ÉTUDES DE LA SUBTHALAMOTOMIE COMME TRAITEMENT DES DYSKINÉSIES CHEZ LE PRIMATE PARKINSONIEN

Thèse

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Résumé court

La présente thèse comprend une étude des mécanismes neurochimiques d'une approche chirurgicale, la subthalamotomie, pour le traitement de la maladie de Parkinson et les dyskinésies induites à la L-DOPA. Nous avons cherché à identifier, à l'aide de quelques hypothèses de recherche, les changements biochimiques dans les ganglions de la base induits par la lésion du noyau sous-thalamique. Nous avons utilisé un modèle de singe parkinsonien traité à la L-DOPA et ayant reçu une subthalamotomie unilatérale. Nos résultats démontrent que la subthalamotomie potentialise la réponse à faible dose de L-DOPA et que cette potentialisation serait entre autre régulée par le récepteur dopaminergique D_1 et les récepteurs glutamatergiques métabotropiques. Ces données apportent de nouveaux éléments aidant à mieux comprendre les mécanismes de cette chirurgie pour le traitement des dyskinésies induites à la L-DOPA. De telles connaissances ouvrent la porte à de nouvelles stratégies pour augmenter la réponse chirurgicale du patient.

Résumé long

La lésion du noyau sous-thalamique, ou subthalamotomie, est une procédure chirurgicale utilisée chez les patients parkinsoniens réfractaires à la L-DOPA ou qui présentent des dyskinésies induites par cette médication dont les mécanismes d'action restent obscurs. Dans le but de pousser l'étude de ses mécanismes, nous avons utilisé un modèle animal de la maladie de Parkinson, le singe MPTP. L'administration chronique de L-DOPA, médication utilisée chez le patient parkinsonien, induit des effets secondaires comparables à ceux observés chez l'homme, incluant les dyskinésies. Les singes de notre étude présentaient des dyskinésies induites à la L-DOPA, répliquant ainsi la situation clinique pour laquelle certains patients se font offrir une chirurgie. Ensuite, ces singes ont reçu une subthalamotomie unilatérale, dont le côté non-lésé a servi de contrôle intra-animal. La réponse antiparkinsonienne à faible dose de L-DOPA fut potentialisée par la subthalamotomie.

Nous avons étudié par autoradiographie les récepteurs dopaminergiques D_1 et D_2, glutamatergiques ionotropiques NMDA (contenant la sous-unité NR1/NR2B) et AMPA, glutamatergiques métabotropiques mGluR2/3 et mGluR5, ainsi que le transporteur et de la dopamine (DAT) en utilisant respectivement les radioligands sélectifs [^{3}H]-SCH-23390, [^{3}H]-Raclopride, [^{3}H]-Ro 25-6981, [^{3}H]-Ro 48-8587, [^{3}H]-LY-341495, [^{3}H]-ABP688, et [^{125}I]-RTI-121. L'ARN messager des récepteurs D_1, D_2 et de la préproenképhaline furent mesurés par hybridation *in situ* avec des sondes oligonucléotidiques pour l'ARNm et l'ARNm de la préprodynorphine avec une sonde ribonucléotidique. Nous avons aussi mesuré les concentrations de dopamine et ses métabolites par chromatographie liquide à haute performance. Finalement, nous avons mesuré les protéines de signalisation intracellulaire ERK1 et ERK2 et leurs formes phosphorylées, ainsi que la protéine DARPP-32 par immunobuvardage de type Western. Nos résultats démontrent que le récepteur dopaminergique D_1, mais pas le récepteur D_2, ainsi que les deux récepteurs glutamatergiques métabotropiques investigués participeraient à la réponse comportementale de la subthalamotomie. Ces données suggèrent que la potentialisation de la réponse à la L-DOPA suivant la subthalamotomie serait due principalement à des changements dans la

voie directe du modèle des ganglions de la base et des voies de sortie du noyau sous-thalamique. Nos résultats ouvrent de nouvelles voies d'exploration sur la subthalamotomie, ainsi que vers d'autres chirurgies offertes aux patients, qu'elles soient lésionnelles ou de stimulation.

Thesis Abstract

Lesion of the subthalamic nucleus, also called subthalamotomy, is surgical therapy offered to parkinsonian patients refractory to L-DOPA or for whom L-DOPA-induced dyskinesias become disabling. Its mechanisms remain however largely unknown. In order to better understand the biochemical and cellular changes underlying subthalamotomy, we used an Parkinson's disease animal model, the MPTP monkey. Chronic administration of L-DOPA in this animal model induces dyskinesias, as those seen in parkinsonian patients. The monkeys used in this study displayed such side effects and took part of different pharmacological trials to reduce these dyskinesias before undergoing surgery. Thus, we replicated the clinical situation where patients receive such surgery when all the other pharmacological treatments have failed. These monkeys received a unilateral subthalamotomy, the non-lesioned side served as an intra-animal control. Antiparkinsonian response to low dose of L-DOPA was potentiated by subthalamotomy.

Then, we studied by autoradiography the D_1 and D_2 dopaminergic receptors, ionotropic NMDA (NR1/NR2B) and AMPA, metabotropic mGluR2/3 and mGluR5 glutamatergic receptors, and the dopaminergic transporter (DAT) using respectively the selective radioligands [^{3}H]-SCH-23390, [^{3}H]-Raclopride, [^{3}H]-Ro 25-6981, [^{3}H]-Ro 48-8587, [^{3}H]-LY-341495, [^{3}H]-ABP688 and [^{125}I]-RTI-121. We measured by *in situ* hybridization the D_1, D_2 and preproenkephalin mRNAs using oligonucleotides as well as preprodynorphin mRNA using a riboprobe. We also assessed the dopamine and its metabolites by high-performance liquid chromatography. Finally, we measured the proteins ERK1 and ERK2, involved in intracellular signaling, and their respective phosphorylation state, as well as DARPP-32 by Western blot. Our results show that the dopamine D_1 receptor, but not D_2, as well as the metabotropic glutamate receptors are involved in the behavioral effects of subthalamotomy. This data suggest that the potentiation of response to L-DOPA after subthalamotomy would be due to changes in the direct pathway of the model of basal ganglia and in the subthalamic output. Our results open new and exciting pathways to explore on subthalamotomy, as well as other surgeries that are offered to disabled

patients with movement disorders, whether these surgeries are lesional or with implantable stimulation devices.

Avant-propos

Durant ces quatre années de doctorat, plusieurs personnes ont joué un rôle dans le déroulement de mes recherches. Sans leur support, cette thèse ne serait pas ce qu'elle est aujourd'hui.

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Contribution des auteurs

Chapitre 5

Ce chapitre est un article de recherche originale publiée dans la revue scientifique *Journal of Neurosurgery* sous la référence : Jourdain VA, Grégoire L, Morissette M, Morin N, Parent M, Di Paolo T. Potentiation of response to low-doses of levodopa in MPTP-injected monkeys by chemical unilateral subthalamotomy. J Neurosurg (2013) 118;1:180-191.

Contribution : Design expérimental (Jourdain, Di Paolo), les expériences et chirurgies (Jourdain, Grégoire, Parent), acquisition des données (Jourdain, Grégoire, Morin, Morissette), les analyses statistiques et interprétation (Jourdain, Grégoire, Di Paolo), rédaction de l'article (Jourdain), révision de l'article (tous les auteurs), approbation finale de l'article (Di Paolo), supervision de l'étude (Di Paolo).

Chapitre 6

Ce chapitre est un article de recherche originale en préparation sous la référence : Jourdain VA, Morin N, Morissette M, Grégoire L, Di Paolo T. Dopamine receptors and subthalamotomy-associated improved motor response in parkinsonian monkeys.

Contribution : Design expérimental (Jourdain, Di Paolo), les expériences (Jourdain, Morissette, Morin), acquisition des données (Jourdain), les analyses statistiques et interprétation (Jourdain, Grégoire, Di Paolo), rédaction de l'article (Jourdain), révision de l'article (tous les auteurs), approbation finale de l'article (Di Paolo), supervision de l'étude (Di Paolo).

Chapitre 7

Ce chapitre est un article de recherche originale en préparation sous la référence: Jourdain VA, Grégoire L, Morin N, Morissette M, Di Paolo T. Modulation of glutamate receptors in dyskinetic MPTP monkeys receiving a unilateral subthalamotomy.

Contribution : Design expérimental (Jourdain, Di Paolo), les expériences (Jourdain, Morissette, Morin), acquisition des données (Jourdain), les analyses statistiques et interprétation (Jourdain, Grégoire, Di Paolo), rédaction de l'article (Jourdain), révision de l'article (tous les auteurs), approbation finale de l'article (Di Paolo), supervision de l'étude (Di Paolo).

Appendice 1

Cet appendice est un article de revue de littérature sous presse dans la revue scientifique *Journal of Neurosurgery* sous la référence : Jourdain VA, Schechtmann G, Di Paolo T. The role of the subthalamic nucleus and subthalamotomy in the treatment of Parkinson's disease.

Contribution : Rédaction de l'article (Jourdain, Schechtmann), révision de l'article (tous les auteurs), approbation finale de l'article (Di Paolo).

Appendice 2

Cet appendice est un article de revue de littérature sous invitation dans la revue scientifique *Experimental Neurology* sous la référence : Morin N*, Jourdain V*, Di Paolo T. Modeling dyskinesia in animal models of Parkinson disease. Exp Neurol (2013) doi : 10.1016/j.expneurol.2013.01.024.

Contribution : Rédaction de l'article (tous les auteurs avec une contribution égale de Morin et Jourdain), révision de l'article (tous les auteurs), approbation finale de l'article (Di Paolo).

Appendice 3

Cet appendice est un chapitre de livre en révision sous invitation dans le livre de référence *Levodopa-induced dyskinesia* sous la référence : Jourdain V*, Morin N*, Di Paolo T. Chapter 9 – Dopamine Receptors and LID, in Fox S, Brotchie J (eds) : **Levodopa-induced dyskinesia**. Berlin : Springer.

Contribution : Rédaction de l'article (tous les auteurs avec une contribution égale de Jourdain et Morin), révision de l'article (tous les auteurs), approbation finale de l'article (Di Paolo).

Table des matières

Liste des figures

Liste des tables

Liste des abréviations

5-HT	Sérotonine
6-OHDA	6-hydroxydopamine
AC	Adénylyl cyclase
AChE	Acetylcholinesterase
AMP	Adénosine monophosphate
ARN	Acide ribonucléique
ATP	Adénosine triphosphate
AMPA	Acide α-amino-3-hydroxy-5-méthyl-4-isoxazolepropionique
ANOVA	Analyse de variance
BG	Basal ganglia (ganglions de la base)
BHE	Barrière hémato-encéphalique
CM	Noyau centromédian du thalamus
CN	Noyaux profonds du cervelet
COMT	Catéchol-*O*-méthyltransférase
DA	Dopamine
DARPP-32	DA- and cAMP-regulated phosphoprotein of 32kDa
DAT	Dopamine transporter (transporteur de la dopamine)
DBS	Deep brain stimulation (stimulation cérébrale profonde)
DDC	Dopa décarboxylase
DOPAC	Acide 3,4-dihydroxyphénylacétique
DPMP	Déhydro-4-phényl-*N*-méthylpipéridine
ERK	Extracellular signal-regulated kinase
GABA	Acide γ-aminobutyrique
GPe	Globus Pallidus pars externa
GPi	Globus Pallidus pars interna
H_1	Fasciculus thalamique
H_2	Fasciculus lenticularis
HFS	High-frequency stimulation (stimulation à hautes fréquences)
HPLC	High-performance liquid chromatography
HPMP	4-hydroxy-4-phényl-*N*-méthylpipéridine
HVA	Acide homovanillique
Hz	Hertz
IEG	Immediate-early genes
L-Dopa	Lévodopa, L-3,4-dihydroxyphenylalanine
LID	Dyskinésies induites à la lévodopa
LDME	L-DOPA methylester
LTD	Dépotentialisation à long-terme
LTP	Potentialisation à long-terme
MAO	Monoamine oxydase
MD	Noyau médiodorsal du thalamus
MER	Micro-enregistrement neuronal
MFB	Faisceaux télencéphaliques médians
MI	Cortex moteur primaire
MPDP+	1-méthyl-4-phényl-2,3-dihydropyridinium

MPTP	1-méthyl-4-phényl-1,2,3,6-tétrahydropyridine
MPP+	1-méthyl-4-phénylpyridinium
MPPP	1-méthyl-4-phényl-4-propionoxypipéridine
MSN	Neurones de calibres moyens épineux
NMDA	N-methyl-D-aspartate
NO	Oxyde nitrique
OONO-	Peroxynitrite
PBS	Sodium Phosphate buffer
PD	Maladie de Parkinson, Parkinson's disease
PET	Tomographie par émission de positrons
Pf	Noyau parafasciculaire du thalamus
PM	Cortex pré-moteur
PPD	Préprodynorphine
PPE	Préproenképhaline
PPN	Noyau péducunlopontin
PPNc	Noyau péducunlopontin pars compacta
PPNd	Noyau péducunlopontin pars dissipata
PVP	Pallidotomie postéroventrale
SERT	Transporteur de la sérotonine
SMA	Aire motrice supplémentaire
SNc	Substantia nigra pars compacta
SNcd	Partie dorsale de la substantia nigra pars compacta
SNcv	Partie ventrale de la substantia nigra pars compacta
SNr	Substantia nigra pars reticulata
SP	Substance P
STN	Subthalamic nucleus
TH	Tyrosine hydroxylase
TRIS	Tris-[hydroxyméthyl]-aminométhane
VA	Noyau ventral antérieur du thalamus
VAL	Partie latérale du noyau ventral antérieur du thalamus
VAM	Partie médiane du noyau ventral antérieur du thalamus
VApc	Partie parvicellulaire du noyau ventral antérieur du thalamus
VIM	Noyau ventrointermédian du thalamus
VL	Noyau ventral latéral du thalamus
VLc	Partie caudale du noyau ventral latéral du thalamus
VLo	Partie orale du noyau ventrolatéral du thalamus
VPLo	Partie orale du noyau postérolatéral du thalamus (VIM selon l'atlas de Hassler)
VMAT	Transporteur vésiculaires des monoamines
VMT	Tegmentum mésencéphalique ventromédian
VTA	Aire tegmentaire ventrale

PARTIE I. INTRODUCTION GÉNÉRALE ET HYPOTHÈSES DE RECHERCHE

As long as our brain is a mystery, the universe, the reflection of the structure of the brain will also be a mystery

- Santiago Ramón y Cajal

Chapitre 1. Anatomie structurelle et fonctionnelle des ganglions de la base

1.1 Introduction générale

Les ganglions de la base (BG), ensemble de structures sous-corticales, sont les principaux acteurs de la planification et la coordination du mouvement (Haber *et coll.*, 2012). Un dérèglement dans une des structures des BG peut se traduire sous la forme de troubles du mouvement (Obeso et Lanciego, 2011). De ces derniers, il existe les formes hyperkinétique ou hypokinétique, telles que la maladie d'Huntington et la maladie de Parkinson (PD) respectivement (Albin *et coll.*, 1989).

Les troubles du mouvement sont des désordres connus que chez l'humain, mais peuvent être reproduits chez certains animaux par des traitements pharmacologiques ou par transformations génétiques. Il n'existe encore aujourd'hui aucun traitement curatif de la PD, qui est caractérisée par une pauvreté du mouvement. La L-DOPA, introduite dans les années 1960 (Birkmayer et Hornykiewicz, 1961), est le traitement pharmacologique de choix (Goetz *et coll.*, 2005). Toutefois, son utilisation à long-terme induit des mouvements involontaires, tels que les dyskinésies (LID) (Markham, 1971). Les LID seraient le produit de la stimulation pulsatile des récepteurs dopaminergiques à des doses non-physiologiques chez un patient ayant une dénervation dopaminergique importante (Jenner, 2008).

Le noyau sous-thalamique (STN), structure importante des BG, est la cible thérapeutique de choix pour deux traitements chirurgicaux pour la PD, soient la subthalamotomie et la stimulation cérébrale profonde (DBS) (Walter et Vitek, 2004). Les mécanismes de ces deux procédures neurochirurgicales sont encore peu connus. Cette thèse s'est penchée sur la subthalamotomie. Une meilleure compréhension des changements biochimiques suivant cette chirurgie permettrait une potentialisation de la réponse à ce traitement et améliorer la condition du patient.

À moins que mentionné, la présente thèse se basera sur des données obtenues chez l'humain et le primate non-humain, étant donné la nature des recherches qui y seront présentées et pour éviter la confusion entre les espèces (rongeurs et primates).

1.2 Ganglions de la base

> *[…] the ganglia situated in the base of the brain still, to a large extent, retain the characteristic of basements-viz., darkness.* (Wilson, 1925)

Les BG sont un regroupement de structures sous-corticales architecturalement et chimiquement organisées qui sont impliquées dans le contrôle du comportement psychomoteur (Figure 1.1). Initialement, les BG étaient restreints au striatum et aux deux segments du globus pallidus (Haber *et coll.*, 2012). Il est maintenant considéré que la substance noire et le STN sont des structures intrinsèques aux BG. Finalement, le thalamus et le noyau pédunculopontin ne sont pas considérés comme faisant partie de ce groupe de structures sous-corticales (Haber *et coll.*, 2012), mais ils y jouent néanmoins un rôle important dans la régulation de l'activité fonctionnelle (Geula et Mesulam, 2012, Mai et Forutan, 2012). Cette section présentera chacune de ces structures en terme de morphologie, connexions, interactions et neurochimie.

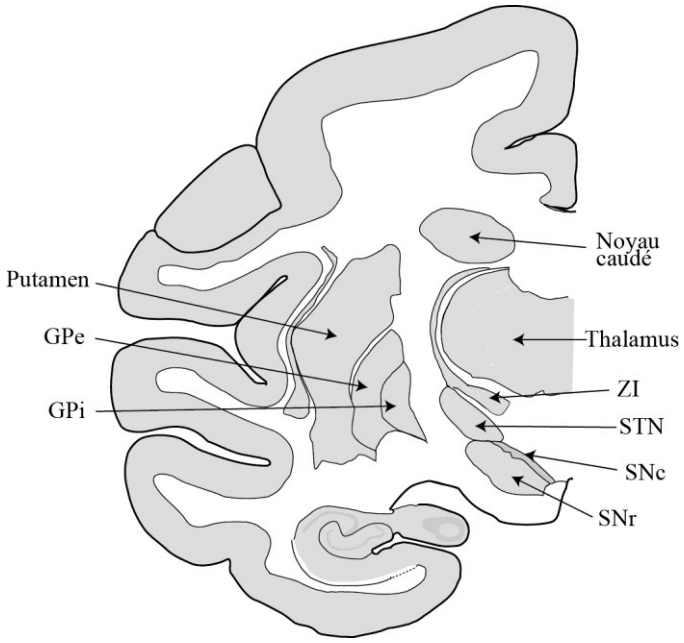

Figure 1.1 Ganglions de la base chez le primate. GPe: globus pallidus externe, GPi: globus pallidus interne, SNc: substance noire pars compacta, SNr: substance noire pars reticulata, STN: noyau sous-thalamique, ZI: zona incerta

1.2.1 Striatum

Le striatum (appelé neostriatum dans la vieille littérature) est la plus grosse structure des BG et la principale porte d'entrée de ceux-ci. Rostralement, le striatum se présente comme une structure unique, alors que caudalement le passage des fibres de la capsule interne le subdivise en une partie médiane, le noyau caudé, et une partie latérale, le putamen (Parent et Carpenter, 1996). Le noyau caudé prend la forme allongée qui suit de très près les ventricules latéraux. Dans sa portion très antérieure, la « tête » du noyau caudé est à sa pleine grosseur et est fusionné avec le putamen (Szabo et Cowan, 1984). Le putamen constitue la plus grosse partie du striatum, se situe plus latéralement que le noyau caudé et prend une forme lenticulaire (Parent et Carpenter, 1996). La capsule interne sépare les deux composantes du striatum. Médialement au putamen se retrouve le globus pallidus externe, séparé par la lame médullaire externe (Parent et Carpenter, 1996).

Le striatum se compose principalement de neurones de calibres moyens épineux (medium-sized spiny neurons, MSN), mais aussi d'un faible nombre d'interneurones de moyen ou de gros calibre (Kawaguchi *et coll.*, 1995). Les MSN constituent la grande majorité des neurones de projection du striatum (Graveland et DiFiglia, 1985). Ils forment des contacts synaptiques symétriques, contenant du GABA, avec principalement le complexe pallidal et la substance noire (Smith *et coll.*, 1998). Il est généralement admis que les cellules striatales de projection colocalisent les neuropeptides substance P/dynorphine ou enképhaline avec le GABA et forment deux voies de projection distinctes vers le globus pallidus interne (GPi) et le globus pallidus externe (GPe) respectivement, pour former la voie directe et indirecte du modèle des ganglions de la base (voir section 3.3). Des études ont démontré que cette distinction n'est pas aussi claire, car de l'enképhaline fut trouvée dans le GPi et de la substance P dans le GPe (Haber et Watson, 1985). De plus, la plupart des neurones si ce n'est pas tous les neurones du striatum projettent au GPe et qu'environ la moitié projettent strictement au GPe tandis que l'autre moitié auraient des collatérales vers le GPi et la substance noire pars reticulata (Kita, 2007, Parent *et coll.*, 1995a). La collatéralisation striatofugale est complexe et démontre que plusieurs types de neurones arborisent une ou plusieurs structures (Lévesque et Parent, 2005b).

Le striatum est fonctionnellement hétérogène; l'on y retrouve trois territoire distincts reliés chacun à une fonction spécifique, soit les fonctions sensorimotrice, associative et

motrice (Parent et Hazrati, 1995a). La portion sensorimotrice est de loin la plus importante et représente la quasi-totalité du volume total du putamen caudal. Elle reçoit des projections massives excitatrices provenant du cortex (pour un élégant sommaire, voir (Smith, 2011)). Ces projections corticostriatales se distribuent de manière hétérogène au niveau du striatum en striosomes et en matrice extrastriosomale. Ces deux compartiments du striatum se distinguent, entre autres, à partir du niveau d'expression d'acétylcholinestérase (AChE) et de leurs projections afférentes et efférentes distinctes. Les striosomes sont "pauvres" en AChE, mais expriment abondamment différents récepteurs aux opiacés. Cependant, la matrice entourant les striosomes est "riche" en AChE (Graybiel, 1983, Graybiel, 1990, Graybiel et Ragsdale, 1978). D'autre part, les striosomes et la matrice extrastriosomale reçoivent une innervation corticale distincte. En effet, les striosomes reçoivent principalement une afférence préfrontale et sensorimotrice (Eblen et Graybiel, 1995, Flaherty et Graybiel, 1991), tandis que la matrice extrastriosomale une innervation provenant du cortex occipital, pariétal, frontal et sensorimoteur (Flaherty et Graybiel, 1991, 1993, 1994). Conséquemment, cette hétérogénéité structurelle du striatum suggère une différentiation fonctionnelle entre les deux divisions (Holt *et coll.*, 1997, Selemon *et coll.*, 1994). En plus de recevoir des afférences corticales, le striatum est aussi largement innervé par le noyau centromédian/parafasciculaire du thalamus (Parent et Parent, 2005) et la substance noire pars compacta (Lavoie *et coll.*, 1989). Chez le rat, les terminaisons dopaminergiques se retrouvent proches de celles provenant du cortex (Wang et Pickel, 2002), ce qui aurait un effet modulateur sur l'influence glutamatergique corticale. Finalement, les deux segments du globus pallidus (Beckstead, 1983, Sato *et coll.*, 2000a, Spooren *et coll.*, 1996), le STN (Smith *et coll.*, 1990), le noyau raphé (Lavoie et Parent, 1990, Parent *et coll.*, 2011) et le noyau pédunculopontin (Lavoie et Parent, 1994c, Nakano *et coll.*, 1990) projettent au striatum chez le primate, mais à moindre mesure.

1.2.2 Globus pallidus

Le globus pallidus (appelé paleostriatum dans la vieille littérature) consiste en deux segments similaires qui sont des dérivés diencéphaliques. Morphologiquement, les cellules des deux segments (interne et externe) sont similaires (Fox *et coll.*, 1974), principalement ce sont des neurones relativement larges présentant des dendrites avec peu

d'embranchements et des épines éparses. Le pallidum est composé de plusieurs couches de neurones aplatis dont les dendrites sont orientées vers les fibres afférentes (Percheron *et coll.*, 1984). Toutefois, les neurones de chaque segment présentent des fonctions et afférences différentes.

1.2.2.1 Globus pallidus pars interna (GPi)

Le GPi est séparé latéralement du GPe par la lame médullaire interne, tandis que la capsule interne l'isole médialement de la substance noire et du STN. Le GPi est divisé dans des portions médiales et latérales par des fibres verticales provenant de l'ansa lenticularis (Parent et Carpenter, 1996). Une telle division pourrait refléter le fait que les neurones de projections du GPi sont plus ou moins ségrégés selon leur cible d'efférence. En effet, les structures efférentes pallidales sont innervées par l'une des projections, qui sont l'ansa lenticularis, le fasciculus lenticularis (aussi appelé H_2) et les fibres pallidotegmentales (Parent et Carpenter, 1996, Shink *et coll.*, 1997). Les fibres de l'ansa lenticularis, qui proviennent de la partie latérale du GPi, forment une bandelette qui passe ventromédialement et rostralement au GPi et qui contourne la capsule interne et le noyau sous-thalamique pour fusionner avec le H_2 dans les champs H de Forel. De son côté, le fasciculus lenticularis provient de la partie médiale et traverse la capsule interne pour former une bandelette ventrale à la zona incerta. Le fasciculus lenticularis se fusionne avec l'ansa lenticularis pour former le fasciculus thalamique (H_1) et innerve différents noyaux thalamiques (Schaltenbrand et Wahren, 1977). Ces projections pallidothalamiques sont topographiques car elles maintiennent leur intégrité fonctionnelle dans le thalamus, suggérant des différences fonctionnelles (Baron *et coll.*, 2001, Kuo et Carpenter, 1973). Les régions pallidales qui reçoivent des efférences sensorimotrices du striatum projettent vers le la portion latérale du noyau ventrolatéral (VL) du thalamus, tandis que les efférences associatives sont retransmises aux noyaux ventral antérieur (VA) et médiodorsal (MD) du thalamus (Parent *et coll.*, 2001). Certaines de ces fibres pallidothalamiques projettent des collatérales qui se terminent dans les noyaux intralaminaires, centromédian (CM) et parafasciculaire (Pf) (Parent *et coll.*, 2001). Les fibres pallidotegmentales se terminent dans le noyau pédunculopontin (PPN). Ses projections thalamiques et pédunculonpontine confèrent au GPi un rôle dans la sortie d'information des BG. Le GPi est récipiendaire d'afférences principalement sous-thalamiques (Parent et Parent, 2007) et striatales (Parent

et coll., 1995a). Il est aussi bien connu que le GPi est profusément innervé par le noyau raphé (Parent *et coll.*, 2011) et le PPN (Lavoie et Parent, 1994c).

1.2.2.2 Globus pallidus pars externa (GPe)

Les lames médullaires externe et interne forment respectivement les bordures latérales et médiales du GPe, les séparant du striatum et du GPi (Parent et Carpenter, 1996). Le GPe projette principalement au STN via le fasciculus subthalamique, qui est une bandelette de fibres qui comprend les axones pallidosubthalamiques ainsi que les fibres subthalamopallidales (Shink *et coll.*, 1996). Le STN, en retour, projette aussi vers le GPe (Carpenter *et coll.*, 1981b). Cette connexion réciproque confèrerait au GPe un rôle dans le contrôle de l'activité sous-thalamique. De plus, environ 30% des neurones du GPe projettent strictement vers le striatum (Kita *et coll.*, 1999, Sato *et coll.*, 2000a), tandis que le GPi, le mésencéphale et le thalamus sont des structures recevant une innervation du GPe par projection directe ou par collatérales (Asanuma, 1994, Beckstead, 1983, Hazrati et Parent, 1991b, Hazrati *et coll.*, 1990, Kita *et coll.*, 1999, Parent *et coll.*, 1991). En termes d'afférences, le GPe reçoit des innervations dopaminergiques, cholinergiques et sérotoninergiques de la SNc, du PPN et du noyau raphé respectivement (Charara et Parent, 1994, Lavoie et Parent, 1994c, Lavoie *et coll.*, 1989, Parent *et coll.*, 2011). Des afférences corticopallidales furent démontrées chez le rat, mais aucune étude n'a pu le démontrer chez le primate (Naito et Kita, 1994). Tout comme le GPi, les projections du GPe sont organisées de manière topographique pour le maintien fonctionnel au-travers des structures cibles (Mink, 1996, Nambu, 2011).

1.2.3 Substance noire pars reticulata (SNr)

La substance noire est une structure de forme ovale qui se retrouve dorsalement aux pédoncules cérébraux, ventralement au STN, antérieurement au noyau rouge et antérolatéralement à l'hypothalamus latéral (Parent et Carpenter, 1996). Selon des critères chimique et cytoarchitecturel, la substance noire se divise en deux groupes de cellules, soient la substance noire pars compacta (SNc) et la substance noire pars reticulata (SNr) (Poirier *et coll.*, 1983). Bien que cette dernière est une structure bien définie, elle peut être considérée comme une extension antéromédiale du GPi en prenant compte de sa morphologie, ses connexions, sa physiologie et sa neurochimie (Percheron *et coll.*, 1994,

Percheron *et coll.*, 1984, Yelnik *et coll.*, 1987). En effet, les neurones de la SNr, présentent des dendrites longues et épaisses qui sont recouvertes de contacts synaptiques (Yelnik *et coll.*, 1987). Ils déchargent de façon continue à une fréquence aussi similaire au GPi, soit environ 50 à 70 Hz (Schultz, 1986, Wichmann *et coll.*, 1999). Finalement, en plus de posséder les mêmes connections thalamiques (principalement le VA) que le GPi, la SNr latérale projette vers le colliculus supérieur pour le contrôle du mouvement des yeux (Hikosaka et Wurtz, 1983). Malgré ces similitudes, les cellules de la SNr proviennent d'une population différente du GPi tel que démontré dans le développement embryonnaire chez le rat (Marchand et Lajoie, 1986, Marchand et Poirier, 1983).

1.2.4 Substance noire pars compacta (SNc)

La SNc est facilement identifiable par sa coloration noire provenant d'un sous-produit de la synthèse de la dopamine (DA), la neuromélanine (Double *et coll.*, 2008). Cette structure joue un rôle crucial dans le mouvement. La dégénérescence de ces cellules est un fait saillant dans la PD (voir section 2.3). La SNc se divise en deux feuillets ou couches, soit la partie dorsale (SNcd) et la partie ventrale (SNcv). La SNcv comprend les colonnes cellulaires et densocellules, ces dernières sont particulièrement sensibles à une dégénérescence induite par la neurotoxine 1-méthyl-4-phényl-1,2,3,6-tétrahydropyridine (MPTP) (voir section 2.4.2) et dans la PD (Lavoie et Parent, 1991a, Pifl *et coll.*, 1991). La SNcd est significativement plus large que son homologue SNcv, mais les deux comportent un nombre similaire de cellules dopaminergiques (Hardman *et coll.*, 2002). La cible principale de la SNc est le striatum (Lavoie *et coll.*, 1989). Il semble y exister une connexion réciproque entre la SNc et le striatum. En effet, chaque neurone de la SNc reçoit une innervation d'une centaine de neurones striataux (Percheron *et coll.*, 1994). La SNcd reçoit principalement des afférences associatives du noyau caudé et du putamen antérieur, tandis que la SNcv reçoit une innervation associative et sensorimotrice (Haber *et coll.*, 2000). Plus particulièrement, la partie ventrolatérale du SNcv et les parties sensorimotrices dorsolatérales du putamen sont interconnectées. En retour, chaque neurone de la SNc couvre jusqu'à 5% du territoire striatal, innervant autant la matrice que les striosomes, tel que mesuré chez le rat (Matsuda *et coll.*, 2009).

En plus de ses connexions avec le striatum, la SNc reçoit des projections pallidales ventrales, qui terminent principalement dans la région densocellulaire (Haber *et coll.*, 1993). De plus, des afférences du PPN se terminent dans la SNc et forment des contacts sur les corps cellulaires de la SNcd (Lavoie et Parent, 1994a). Des terminaisons sérotoninergiques provenant du noyau raphé ont été démontré dans la SNc, mais à moindre mesure que la SNr (Parent *et coll.*, 2011). En retour, la SNc projette vers les deux segments du globus pallidus (Lavoie *et coll.*, 1989), le STN (Lavoie *et coll.*, 1989), le PPN (Rolland *et coll.*, 2009), le noyau raphé (Moore *et coll.*, 2003) et le thalamus (Freeman *et coll.*, 2001).

L'aire tegmentaire ventrale (VTA) et les champs rétrorubraux se situent respectivement dorsalement et médialement à la SNcd. La VTA est impliquée dans le système de la récompense (Ikemoto, 2007) et dans les fonctions cognitives (Goldman-Rakic *et coll.*, 2004). Malgré le fait que les champs rétrorubraux sont considérés comme une partie intégrante du système mésencéphalique (Björklund et Dunnett, 2007), elle demeure la structure la moins étudiée. Ces deux structures dopaminergiques innervent aussi le striatum (Deutch *et coll.*, 1988, Francois *et coll.*, 1999, Ikemoto, 2007), mais il ne semble pas exister une connectivité réciproque. Les champs rétrorubraux pourraient jouer un rôle dans le contrôle des mouvements orofaciaux (von Krosigk *et coll.*, 1992) et qu'une perte de cellules dans cette structure pourrait contribuer à la réduction de l'expression faciale (*mask-like face*) chez le patient parkinsonien (Spooren *et coll.*, 1993). En prenant compte de la nature peu motrice de ces deux structures mésencéphaliques, les connexions fonctionnelles ne seront pas révisées dans cette présente thèse (pour plus d'informations sur ce sujet, voir (Halliday *et coll.*, 2012)).

1.2.5 Noyau sous-thalamique (STN)

Le STN est une structure biconvexe encapsulée par des bandes majeures de fibres (Parent et Hazrati, 1995b). Dorsalement se situent la zona incerta et le fasciculus H_2, qui séparent le STN du VL thalamique et des radiations prélemniscales (Parent et Carpenter, 1996). Latéralement, la capsule interne sépare le STN du GPi (Parent et Carpenter, 1996). Les champs H de Forel et la substance noire forment respectivement les bordures rostromédiales et ventrales du STN (Parent et Carpenter, 1996). Chez le macaque, deux

types de neurones de projections et un type d'interneurones ont été isolés (Rafols et Fox, 1976). Une étude comparative a démontré une augmentation du nombre de cellules et du volume du STN en partant du rat, chez certains primates et l'humain (Hardman *et coll.*, 2002). Le STN du macaque contenant 154 000 neurones pour un volume total de 34mm^3.

Il fut longtemps reconnu que le STN se divisait en trois parties selon leurs efférences : les neurones de la partie dorsolatérale projettant vers les structures sensorimotrices (75-80%), les neurones de la portion ventromédiales feraient partie des voies associatives (15-20%) et les neurones de la portion de la pointe médiale (5-10%) projettant vers des structures impliquées dans le système limbique (Parent et Hazrati, 1995b, Parent et Smith, 1987). Une revue récente de littérature a remis en question ce modèle de tripartite du STN (Keuken *et coll.*, 2012). Les auteurs de cette étude ont proposé que le STN pourrait être encore sous-divisé, surtout considérant les cinq circuits parallèles, impliquant aussi le STN, précédemment proposé par Alexander et Crutcher (Alexander et Crutcher, 1990). Les deux segments du globus pallidus sont certainement les cibles majeures d'efférences du STN (Carpenter et Strominger, 1967, Nauta et Cole, 1978, Smith *et coll.*, 1990). Les fibres subthalamopallidales sont organisées de manière topographique et se terminent dans les deux segments pallidaux, formant au moins deux bandes verticales dans chaque segment (Parent et Hazrati, 1995b) très similaires à celles produits par les fibres striatopallidales (Parent et Hazrati, 1995a). De plus, les axones du STN arborisent de larges portions du pallidum et convergeant avec les afférences striatales (Parent et Hazrati, 1995b). La SNr est une des cibles principales du tiers ventromédian efférents du STN (Carpenter et Strominger, 1967). D'un autre côté, la VTA et la SNc seraient innervées par la pointe médiale du STN (Smith *et coll.*, 1990). De plus, l'arborisation axonale émergeant du STN est complexe. En effet, environ 25% des neurones innervant la SNr projettent vers le GPe, le GPi ou les deux (Sato *et coll.*, 2000b). Près de la moitié des neurones subthalamofugaux innervent les deux segments pallidaux (Sato *et coll.*, 2000b). Certains axones atteignent le striatum (Carpenter et Strominger, 1967, Nauta et Cole, 1978), par collatérales de la voie subthalamonigrale (Parent et Smith, 1987) ou peut-être par voie directe (Sato *et coll.*, 2000b). Il semblerait toutefois que ces collatérales vers le striatum proviennent de populations neuronales différentes que celles se dirigeant vers le pallidum (Parent et Smith, 1987). Chez le rat, le STN projette vers le PPN (Granata et Kitai, 1989,

Jackson et Crossman, 1981b) et peut-être vers le cortex cérébral (Jackson et Crossman, 1981a) et la moelle épinière (Takada *et coll.*, 1987), mais aucune étude chez le primate n'a pu confirmer ces connexions.

L'afférence majeure au STN provient du GPe (Carpenter *et coll.*, 1981a, Shink *et coll.*, 1996). Les boutons GABAergiques de la voie pallidosubthalamique couvrent complètement le périkarya des neurones de projections du STN, ainsi que leurs dendrites (Carpenter *et coll.*, 1981b, Nauta et Mehler, 1966, Shink *et coll.*, 1996). Le STN reçoit aussi des afférences corticales, somatotopiquement organisées pour l'aire moteur primaire et topographiquement pour les aires pré-motrice et motrice supplémentaire (Künzle, 1978, Monakow *et coll.*, 1978). Cette voie corticosubthalamique est dénommée hyperdirecte (Nambu *et coll.*, 2002) et jouerait un rôle régulateur dans le modèle des BG (voir sections 3.3 et 3.4). Le PPN envoie bilatéralement des efférences glutamatergiques/cholinergiques vers le STN (Lavoie et Parent, 1994b, c). Le thalamus intralaminaire (voir section 1.2.6.2) projette vers le STN, tel qu'observé chez le rat (Sugimoto et Hattori, 1983, Sugimoto *et coll.*, 1983) et le primate (Sadikot *et coll.*, 1992a). Le STN reçoit aussi des afférences de la SNc (Francois *et coll.*, 2000, Lavoie *et coll.*, 1989, Prensa *et coll.*, 2000) et profusément du noyau raphé (Lavoie et Parent, 1990, Parent *et coll.*, 2011). En somme, le STN présente beaucoup de connexions réciproques avec différentes structures clés des BG (Shink *et coll.*, 1996), lui conférant ainsi un rôle important dans la transmission des informations motrices. En effet, considérant son activité excitatrice, le STN est reconnu pour être une force d'entraînement (Kitai et Kita, 1987).

1.2.6 Thalamus

Le thalamus est une structure qui ne fait pas partie des BG, mais possède des fonctions de relai entre le cortex et ces structures sous-corticales (Guillery et Sherman, 2002). Il se divise en une multitude de noyaux qui se différencient par leurs fonctions, connexions et architecture respectives. Dans le cadre de cette thèse, ce seront les divisions motrices des régions ventrale et intralaminaire qui seront exposées. Il est important de noter que différents atlas sur le thalamus furent publiés (Hassler, 1959, Ilinsky et Kultas-Ilinsky, 2001, Jones, 2007, Olszewski, 1952, Percheron, 2004), chacun utilisant sa propre terminologie et division, ajoutant ainsi à la complexité même du thalamus. Pour réduire la

confusion entre les termes et les sous-structures thalamiques, certains auteurs ont tenté d'arriver à un consensus dans la nomenclature (Krack *et coll.*, 2002, Macchi et Jones, 1997). Dans un souci d'uniformité avec l'aspect clinique, la présente section se basera sur les atlas de (Percheron, 2004) et de (Mai et Forutan, 2012).

1.2.6.1 Thalamus ventral

La portion motrice du thalamus latéral (Figure 1.2) se divise en deux sous-structures, soient le noyau ventral antérieur (VA) et le noyau ventrolatéral (VL). Le VA est le territoire thalamique qui est la cible principale des afférences des BG (Ilinsky et Kultas-Ilinsky, 1987, Ilinsky *et coll.*, 1993). Il se situe dans la portion rostrale du thalamus latéral.

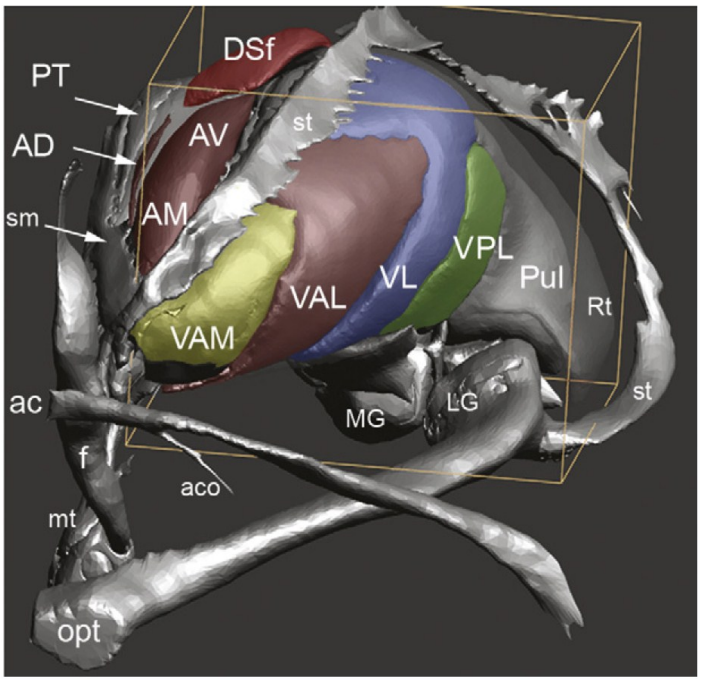

Figure 1.2 Thalamus ventral démontrant le VAM, VAL et VL (Figure tirée de (Mai et Forutan, 2012))

L'organisation et topographie de la voie nigrothalamique chez le primate furent largement étudiées (François *et coll.*, 2002, Sakai *et coll.*, 1996). Cette voie se termine principalement dans le VA médial (VAM), mais aussi dans le médiodorsal (MD) et les noyaux intralaminaires. La majeure partie des efférences du VAM se termine dans le cortex préfrontal (Tanibuchi *et coll.*, 2009). Le VA latéral (VAL) est la cible thalamique principale de la portion médiale du GPi via le fasciculus thalamique H_1 (Ilinsky et Kultas-Ilinsky,

1987, Kim *et coll.*, 1976, Kuo et Carpenter, 1973, Parent *et coll.*, 1999b). En retour, le VAL projette vers trois aires corticales (Nakano *et coll.*, 1993), soient le cortex prémoteur (Morel *et coll.*, 2005, Stepniewska *et coll.*, 2007, Strick, 1976), l'aire motrice supplémentaire (Akkal *et coll.*, 2007, Morel *et coll.*, 2005) et le cortex moteur primaire (Kultas-Ilinsky *et coll.*, 1997). Le noyau VL, aussi dénommé ventrointermédian (VIM) selon différents auteurs (Hassler, 1959, Percheron, 2004), est la portion thalamique qui reçoit les afférences motrices des pédoncules cérébelleux supérieurs via les projections cérébellothalamiques (van Kan *et coll.*, 1993). Les neurones du VL (tremor cells) peuvent se synchroniser à certaines fréquences, ce qui provoque du tremblement chez le patient (Ohye *et coll.*, 1993, Tasker *et coll.*, 1982). Tout comme le VA, le VL projette vers le cortex moteur primaire (Hoover et Strick, 1999, Lu *et coll.*, 2007), l'aire prémotrice (Hashimoto *et coll.*, 2010, Nakano *et coll.*, 1993) et l'aire motrice supplémentaire (Akkal *et coll.*, 2007, Nakano *et coll.*, 1993).

1.2.6.2 Thalamus intralaminaire

Le thalamus intralaminaire se compose de trois noyaux, soient le noyau centromédian (CM), le noyau parafasciculaire (Pf) et le noyau subparafasciculaire (Figure 1.3). Chez l'humain, le CM et le Pf sont souvent combinés ensemble dû à leur connectivité similaire (Sadikot et Rymar, 2009, Smith *et coll.*, 2009), malgré leurs différences structurelles. Le complexe CM/Pf se situe ventralement au MD et dorsalement à la zona incerta, cette dernière qui sépare le noyau rouge du thalamus (Percheron *et coll.*, 1996). Le Pf se situe médialement au CM et apparaît comme son extension. Le complexe CM/Pf se compose de trois types de neurones de projections. Le premier type de neurones projettent vers le striatum, le Pf préférentiellement au territoire associatif, tandis que le CM arborise le territoire moteur du striatum (Parent et Parent, 2005).

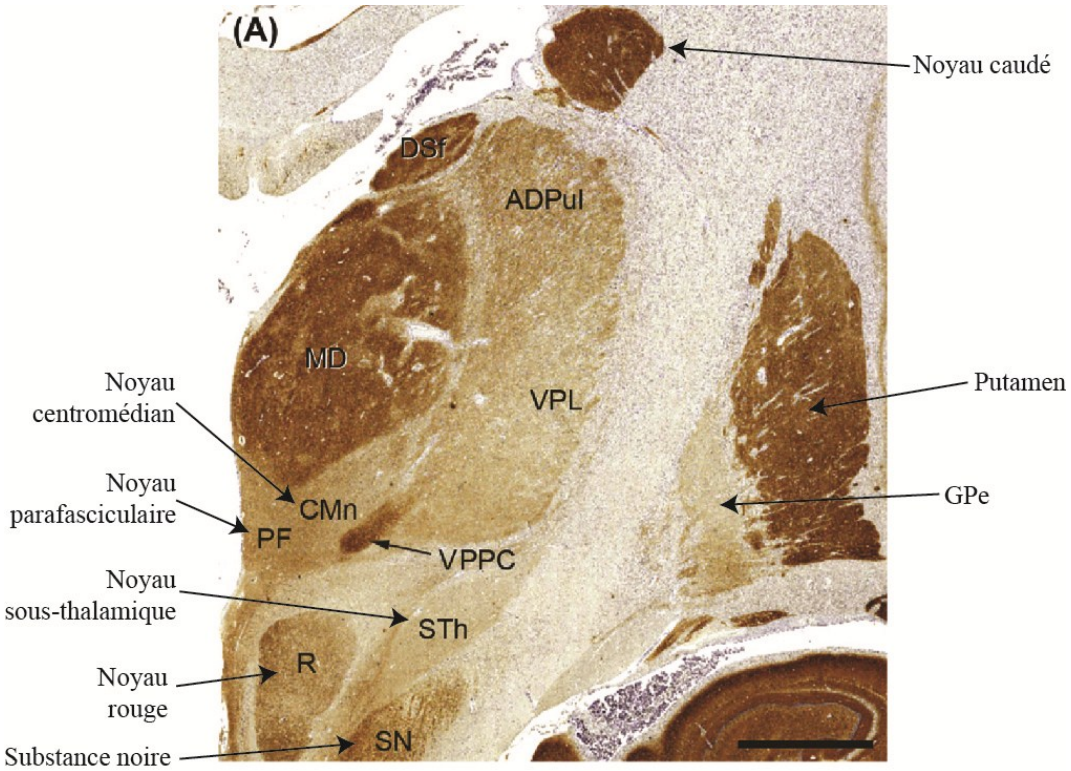

Figure 1.3 Thalamus intralaminaire ainsi que certaines structures des ganglions de la base, coloration immunoréactive pour synaptophysine (Figure adaptée de (Mai et Forutan, 2012))

Il est intéressant de noter que les terminaisons thalamostriatales se situent sur les dendrites et non pas sur les épines dendritiques comme les voies corticostriatales (Smith *et coll.*, 2004). Le second type de neurones projettent vers les couches V et VI du cortex cérébral, le Pf projettant vers les aires préfrontales et le CM vers les aires motrices et pré-motrices (Parent et Parent, 2005). Le dernier type de neurones projettent au striatum et au cortex cérébral (Parent et Parent, 2005). D'autre part, le CM/Pf a des connections avec le GPe, le GPi, le STN, la VTA, la zona incerta, la formation réticulée et la substance noire (Catsman-Berrevoets et Kuypers, 1978, Kuo et Carpenter, 1973, Parent et Parent, 2005, Russchen *et coll.*, 1987, Tandé *et coll.*, 2006).

1.2.7 Noyau pédunculopontin (PPN)

Le PPN est une population de neurones neurochimiquement et morphologiquement hétérogènes se situe caudalement au noyau rouge et à la substance noire (Mesulam *et coll.*, 1989, Pahapill et Lozano, 2000). Tout comme le thalamus, elle ne fait pas partie des BG.

Toutefois, certaines caractéristiques électrophysiologiques et fonctionnelles leur sont communes et sont hautement interconnectés, ce qui pourrait indiquer que le PPN et la substance noire sont moins distincts fonctionnellement que cru auparavant (Mena-Segovia *et coll.*, 2004). Le PPN fait partie de la formation réticulée et la grande majorité de ses neurones se retrouvent dorsolatéralement dans la pars compacta (PPNc), formant une des rares structures avec des bordures relativement bien délimitées (Olszewski et Baxter, 1954). Les neurones cholinergiques représentent plus de 90% des neurones de la PPNc et entre 25 et 75% de la PPN pars dissipata (PPNd) (Mesulam *et coll.*, 1989). Le PPNd se situe tout au long de l'axe rostrocaudal de la portion pontique et mésencéphalique du tronc cérébral. Le PPN reçoit des afférences du cervelet (Hazrati et Parent, 1992), du GPi (Harnois et Filion, 1982, Hazrati et Parent, 1991a) et, chez le rat, de la SNr (Spann et Grofova, 1991). Les afférences pallidotegmentales se terminent préférentiellement sur les neurones non-cholinergiques de la PPNd, ne connectant peu ou pas sur les neurones cholinergiques des deux segments du PPN (Shink *et coll.*, 1997). Plus de 80% des neurones du GPi qui projettent vers le PPN et le VL via des collatérales (Harnois et Filion, 1982) et que le diamètre de la collatérale vers le PPN est plus large que celle vers le thalamus (communication personnelle par A. Parent, cité par (Pahapill et Lozano, 2000)), suggérant que le PPN serait la cible principale de la sortie pallidale. Les projections nigrales ne semblent pas se terminer qu'exclusivement sur les neurones non-cholinergiques du PPNd, tel que mesuré chez le rat (Spann et Grofova, 1991). Le PPN reçoit aussi des afférences du cortex moteur (Matsumura *et coll.*, 2000). Des projections provenant du STN (Granata et Kitai, 1989) et de la moelle épinière (Grunwerg *et coll.*, 1992) furent démontrées chez le rat, mais il n'existe pas encore de données sur de telles connections chez le primate. En retour, le PPN projette vers le STN, le GPi, la SNc, le cortex cérébral, le striatum, le thalamus, la moelle épinière, ainsi que d'autres structures du tronc cérébral chez le rat et le primate (Lavoie et Parent, 1994c, Parent *et coll.*, 1999a); pour un sommaire, voir : (Inglis et Winn, 1995, Pahapill et Lozano, 2000). D'autre part, environ 40% des neurones du PPN qui projettent vers les BG projettent de façon contralatérale (Lavoie et Parent, 1994c). Tout comme le STN, les connexions du PPN avec les BG, le thalamus et la moelle épinière lui confèrent un rôle important dans l'intégration des informations motrices et un rôle de carrefour dans la transmission de ces informations.

1.3 Modèle des ganglions de la base

Une connaissance exacte de l'organisation anatomique et fonctionnelle des BG est essentielle pour la compréhension de leur fonctionnement dans des conditions normales, mais aussi pathologiques. À la fin des années 80, un modèle fonctionnel des BG a vu le jour (Albin *et coll.*, 1989, DeLong, 1990), ce qui a soulevé de nouvelles approches thérapeutiques dont pour la PD. Selon ce modèle, les BG seraient organisés de manière à former deux voies ségréguées, soient la voie directe et la voie indirecte. La voie directe comprend les neurones striataux qui expriment les récepteurs excitateurs dopaminergiques D_1 et co-expriment les neuropeptides dynorphine et substance P, projettent vers le GPi et la SNr (voie striatonigrale). Cette voie favoriserait le mouvement. À l'opposé, les neurones striatofugaux de la voie indirecte expriment les récepteurs inhibiteurs D_2 et co-expriment le neuropeptide enképhaline, projettent vers le GPe (voie striatopallidale) et favoriseraient un contrôle inhibiteur du mouvement. Le STN reçoit des projections du GPe, pour ensuite projetter vers le GPi et ainsi fermer la boucle des BG (Figure 3.1).

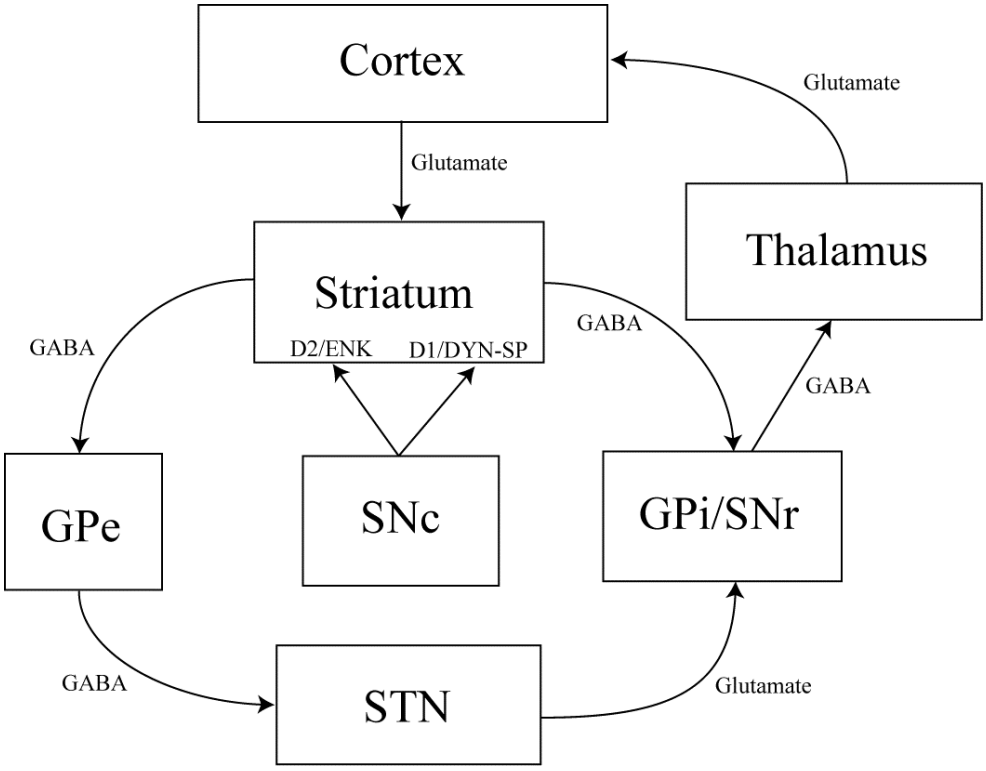

Figure 1.4 Modèle des ganglions de la base chez un sujet sain

Dans le cadre de la PD, la perte neuronale de la SNc provoque deux phénomènes opposés, soient une hypoactivation de la voie « pro-mouvement » et une hyperactivation de la voie indirecte « anti-mouvement ». En conséquence, les voies de sortie des BG (GPi et SNr) deviennent hyperactives par une baisse des afférences GABAergiques du striatum et d'une augmentation des afférences glutamatergiques du STN. Cette hyperactivité GPi/SNr résulterait en une surinhibition des cellules thalamiques, et conséquemment une réduction de l'apport glutamatergique vers le cortex (Figure 3.2).

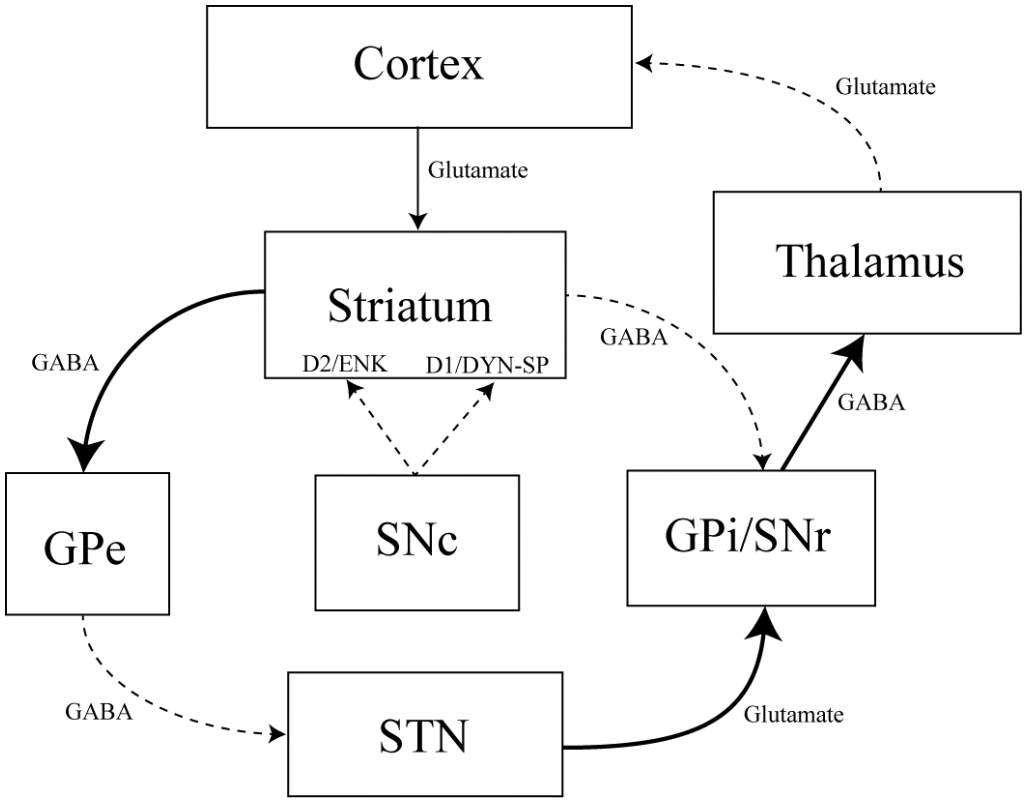

Figure 1.5 Modèle des ganglions de la base chez un sujet parkinsonien

1.4 Neurochimie des ganglions de la base

La section précédente a passé en revue l'anatomie fonctionnelle des BG. Chacune des structures présentées occupe un rôle qui lui est propre dans des conditions physiologiques normales. En complément, la prochaine section présentera brièvement l'expression des récepteurs et leurs fonctions dans les principaux systèmes neurochimiques des BG, soient les systèmes dopaminergique, glutamatergique, peptidergique, GABAergique, cholinergique et sérotoninergique.

1.4.1 Système dopaminergique

Les récepteurs à la DA sont couplés à des protéines G et se divisent en deux familles, soient les D_1-like (D_1 et D_5) et les D_2-like (D_2, D_3 et D_4), selon leurs propriétés biochimique et pharmacologique, ainsi que leur activité physiologique (Missale *et coll.*, 1998). Parmi ces cinq récepteurs, les sous-types D_1 et D_2 sont les plus abondants dans les BG et aussi les plus étudiés (Beaulieu et Gainetdinov, 2011). Ces deux récepteurs sont bien reconnus pour leur rôle dans les activités locomotrices (Centonze *et coll.*, 2003). En effet, l'invalidation pour le récepteur D_2 et des modifications génétiques pour le récepteur D_1 chez la souris provoque des troubles moteurs et de locomotion (Baik *et coll.*, 1995b, Dracheva et Haroutunian, 2001, Tinsley *et coll.*, 2009). Le récepteur D_3 exerce une activité inhibitrice modérée soit par son activation présynaptique en tant qu'autorécepteur (Joseph *et coll.*, 2002) ou post-synaptique (Sibley, 1999). Les récepteurs D_4 et D_5, de par leur expression limitée dans les BG, ne semblent pas jouer un rôle important dans la locomotion (Missale *et coll.*, 1998, Rondou *et coll.*, 2010). Le récepteur D_1 est strictement post-synaptique et a des fonctions excitatrices par l'activation de l'adénosine monophosphate (AMP) cyclique (cAMP) et de l'adénylyl cyclase (AC), tandis que les récepteurs D_2 sont exprimés autant par les terminaisons pré-synaptiques (la forme courte du récepteur) et par les cellules post-synaptiques (la forme longue) et ont un rôle inhibiteur en désactivant la cAMP et l'AC (Beaulieu et Gainetdinov, 2011, Kebabian et Calne, 1979, Missale *et coll.*, 1998).

La source principale de DA dans les BG est certainement la SNc et le striatum est la structure principalement ciblée par ces projections dopaminergiques. En effet, le striatum abonde de varicosités axonales réactives à la tyrosine hydroxylase (TH), ce qui indique une innervation dopaminergique importante (Lavoie *et coll.*, 1989). La partie dorsale du striatum démontre aussi des zones pauvres en immunoréactivité pour la TH (Graybiel *et coll.*, 1987). Ces zones pauvres en innervation dopaminergique correspondent aux striosomes (Graybiel et Ragsdale, 1978). Dans des conditions normales, la DA est distribuée de manière hétérogène entre la matrice extrastriosomale et les compartiments striosomaux (Prensa *et coll.*, 2000). Les afférences corticales et nigrales sembleraient converger sur les MSN striataux, formant des contacts monosynaptiques (Parent *et coll.*, 1995b). L'afférence dopaminergique aurait des effets modulateur ou inhibiteur de

l'afférence excitatrice corticostriatale (Freund *et coll.*, 1984). Les taux de DA dans le striatum diminuent largement (>80% de perte à l'apparition des symptômes) dans la PD (voir section 2.3). Deux voies striatofugales émergent des récepteurs D_1 et D_2, soient les voies directe et indirecte respectivement. Ces deux voies ségréguées forment le modèle des BG (voir section 3.3).

Les récepteurs dopaminergiques sont aussi exprimés dans d'autres structures des BG, dont le complexe pallidal. En effet, le GPi et le GPe contiennent plusieurs varicosités axonales et fibres immunoréactives pour la TH (Lavoie *et coll.*, 1989). Les neurones de la voie nigropallidale passent le long des deux voies de sortie des GP, soient le fasciculus lenticulaire et l'ansa lenticularis. Les fibres nigropallidales s'arborisent profusément dans le GPi, mais plus modestement dans le GPe (Lavoie *et coll.*, 1989). Quelques fibres nigrostriatales envoient des collatérales vers le complexe pallidal (Charara et Parent, 1994, Parent *et coll.*, 1990). L'innervation dopaminergique du GPi provient d'une population de la SNc qui est différente de celle de la voie nigrostriatale (Smith *et coll.*, 1989). Le récepteur D_1 est largement plus exprimé dans le GPi comparativement à son homologue, le GPe (Boyson *et coll.*, 1986, Richfield *et coll.*, 1989), tandis que l'opposé est observé pour le D_2. Toutefois, certains auteurs n'ont pas observé le récepteur D_2 dans le complexe pallidal, ni le D_1 dans le GPe (voir chapitre 5). Les niveaux de DA sont 5 fois plus élevés dans le GPe que dans le GPi et ces niveaux diminuent entre 50 et 85% dans la PD (Hornykiewicz, 2001, Jan *et coll.*, 2000).

Le STN est innervé par les fibres dopaminergiques (Rinvik *et coll.*, 1979). Cette structure est entourée des fibres nigrostriatales et nigropallidales, mais très peu d'entre elles y pénètrent (Lavoie *et coll.*, 1989). Chez le rat, les récepteurs D_1 et D_2 sont fortement exprimés dans le STN (Brown *et coll.*, 1979, Martres *et coll.*, 1985, Savasta *et coll.*, 1986). Mais ces derniers sont beaucoup plus faiblement exprimés chez l'humain (Camps *et coll.*, 1989, Cortés *et coll.*, 1989), ce qui coincide avec leur ARN messager qui y est faiblement ou nullement détecté (Augood *et coll.*, 2000, Hurd *et coll.*, 2001, Svenningsson et Le Moine, 2002). Chez les patients parkinsoniens, ainsi que chez le singe MPTP, la DA dans le STN diminue entre 50 et 65% (Francois *et coll.*, 2000, Hornykiewicz, 2001).

En dernier lieu, le transporteur de la dopamine (DAT) est largement exprimé par les cellules dopaminergiques pré-synaptiques dans le striatum, plus particulièrement dans les

divisions motrices (Ciliax *et coll.*, 1999, Hersch *et coll.*, 1997, Nirenberg *et coll.*, 1996). Il est aussi exprimé de manière hétérogène dans la substance noire, où la partie latérale de la SNc (qui projette vers la partie sensorimotrice) exprime plus abondamment le DAT que la partie médiane et la VTA (Donnan *et coll.*, 1991, Reyes *et coll.*, 2013). Cette différence dans l'expression du transporteur explique entre autres pourquoi les cellules de la SNcv sont plus vulnérables au MPTP, car cette neurotoxine est recaptée par le DAT (voir 2.4.2.2). Le DAT est intrinsèquement relié à la PD, car sa mesure représente le taux de dénervation dopaminergique (Brooks et Pavese, 2011) et fournit des informations sur l'intégrité fonctionnelle des cellules dopaminergiques pré-synaptiques (Lee *et coll.*, 2000, Tedroff *et coll.*, 1999).

1.4.2 Système glutamatergique

Le glutamate est le neurotransmetteur excitateur principal du système nerveux central, où il est utilisé par 70% des synapses (Platt, 2007). Les aires motrices du cortex cérébral, le thalamus et le PPN sont les sources extrinsèques majeures de glutamate dans les BG (Lavoie et Parent, 1994b, McFarland et Haber, 2000, Parent et Hazrati, 1995a, Smith *et coll.*, 2009), tandis que le STN en est la seule source intrinsèque (Smith et Parent, 1988). Les récepteurs glutamatergiques sont soit ionotropiques (NMDA, AMPA et kainate), soit métabotropiques (mGlu1-8) (Foord *et coll.*, 2005). Chacun des récepteurs glutamatergiques a ses propres fonctions, mais ils peuvent aussi interagir entre eux et contribuer à l'excitabilité neuronale (Meldrum, 2000).

Le STN est la seule structure excitatrice des BG et aussi la seule à utiliser le glutamate dans ses projections (Smith et Parent, 1988). Le STN exprime les sous-types de récepteurs métabotropiques mGlu1 à mGlu5, sauf le mGlu4 (Testa *et coll.*, 1994, Wang *et coll.*, 2000), ainsi que les sous-unités GluR1 à GluR3 du récepteur AMPA (Wang *et coll.*, 2000). Les récepteurs NMDA et kainate le sont aussi, à des niveaux faibles à modérés (Smith *et coll.*, 2001). La suractivité sous-thalamique dans la PD est considérée comme l'un des éléments importants dans l'apparition des signes cardinaux (voir section 2.1). Toujours dans la PD, le niveau de glutamate dans le STN est légèrement augmenté (Hornykiewicz, 2001) et il n'y a pas de dégénérescence cellulaire (Hardman *et coll.*, 1997).

Les deux cibles principales du STN, soient le GPi et le GPe, expriment évidemment des récepteurs au glutamate et ce, de façon très similaire. En effet, les sous-unités GluR1 à GluR4 du récepteur AMPA et toutes les unités du récepteur NMDA sont aussi exprimés, mais à moindre intensité que dans le striatum (Kosinski *et coll.*, 1998, Smith *et coll.*, 2001). L'ARNm des récepteurs métabotropiques mGlu1 à mGlu5 sont faiblement marqués dans le pallidum du rat (Testa *et coll.*, 1994), mais les récepteurs du groupe I (mGlu1 et mGlu5) y sont fortement marqués chez le singe (Smith *et coll.*, 2000, Smith *et coll.*, 2001). Malgré la suractivité du STN, les niveaux de glutamate dans le pallidum sont normaux ou légèrement augmentés dans la PD (Hornykiewicz, 2001). Il faut aussi considérer que chez le primate, le PPN projette aux segments du globus pallidus (Lavoie et Parent, 1994c) et serait une source potentielle de glutamate (Lavoie et Parent, 1994b); le cortex cérébral et le thalamus n'y projetant pas (Carpenter, 1989).

Le striatum est la structure recevant le plus de glutamate parmi les BG (Hornykiewicz, 2001). Les récepteurs AMPA GluR1 à GluR4 sont largement exprimés dans le striatum chez le rat (Bernard *et coll.*, 1996). Le striatum est la structure des BG qui exprime le plus fortement le récepteur NMDA (Ravenscroft et Brotchie, 2000) et toutes les cellules striatales l'expriment chez l'humain (Küppenbender *et coll.*, 2000). On y retrouve notamment toutes les sous-unités du récepteur NMDA (Küppenbender *et coll.*, 2000). Tous les récepteurs métabotropiques au glutamate sont aussi exprimés dans le striatum (Mao *et coll.*, 2013, Testa *et coll.*, 1994), mais plus particulièrement le mGlu5 (Smith *et coll.*, 2001). Dans la PD, les niveaux de glutamate augmentent dans le striatum et de façon plus marquée dans la partie dorsolatérale (Hornykiewicz, 2001). Cette sous-division striatale est celle principalement affectée par la dégénérescence dopaminergique. Les terminaux corticostriataux expriment l'auto-récepteur D_2 (Bamford *et coll.*, 2004). L'administration de DA ou d'agonistes D_2 inihibe la relâche glutamatergique, tandis qu'un agoniste D_1 n'a pas cet effet (Yamamoto et Davy, 1992). On peut donc présumer que l'augmentation de glutamate dans le striatum dans la PD provient de la perte des récepteurs D_2 (Morari *et coll.*, 1998). Une augmentation de l'activité glutamatergique est aussi observée dans les LID (voir section 4.1.3.3).

La grande majorité des cellules dopaminergiques de la SNc expriment tous les sous-types du récepteur AMPA et la sous-unité NMDA/NR1 (Paquet *et coll.*, 1997), tandis que

les sous-unités NR2A, NR2B et NR2C du récepteur NMDA sont peu ou pas exprimées dans la SNc (Counihan *et coll.*, 1998, Paquet *et coll.*, 1997). Les niveaux d'ARNm des récepteurs glutamatergiques sont faibles dans la substance noire, les récepteurs mGlu1 et mGlu3 se démarquant légèrement des autres chez le rat (Testa *et coll.*, 1994). La forte présence de récepteurs ionotropiques dans la SNc a ouvert la possibilité d'une hypothèse d'excitotoxicité glutamatergique qui contribuerait à la dégénérescence dans la PD (Greene et Greenamyre, 1996). Toutefois, cette hypothèse ne fut jamais démontrée clairement en clinique et en pré-clinique (Henchcliffe et Beal, 2007). La suractivité du STN dans la PD a été suggérée comme un effet compensatoire pour pallier à la baisse dopaminergique à travers la voie subthalamo-nigrale (Bezard *et coll.*, 1999a). Par contre, les niveaux de glutamate chez le patient parkinsonien demeurent inchangés (Hornykiewicz, 2001).

1.4.3 Système peptidergique

Les BG contiennent une large gamme de peptides neuroactifs (Graybiel, 1986). Contrairement aux neurotransmetteurs classiques, il n'existe pas de processus de reprise ou de recyclage des peptides après l'activation des récepteurs. En conséquence, le remplacement de ces peptides se fait par une nouvelle synthèse par les neurones (Dockray, 1995). Parmi les structures des BG, le striatum est la structure principale de synthèse de neuropeptides (Graybiel, 1986). Les neuropeptides peuvent agir comme neurotransmetteurs, neuromodulateurs et facteurs neurotrophiques (Chen *et coll.*, 2004). Les neuropeptides les plus étudiés sont la neurokinine substance P et les opioïdes enképhaline et dynorphine. Des études par hybridation *in situ* et immunohistochimie ont clairement démontré la présence de neurokinines et d'opioïdes dans les ganglions de la base, principalement dans le striatum, les globus pallidus et la substance noire (pour une revue complète, voir (Samadi *et coll.*, 2007)). La SP et la dynorphine sont exprimées par les neurones de la voie directe projettant au GPi, tandis que l'enképhaline est exprimée principalement par les neurones de la voie indirecte. Consistent avec ces observations, les souris invalidées pour le récepteur D_1 expriment moins la dynorphine et la SP, tandis que les souris invalidées pour le récepteur D_2 ont une baisse de l'expression de l'enképhaline (Baik *et coll.*, 1995a, Drago *et coll.*, 1994, Xu *et coll.*, 1994). Les neurokinines pourraient jouer un rôle neuroprotecteur des cellules dopaminergiques par un un processus

antiglutamatergique (Chen *et coll.*, 2004). Une baisse de la SP et de son récepteur fut démontrée dans le striatum et la substance noire chez le patient parkinsonien (Levy *et coll.*, 1995, Tenovuo *et coll.*, 1990, Tenovuo *et coll.*, 1984). Une étude récente a toutefois démontré que la SP striatale n'est pas affectée chez le singe exposé au MPTP traité ou non avec la L-DOPA (Tamim *et coll.*, 2010). D'un autre côté, la dynorphine, qui est exprimée par les mêmes neurones diminue légèrement avec le MPTP, mais augmente significativement avec la L-DOPA (Tamim *et coll.*, 2010, Tel *et coll.*, 2002). Le traitement au MPTP chez le primate augmente siginificativement la synthèse d'ARNm de l'enképhaline (Asselin *et coll.*, 1994, Augood *et coll.*, 1989, Morissette *et coll.*, 2006, Morissette *et coll.*, 1997, Morissette *et coll.*, 1999) et augmentée de nouveau avec le traitement à la L-DOPA (Herrero *et coll.*, 1995, Jolkkonen *et coll.*, 1995, Morissette *et coll.*, 2006, Tamim *et coll.*, 2010). L'augmentation des neuropeptides enképhaline et dynorphine serait reliée aux LID. En effet, il existe une corrélation positive entre l'expression de LID et la synthèse des neuropeptides (Cenci *et coll.*, 1998, Henry *et coll.*, 2003). D'autres neuropeptides sont aussi présents dans les BG (neurotensine, neuropeptide Y, somatostatine, etc.), toutefois, ils ne seront pas revus dans cette présente thèse dû à leur rôle minime dans la PD et les LID (Samadi *et coll.*, 2007).

1.4.4 Système GABAergique

L'acide γ-aminobutyrique (GABA) est le neurotransmetteur inhibiteur le plus utilisé dans le cerveau et plus particulièrement dans les BG. En effet, toutes les structures qui forment les BG, sauf le STN et la SNc, utilisent le GABA comme neurotransmetteur principal (Samadi *et coll.*, 2007). Les récepteurs GABAergiques se divisent en récepteurs pentamériques ionotropiques, $GABA_A$ et $GABA_C$, et en récepteurs métabotropiques $GABA_{B1}$ et $GABA_{B2}$ (Waldvogel *et coll.*, 2004).

Chez l'humain, les MSNs GABAergiques constituent environ 85% des cellules striatales, le restant étant des interneurones présentant différents phénotypes (Cicchetti *et coll.*, 1998). La quasi-totalité de l'innervation GABAergique dans le striatum serait une dérivation intrinsèque des interneurones ou de collatérales des MSNs (Rao, 2007). Tout comme le glutamate, les niveaux de GABA sont élevés dans le striatum de patients parkinsoniens et de façon plus prononcée dans la partie dorsolatérale motrice (Kish *et coll.*,

1986). Cette hausse serait inversement proportionnelle à la perte dopaminergique (Hornykiewicz, 2001, Kish *et coll.*, 1986). Toutefois, les liaisons spécifiques aux récepteurs $GABA_A$ et $GABA_B$ sont inchangées dans le striatum de singes MPTP comparativement à des singes contrôles, qu'ils soient traités ou non à la L-DOPA (Calon *et coll.*, 1995, Calon *et coll.*, 2000b). Par contre, chez les patients parkinsoniens, on observe une baisse significative du récepteur $GABA_B$ comparativement à des sujets sains (Calon *et coll.*, 2003a).

Le GPe est fortement innervé par des projections GABAergiques, provenant principalement des neurones striatofugaux co-localisant l'enképhaline (Haber et Watson, 1985). La lésion dopaminergique par le MPTP provoque une augmentation de la relâche de GABA dans le GPe par les neurones de la voie indirecte (Soghomonian et Laprade, 1997). Cette observation est similaire chez le patient parkinsonien, mais à moindre mesure (Kish *et coll.*, 1986). Les récepteurs $GABA_A$ et $GABA_B$ dans le GPe suivent le même patron que celui du striatum chez le patient parkinsonien (Calon *et coll.*, 2003a).

L'afférence GABAergique principale dans le GPi provient du striatum, mais le GPe aussi l'innerve (Hazrati *et coll.*, 1990). Ces neurones striatofugaux de la voie directe (section 3.3) co-localisent la dynorphine (Haber et Watson, 1985). La lésion au MPTP provoque une augmentation de l'ARNm d'une enzyme de synthèse du GABA (GAD67) dans le GPi, qui est corrigée avec l'administration de L-DOPA (Herrero *et coll.*, 1996). Chez les patients parkinsoniens, les niveaux de GABA dans le GPi sont aussi élevés comparativement à des sujets sains (Hornykiewicz, 2001, Kish *et coll.*, 1986). Les récepteurs $GABA_A$ dans le GPi présentent une distribution similaire à celle du GPe (Rao, 2007). Chez les patients parkinsoniens, la liaison spécifique au $GABA_A$ est augmentée après l'apparition des dyskinésies, ce qui coïncide avec l'augmentation de l'ARNm d'enképhaline striatal (Calon et Di Paolo, 2002). Chez le singe, le récepteur $GABA_B$ aussi augmente dans le GPi avec le MPTP (Calon *et coll.*, 2000b).

Le STN est le récipiendaire principal de l'efférence GABAergique du GPe (Carpenter et Jayaraman, 1990), mais le STN reçoit aussi du GABA de la région mésopontine (probablement du PPN) chez le rat (Bevan et Bolam, 1995). Le STN comporte aussi une faible proportion d'interneurones GABAergiques chez l'humain (Lévesque et

Parent, 2005a). Comparativement aux autres structures des BG, les niveaux de GABA demeurent inaffectés dans la PD (Hornykiewicz, 2001, Kish *et coll.*, 1986).

1.4.5 Système cholinergique

Les récepteurs à l'acétylcholine se divisent en deux familles, soient les récepteurs métabotropiques muscariniques (M1 à M5) et les récepteurs ionotropiques nicotiniques (Foord *et coll.*, 2005). Les récepteurs nicotiniques sont des pentamères qui, dans le cerveau proviennent de combinaisons homo- ou hétéromériques de 12 sous-unités (α2 à α9, β2 à β4 et γ) (Changeux *et coll.*, 1998). La source cholinergique d'innervation des BG provient de projections ascendantes du PPN, situé dans le tronc cérébral (Lavoie et Parent, 1994b). Les fibres cholinergiques innervent abondamment la plupart, sinon la totalité des noyaux thalamiques (Steriade *et coll.*, 1988). La SNc est de loin la plus innervée par le système cholinergique parmi les BG (Lavoie et Parent, 1994a, c). Chez le rat, les neurones de cette voie péducunlonigrale arboriserait aussi le thalamus, probablement par l'entremise de collatérales (Oakman *et coll.*, 1999). La majorité des récepteurs nicotiniques sont exprimés de manière pré-synaptique, ce qui faciliterait la relâche de DA dans le striatum (Rao, 2007). En effet, on observe une baisse de la liaison spécifique de [^{3}H]-nicotine chez les patients parkinsoniens (Court *et coll.*, 2000).

Les interneurones géants non-épineux comptent pour 2% des neurones striataux et forment la source exclusive d'innervation cholinergique au striatum (Zhou *et coll.*, 2002). Ils font contact avec les neurones des voies de sortie du striatum (Pisani *et coll.*, 2003). Chez le singe MPTP, ces neurones démontrent une activité oscillatoire similaire aux fréquences de tremblement (Raz *et coll.*, 2001), suggérant qu'ils sont impliqués dans le génèse du tremblement chez le patient parkinsonien.

Le GPe est faiblement innervé par le PPN (Garcia-Rill, 1991, Lavoie et Parent, 1994c). Chez l'humain, tous les types de récepteurs muscariniques sont exprimés (Piggott *et coll.*, 2002). La liaison spécifique à ces récepteurs demeure inchangée dans la PD (Piggott *et coll.*, 2003). Comparativement à son homologue, le GPi démontre une plus forte innervation cholinergique (Lavoie et Parent, 1994c). Le récepteur muscarinique M4 est profusément exprimé, mais pas son ARNm, ce qui indique qu'il serait exprimé sur les terminaisons GABAergiques du striatum (Yan *et coll.*, 2001). La liaison spécifique pour les

récepteurs muscariniques sont fortement augmentée dans la PD (Griffiths *et coll.*, 1990), phénomène compensatoire probablement dû à une perte de la neurotransmission cholinergique du PPN.

En dernier lieu, le STN est aussi profusément innervé par le PPN (Lavoie et Parent, 1994c) et, d'après certaines données obtenues chez le rat, cette innervation serait de nature cholinergique (Bevan et Bolam, 1995). Le récepteur α7-nicotinique est fortement exprimé dans le STN chez le rat (Schulz *et coll.*, 1991). Les récepteurs α4β2 et α6β2 sont modérément exprimés chez l'humain et sont diminués dans la PD (Pimlott *et coll.*, 2003). Des études en électrophysiologie ont toutefois suggéré un rôle limité des récepteurs nicotiniques dans le STN (Feger *et coll.*, 1979). À l'opposé, les récepteurs muscariniques sembleraient avoir un rôle important dans la régulation de l'activité sous-thalamique, plus particulièrement le récepteur M3 car il y est fortement exprimé et synthétisé chez le rat (Levey *et coll.*, 1994, Weiner *et coll.*, 1990).

1.4.6 Système sérotoninergique

Le système sérotoninergique a un rôle neuromodulateur dans les BG (Soubrié *et coll.*, 1984). Les fibres sérotoninergiques originent du noyau raphé dorsal et médian et empruntent les faisceaux télencéphaliques médians (*medial forebrain bundle*; MFB) pour se rendre aux BG (Parent *et coll.*, 2011). Il existe sept familles de récepteurs à la 5-HT (5-HT_1-5-HT_7) et 14 différents récepteurs (Foord *et coll.*, 2005, Huot *et coll.*, 2011). Tous ces récepteurs, sauf le 5-HT_3 qui est un récepteur ionique, sont des récepteurs métabotropiques couplés à une protéine G (Barnes et Sharp, 1999).

La substance noire est de loin la structure recevant le plus d'innervation sérotoninergique dans les BG (Lavoie et Parent, 1990). Les fibres sérotoninergiques passent dans la partie dorsale de la substance noire et arborisent largement dès leur entrée dans la structure (Lavoie et Parent, 1990). Les axones provenant du noyau raphé dorsal terminent de manière plus dense dans les tiers caudaux et latéraux que les tiers rostraux et médiaux de la substance noire (Lavoie et Parent, 1991b, Parent *et coll.*, 2011). Fait intéressant, ce sont ces régions nigrales qui dégénèrent dans les premiers stades de la PD et seraient les plus vulnérables aux neurotoxines (Betarbet *et coll.*, 2000, Damier *et coll.*, 1999). Les terminaisons axonales se terminent plus souvent dans la SNr que dans la SNc (Lavoie et

Parent, 1990). Les neurones qui projettent à la substance noire projettent aussi vers le striatum via des collatérales chez le rat (van der Kooy et Hattori, 1980). Chez le rat, les synapses sérotoninergiques terminant dans la SNc sont asymétriques et projettent directement sur les cellules dopaminergiques (Nedergaard *et coll.*, 1988), suggérant que la 5-HT puisse altérer l'activité des neurones qui projettent vers le striatum (Parent *et coll.*, 1995b).

Le complexe pallidal est largement innervé par les fibres sérotoninergiques, qui arborisent plus abondament le GPi que le GPe (Mori *et coll.*, 1985). Des niveaux élevés de 5-HT furent démontrés dans le pallidum de singes (Shannak et Hornykiewicz, 1980) et d'humains (Walsh *et coll.*, 1982). En effet, le globus pallidus a été rapporté comme étant la structure des BG où la synthèse de 5-HT était la plus élevée (Bacopoulos *et coll.*, 1979). Tout comme dans la SNc, les synapses sérotoninergiques y sont asymétriques et se retrouvent sur les dendrites post-synaptiques (Pasik *et coll.*, 1984a, Pasik *et coll.*, 1984b). D'autre part, la 5-HT exerce des influences pré- et post-synaptiques dans le pallidum (Rav-Acha *et coll.*, 2008). La 5-HT modulerait négativement la relâche de GABA par des mécanismes pré-synaptiques, tandis qu'elle activerait l'hyperpolarisation des canaux cations post-synaptiques (Rav-Acha *et coll.*, 2008).

Le STN est aussi abondament innervé par les fibres sérotoninergiques, légèrement plus intense dans le STN médial chez l'humain (Wallman *et coll.*, 2011), tandis que l'opposé serait présent chez le primate (Lavoie et Parent, 1990). Le STN contient aussi des quantités significatives de 5-HT, tel que mesuré chez le primate (Cross et Joseph, 1981) et l'humain (Walsh *et coll.*, 1982). Le rôle exact de l'afférence sérotoninergique dans le STN reste à être élucidé, mais il fut démontré que la 5-HT inhibe les voies excitatrices corticosubthalamiques et les voies GABAergiques provenant du complexe pallidal en agissant au niveau pré-synaptique (Shen et Johnson, 2008).

Comparativement au complexe pallidal et à la substance noire, le striatum reçoit une innervation sérotoninergique beaucoup moins dense. Les divisions associatives et motrices du striatum sont moins innervées que la partie limbique et le noyau accumbens (Lavoie et Parent, 1990). Tout comme pour l'innervation dopaminergique, le striatum présente des zones "pauvres" en immunoréactivité pour la 5-HT. Ces dernières correspondent aux mêmes zones pauvres en DA (section 1.4.1) et seraient aussi reliées aux striosomes

(Graybiel et Ragsdale, 1978). Par conséquent, les afférences dopaminergiques et sérotoninergiques chez le primate arboriseraient plus abondamment la matrice extrastriosomale que les striosomes (Parent *et coll.*, 1995b). Une importante perte de DA striatal (>80%) chez le patient parkinsonien est accompagnée d'une baisse de 50% des niveaux de 5-HT (Wilson *et coll.*, 1996), baisse qui devient encore plus importante lorsque que le patient présente des symptômes dépressifs (Kish, 2003). En dernier lieu, l'innervation sérotoninergique du thalamus est similaire, sinon plus importante dans certains noyaux, à celle du striatum (Lavoie et Parent, 1991b). Le noyau CM/Pf est bien innervé, tandis que les noyaux VL et VA sont faiblement à modérément innervés (Lavoie et Parent, 1991b). Toutefois, le rôle de cette innervation reste à être élucidée.

CHAPITRE 2. MALADIE DE PARKINSON

La PD est une condition neurodégénérative qui affecte environ 100 000 canadiens (Canada, 2003). L'âge est le facteur de risque le plus consistent (Collier *et coll.*, 2011). En effet, 0.3% de la population mondiale est affectée, dont 1% à 60 ans et 3% à 80 ans (de Lau et Breteler, 2006). Un des impacts majeurs de cette maladie se traduit par une mortalité entre deux et trois fois plus élevée chez les patients parkinsoniens comparativement à une population contrôle (Bennett *et coll.*, 1996, Louis *et coll.*, 1997), ce qui en résulte en une diminution de l'espérance de vie (Morens *et coll.*, 1996). Il est même prédit que les maladies neurodégénératives (démences, maladie du neurone moteur et PD) deviendront la deuxième cause de mort chez les personnes âgées en 2040, dépassant ainsi le cancer (Lilienfeld et Perl, 1993).

2.1 Manifestations cliniques

Les manifestations cliniques de la PD furent décrits pour la première fois il y a près de 200 ans. Le médecin britannique James Parkinson décrivait la *paralysis agitans* comme étant « *[an] involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured* » (Parkinson, 2002). Une telle représentation met en évidence la pauvreté du mouvement dans un tel syndrome. Les travaux de divers neurologues, notamment Jean-Martin Charcot, ont permis une meilleure description de la maladie. C'est ce dernier qui renomma cette pathologie en honneur du docteur Parkinson (Lees, 2007). La PD se caractérise aux premiers abords par une pauvreté du mouvement et du tremblement, signes cardinaux *sine qua non* menant au diagnostique de la PD. La prochaine section décrira chacune de ces manifestions motrices, puis suivra une brève description des symptômes non-moteurs de la PD.

2.1.1 Le tremblement de repos

Le tremblement de repos est probablement l'aspect le plus facile à identifier chez le patient parkinsonien et est souvent la raison de la consultation d'un patient (Shahed et

Jankovic, 2007). Il est généralement unilatéral, se manifeste au repos et a une fréquence de 4 à 6 Hz. Les premiers symptômes de tremblement de main ressemblent à un roulement de dés (*pill-rolling*) unilatéral et, au fur et à mesure que la maladie progresse, ce tremblement se transpose du côté opposé (Shahed et Jankovic, 2007). Le tremblement peut aussi se manifester au niveau du visage (lèvres et la mâchoire), mais affecte rarement le cou et la tête (Jankovic, 2008). Le tremblement de repos, comme son nom l'indique, disparait durant l'exécution d'un mouvement, ce qui le distingue du tremblement essentiel (Crawford et Zimmerman, 2011), et pendant le sommeil, tandis que le stress, la marche et une exécution manuelle bilatérale l'accentuent (Shahed et Jankovic, 2007). La très faible occurrence du tremblement de repos chez les autres syndromes parkinsoniens (Hobson, 2003) est un symptôme utile pour le diagnostique. Certains patients présentent aussi un tremblement postural, qui est plus débilitant que le tremblement de repos et apparaitrait comme la première manifestation de la maladie (Jankovic *et coll.*, 1999). Toutefois, le tremblement serait absent entre 23% et 30% des patients parkinsoniens (Hughes *et coll.*, 1993, Jankovic, 2008), quoiqu'une étude clinicopathologique prospective a démontré que tout patient parkinsonien présentent du tremblement un moment au cours de leur maladie (Rajput *et coll.*, 1991).

2.1.2 La bradykinésie

La bradykinésie réfère à la lenteur d'exécution d'un mouvement. Elle est le symptôme le plus caractéristique de la PD. Elle consiste en des difficultés dans la planification, la préparation, l'initiation et l'exécution du mouvement. Elle est certainement apparente lors de mouvements séquentiels ou simultanés (Berardelli *et coll.*, 2001). Le terme « bradykinésie » est souvent utilisé avec les mots akinésie et hypokinésie. L'akinésie réfère à l'incapacité à initier un mouvement spontané, tandis que l'hypokinésie serait associé à la lenteur du mouvement mais aussi à une réduction de l'amplitude du mouvement, comme la micrographie (Berardelli *et coll.*, 2001). Lors des premières manifestations de la bradykinésie, le patient se voit effectuer des tâches de la vie quotidienne avec lenteur, principalement toute tâche demandant une motricité fine, tel qu'attacher un bouton (Ringendahl, 2002). La bradykinésie varie selon l'état émotionnel du patient. En effet, un élément externe excitateur peut provoquer un déclenchement moteur

qui serait considéré comme normal chez un sujet sain (Ballanger *et coll.*, 2006), comme attraper une balle ou même courir lors d'une urgence (Souques, 1921). Ce paradoxe cinétique démontre que les programmes moteurs demeurent intacts et que le patient démontre une difficulté à les initier sans un signal externe. Finalement, le degré de dénervation dopaminergique serait le facteur pathophysiologique qui corrèle le plus à la bradykinésie (Vingerhoets *et coll.*, 1997). Des études effectuées par tomographie par émission de positrons (PET) ont démontré qu'une baisse de la recapture de [^{18}F]-fluorodopa dans le striatum était proportionnelle à la bradykinésie (Lozza *et coll.*, 2002). D'ailleurs, il est bien documenté que la mort neuronale est un processus normal du vieillissement (Fearnley et Lees, 1991) et que la bradykinésie observée chez des sujets âgés non parkinsoniens (>80 ans) serait aussi associée avec une baisse de neurones dopaminergiques (Ross *et coll.*, 2004).

2.1.3 La rigidité

La rigidité est un symptôme caractérisé par une augmentation de la résistance lors de mouvements, qui peut être source de douleur musculo-squelettique chez le patient (Ha et Jankovic, 2011). La rigidité est souvent accompagnée par une non-fluidité du mouvement, phénomène appelé « roue dentée » (*cogwheel effect*) lors de mouvements passifs d'un membre (Ghiglione *et coll.*, 2005). Le *cogwheel effect* est surtout présent lorsque le patient présente du tremblement de repos et se manifeste autant de façon proximale (cou, épaule) que distale (poignet, cheville). Des mouvements volontaires contralatéraux augmentent significativement la rigidité musculaire (Mendonça et Jog, 2008). Finalement, la rigidité pourrait aussi causer d'autres problèmes moteurs de la PD, dont les troubles de posture.

2.1.4 Les troubles de posture et de la démarche

Certains patients présentent de l'instabilité et des difformités posturales. En effet, une flexion extrême du cou (*dropped head*), du tronc (camptocormie) et scoliose résulteraient d'une rigidité des membres impliqués (Ashour et Jankovic, 2006, Djaldetti et Melamed, 2006). La camptocormie provient d'une flexion importante de la partie thoracolombaire de la colonne vertébrale. Cette condition s'exacerbe lors de la marche, mais se dissipe lorsque le patient s'asseoit ou s'appuie sur un mur (Azher et Jankovic, 2005). D'autres patients ont une difformité axiale qui se manifeste seulement lorsqu'ils sont

assis ou debouts, avec une inclinaison du tronc, appelé syndrome de Pise (Tassorelli *et coll.*, 2011, Villarejo *et coll.*, 2003). Ce type de symptôme est aussi présent, quoique très rare, après certaines chirurgies (Su *et coll.*, 2002).

L'instabilité posturale est due à une perte des réflexes posturaux et arrive tardivement dans la maladie. Elle est, conjointement avec le phénomène d'astasie-abasie (*freezing of gait*), la cause principale des chutes chez le patient parkinsonien, contribue aux problèmes indirects de la maladie (i.e. fracture de la hanche) et engendre du stress (Adkin *et coll.*, 2003, Bloem *et coll.*, 2004). Le *freezing of gait*, quant à lui, est une forme d'akinésie présente chez près de la moitié des patients parkinsoniens (Macht *et coll.*, 2007), affectant surtout les jambes durant la marche, mais aussi les bras et les paupières (Boghen, 1997). Cette akinésie est spontanée et transitoire, durant généralement moins de 10 secondes. Pendant cette période, le patient est incapable de bouger. Le *freezing of gait* se manifeste au début de la marche (forme d'hésitation) ou lors d'un mouvement spécifique, tel que tourner ou à la marche d'une intersection d'une rue achalandée. Le *freezing of gait* serait conséquent d'une dysfonction du PPN (Karachi *et coll.*, 2010). Malheureusement, les traitements classiques pharmacologiques et chirurgicaux (voir Chapitre 3) améliorent peu les troubles axiaux (Giladi, 2001, Giladi *et coll.*, 1997), ce qui laisse une place à de nouvelles avenues thérapeutiques pour l'abolition ou du moins la réduction de ces troubles de posture et de démarche.

2.1.5 Autres troubles moteurs

Certains patients vont exhiber d'autres affectations motrices qui résulteraient des signes cardinaux de la PD. En effet, des patients vont présenter des difficultés à articuler (dysarthrie), à avaler (dysphagie), une réduction de la parole (hypophonie) et de l'expression faciale (*mask-like face*), symptômes partiellement expliqués par une rigidité et bradykinésie orofaciale (Hunker *et coll.*, 1982). D'autre part, des anomalies neuro-ophtamologiques peuvent aussi survernir, telles qu'une diminution du réflexe de clignement des yeux, du blépharospasme et un larmoiement excessif (Biousse *et coll.*, 2004).

2.2 Troubles non-moteurs

Nonobstant le fait que la PD se caractérise principalement par des symptômes moteurs, la grande majorité des patients va présenter des troubles non-moteurs reliés directement à la maladie, mais aussi induits par les traitements pharmacologiques. Il est possible de les regrouper en troubles neuropsychiatriques, fonctionnels et sensoriels. Cette section passera brièvement en revue les principaux symptômes non-moteurs.

La dépression est le trouble neuropsychiatrique le plus fréquent chez les patients parkinsoniens. En effet, près de 50% de cette population vont présenter des symptômes dépressifs au cours de leur maladie (Tandberg *et coll.*, 1996) et ceci est associé à une baisse de la qualité de vie du patient (Schrag *et coll.*, 2000). Ce pourcentage est largement plus élevé que dans la communauté âgée de 60 ans et plus, se retrouvant aux alentours de 10 à 15% (Beekman *et coll.*, 1999). Certaines évidences démontrent que les symptômes dépressifs pourraient précéder l'apparition des troubles moteurs par plusieurs années (Leentjens *et coll.*, 2003a). Le développement de la dépression pourrait être conséquent d'une perte des cellules sérotoninergiques du noyau raphé. En effet, les patients parkinsoniens avec dépression ont une perte cellulaire plus importante dans cette structure que les patients ne présentant pas de dépression (Paulus et Jellinger, 1991). Les systèmes dopaminergique et noradrénergique pourraient aussi être impliqués. Des études sur leurs transporteurs spécifiques ont démontré des baisses dans diverses structures des BG et le thalamus (Remy *et coll.*, 2005, Weintraub *et coll.*, 2005). Des symptômes dépressifs et suicidaires ont aussi été rapportés chez des patients recevant une stimulation cérébrale profonde du STN (Voon *et coll.*, 2008). Le traitement de la dépression chez le parkinsonien peut se faire avec l'administration d'inhibiteurs sélectifs de la recapture de 5-HT (Chen *et coll.*, 2007), mais certaines études arrivent à des conclusions différentes (Leentjens *et coll.*, 2003b). L'implication noradrénergique semblerait une nouvelle voie à explorer (Takahashi *et coll.*, 2005).

Les patients parkinsoniens peuvent aussi présenter des troubles psychotiques, tels que des hallucinations visuelles et auditives (Chou *et coll.*, 2005, Inzelberg *et coll.*, 1998). La prise de médication dopaminergique est le facteur de risque le plus important. En effet, un patient sur six prenant de la L-DOPA présente des symptômes psychotiques (Yahr *et coll.*, 1969) et ce nombre augmente avec les agonistes dopaminergiques (Papapetropoulos

et Mash, 2005). Les autres facteurs de risque sont l'âge, la durée de maladie, la démence et la polythérapie (Fénelon, 2008). Le fait que les hallucinations et les troubles psychotiques soient reliés à la médication pose un problème dans le traitement. Réduire la médication antiparkinsonienne aurait pour conséquences une détérioration motrice. L'administration de faibles doses de clozapine, un neuroleptique de seconde génération, semblerait avoir des effets bénéfiques sans que l'apport antiparkinsonien de la L-DOPA soit compromis (1999, Pollak *et coll.*, 2004). Finalement, la stimulation cérébrale profonde du STN permet une réduction de la prise de L-DOPA et a pour conséquence la réduction des hallucinations chez les patients (Umemura *et coll.*, 2011).

La quasi-totalité des patients parkinsoniens rapportent des troubles du sommeil, dont une mauvaise qualité du sommeil, de l'insomnie et une difficulté à rester endormi (Comella, 2007). Les neurones sérotoninergiques, noradrénergiques et cholinergiques des noyaux raphé, locus coeruleus et pédunculopontin respectivement, sont impliqués dans le sommeil (Arnulf *et coll.*, 2010, Bruin *et coll.*, 2012, Comella, 2007). Un dérèglement dans l'activité de ces structures aurait alors des conséquences directement sur les cycles éveil/sommeil (Sixel-Döring et Trenkwalder, 2011). Divers traitements pharmacologiques, selon le trouble du sommeil dominant, peuvent être prescrits (Bruin *et coll.*, 2012, Sixel-Döring et Trenkwalder, 2011).

Parmi les symptômes non-moteurs autonomiques et périphériques, les troubles gastro-intestinaux font l'objet de plusieurs recherches. Les patients parkinsoniens peuvent présenter des problèmes de motilité intestinale, de gastroparésie et des dysfonctions ano-rectales (Pfeiffer, 2011). Ces symptômes pourraient être expliqués par le fait que 14 à 20% du système nerveux entérique est composé de cellules dopaminergiques (Anlauf *et coll.*, 2003) et que ce sont ces cellules qui dégénèrent dans la PD (voir section 2.3). En effet, l'administration intrapéritonéale (Anderson *et coll.*, 2007) ou intraveineuse (Chaumette *et coll.*, 2009) de la toxine MPTP provoque une perte des cellules dopaminergiques entériques. De plus, les patients parkinsoniens peuvent aussi présenter des dysfonctions sexuelles (Pargeon *et coll.*, 2011), urinaires (Stocchi *et coll.*, 2011), olfactives (Duda et Stern, 2011), ainsi que des troubles sensoriels (Lim et Evans, 2011). Cet amalgame de troubles non-moteurs démontre que la PD ne se limite pas seulement au système

dopaminergique, mais bien qu'elle soit un désordre multisystémique. La prochaine section révisera les systèmes neuronaux impliqués en termes neuropathologiques.

2.3 Manifestation neuropathologique

La PD se caractérise par une perte progressive et sélective mais hétérogène de certaines populations de neurones. Ce sont les neurones dopaminergiques de la SNc qui sont principalement reconnus pour dégénérer dans la PD (Pavese *et coll.*, 2011), mais les neurones des systèmes sérotoninergiques, cholinergiques et noradrénergiques sont aussi affectés (voir ci-bas). Toutefois, la PD n'affecte pas toutes les projections dopaminergiques. En effet, ce sont surtout les neurones du tiers ventrolatéral de la SNc, projettant vers le striatum dorsolatéral, qui dégénèrent le plus (Kish *et coll.*, 1988), avec une perte estimée entre 60 à 70% quand les premiers symptômes de la PD apparaissent, puis suivent les neurones du tiers ventromédian (Fearnley et Lees, 1991). Ce patron de dégénérescence dopaminergique semble spécifique à la PD. Le patron de perte dopaminergique dans le processus normal de vieillissement est opposé à ce dernier dont les parties dorsales sont les plus affectées (Fearnley et Lees, 1991) et ce patron diffère aussi des autres conditions de dégénérescence neuronale (Fearnley et Lees, 1990, 1991). Le patron de perte neuronale dans la PD corrèle avec les niveaux d'ARN messagers pour le DAT dans la SNc (Uhl *et coll.*, 1994). Au fur et à mesure que la PD progresse, les cellules nigrales de la SNc médiale, qui projettent vers le noyau caudé, dégénèrent et ceci pourrait participer aux troubles cognitifs (Gibb et Lees, 1991). La perte neuronale est un processus normal de vieillissement. En effet, il fut démontré récemment que des singes agés démontrait des symptômes parkinsoniens, une perte cellulaire et une perte striatale de DA, sans même avoir être exposés à la neurotoxine MPTP (Hurley *et coll.*, 2011). Dans le cas de la PD, on observe une perte des cellules de la SNc six à dix fois plus rapide que dans un vieillissement normal (McGeer *et coll.*, 1988). Cette perte neuronale est estimée à environ 5 à 8% du nombre de cellules par décennie (Vingerhoets *et coll.*, 1994a).

Il fut proposé relativement récemment une sous-division à la PD selon la symptomatologie et la réponse à la médication, mais aussi qui coïncide avec une dégénérescence dopaminergique différente (Rajput *et coll.*, 2009). Dans le type akinétique-rigide, ce sont surtout les neurones de la SNc ventrolatérale qui dégénèrent

comparativement à la partie médiane (Paulus et Jellinger, 1991). Il existe une corrélation négative entre le nombre de cellules de la SNc ventrolatérale, la sévérité des symptômes et la perte de DA dans le striatum (Ma *et coll.*, 1997). Contrairement au type akinétique-rigide, le type avec une dominance de tremblements présente une perte neuronale globale moins importante et plus uniforme entre les divisions latérales et médiales de la SNc (Paulus et Jellinger, 1991). D'autre part, il fut démontré que le type avec prédominance de tremblement présentait des pertes importantes des cellules dopaminergiques des champs périrétrorubraux (A8) et de la VTA (A10) (Percheron *et coll.*, 1994). Ces deux structures dopaminergiques projettent au striatum, mais aussi vers le thalamus VL (Deutch *et coll.*, 1988). La perte de DA dans le thalamus VL pourrait être une des causes possibles de la synchronisation de cette région et de l'induction du tremblement (Taha *et coll.*, 1997). Nonobstant leurs différences en terme de neurodégénérescence neuronale, les deux types de PD répondent différemment à la médication. En effet, les patients qui présentent un type avec prédominance de tremblements répondent mieux à la L-DOPA que ceux avec un type akinétique-rigide (Rajput *et coll.*, 2009). Cette meilleure réponse antiparkinsonienne est aussi accompagnée d'un plus haut taux de baisse de réponse en fin de dose (*wearing-off*, voir section 4.1.1). D'un autre côté, le type akinétique-rigide risque beaucoup plus de développer une démence (Rajput *et coll.*, 2009). Finalement, il existe un type mixte, beaucoup plus fréquent que les deux autres, qui présentent le mélange entre akinétique-rigide et avec prédominance de tremblements (Rajput *et coll.*, 2009). Il n'y a pas de différences entre les trois types pour ce qui est des autres effets secondaires à la médication (voir section 4.1) ou pour les troubles de la démarche.

Le noyau raphé dorsal est la structure innervant les BG et le thalamus avec de la 5-HT (section 1.4.6). Dans la PD, on observe une perte entre 25 et 45% des cellules sérotoninergiques (Halliday *et coll.*, 1990, Paulus et Jellinger, 1991), ce pourcentage augmentant chez les patients parkinsoniens qui présentent des signes dépressifs (Paulus et Jellinger, 1991). Il y a aussi dégénérescence des neurones cholinergiques du PPNc. En effet, il existe une perte entre 35 et 60% de ces cellules (Hirsch *et coll.*, 1987, Zweig *et coll.*, 1989a) et cette baisse est corrélée avec la perte dopaminergique (Zweig *et coll.*, 1989b). Cette baisse cholinergique semblerait jouer dans les troubles de démarche et dans la baisse de locomotion, car ces symptômes sont associés à une réduction de l'activité du

PPN (Pahapill et Lozano, 2000). Le locus coeruleus est la source principale d'innervation noradrénergique participant dans l'état d'éveil (Berridge *et coll.*, 2012). Dans la PD, on observe une perte d'environ 60% des neurones du locus coeruleus caudal (Mann *et coll.*, 1983), qui projettent vers la moelle épinière et le cervelet, avec des pertes plus importantes chez le type akinétique-rigide de la PD (Jellinger, 1991). Une co-morbidité avec des troubles cognitifs amplifie cette perte (Chan-Palay et Asan, 1989). Cette perte noradrénergique pourrait avoir un impact sur les troubles du sommeil chez les patients parkinsoniens. Considérant les pertes neuronales de ces différents systèmes et structures, la PD est clairement une maladie neurodégénérative multi-systémique.

En plus de la perte des neurones, des agrégats anormaux de la protéine α-synucléine, appelés corps de Lewy (Del Tredici et Braak, 2012), se forment à l'intérieur des neurones partout dans le cerveau (Braak *et coll.*, 1996), plus particulièrement dans le tronc cérébral et dans le cortex. La formation de ces inclusions neuronales dans la pathogénèse de la PD et leur rôle dans le processus neurodégénératif demeurent obscurs, quoique certains auteurs lui attribueraient un rôle cytoprotecteur dans la PD (Wakabayashi *et coll.*, 2007). D'autre part, la présence de corps de Lewy n'est pas spécifique à la PD, ils sont aussi observables dans d'autres maladies neurodégénératives (Trojanowski et Lee, 2007) et dans certaines formes de démence (Meeus *et coll.*, 2012).

2.4 Modèles parkinsoniens

2.4.1 6-OHDA

L'étude chez les rongeurs pour la PD par administration de neurotoxines ciblant les cellules dopaminergiques a débuté avec une toxine dérivée de la DA, la 6-hydroxydopamine (6-OHDA, (Ungerstedt, 1968)). Ne passant peu ou pas la barrière hémato-encéphalique (BHE), elle doit être injectée par stéréotaxie dans la SNc, dans le site terminal de la DA, le striatum, ou dans les fibres les reliant, soient les faisceaux télencéphaliques médians (Ungerstedt, 1968, Winkler *et coll.*, 2002). Habituellement, une lésion dopaminergique complète est produite unilatéralement seulement, car une lésion totale bilatérale provoque une dysfonction nutritionnelle (Ungerstedt, 1971). Conséquemment, les rongeurs ont besoin d'une alimentation par gavage et des soins constants (Sakai et Gash, 1994). L'avantage d'utiliser ce modèle unilatéral est la

reproductibilité de la lésion et avoir le côté non-lésé comme contrôle. De plus, la déplétion dopaminergique induite par cette neurotoxine se traduit par des changements morphologiques et électrophysiologiques similaires à ceux observés chez l'humain (Breit *et coll.*, 2006). Toutefois, contrairement à l'humain, il n'y a pas d'évidences que la 6-OHDA induit des corps de Lewy (Schober, 2004). La 6-OHDA est principalement utilisée chez le rongeur, mais est aussi utilisée chez les primates de petite taille, tel que le ouistiti (Henderson *et coll.*, 1998).

Quoique le mécanisme de la toxicoté de la 6-OHDA ne soit pas complètement élucidé, il est généralement admis qu'elle provoque une dégénérescence neuronale par stress oxydatif et altération de la respiration mitochondriale. Brièvement, elle est recaptée par le DAT et rendue dans la cellule dopaminergique, la 6-OHDA peut s'oxyder et former des molécules oxygénées réactives, telle que le peroxyde d'hydrogène. De plus, elle réduit le nombre d'enzymes anti-oxydantes et interagit avec les complexes I et IV de la chaine de respiration mitochondriale (Blandini *et coll.*, 2008). L'une des utilisations principales du modèle 6-OHDA est pour l'étude des LID. Quoique l'appellation dyskinésie fut fortement critiquée, certains auteurs préfèrent utiliser le terme « mouvements involontaires anormaux » (Cenci *et coll.*, 1998). Ces derniers se traduisent par une rotation du côté contralatéral à la lésion dopaminergique et par trois mouvements stéréotypiques qui prennent forme de mouvements répétitifs des membres supérieurs, une dystonie axiale et des dyskinésies orofaciales.

2.4.2 MPTP

Avant l'introduction des neurotoxines chez le primate, un modèle lésionnel avait été développé pour l'étude de la PD (Poirier *et coll.*, 1975, Sourkes et Poirier, 1966). En effet, certains chercheurs s'étaient penchés sur le tegmentum mésencéphalique ventromédian (VMT), qui correspond essentiellement à la VTA, pour des lésions électrolytiques ou par radiofréquences. Cette aire projette des afférences dopaminergiques vers le striatum (Koob *et coll.*, 1975). Ce modèle présentait des tremblements ainsi que des dyskinésies s'apparentant à des LIDs (Battista *et coll.*, 1971, Poirier, 1960), ces dernières étaient augmentées par l'administration de L-DOPA. Par contre, la présentation des symptômes variait selon la lignée de primate utilisée (Bédard *et coll.*, 1983).

Le premier cas rapporté d'induction d'un syndrome parkinsonien chez l'humain remonte à la fin des années 1970 (Davis *et coll.*, 1979). Un patient avait développé les symptômes parkinsoniens après des injections intramusculaires et intraveineuses auto-administrées provenant d'une mauvaise synthèse d'héroïne synthétique. Ce patient avait une bonne réponse à la L-DOPA. Les auteurs de l'étude ont reproduit les étapes de synthèse et ont obtenu un mélange de 1-méthyl-4-phényl-4-propionoxypipéridine (MPPP, héroïne synthétique), de 4-hydroxy-4-phényl-*N*-méthylpipéridine (HPMP) et de dehydro-4-phényl-*N*-méthylpipéridine (DPMP). Cette dernière substance fut d'abord synthétisée au milieu du 20^{ième} siècle (Ziering et Berger, 1947). L'histoire entre le MPTP et le parkinsonisme remonte toutefois aux années 1950. Des injections sous-cutanées de 0.5 mg/kg chez deux singes provoquèrent une rigidité des membres supérieurs au bout de 24 à 48 heures et une immobilité complète 68 heures après une injection de 2.0 mg/kg; ces deux singes furent retrouvés morts au bout de 12 et 24 jours (Langston *et coll.*, 1984). Dans le cadre de la même investigation, des doses variant de 50 à 300 mg de MPTP furent données quotidiennement à des humains pendant 3 semaines. Toutefois, ce projet fut abandonné quand deux des six sujets décédèrent lors des essais cliniques. Ironiquement, le MPTP était investigué comme agent antiparkinsonien (Langston *et coll.*, 1984). Malgré cela, l'article de Davis et ses collaborateurs (1979) passa un peu sous le silence jusqu'en 1983 où une série de six toxicomanes furent admis pour un profond syndrome parkinsonien (Langston *et coll.*, 1983). L'induction d'un tel syndrome fut reproduite chez le primate la même année (Burns *et coll.*, 1983). Cette induction peut se faire par injection/diffusion sous-cutanée (Soghomonian *et coll.*, 1994), intra-musculaire (Mounayar *et coll.*, 2007), intraveineuse (Palombo *et coll.*, 1991) et intra-carotide (Guttman *et coll.*, 1990). Cette dernière voie d'administration crée un modèle hémi-parkinsonien, comparativement aux autres qui donnent un parkinsonisme bilatéral. La découverte de cette neurotoxine a permis l'étude d'un modèle fiable de la PD et est encore aujourd'hui fortement utilisée (Fox et Brotchie, 2010).

2.4.2.1 Symptômes et neurodégénérescence

Pour valider l'utilisation de cette neurotoxine pour l'étude de la PD, une des premières questions qui s'est posée était à savoir si le MPTP provoquait une dégénérescence similaire à celle observée chez un patient parkinsonien. Il fut alors

démontré par autoradiographie chez le singe que le putamen était plus vulnérable que le noyau caudé au MPTP et de façon plus marquée dans les parties postérieures du striatum (Moratalla *et coll.*, 1992). Toutefois, le patron de dégénérescence dopaminergique serait différent chez l'humain; le putamen et le noyau caudé démontrant une dégénérescence similaire (Snow *et coll.*, 2000). Chez des humains exposés à des faibles doses de MPTP mais ne présentant peu ou pas de symptômes parkinsoniens, une baisse partielle de l'activité striatale fut mesurée par PET comparativement à des sujet contrôles, les patients parkinsoniens ayant une baisse plus importante (Calne *et coll.*, 1985). Cette observation *in vivo* démontre qu'une dégénérescence dopaminergique est présente avant que les symptômes apparaissent. Des changements dans l'activité neuronale provenant du cortex moteur, du pallidum et du STN pourraient être à l'origine de telles compensations (Bezard *et coll.*, 2001b). D'autre part, les humains exposés au MPTP ont une dégénérescence dopaminergique plus rapide que des sujets contrôles et ce plusieurs années après l'injection de cette neurotoxine (Vingerhoets *et coll.*, 1994b), démontrant ainsi que les cellules exposées au MPTP demeurent plus vulnérables que celles qui ne furent pas exposées. Cette vulnérabilité pourrait être entre autre expliquée par un processus neuroinflammatoire, car la présence de microglie réactive fut démontrée après une longue période post-exposition au MPTP chez le primate (McGeer *et coll.*, 2003). Les symptômes parkinsoniens conséquents à une administration de MPTP vont varier pour chaque singe (Eidelberg *et coll.*, 1986), reproduisant ainsi la situation clinique où chaque patient présente un patron de symptômes qui lui est propre (Jankovic *et coll.*, 1990). Le dosage individuel est un aspect important à considérer à cause de la variabilité inter-animale dans la sensibilité au MPTP, l'âge étant un facteur important dans la réponse au MPTP (Ovadia *et coll.*, 1995). Finalement, certains primates exposés au MPTP récupèrent une fonction motrice après quelques mois (Eidelberg *et coll.*, 1986), nécessitant des injections supplémentaires de MPTP. Tirant profit de cette récupération, il est donc possible d'étudier les mécanismes compensatoires dans les premiers stades de la PD (Mounayar *et coll.*, 2007).

2.4.2.2 Mécanismes

Après son administration, le MPTP passe la barrière hémato-encéphalique pour être converti en 1-méthyl-4-phényl-2,3-dihydropyridinium (MPDP+) par l'enzyme monoamine oxidase B (MAO-B) présente dans les astrocytes (Ransom *et coll.*, 1987). Le MPDP+

s'oxyde spontanément pour former le 1-méthyl-4-pyridinium (MPP+). C'est sous cette forme que s'exerce la toxicité du MPTP. Le MPP+ est alors recapté par les cellules qui expriment le DAT, soit principalement les cellules de la SNc (Javitch *et coll.*, 1985). Cette étape semble cruciale car aucune toxicité du MPP+ n'a été observé chez les souris n'exprimant pas le DAT (Bezard *et coll.*, 1999b, Gainetdinov *et coll.*, 1997).

À l'intérieur de la cellule, le MPP+ inhibe le complexe I de la chaîne de transport d'électrons dans la mitochondrie, ce qui produit une déplétion d'adénosine triphosphate (ATP), source d'énergie cellulaire. Toutefois, la toxicité du MPP+ sur les cellules dopaminergiques ne semble pas conséquente d'une simple baisse énergétique. Le MPP+ génère aussi la formation de radicaux superoxides dans le cytosol (Cleeter *et coll.*, 1992, Przedborski *et coll.*, 1992, Wu *et coll.*, 2003). De plus, le MPP+ induit, indirectement par des processus inflammatoires, une production d'oxide nitrique (NO) dans les cellules gliales (Hunot *et coll.*, 1999). Le NO est une molécule lipophile qui passe facilement à travers les membranes cellulaires et diffuse facilement dans les milieux intra- et extracellulaires (Lancaster, 1996). Dans les neurones, le NO et les radicaux superoxides peuvent interagir pour former du peroxynitrite (OONO-), une molécule oxydante très réactive (Ischiropoulos et al-Mehdi, 1995). La TH, l'enzyme limitante dans la synthèse des catécholamines, est inactivée par le OONO- par un processus de nitration (Kuhn *et coll.*, 1999). La DA est une molécule qui peut s'auto-oxider et est sensible aux radicaux libres intracellulaires, participant au stress oxidatif cellulaire (Hirrlinger *et coll.*, 2002, Slivka et Cohen, 1985). Elle est aussi la cible du peroxynitrate (LaVoie et Hastings, 1999). Tous ces processus participent à la mort de la cellule dopaminergique. Les cellules dopaminergiques de la VTA et noradrénergiques du locus coeruleus sont aussi affectées par le MPTP mais à moindre mesure (Forno *et coll.*, 1986, Mitchell *et coll.*, 1985). En résumé, le MPTP a des propriétés qui, par des processus d'oxidation, de nitration et d'inhibition de la respiration cellulaire, sont toxiques pour les cellules dopaminergiques.

Une des signatures importantes du diagnostic *post-mortem* de PD est la présence de corps de Lewy (voir section 2.3). Malgré le fait que le MPTP réplique quasiment de façon parfaite la mort des cellules dopaminergiques et un comportement moteur similaire, les primates et les humains exposés au MPTP ne développement pas ces corps de Lewy et ce

même après une très longue période de survie (Halliday *et coll.*, 2009, Langston *et coll.*, 1999), démontrant ainsi une des seules limites de ce modèle.

2.4.3 Autres toxines et modèles génétiques de la PD

Après la découverte du MPTP, les études sur les toxines environnementales ont explosé et des études épidémiologiques ont proposé un lien entre les toxines et la PD (Ascherio *et coll.*, 2006, Freire et Koifman, 2012). Des études effectuées à l'aide de tissus *post-mortem* ont démontré la présence d'une dysfonction mitochondriale chez les patients parkinsoniens (Hattori *et coll.*, 1991, Schapira *et coll.*, 1990). La roténone, un agent organique naturel, fut utilisé comme pesticide et pour contrôler la population de poissons nuisibles dans les lacs et les réservoirs (Martinez et Greenamyre, 2012), inhibe systématiquement le complexe I mitochondrial. Il fut dernièrement associé à la PD chez l'humain (Tanner *et coll.*, 2011). Toutefois, certains auteurs ont démontré une toxicité non-spécifique, le rendant moins attrayant pour l'étude de la PD (Lapointe *et coll.*, 2004).

Le paraquat, un herbicide avec une similarité moléculaire au MPTP, fut aussi associé à un développement de PD (Tanner *et coll.*, 2011). Il s'attaque, tout comme le MPTP, au complexe I mitochondrial (Martinez et Greenamyre, 2012). Comparativement au MPTP, le paraquat est une neurotoxine moins « efficace » en terme de dénervation dopaminergique. Elle induit une moins forte déplétion des terminaisons nerveuses dopaminergiques dans le striatum et une atteinte motrice plus modérée (Brooks *et coll.*, 1999, McCormack *et coll.*, 2002). Le paraquat, utilisé chez le rongeur, apparatrait comme un bon modèle pour la phase pré-clinique de la PD (Martinez et Greenamyre, 2012).

Le Maneb est un fongicide qui a aussi été relié à un développement de syndrome parkinsonien chez l'humain. Peu de chose est connu sur le maneb, mais son administration chez la souris provoque un déficit moteur (Morato *et coll.*, 1989), potentialise les effets neurotoxiques du MPTP (Takahashi *et coll.*, 1989) et a des interactions synergétiques avec le paraquat (Thiruchelvam *et coll.*, 2000). Fait intéressant, comparativement au MPTP, les neurotoxines roténone, paraquat et maneb vont provoquer l'accumulation d'α-synucléine, ressemblant aux corps de Lewy (Hisahara et Shimohama, 2011).

Le trichloroéthylène, un agent dégraissant très utilisé, est un contaminant environnemental courant (Martinez et Greenamyre, 2012). Tout comme les autres

neurotoxines, il inhibe la chaine respiratoire du complexe I et il a été récemment associé au développement de la PD après une exposition chronique (Gash *et coll.*, 2008). Toutefois, très peu est connu de cette toxine et d'autres études seront nécessaires pour établir sa place en tant que modèle de la PD (Martinez et Greenamyre, 2012). L'exposition à différents solvants et autres pesticides peuvent aussi déclencher un dévelopement d'un syndrome parkinsonien (pour une revue complète récente, voir (Pezzoli et Cereda, 2013)).

En dernier lieu, l'étude génétique des patients parkinsoniens a mené au développement de modèles génétiques de la PD. Plusieurs modèles animaux, de la drosophile jusqu'au singe, transgéniques ou invalidés (« *knock-out* ») pour différents gènes impliqués dans la PD sont maintenant disponibles (Hisahara et Shimohama, 2011). Pour chacun des modèles animaux, certaines caractéristiques de la PD (perte des cellules dopaminergiques, inclusion de corps de Lewy, déficit moteur répondant à la L-DOPA) sont présentes ou absentes (pour une revue complète, voir (Hisahara et Shimohama, 2011)).

CHAPITRE 3. TRAITEMENTS PHARMACOLOGIQUES ET CHIRURGICAUX

3.1 Traitements pharmacologiques

Cinquante ans après son introduction, la L-DOPA, précurseur métabolique immédiat de la DA, demeure la médication la plus efficace et la plus utilisée comme thérapie de remplacement pour le traitement de la PD (Goetz *et coll.*, 2005). D'autres traitements pharmacologiques sont aussi disponibles, dont les agonistes dopaminergiques et d'autres médications adjuvantes à la L-DOPA, comme traitement symptomatologiques (Fox *et coll.*, 2011). Certains patients ont recours à des procédures chirurgicales pour diverses raisons (mauvaise réponse à la médication, effets secondaires importants, symptômes réfractaires comme le *freezing of gait*) (Bronstein *et coll.*, 2011, Giladi, 2001, Giladi *et coll.*, 1997). Parmi ces chirurgies offertes, on compte principalement les lésions, la stimulation cérébrale profonde et les transplantations cellulaires. La prochaine section passera en revue la L-DOPA, les agonistes dopaminergiques les plus fréquemment utilisés, ainsi que les diverses chirurgies offertes aux patients.

3.1.1 Historique

La L-DOPA, ou L-3,4-dihydroxyphénylalanine, fut isolée au début du vingtième siècle à partir de fèves (Torquati, 1913). Cette molécule est biologiquement inactive et doit être convertie en DA par l'enzyme dopa décarboxylase (DDC), découverte en 1938 (Holtz, 1939). Toutefois, la fonction de la DA n'était pas encore connue (Hornykiewicz, 2002). Ce n'est que deux décennies plus tard que fut démontrée la présence de DA dans le cerveau chez les mammifères (Montagu, 1957, Weil-Malherbe et Bone, 1957) et principalement dans le noyau caudé et dans le putamen (Sano *et coll.*, 1959). Cette dernière observation démontrait un lien possible entre la DA et les fonctions motrices. L'étude classique de Carlsson en 1957 démontrait que l'administration de L-DOPA renversait l'akinésie induite par réserpine chez le lapin (Carlsson *et coll.*, 1957). Une étude chez des patients souffrant de désordres des BG démontra une baisse radicale de DA au niveau striatal seulement chez les patients parkinsoniens, tandis que les niveaux dopaminergiques demeuraient inchangés

chez les patients avec la maladie d'Huntington (Ehringer et Hornykiewicz, 1960). Les premiers essais cliniques avec de la L-DOPA chez le parkinsonien démontrèrent un effet bénéfique sur l'akinésie (Birkmayer et Hornykiewicz, 1961), tandis qu'aucune amélioration n'était observable avec des composés analogues (Birkmayer et Hornykiewicz, 1962). Une étude chronique prouva son efficacité à long terme (Cotzias *et coll.*, 1967), ouvrant ainsi de manière définitive la voie de la L-DOPA comme traitement principal de la PD.

3.1.2 Mode d'administration et biodisponibilité

Lors des premiers essais cliniques, les patients recevaient des doses très élevées de L-DOPA (4.5 à 8 grammes par jour) (Cotzias *et coll.*, 1969). À de telles doses, les patients présentaient des effets bénéfiques, mais aussi des effets secondaires dont des nausées et des mouvements involontaires (Cotzias *et coll.*, 1969, Cotzias *et coll.*, 1967). Ceci était avant la découverte d'enzymes qui métabolisaient la L-DOPA en périphérie, ainsi que l'addition d'inhibiteur de ces enzymes à la L-DOPA (Tissot *et coll.*, 1969). Ces inihibiteurs (carbidopa et benserazide) sont maintenant présents *de facto* dans la médication fournie au patient, sous différentes formulations (Strecker et Schwarz, 2008). La L-DOPA est aujourd'hui administrée principalement par voie orale. Il existe toutefois d'autres voies d'administration. La L-DOPA methylester est une forme injectable (Cooper *et coll.*, 1984) qui doit être accompagnée d'inhibiteurs de DDC. L'avantage de cette voie est que sous cette forme, la réponse est plus stable et évite un passage dans le foie. L'administration de DA et d'agonistes dopaminergiques directement dans le striatum fut déjà explorée (de Yebenes *et coll.*, 1988, de Yebenes *et coll.*, 1987, Velasco Suárez et Escobedo, 1970), mais l'efficacité ne fut pas celle escomptée et les problèmes reliés au matériel installé ont vite fait abandonnée cette voie. Plus récemment, l'infusion gastro-intestinal (Duodopa) fut explorée et semblerait avoir un avenir prometteur comme voie d'administration de L-DOPA (Fernandez *et coll.*, 2013).

Lorsqu'administrée, la L-DOPA orale est absorbée par l'intestin et passe rapidement dans le plasma où sa concentration va être à son apogée après 0.8 heure post-dose (Olanow *et coll.*, 1991). La fraction cérébrale de L-DOPA, mesurée dans le liquide céphalorachidien, est d'environ 12% de la concentration plasmatique et va être à son maximum près de 2 heures post-dose (Olanow *et coll.*, 1991). Les effets bénéfiques de la L-DOPA sont

hautement corrélés avec la concentration plasmatique (Muenter et Tyce, 1971, Olanow *et coll.*, 1991). Toutefois, l'efficacité de L-DOPA peut être influencée par la diète du patient; les protéines réduisant entre autre son absorption (Tsui *et coll.*, 1989), car elles compétitionnent pour le transport membranaire (Nutt et Fellman, 1984). Rendue dans la cellule, la L-DOPA est convertie en DA par la DDC puis est stockée dans les vésicules en attente d'être relâchée dans la fente synaptique.

L'utilisation de la L-DOPA comme thérapie de remplacement pour la perte de DA est très efficace pour l'amélioration des signes cardinaux de la PD (Neurology, 1993) et demeure encore aujourd'hui le traitement standard pharmacologique (Goetz *et coll.*, 2005). Tous les patients bénéficient de cette pharmacothérapie, peu importe le stade de développement de la maladie (Fahn, 1999). Les améliorations fonctionnelles sont doses-dépendantes et toute dose de L-DOPA donne de meilleurs résultats que l'administration d'un placebo (Fahn *et coll.*, 2004).

3.1.3 Agonistes dopaminergiques

En plus de la L-DOPA, il existe sur le marché un amalgame d'agonistes dopaminergiques qui peuvent être utilisés comme monothérapie ou en complément avec la L-DOPA. Les agonistes furent introduits comme compléments pour réduire les effets secondaires induits par la L-DOPA (Fischer, 1995). En effet, les doses de L-DOPA étaient réduites entre 20 et 30%, réduisant du même coup les effets secondaires (Brooks, 2000). Contrairement à la L-DOPA, les agonistes ne sont pas stockés dans les neurones pré-synaptiques et possèdent en général des demie-vies plus longues que la L-DOPA (Olanow *et coll.*, 2009). Cette dernière caractéristique pourrait entre autre expliquer pourquoi les agonistes induisent moins de LID que la L-DOPA. D'autre part, les agonistes ne sont pas métabolisés par des mécanismes oxidatifs et n'engendrent pas la formation de radicaux libres comparativement à la L-DOPA (Brooks, 2000). Il fut donc proposé de retarder l'introduction de la L-DOPA et utiliser des agonistes pour éviter une progression plus rapide de la PD et réduire les risques de développement des effets secondaires (2000, Siderowf et Stern, 2003). Quoique des études récentes arrivent à des conclusions contraires après un traitement chronique (Katzenschlager *et coll.*, 2008, Schapira *et coll.*, 2013), remettant ainsi en question ce paradigme. Les agonistes se divisent en dérivés d'ergoline et

les non-ergolines. Les premiers dérivés d'ergoline agissaient principalement sur les récepteurs de la famille D_2 (D_2-D_4), dont entre autres la pergolide, la cabergoline et la bromocriptine (Brooks, 2000). Plus récemment, des agonistes n'étaient pas des dérivés d'ergoline apparurent sur le marché, dont le pramipexole et le ronipirole. Chacun de ces agonistes présente un profil pharmacologique qui lui est distinct et va avoir des interactions agonistes ou antagonistes avec les systèmes de neurotransmission (pour revue, voir (Fox *et coll.*, 2011))

Des agonistes D_1 furent testés chez le primate parkinsonien et semblent avoir des effets bénéfiques sur les symptômes parkinsoniens avec peu d'expression de LID comparativement à des agonistes D_2 (Blanchet *et coll.*, 1993). Toutefois, ces effets s'estompaient rapidement après quelques administrations, probablement à cause d'une internalisation ou d'une désensibilisation des récepteurs (Blanchet *et coll.*, 1996b). À ce jour, il n'existe pas sur le marché des agonistes spécifiques pour le récepteur D_1. Il existe l'apomorphine, agoniste injectable par voie sous-cutanée agissant sur les récepteurs D_1 et D_2, qui est utilisé lors des chirurgies pour la PD (Hutchinson *et coll.*, 1997). Bien que les agonistes induisent moins de complications motrices que la L-DOPA, il reste toutefois qu'ils demeurent moins efficaces en termes de bénéfices antiparkinsoniens et ont des profils d'effets secondaires importants (nausée, hypotension, hallucinations, somnolence, etc.) (Brooks, 2000).

3.1.4 Autres agents antiparkinsoniens

Les autres agents pharmacologiques ne jouent pas directement sur la neurotransmission, contrairement à la L-DOPA et les agonistes dopaminergiques (Strecker et Schwarz, 2008). Parmi les autres agents, on retrouve les inhibiteurs d'enzymes de dégradation de la DA. L'enzyme monoamine oxidase de type B (MAO-B) dégrade la DA en acide 3,4-dihydroxyphénylacétique (DOPAC) (Jankovic et Poewe, 2012). En inhibant la MAO-B, on augmente ainsi les concentrations de DA dans la fente synaptique (Abdel-Salam, 2008). La Sélégiline et la Rasagiline sont deux inhibiteurs irréversibles de la MAO-B et peuvent être utilisés comme monothérapie dans les premiers stades de la PD (Chen, 2006), retardant ainsi l'introduction de la L-DOPA de 9 à 12 mois (Shoulson, 1998). La Rasagiline, lorsque donnée avec de la L-DOPA chez les patients parkinsoniens avec un

stade avancé peut réduire les LID et le *wearing-off* (Group, 2005, Oldfield *et coll.*, 2007). La deuxième enzyme de dégradation ciblée pour la PD est la catéchol-*O*-méthyltransférase (COMT) (Abdel-Salam, 2008). La COMT va dégrader la DA en 3-méthoxytyramine, mais aussi la DOPAC en acide homovanillique (HVA) (Espinoza *et coll.*, 2012). Les inhibiteurs de la COMT (tolcapone et entacapone) permettent une réduction de L-DOPA entre 30 et 50%, car ils réduisent le catabolisme de la DA (Müller *et coll.*, 2006). Les inhibiteurs de la COMT sont utilisés comme traitement complémentaire à la L-DOPA chez les patients qui présentent des fluctuations motrices (Group, 1997). Lors de son introduction, les inhibiteurs d'enzymes de dégradation de la DA peuvent exacerber les LID dû à leurs activités pro-dopaminergiques (Mizuno *et coll.*, 2007), mais ces LID cessent après un réajustement de la médication.

L'amantadine, un antagoniste du récepteur NMDA, peut aussi être utilisé dans la PD (Hubsher *et coll.*, 2012). Quoique son mécanisme d'action ne soit pas complètement élucidé, son activité antiparkinsonienne pourrait provenir de son action pré-synaptique sur les cellules dopaminergiques en favorisant la relâche de DA et en inhibant sa recapture, ainsi qu'en agissant post-synaptiquement sur les récepteurs post-synaptiques D_2 (Abdel-Salam, 2008). Cette activité antiparkinsonienne est faible, rendant l'amantadine utile dans les premiers stades de la PD. D'un autre côté, son activité anti-glutamatergique le rend attrayant pour le traitement des LID, car ces dernières sont entre autres dues à une hyperactivité glutamatergique (voir section 4.1.3.3). Les troubles cognitifs associés à la prise d'amantadine et le développement de tolérance sont des facteurs à considérer dans l'utilisation de cette médication (Schapira *et coll.*, 2006).

En dernier lieu, des drogues anticholinergiques furent introduites bien avant la L-DOPA, soit au milieu du 19^{ième} siècle (Olanow *et coll.*, 2009). Elles exercent des actions antiparkinsoniennes très modestes et souvent ne suffisent pas comme traitement primaire (Olanow *et coll.*, 2001). De plus, leur profil d'effets secondaires (assèchement des mucueuses, troubles urinaires et intestinaux, sédation et étourdissements) limitent leur utilisation (Schapira *et coll.*, 2006). Pour des informations plus approfondies sur les agonistes dopaminergiques ainsi que les autres agents pharmacologiques, voir (Olanow *et coll.*, 2009).

3.2 Traitements chirurgicaux

Les traitements chirurgicaux pour les troubles du mouvement, incluant la PD et les dyskinésies, ont précédé les traitements pharmacologiques et ont suscité beaucoup de controverse. En effet, des lésions ont été produites au niveau des cortex moteur primaire et pré-moteur (Bucy, 1966, Horsley, 1909) ou de la portion dorsale du faisceau latéral de la moelle épinière (Foerster, 1913, Puusep, 1930) pour le traitement des dyskinésies avec une amélioration considérable. Par contre, ces abolitions étaient associées à d'autres troubles moteurs importants, dont l'hémiparésie contralatérale (Carpenter *et coll.*, 1960, Carpenter et Mettler, 1951). La neurochirurgie stéréotaxique, introduite en 1947 avec les travaux de Spiegel et Wycis (Spiegel *et coll.*, 1947), avait pour but d'atteindre des structures profondes dans le cerveau avec une haute précision tout en gardant les structures adjacentes intactes, telle que décrite par Horsley et Clarke au début du 20ième siècle :

> *« An essential preliminary, therefore, to further progress was to find some method which would satisfy these conditions, viz., a means of producing lesions which should be accurate in position, limited to any desired degree of extent, and involving as little injury as possible to other structures »* (Horsley et Clarke, 1908)

Aujourd'hui, il existe trois types de chirurgies, soient les lésions, la stimulation cérébrale profonde (deep brain stimulation, DBS) et les transplantations de cellules souches (Walter et Vitek, 2004). Le GPi, le thalamus et le STN sont les trois cibles principales pour les chirurgies lésionnelles, mais aussi pour le DBS (Jourdain et Schechtmann, 2013). Cette présente section passera brièvement en revue chacune de ces chirurgies lésionnelles et de stimulation, ainsi que les transplantations de cellules souches.

3.2.1 Pallidotomie

Avant l'introduction de la L-DOPA, la lésion du GPi ou pallidotomie était une procédure commune pour le traitement de la PD. Les premiers travaux par Lars Leksell dans les années 1950 étaient basés sur des observations cliniques avec un déplacement de la lésion vers la partie postérieure et ventrale du GPi (Svennilson *et coll.*, 1960). Cette portion

sensorimotrice du GPi fut confirmée *a posteriori* avec des données anatomiques chez le primate (Percheron *et coll.*, 1984). Cette chirurgie s'est vue tomber en hibernation jusqu'en 1992, lorsqu'un groupe de Suède a « ressuscité » la pallidotomie postéroventrale (PVP) pour le traitement des symptômes cardinaux (Laitinen *et coll.*, 1992), mais aussi pour une condition qui n'était pas présente dans les années où la pallidotomie prédominait, soient les LID. Ce sont les patients avec un état cognitif normal qui présentent des LID et des fluctuations motrices qui bénéficient le plus de la PVP (Kleiner-Fisman *et coll.*, 2010). Les effets sur les LID sont les plus spectaculaires. En effet, les patients voient leurs LID diminuées par 86% un an après une PVP unilatérale (Alkhani et Lozano, 2001). D'un autre côté, l'akinésie, le tremblement et les troubles de la démarche sont aussi améliorés, mais à moindre mesure (Valldeoriola *et coll.*, 2002). Le fait que le GPi soit une large structure (Hardman *et coll.*, 2002), le site et la grosseur de la lésion influencent beaucoup sur l'efficacité de la pallidotomie sur les symptômes cardinaux (Gross *et coll.*, 1999). Finalement, la médication requise pour les troubles moteurs chez le patient parkinsonien demeure peu affectée (Guridi *et coll.*, 2008). Il est généralement admis que ce sont les patients présentant des symptômes asymétriques qui bénéficient le plus de la PVP (Kleiner-Fisman *et coll.*, 2010). En effet, la PVP unilatérale est normalement pratiquée, car une lésion bilatérale augmente les risques de problèmes cognitifs et de langage (Counihan *et coll.*, 2001, York *et coll.*, 2007) et la deuxième PVP contralérale n'est jamais aussi efficace que la première (De Bie *et coll.*, 2002). La PVP est aussi très efficace comme approche dans le traitement des dystonies et est plus souvent pratiquée que les autres chirurgies lésionnelles pour cette pathologie (Jourdain et Schechtmann, 2011).

3.2.2 Thalamotomie

La thalamotomie que l'on connaît aujourd'hui fut introduite par Hassler et Riechert (Hassler et Riechert, 1954). Les neurones du VIM (ou VL) sont largement connectés avec le cervelet et présentent une activité électrique particulière (voir section 1.2.6.1). L'ablation de cette région, la thalamotomie, fut donc introduite pour l'abolition du tremblement (Hassler et Riechert, 1954). Une lésion d'un volume entre 40 et 60 mm^3 est suffisante pour l'arrêt d'un tremblement chez le parkinsonien (Ohye, 2009). Lorsque le microenregistrement neuronal est utilisé, il est possible de bien circonscrire la région à léser

et les patients sont complètement soulagés de leurs tremblements. Cette nette amélioration dure dans le temps, avec une abolition complète des symptômes après 5 ans post-thalamotomie étant comparable à la stimulation cérébrale profonde (Schuurman *et coll.*, 2008). Le tremblement est certainement le symptôme principal pour lequel une thalamotomie est proposée (Ohye, 2009). Elle est peut aussi être pratiquée pour réduire la rigidité chez le parkinsonien (Ohye, 2000). Dans cette situation, le VIM est localisé par microenregistrement neuronal et la lésion est pratiquée antérieurement, soit dans le ventrooralis, parce que, contrairement au VIM, ce dernier noyau thalamique ne présente pas de patron électrique qui lui est spécifique (Vitek *et coll.*, 1994). La lésion thalamique est normalement pratiquée par électrocoagulation, mais certains centres utilisent la radiochirurgie de type gamma knife (Ohye *et coll.*, 2012, Young *et coll.*, 1998). Son avantage principal est qu'il n'y a aucune pénétration mécanique dans le cerveau, évitant ainsi les hémorragies intracérébrales et permet d'opérer des patients plus âgés qui ne seraient pas autrement candidats à la chirurgie (Kooshkabadi *et coll.*, 2013). Toutefois, cette dernière technique ne semble pas reproduire les effets avec la même efficacité (Pan *et coll.*, 1996) et les effets se font voir après plusieurs mois (rarement avant 3 mois) dus à la technique (Ohye *et coll.*, 2012). Les complications transitoires post-thalamotomie sont présentes dans près de 70% des cas, qui incluent dystonie, confusion, troubles du langage et sensoriels (Fox *et coll.*, 1991, Jankovic *et coll.*, 1995). Les effets secondaires permanents à la thalamotomie sont relativement rares. Environ 5% des patients lésés vont présenter des paresthésies au niveau des lèvres ou au bout des doigts (Ohye, 2009). Certains patients peuvent présenter un sentiment de légèreté du membre contralatéral à la lésion (Ohye, 2009). La thalamotomie unilatérale est aussi fréquemment utilisée que la pallidotomie unilatérale pour la PD (Jourdain et Schechtmann, 2011). D'autre part, la thalamotomie bilatérale est rarement appliquée car plusieurs patients développent des troubles du langage, telles que l'aphasie (Ohye, 2009).

3.2.3 Subthalamotomie

Comparativement à ses deux homologues lésionnels, la subthalamotomie est la moins documentée et la moins pratiquée (Jourdain et Schechtmann, 2013). Elle ne fait pas partie des lignes directrices dictées par la société pour les troubles du mouvement

(*Movement Disorder Society*) à cause du manque d'évidences (Fox *et coll.*, 2011). Cette exclusion des recommandations lui confère un statut de chirurgie expérimentale et explique en partie le faible taux de pratique de cette chirurgie. Cela n'empêche pas que cette chirurgie soit efficace pour le traitement de la PD et les LID. En fait, deux études randomisées ont permis de démontrer que la subthalamotomie unilatérale et bilatérale pouvaient être aussi efficaces que les chirurgies recommandées, soient la PVP unilatérale et le STN-DBS bilatéral respectivement (Çoban *et coll.*, 2009, Merello *et coll.*, 2008). Toutefois, le faible nombre de patients recrutés dans ces deux études ne fut pas suffisant pour qu'elles soient considérées dans les lignes directrices. Le premier appendice de cette thèse est une revue de littérature portant sur le rôle du STN et de sa lésion dans le cadre de la PD.

3.2.4 Stimulation cérébrale profonde

Le DBS est aujourd'hui l'un des meilleurs traitements offerts aux patients qui présentent des effets secondaires importants à la médication ou qui sont réfractaires à cette dernière (Fasano *et coll.*, 2012). Le patient se voit implanté des électrodes uni- ou bilatéralement, en fonction du besoin et de la pathologie. Ces électrodes, connectées à une batterie-générateur, génèrent un courant électro-magnétique qui va modifier l'activité des cellules et fibres avoisinantes (pour d'excellentes revues de littérature sur les mécanismes d'action, voir : (Albert *et coll.*, 2009, Liu *et coll.*, 2008, Montgomery et Gale, 2008). Le DBS présente plusieurs avantages comparativement aux lésions. Tout d'abord, il y a la possibilité de modifier les paramètres de stimulation en fonction de la réponse du patient, mais aussi en fonction de la progression de la maladie lorsqu'elle est dégénérative comme la PD (Benabid *et coll.*, 2009). De plus, c'est une chirurgie qui est dite minimalement invasive, car l'introduction des électrodes de stimulation cause peu de dommage mécanique (les électrodes sur le marché nord-américain ont présentement un diamètre de 1.27mm) et que la stimulation peut être arrêtée en tout moment tandis que dans le cas la lésion, le tissu cérébral est détruit et on ne peut pas revenir à un état initial (Kringelbach *et coll.*, 2007). D'un autre côté, le DBS est un système implantable, donc des complications post-opératoires reliées au matériel, dont la migration ou bris des électrodes, infection du système et l'érosion cutanée (Blomstedt et Hariz, 2005). D'autre part, certains facteurs

limitent l'utilisation du DBS. En effet, l'accès aux soins de santé publique ou un accès à montant monétaire important (un système de DBS coûte au-delà de 40 000$ (McIntosh *et coll.*, 2003, McIntosh, 2011)), une distance trop importante avec l'hôpital d'attache pour les suivis post-opératoires et d'ajustements, ainsi que certaines contraindications neuropsychiatriques (démence, dépression, troubles psychotiques) sont autant de raisons de considérer les lésions chez ces patients (Hooper *et coll.*, 2008).

Le choix de la cible pour l'implantation d'électrodes se fait principalement selon la symptomatologie du patient. Le STN est de loin la cible la plus utilisée dans la PD et le traitement des dyskinésies (Jourdain et Schechtmann, 2013). Après l'implantation, les patients se voient réduire leur médication d'environ 60% et conséquemment leur LID par >60% (Krack *et coll.*, 2003). Ces effets restent bénéfiques aux patients 10 ans après l'opération (Castrioto *et coll.*, 2011). Les patients ont des améliorations importantes au niveau de la rigidité, de l'akinésie, des fluctuations motrices et de leur tremblement sans médication (Limousin *et coll.*, 1998). D'autre part, la réduction de médication abaisse les hallucinations chez les patients qui présentent des psychoses induites à la L-DOPA (Umemura *et coll.*, 2011). D'un autre côté, certains patients peuvent développer des problèmes cognitifs ou dépressifs suivant la chirurgie (Deuschl *et coll.*, 2006, Voon *et coll.*, 2008). Le GPi offre des bénéfices fonctionnels similaires à ceux obtenus avec le STN-DBS (Follett *et coll.*, 2010), sauf pour la réduction de médication, qui reste inchangée (Anderson *et coll.*, 2005). Le GPi est aussi très utilisé dans le cadre de dystonie (Coubes *et coll.*, 2000). Le VIM est la troisième cible principale pour le DBS (Jourdain et Schechtmann, 2013, Walter et Vitek, 2004). Contrairement au GPi et au STN, le VIM n'a peu ou pas d'effet sur les LID (Guridi *et coll.*, 2008), mais est très efficace sur le tremblement parkinsonien (réduction de plus de 80%) et le tremblement essentiel (Katayama *et coll.*, 2005). Le PPN est présentement une cible prometteuse pour les troubles de la démarche et de posture (Ferraye *et coll.*, 2010). Contrairement aux autres cibles de DBS dont on retrouve une augmentation de l'activité neuronale, les neurones du PPN dégénèrent (section 1.2.7) et l'activité globale est réduite. En effet, une lésion du PPN reproduit une akinésie parkinsonienne chez le primate (Kojima *et coll.*, 1997). Une stimulation à basse fréquence est donc utilisée (Stefani *et coll.*, 2007). L'avantage de stimuler le PPN est qu'il est possible de la jumeler avec la stimulation d'autres structures (Stefani *et coll.*, 2007) et

permet de mieux gérer une polysymptomatologie (i.e. LID et *freezing of gait*). Finalement, la zona incerta (Plaha *et coll.*, 2006) et le CM/Pf (Peppe *et coll.*, 2008) sont d'autres cibles thérapeutiques pour le DBS, mais peu utilisées (Jourdain et Schechtmann, 2013) et demeurent des cibles exploratoires.

Le concept du DBS généralement accepté aujourd'hui est attribuable au Dr. Benabid à cause de sa réintroduction en 1987 (Benabid *et coll.*, 1987). Il faut tout de même se rappeler qu'historiquement, la stimulation cérébrale profonde fut utilisée comme traitement non pas seulement pour les troubles du mouvement (Bechtereva *et coll.*, 1975), mais aussi pour l'épilepsie (Cooper *et coll.*, 1980), la douleur (Mazars *et coll.*, 1974), les troubles psychiatriques (Sem-Jacobsen et Styri, 1972) et de comportement (Delgado, 1964). Aujourd'hui, les troubles du mouvement (PD, tremblement essentiel, dystonie) demeurent l'indication principale de l'utilisation du DBS (Lozano et Lipsman, 2013), mais il y a beaucoup de nouvelles avenues qui incluent les troubles neuropsychiatriques (dépression, troubles obsessionnels-compulsifs, le syndrome de Tourette, l'aggressivité, syndrome de Lesch-Nyhan, etc.) et les troubles neurologiques (douleur, épilepsie, migraines, maladie d'Alzheimer) (Ashkan *et coll.*, 2013, Lozano et Lipsman, 2013, Robison *et coll.*, 2012).

3.2.5 Transplantation cellulaire

La transplantation cellulaire est un traitement expérimental, dont le rationnel serait de remplacer les neurones dopaminergiques qui dégénèrent dans la PD. Elle se fait à partir de cellules souches qui sont introduites par stéréotaxie dans le striatum (Isacson et Kordower, 2008). Ces cellules injectées, dont le stade de développement cellulaire varie selon le laboratoire, se développeraient avec un phénotype dopaminergique (Isacson et Kordower, 2008). Un pourcentage très faible de ces cellules survie, mais celles qui survivent le font pour une longue période (Mendez *et coll.*, 2008). Des patients ont vu leurs symptômes parkinsoniens améliorés, mais au détriment d'apparition de dyskinésies sans L-DOPA (Politis *et coll.*, 2011). Toutefois, la *Movement Disorder Society* n'approuve aucunement cette procédure autant pour les résultats engendrés que pour les risques encourus (Fox *et coll.*, 2011).

3.3 Paradoxes et remise en question du modèle

Le modèle des BG a permis une explication simple de la pathophysiologie des troubles du mouvement. Depuis son introduction en 1990 (Albin *et coll.*, 1989, DeLong, 1990), les recherches sur la circuiterie se sont multipliées et la compréhension sur la fonction des BG a largement changé depuis. Toutefois, ces nouveaux éléments n'ont jamais été intégrés au modèle, le rendant désuet. D'autre part, certains phénomènes observés vont dans le sens contraire du modèle. La présente section couvrira les connaissances non intégrées au modèle, touchant particulièrement le STN, qui seront nécessaires à une meilleure compréhension et amènera le lecteur à reconsidérer le modèle.

Le striatum reçoit une afférence importante corticale (voir section 1.2.1), principalement du cortex moteur primaire (MI), de l'aire motrice supplémentaire (SMA) et du cortex pré-moteur (PM) (Künzle, 1975, 1978). Les voies de sortie des BG (GPi et SNr) passent par la partie orale du noyau ventrolatéral (VLo) et la partie parvicellulaire du noyau ventral antérieur (VApc) du thalamus avant d'atteindre les MI, SMA et PM (Sakai *et coll.*, 1996, Sakai *et coll.*, 2002). Le cervelet est connu pour son rôle dans la synchronisation et la coordination des mouvements (Manto, 2008). Les noyaux profonds du cervelet (*deep cerebellar nuclei*, CN) jouent aussi un rôle dans le contrôle cortical avec des afférences à la partie orale du noyau postérolatéral (VPLo) et la partie caudale du noyau ventral latéral (VLc) du thalamus (Sakai *et coll.*, 1996). Ces deux structures thalamiques aussi projettent aux mêmes structures corticales précédemment mentionnées (MI, SMA et PM), ce qui suggère que les afférences des BG et les afférences cérébelleuses atteignent le cortex de manière parallèle et indépendante (Sakai *et coll.*, 2002). Une microstimulation des aires thalamiques recevant une innervation cérébelleuse provoque des mouvements, tandis qu'une stimulation du VLo et VApc ne provoque aucune réponse (Buford *et coll.*, 1996, Vitek *et coll.*, 1996). Donc, la fonction de ces deux afférences et leur interaction dans le cortex reste à être élucidées.

Le modèle des BG se compose de deux voies ségréguées, la voie directe (pro-mouvement) et la voie indirecte (anti-mouvement). Plusieurs études ont démontré la présence d'une troisième voie (Monakow *et coll.*, 1978, Nambu *et coll.*, 2000), surnommée hyperdirecte. Cette projection cortico-subthalamique transmet un signal excitateur pour le GPi et la SNr plus rapide que celle de la voie indirecte. Chez un individu sain, la voie

hyperdirecte serait impliquée dans l'élimination de signaux non pertinents ou lors de changements rapides dans la planification motrice (Leblois *et coll.*, 2006). Dans un état parkinsonien, cette afférence pourrait participer à la suractivation du STN. En effet, le modèle des BG prédit une hypoactivation du GPe, ce qui aurait pour conséquence d'alléger la charge inhibitrice GABAergique sur le STN. Toutefois, des études histochimiques ont démontré que l'activité structurelle du GPe chez le primate et des patients parkinsoniens était soit similaire, soit augmentée comparativement à leurs contrôles respectifs (Guridi *et coll.*, 1996, Levy *et coll.*, 1997, Soghomonian *et coll.*, 1994). Ce qui indique que l'afférence inhibitrice exercée par le GPe sur le STN n'est pas altérée dans un état parkinsonien, contrairement à ce qui est prédit par le modèle. L'hyperactivation du STN pourrait donc être expliquée par une augmentation de la voie hyperdirecte cortico-subthalamique, mais aussi par des afférences glutamatergiques du noyau Pf du thalamus, malgré que cette projection thalamique ne semble pas avoir exercer une grande influence sur le STN (Carpenter *et coll.*, 1965).

Toujours selon le modèle des BG, les GPi et GPe sont les deux structures recevant les fibres striatofugales pour former la voie directe et indirecte (Albin *et coll.*, 1989). Des données récentes en traçage neuronal démontrent clairement que les projections striatales sont beaucoup plus complexes que cru auparavant. En effet, une proportion importante d'axones sortant du putamen projettent autant au GPe, au GPi et même à la SNr à travers de collatérales (Lévesque et Parent, 2005b, Parent *et coll.*, 1995a). D'autre part, le GPe et le GPi furent longtemps reconnues pour avoir deux fonctions différentes selon leur emplacement dans le modèle des BG, malgré leur grande similarité anatomique, chimique et cellulaire (Kita *et coll.*, 2004, Tachibana *et coll.*, 2008). De plus, le GPe et le GPi sont interconnectés par des projections directes du GPe vers le GPi (Hazrati *et coll.*, 1990). Finalement, le STN projette vers le GPe et le GPi et certains de ses axones projettent aux deux structures pallidales à travers de collatérales (Parent et Parent, 2007).

Le modèle des BG prédit une innervation dopaminergique seulement dans le striatum, dont l'expression des récepteurs D_1 et D_2 détermine les voies directe ou indirecte. Des données récentes démontrent toutefois que des cellules striatales expriment les deux types de récepteurs à la DA (Aizman *et coll.*, 2000) et que ces deux derniers peuvent se coupler et former un récepteur hétéromère (Hasbi *et coll.*, 2011). De plus, on retrouve des

projections dopaminergiques dans le GPi, le GPe et le STN provenant de la SNc (Lavoie *et coll.*, 1989, Prensa *et coll.*, 2000). D'autre part, la 5-HT provenant du noyau raphé agit comme modulateur dans la plupart des structures des BG (Parent *et coll.*, 2011, Wallman *et coll.*, 2011). Tous les éléments soulevés démontrent que les BG ne sont pas seulement un regroupement de structures connectées de manière séquentielle comme le suggère le modèle, mais bien comme un réseau beaucoup plus complexe qu'initialement suggéré d'interconnections excitatrices et inhibitrices, dont le rôle et l'importance de chacune reste à bien définir.

En dernier lieu, l'effet antidyskinétique est l'apport clinique le plus constant dans le temps lors de la subthalamotomie chez le patient parkinsonien (voir table 1 de l'appendice 1). Il est maintenant bien connu que l'activité neuronale du GPi est hyperactive dans un état parkinsonien et devient quasiment complètement supprimée lors de dyskinésies (Hutchinson *et coll.*, 1997, Papa *et coll.*, 1999). Théoriquement, la baisse d'une afférence glutamatergique lors d'une subthalamotomie ou une lésion du GPi aurait pour conséquences de réduire cette activité neuronale du GPi à un niveau presque nul et ainsi exacerber les dyskinésies par la sous-inhibition de la voie thalamocorticale. Cependant, c'est le contraire qui est observé. Une activité oscillatoire de basse fréquence dans le GPi pourrait en être la cause en créant un signal spécifique pour l'apparition des dyskinésies (Silberstein *et coll.*, 2003). Une synchronisation cellulaire dans les mêmes fréquences (4 à 11 Hz) est aussi observée dans le STN chez les patients lorsqu'ils présentent des dyskinésies (Alonso-Frech *et coll.*, 2006). Le STN semblerait donc jouer un rôle important dans la génération de ces activités oscillatoires dans le GPi et participer aux dyskinésies. Donc, l'effet antidyskinétique de la subthalamotomie ou la pallidotomie serait attribuable à l'interruption des activités anormales et oscillatoires dans le GPi.

CHAPITRE 4. PROBLÉMATIQUES ET HYPOTHÈSES DE RECHERCHE

4.1 Effets secondaires de la L-DOPA

Les premières années de traitement à la L-DOPA sont souvent appelées la période de "lune de miel", car le patient retrouve ses capacités motrices sans effets secondaires importants (Rascol *et coll.*, 2003). Malheureusement, avec la prise chronique de L-DOPA et la progression de la PD, des effets secondaires moteurs apparaissent. Ces troubles indésirables, qui feront l'objet de cette présente section, sont le *wearing-off*, les fluctuations motrices et les LID.

4.1.1 Baisse de réponse en fin de doses (*wearing-off*)

Le *wearing-off* est souvent la première complication motrice à se manifester (Stacy *et coll.*, 2005). Elle se caractérise par une réduction de la durée de la réponse antiparkinsonienne de la L-DOPA et une ré-émergence prévisible d'un ou plusieurs signes cardinaux de la PD (Stacy *et coll.*, 2005). Cet effet secondaire apparaît après plusieurs mois ou années de traitements (Pahwa et Lyons, 2009) et la totalité des patients parkinsoniens vont présenter du *wearing-off* après 5 ans (Stacy *et coll.*, 2005). Ce phénomène est aussi observable chez le primate ayant une importante déplétion de cellules dopaminergiques induite par le MPTP (Grégoire *et coll.*, 2008). Certains auteurs ont suggéré que le *wearing-off* serait conséquent d'une perte de la capacité d'emmagasinage de DA dans les terminaisons pré-synaptiques (Stacy *et coll.*, 2005). Toutefois, contrairement au patient parkinsonien, le *wearing-off* se manifeste très rapidement (~2 semaines) après l'introduction de la L-DOPA chez les singes MPTP très dénervés (Grégoire *et coll.*, 2008, Morin *et coll.*, 2013a) et relativement rapidement (<9 mois) chez des humains exposés au MPTP (Ballard *et coll.*, 1985). D'autre part, il fut observé qu'un début précoce de PD et de fortes doses requises de L-DOPA étaient des facteurs de risque pour le développement de *wearing-off* (Jankovic, 2005). Finalement, l'administration de l'agoniste D_1/D_2 apomorphine, qui agit indépendamment des terminaisons pré-synaptiques de la voie nigrostriatale, a permis de démontrer que les mécanismes du *wearing-off* sont bel et bien en

fonction de la progression de la PD (Mouradian *et coll.*, 1988), mais seraient plus post-synaptiques que pré-synaptiques (Bravi *et coll.*, 1994). Les récepteurs ionotropiques glutamatergiques AMPA et NMDA, qui sont post-synaptiques, pourraient jouer un rôle dans la pathogénèse du *wearing-off* (Calon *et coll.*, 2003b). En effet, l'antagoniste amantadine pour le récepteur NMDA est connu pour réduire la durée antiparkinsonienne de la L-DOPA (Blanchet *et coll.*, 1998, Grégoire *et coll.*, 2013). Différents traitements pharmacologiques ou chirurgicaux sont disponibles pour les patients présentant du *wearing-off* (Pahwa *et coll.*, 2006).

4.1.2 Fluctuations motrices

Les fluctuations motrices *on-off* sont des variations de la réponse antiparkinsonienne durant une dose de L-DOPA, un phénomène similaire à un mouvement de yo-yo, durant lesquelles le patient passe d'un état « *on* » avec ou sans LID à un état « *off* » akinétique (Duvoisin, 1974). Elle apparaît chez 15 à 40% des patients après 2 à 3 ans de traitement à la L-DOPA (Sweet et McDowell, 1974). Contrairement aux baisses de réponse en fin de dose, les fluctuations *on-off* sont non-reliées à la dose ou au moment de la prise de L-DOPA (Chase *et coll.*, 1990). Les périodes « *off* » durent entre 15 minutes et 2 heures (Marsden et Parkes, 1976), durant lesquelles les signes parkinsoniens réapparaissent et beaucoup de patients vont aussi présenter des torsions dystoniques accompagnées ou non de douleurs dans les membres et au dos (Lees, 1989). Les patients ne semblent pas présenter de dyskinésies pendant les périodes « *off* » (Duvoisin, 1974). Le phénomène des fluctuations *on-off* pourrait être attribuable à un excès de DA qui provoquerait un blocage de dépolarisation des récepteurs dopaminergiques striataux (Marsden et Parkes, 1976). L'absorption et les taux plasmatiques de L-DOPA sont aussi des acteurs importants dans les fluctuations motrices (Nutt *et coll.*, 1984). En conséquence, les infusions constantes de L-DOPA par voie intraveineuse furent explorées avec des résultats prometteurs (Hardie *et coll.*, 1984, Quinn *et coll.*, 1982). D'autres auteurs ont suggéré un changement dans la sensibilité des récepteurs dopaminergiques malgré un apport de L-DOPA au cerveau et une synthèse de DA adéquats (Fahn, 1974). Il fut alors suggéré de réduire graduellement la dose de L-DOPA (Barbeau, 1974) ou même l'arrêt temporaire de prise de L-DOPA (Direnfeld *et coll.*, 1978). Par leur nature imprévisible, il n'existe pas de modèles animaux

d'oscillations *on-off*, rendant leur étude pathophysiologique très difficile. Les traitements sont d'ailleurs très limités. L'agoniste dopaminergique bromocriptine utilisé en monothérapie chez les patients non-exposés à la L-DOPA ne semblait pas induire ces fluctuations (Lees et Stern, 1981).

4.1.3 Dyskinésies

Les LID sont des mouvements involontaires choréiformes et dystoniques induits par une prise chronique de L-DOPA (Markham, 1971). Un patient décrivait ses dyskinésies à son médecin ainsi : « *my limbs behaving as if controlled by a drunken marionette master* » (Lees, 1989). Cette description met l'emphase sur l'aspect involontaire et incontrôlable des dyskinésies. Plus de la moitié (55%) des patients vont présenter des LID après 5 ans de traitement (Hely *et coll.*, 1994) et la quasi-totalité des patients vont être affectés après 15 ans (Hely *et coll.*, 2005). Les membres inférieurs et supérieurs, le tronc et le visage peuvent être affectés (Nutt, 1990) et chaque patient présente un patron de dyskinésies qui lui est propre (Luquin *et coll.*, 1992b). Le problème majeur de cette complication motrice est dû au fait qu'elle est directement reliée à la prise de médication antiparkinsonienne. Donc, une baisse de la médication réduirait les LID mais à la réapparition des symptômes parkinsoniens, ce qui est peu souhaitable pour le patient. En effet, les patients préfèrent présenter des LID que voir leur motricité diminuée (Encarnacion et Hauser, 2008). Une seconde stratégie fut tentée, soit un arrêt de prise de L-DOPA (*drug holiday*) sur une période donnée (Direnfeld *et coll.*, 1978, Mayeux *et coll.*, 1985). Malheureusement, les LID réapparaissent avec la même intensité qu'avant la médication soit cessée. Cette observation démontre que la L-DOPA provoque des changements permanents, ou du moins persistants, dans le cerveau. Une troisième stratégie fut de retarder le début de la prise de L-DOPA. Par contre, des études ont démontré que les patients recevant un placebo ont vu leur état parkinsonien détériorer plus rapidement que ceux recevant de la L-DOPA (Fahn *et coll.*, 2004). Une autre option à cette stratégie est d'administrer des agonistes dopaminergiques (Rascol *et coll.*, 2000) ou des inhibiteurs de la dégradation de la DA (Jankovic et Poewe, 2012). Un suivi de 10 ans a démontré que l'agoniste dopaminergique ropinirole induisait moins de LID que la L-DOPA, mais provoquait beaucoup plus d'effets secondaires neuropsychiatriques (Hauser *et coll.*, 2007). Toutefois, l'administration à long-terme

d'agonistes dopaminergiques semblent aussi "préparer le terrain" pour l'expression des dyskinésies. En effet, le changement d'agonistes pour une administration de L-DOPA provoquent des mouvements involontaires intenses chez le primate parkinsonien (Jackson *et coll.*, 2007, Smith *et coll.*, 2006) et chez l'humain (Katzenschlager *et coll.*, 2008). Cette présente section révisera tout d'abord les conditions *sine qua non* pour le développement et l'expression des dyskinésies. Par la suite, les mécanismes pré- et post-synaptiques seront revus. De plus, le deuxième appendice de cette thèse est une revue de littérature sur les modèles animaux pour l'étude des dyskinésies, incluant le modèle murin et primate (Morin *et coll.*, 2013b).

4.1.3.1 Conditions pour le développement des dyskinésies

Il est généralement admis qu'une perte des cellules dopaminergiques est requise pour le développement des LID. En effet, des patients non-parkinsoniens qui ont reçu chroniquement de la L-DOPA n'ont jamais présenté des LID (Rajput *et coll.*, 1997). Parallèlement, l'administration de hautes doses (jusqu'à 400 mg/kg) de L-DOPA chez le primate normal ne provoque pas l'expression de dyskinésies, mais plutôt des stéréotypies (Mones, 1973, Sassin, 1975). De plus, les LID apparaissent rapidement chez les patients âgés diagnostiqués très tardivement (Varanese *et coll.*, 2011), chez les patients parkinsoniens très dénervés à début précoce de maladie (Schrag *et coll.*, 2000) et chez les patients qui furent exposés à la neurotoxine MPTP (Ballard *et coll.*, 1985). Dans chacun de ces cas, l'état de dénervation dopaminergique est très profond, suggérant qu'une déplétion de DA est nécessaire pour développer des dyskinésies. Des études chez le primate exposé à différentes doses de MPTP a confirmé une corrélation entre l'étendue de la lésion dopaminergique et la sévérité des LID (Di Monte *et coll.*, 2000, Schneider, 1989). Toutefois, la perte des cellules de la SNc ne peut pas être la seule explication, car certains patients (Hely *et coll.*, 2005, Linazasoro *et coll.*, 2009) ou primates parkinsoniens (Aubert *et coll.*, 2005, Guigoni *et coll.*, 2005) ne vont jamais présenter des LID. Les collatérales provenant de la voie nigrostriatale qui innervent les autres structures des BG (Lavoie *et coll.*, 1989), qui expriment aussi des récepteurs dopaminergiques, sont aussi perdus dans la PD (Freeman *et coll.*, 2001). Toutefois, le rôle et l'importance de ces collatérales dans la PD et l'induction des LID est encore inconnu, mais pourrait peut-être aussi y participer.

Dans des conditions normales, les cellules dopaminergiques de la SNc produisent et relâchent de la DA de façon régulière (Berretta *et coll.*, 2010), ce qui maintient un niveau relativement constant de DA dans le striatum. Dans la PD, la perte neuronale de la SNc engendre donc une réduction de l'apport dopaminergique au striatum et le traitement à la L-DOPA est incapable de restaurer cette activité intrinsèque des BG. En effet, l'administration de L-DOPA provoque une stimulation pulsatile et non-physiologique des récepteurs dopaminergiques. En conséquence, des changements mal adaptés se font aux niveaux pré- et post-synaptiques, ce qui se présentent sous forme de dyskinésies chez le patient parkinsonien (Calabresi *et coll.*, 2008).

4.1.3.2 Changements pré- et post-synaptiques dans les LID

Considérant la courte demie-vie de la L-DOPA (environ 1.5 heures) (Fabbrini *et coll.*, 1987), le patient doit prendre sa médication antiparkinsonienne régulièrement. Dans les premiers stades de la maladie, une dose simple de L-DOPA dépasse largement la durée attendue (Fabbrini *et coll.*, 1988). Dans ce cas, la L-DOPA est convertie en DA et est stockée dans les vésicules pré-synaptiques par le transporteur VMAT2 dans les cellules dopaminergiques pour être relâchée au besoin (Dreyer *et coll.*, 2010). Au fur et à mesure que la maladie progresse et que les cellules dopaminergiques meurent, la capacité des cellules restantes de convertir la L-DOPA et de stocker la DA diminuent. La synthèse de DA à partir de L-DOPA se fait alors dans des neurones non-dopaminergiques (Carta *et coll.*, 2007, Melamed *et coll.*, 1980a, b). Cette DA nouvellement synthétisée est relâchée de manière non-physiologique (Obeso *et coll.*, 2000a). En conséquence, les niveaux de DA dans le cerveau de patients à des stades avancés de la maladie fluctuent en fonction des caractéristiques pharmacocinétiques de la L-DOPA et de sa biodisponibilité (Nutt, 2008).
Suivant une dénervation dopaminergique, l'activation des récepteurs dopaminergiques des MSNs par la DA exogène provoque une augmentation significative des voies de signalisation intracellulaire DARPP-32 et ERK, les deux associées au récepteur D_1 (Aubert *et coll.*, 2005). La phosphorylation de ces protéines sont directement reliées aux LID, la voie DARPP-32 dans l'expression et la voie ERK dans le processus de sensibilisation dopaminergique (« *priming* ») (Santini *et coll.*, 2010). Un des éléments les plus importants demeure la dénervation dopaminergique. En effet, une administration aigüe ou chronique de L-DOPA chez le singe contrôle n'induit pas une phosphorylation de ces voies de

signalisation intracellulaire (Santini *et coll.*, 2010). De plus, l'interruption sélective de la voie DARPP-32 dans la voie directe, mais pas celle de la voie indirecte, prévient l'expression des dyskinésies chez la souris invalidée (*knock-out*) conditionnellement pour le DARPP-32 (Bateup *et coll.*, 2010). Il est à noter toutefois que les voies de signalisation ERK ne sont pas qu'impliquées dans les LID et que les changements à court- et long-termes sont complexes (Murphy *et coll.*, 2002). Les récepteurs D1 et les récepteurs ionotropiques au glutamate NMDA sont connus pour interagir physiquement et fonctionnellement (Fiorentini, 2003). Cet oligomère D1/NMDA serait indicatif de l'afférence corticale dans les neurones striatofugaux, et une modification de cet oligomère pourrait conséquemment jouer un rôle dans le développement des LID (Fiorentini *et coll.*, 2008). En effet, les LID sont associées à une altération des sous-unités du récepteur NMDA dans les neurones striataux chez le singe MPTP (Hallett *et coll.*, 2005) et leur redistribution entre un emplacement synaptique et extrasynaptique pourrait faciliter le développement des LID.

Le facteur de régulation transcriptionnel Fos est un marqueur d'activité neuronale bien connu (Sagar *et coll.*, 1988) et est encodé par la famille *fos*, qui sont des gènes activés précocement (« *immediate-early genes* » (IEG)), incluant c-*fos* et *fos*B. L'augmentation de la localisation cellulaire des récepteurs dopaminergiques est associée à une augmentation de c-*fos* dans le striatum (Dragunow et Faull, 1989). Dans un état de dénervation dopaminergique chez le rongeur, l'administration chronique de L-DOPA induisant des LID est aussi associée à une augmentation permanente de *Fos*B (Andersson *et coll.*, 1999, Pavon *et coll.*, 2006). Autre fait intéressant, l'administration d'un agoniste D_1 provoque des augmentations similaires, tandis qu'un agoniste D_2 ne semble pas induire une hausse chez le rongeur et le primate (Doucet *et coll.*, 1996). D'autre part, la surexpression génétique de Δ*Fos*B (forme protéique tronquée de *Fos*B) induit des mouvements involontaires similaires aux LID chez le rat hémiparkinsonien, sans que ces rats aient reçu une médication dopaminergique (Cao *et coll.*, 2010). De plus, il y a une corrélation positive entre le nombre de cellules immunoréactives pour *Fos*B/Δ*Fos*B et la sévérité des mouvements involontaires induits par la L-DOPA chez le rat 6-OHDA (Levandis *et coll.*, 2008).

Finalement, des modifications aberrantes sont observées dans la plasticité synaptique. Deux types de plasticité synaptique se produisent dans les MSN striataux et

ceux-ci modifient l'efficacité de la neurotransmission (Calabresi *et coll.*, 2008): la potentialisation à long-terme (*long-term potentiation*, LTP) et la dépression à long-terme (*long-term depression*, LTD). La stimulation de la voie D_1/DARPP-32 semble être importante dans leur induction, car l'invalidation (*knock-out*) de la protéine DARPP-32 empêche l'apparition autant de la LTP et de la LTD (Calabresi *et coll.*, 2000). La LTP est une augmentation dans l'amplitude d'un potentiel post-synaptique excitateur, phénomène qui apparaît après une stimulation à hautes fréquences par bouffées (*burst firing*) (Centonze *et coll.*, 2003). Dans le striatum, cette entrée excitatrice provient des neurones glutamatergiques corticostriataux (Smith, 2011) et serait dépendante de l'activation des récepteurs D_1 (Centonze *et coll.*, 2003). En effet, le développement de l'hypersensibilité et hyperphosphorylation de DARPP-32 est conséquent de la stimulation dopaminergique (Aubert *et coll.*, 2005, Santini *et coll.*, 2007). DARPP-32 est un puissant inhibiteur de la protéine phosphatase-1, cette dernière régule l'activité des récepteurs glutamatergiques AMPA et NMDA (Greengard *et coll.*, 1999). Alors, une augmentation de la phosphorylation de DARPP-32 permet une dysrégulation des récepteurs ionotropiques au glutamate et préparant ainsi le terrain à l'augmentation de l'afférence excitatrice corticostriatale (Iravani et Jenner, 2011).

À l'opposé de la LTP, la LTD est le résultat d'une stimulation à basse fréquence et aurait pour rôle, entre autres, d'ignorer les signaux non-pertinents (Collingridge *et coll.*, 2010). Chez les rats hémi-parkinsoniens, cette LTP est perdue, mais récupérée avec l'administration de L-DOPA (Picconi *et coll.*, 2003). Toutefois, les rats hémiparkinsoniens avec des mouvements abnormaux involontaires induits à la L-DOPA, cette LTP n'était par récupérée (Picconi *et coll.*, 2003). Ce qui suggère que le mécanisme physiologique permettant d'ignorer les signaux non-pertinents n'est plus présent dans les LID (Picconi *et coll.*, 2003). Ces changements à long-terme dans la plasticité synaptique pourraient expliquer entre autres pourquoi les LID réapparaissent dès la première ré-exposition à la L-DOPA après un arrêt prolongé (« *drug holiday* ») chez les animaux préalablement dyskinétiques (voir appendice 2) et chez le patient parkinsonien (Mayeux *et coll.*, 1985).

En résumé, les changements pré-synaptiques sont un mauvais fonctionnement de stockage et de relâche de la DA. Les changements post-synaptiques sont au niveau 1- des voies de signalisation intracellulaire associées au récepteur D_1 et des récepteurs

ionotropiques au glutamate, 2- dus à une altération dans l'internalisation et expression des récepteurs au glutamate, 3- dus à une altération de l'expression des IEG et 4- dus à une altération de la plasticité synaptique. Pour une analyse plus approfondie, voir (Iravani et Jenner, 2011).

4.1.3.3 Pharmacologie des LID

Ces changements pré- et post-synaptiques dans les LID peuvent se traduire par des changements biochimiques, lesquels peuvent être mesurés *in vivo* chez les patients et par des techniques autoradiographiques et d'hybridation sur des tissus *post-mortem* d'humains et d'animaux parkinsoniens (Borghammer, 2012).

Selon les principes classiques de pharmacologie, on devrait s'attendre à une augmentation de la densité striatale des récepteurs dopaminergiques conséquemment à la dénervation de la voie nigrostriatale et une baisse suivant un traitement dopaminergique (Jenner, 2008). Ce n'est pas toutefois aussi simple et il n'existe pas de consensus en ce qui concerne les changements chez les humains et animaux parkinsoniens qui présentent des LID (Hurley et Jenner, 2006). Mesurés par autoradiographie, les récepteurs D_1 ne changent pas ou baissent chez les patients parkinsoniens traités et non-traités à la L-DOPA (Shinotoh *et coll.*, 1993a, Shinotoh *et coll.*, 1993b) et chez les singes MPTP non-traités (Aubert *et coll.*, 2005, Calon *et coll.*, 1995, Graham *et coll.*, 1993), mais augmentent avec le traitement à la L-DOPA (Aubert *et coll.*, 2005). D'autre part, la distribution cellulaire des récepteurs D_1 est aussi à considérer. En effet, les récepteurs D_1 se retrouvent au niveau de la membrane synaptique une heure après la dernière dose de L-DOPA chez le singe MPTP non-dyskinétique (Guigoni *et coll.*, 2007). Cette distribution est différente chez le singe MPTP dyskinétique où les récepteurs D_1 se retrouvent à la membrane synaptique mais aussi dans des compartiments cytoplasmiques (Guigoni *et coll.*, 2007). Des résultats similaires furent observés chez des patients parkinsoniens traités à la L-DOPA (Muriel *et coll.*, 1999).

D'un autre côté, les récepteurs D_2 augmentent chez les patients parkinsoniens (Lee *et coll.*, 1978, Turjanski *et coll.*, 1997) et singes MPTP non-traités à la L-DOPA(Aubert *et coll.*, 2005, Falardeau *et coll.*, 1988, Gagnon *et coll.*, 1995, Goulet *et coll.*, 2000, Graham *et coll.*, 1993) et reviennent à un niveau normal avec la L-DOPA (Graham *et coll.*, 1993, Lee *et coll.*, 1978). La signalisation intracellulaire démontre clairement une corrélation entre la sévérité des LID et l'état de phosphorylation des protéines intracellulaires (Akt et GSK3β)

associées aux récepteurs D_2 (Morissette *et coll.*, 2010). La protéine intracellulaire RGS9-2 est connue pour moduler la signalisation des récepteurs D_2 (Rahman *et coll.*, 2003). Sa surexpression réduit les dyskinésies induites par un agoniste sélectif pour le récepteur D_2, mais réduit par le fait même son effet antiparkinsonien (Gold *et coll.*, 2007). À notre connaissance, il n'existe pas encore d'étude sur la distribution membranaire versus cytoplasmique des récepteurs D_2 pour les LID.

Lorsque les singes MPTP présentant des LID sont pré-sensibilisés (*primed*), l'administration d'agonistes sélectifs pour les récepteurs D_1 ou D_2 évoquera l'expression de dyskinésies (Blanchet *et coll.*, 1993). De plus, l'administration *de novo* d'agonistes D_1 (Blanchet *et coll.*, 1996a, Goulet *et coll.*, 1996) ou D_2 (Luquin *et coll.*, 1992a) chez le singe MPTP non exposé à la L-DOPA provoque le développement de dyskinésies, démontrant ainsi ces deux récepteurs sont intrinsèquement impliqués dans le développement et l'expression des dyskinésies. Toutefois, les dyskinésies induites par l'administration séparée d'agonistes D_1 ou D_2 ne sont pas aussi intenses que celle provoquées par la L-DOPA, suggérant que la stimulation simultanée des deux récepteurs conduit à des dyskinésies plus importantes (Huot *et coll.*, 2013).

Les récepteurs D_3 et D_4 furent moins souvent l'objet d'études pour le traitement des LID, mais l'administration de leurs antagonistes sélectifs respectifs donne des résutalts prometteurs pour la réduction de l'induction (Visanji *et coll.*, 2009) et l'expression (Huot *et coll.*, 2012) des LID sans toutefois trop nuire aux bénéfices antiparkinsoniens de la L-DOPA. Évidemment, des autres études sont nécessaires pour établir leur rôle dans la PD les LID et peut être leur place dans leur traitement. Le troisième appendice de cette thèse est une revue de littérature sur les récepteurs dopaminergiques et les dyskinésies.

Le modèle des BG suggère une suractivité glutamatergique dans les LID provenant de la voie corticostriatale (Obeso *et coll.*, 2000b). Il est important de se rappeler que le STN, le PPN et le thalamus sont aussi des sources importantes de glutamate dans les BG (section 1.4.2). Consistent avec cette suractivité théorique, plusieurs études *post-mortem* ont démontré des changements importants dans la densité des récepteurs glutamatergiques dans les BG. Les récepteurs NMDA sont des tétramères composés d'au moins une sous-unité NR1, une sous-unité NR2 (NR2A-D) (Dingledine *et coll.*, 1999) et occasionnellement la sous-unité NR3 (Sasaki *et coll.*, 2002). La glycine est un modulateur allostérique positif

pour la sous-unité NR1, tandis que le glutamate se lie aux sous-unités NR2 (Paoletti et Neyton, 2007). Les sous-unités NR2A et NR2B sont celles ayant reçu le plus d'attention dans les LID (Huot *et coll.*, 2013). Chez le singe écureuil, les niveaux striataux de NMDA mesurés par [^{3}H]MK-801 étaient plus bas chez les singes traités à la L-DOPA comparativement aux singes MPTP et contrôles trois jours après la dernière dose de L-DOPA (He *et coll.*, 2000). Les niveaux striataux de récepteurs NMDA présentant la sous-unité NR2B sont diminués chez les singes parkinsoniens comparativement aux contrôles (Hallett *et coll.*, 2005, Ouattara *et coll.*, 2008). Ces niveaux de NMDA/NR2B étaient revenus à des valeurs contrôles chez les singes MPTP dyskinétiques 1 heure (Hallett *et coll.*, 2005) ou 24 heures (Ouattara *et coll.*, 2008) après leur dernière dose de L-DOPA et augmentent huit jours après leur dernière dose de L-DOPA (Hurley *et coll.*, 2005). Chez les patients parkinsoniens, il y a une augmentation de la sous-unité NMDA/NR2B chez ceux qui présentent des complications motrices, incluant les LID et le *wearing-off* comparativement à ceux n'ayant pas de complications à la L-DOPA (Calon *et coll.*, 2003b). Si le blocage de la sous-unité NR2B avec l'antagoniste allostérique Co-101,244/PD-174,494 réduit les LID déjà présentes (Blanchet *et coll.*, 1999), la sous-unité NMDA/NR2A serait, quant à elle, impliquée dans le processus de développement et de présensibilisation des LID (Gardoni *et coll.*, 2012); ce qui pourrait expliquer pourquoi aucun changement ne fut observé dans cette sous-unité chez les patients parkinsoniens présentant des complications motrices (Calon *et coll.*, 2003b).

L'emplacement et l'état de phosphorylation de toutes les sous-unités du récepteur NMDA sont des facteurs importants à considérer dans les LID (Ahmed *et coll.*, 2011, Chase et Oh, 2000) et la stimulation du récepteur D_1 (Dunah et Standaert, 2001, Hallett *et coll.*, 2006) et le STN-DBS (Quintana *et coll.*, 2010) y jouent un rôle déterminant. En effet, chez le rat 6-OHDA euthanasié une heure après la dernière dose de L-DOPA, le nombre de sous-unités NR1 phosphorylées était diminué comparativement aux rats contrôles, mais augmenté comparativement aux rats 6-OHDA non-exposés à la L-DOPA (Napolitano *et coll.*, 2006). De plus, la sous-unité NR2B est redistribuée des sites synaptiques vers des sites extrasynaptiques dans la membrane plasmique dans le striatum de rats 6-OHDA dyskinétiques, tandis que le nombre de sous-unités NR2A post-synaptique augmente (Gardoni *et coll.*, 2006). D'un autre côté, l'hétéromère NR1/NR2B est redistribué vers des

compartiments intracellulaires 12 heures après la dernière dose de L-DOPA chez le rat 6-OHDA. Sa distribution chez les rats dyskinétiques était normale, mais pas son état de phosphorylation (Dunah *et coll.*, 2000, Oh *et coll.*, 1998). Il ne fait aucun doute que les récepteurs NMDA sont impliqués dans les LID. En effet, l'administration d'amantadine, un antagoniste pour le récepteur NMDA, réduit les LID chez le singe (Blanchet *et coll.*, 1998) et chez les patients (Wolf *et coll.*, 2010). Le composé Ro 61-8048 antagonise compétitivement le site NR1, par inhibition de la kynurénine hydroxylase. L'administration de ce composé réduit l'expression (Samadi *et coll.*, 2005) et le développement des LID (Grégoire *et coll.*, 2008). Le traxoprodil, un antagoniste pour les sous-unités NR1A/NR2B, a été démontré pour avoir des effets antidyskinétiques chez les patients parkinsoniens, mais exacerbait la sévérité des LID chez les primates (Nash *et coll.*, 2004). D'un autre côté, le composé CI-1041, un autre antagoniste des sous-unités NR1A/NR2B, a prévenu le développement des LID chez le primate (Hadj Tahar *et coll.*, 2004).

Les récepteurs AMPA chez les singes dyskinétiques sont inchangés au pic de l'effet dopaminergique (Silverdale *et coll.*, 2002) et sont réduits 24 heures après leur dernière dose de L-DOPA (Ouattara *et coll.*, 2010b). Chez l'humain, les baisses d'AMPA ne furent observables que dans le noyau caudé (Calon *et coll.*, 2003b). Ces changements suggèrent un recrutement membranaire des récepteurs AMPA lors d'administration de médication dopaminergique. Tout comme les récepteurs NMDA, l'emplacement des récepteurs AMPA semble jouer un rôle important dans les LID. En effet, les sous-unités Glu2/3 au niveau de la membrane synaptique augmentent chez les singes dyskinétiques comparativement aux contrôles et aux singes MPTP, tandis que la sous-unité Glu1 demeure inchangée (Santini *et coll.*, 2010, Silverdale *et coll.*, 2010). L'administration d'antagonistes pour le récepteur AMPA chez le singe semble efficace pour la réduction des LID (Konitsiotis *et coll.*, 2000, Papa et Chase, 1996, Zuddas *et coll.*, 1992), mais ces résultats ne se sont pas traduits par des améliorations chez l'humain (Lees *et coll.*, 2011). Un des facteurs à considérer est que la plupart des molécules ne sont pas complètement spécifiques pour les récepteurs AMPA. En effet, les différents composés avaient des affinités pour d'autres récepteurs glutamatergiques, mais aussi pour des systèmes non-glutamatergiques (Kobylecki *et coll.*, 2010, Konitsiotis *et coll.*, 2000, Silverdale *et coll.*, 2005). En clinique, l'antagoniste spécifique perampanel n'a pas réduit les LID lors d'une étude de phase II (Eggert *et coll.*,

2010), ce qui lève un sérieux doute sur le blocage des récepteurs AMPA comme cible thérapeutique. Les récepteurs kainate ne semblent pas être impliqués dans les LID, mais auraient un rôle à jouer dans la maladie de Huntington, une autre maladie neurodégénérative hyperkinétique (Rubinsztein *et coll.*, 1997).

Les récepteurs métabotropiques au glutamate font récemment l'objet d'études pour le traitement des LID, principalement à cause de leur localisation dans les BG (Smith *et coll.*, 2001). Des études *post-mortem* sur des tissus de primates et humains ont bien démontré leur dysrégulation dans les LID. En effet, les niveaux de mGlu5 sont augmentés dans le striatum et le pallidum de singes (Samadi *et coll.*, 2008b) et de patients dyskinétiques (Ouattara *et coll.*, 2011) comparativement à leurs contrôles respectifs. Chez le singe parkinsonien, l'administration de différents antagonistes pour le mGlu5 ont démontré une efficacité dans la rédution des LID (Grégoire *et coll.*, 2011, Johnston *et coll.*, 2010a, Morin *et coll.*, 2013a, Rylander *et coll.*, 2010); deux d'entre eux sont testés en clinique (AFQ056 (Berg *et coll.*, 2011) et ADX-48,621 (No. d'essai clinique : NCT01336088)). Contrairement au mGlu5, le blocage de l'autre membre du groupe I des récepteurs métabotropiques au glutamate, le mGlu1, ne prévient (Rylander *et coll.*, 2009) et ne réduit pas (Dekundy *et coll.*, 2006) l'expression des LID, tel que mesuré chez le rat parkinsonien.

Les récepteurs métabotropiques au glutamate mGlu2/3 forment le groupe II (Foord *et coll.*, 2005). Les niveaux de mGlu2/3 augmentent dans le putamen et dans le GPe chez les singes dyskinétiques et non-dyskinétiques comparativement aux singes MPTP, ces derniers n'étant pas différents des contrôles (Samadi *et coll.*, 2008a). Le noyau caudé et le GPi demeurent inchangés par le MPTP et le traitement à la L-DOPA (Samadi *et coll.*, 2008a). Une autre étude chez le primate a démontré aucun changement dans les niveaux striataux et pallidaux de mGlu2/3 avec le MPTP, mais une baisse significative avec la L-DOPA (Morin *et coll.*, 2013c). Le patron chez les patients parkinsoniens fut inverse, les niveaux de mGlu2/3 dans le noyau caudé et dans le GPi étaient plus bas que ceux des contrôles (Samadi *et coll.*, 2009). Aucune différence était observée dans le putamen et le GPe chez l'humain (Samadi *et coll.*, 2009). Un agoniste mGlu2/3 fut testé chez le rat pour prévenir ou réduire les mouvements involontaires anormaux, mais les résultats ne furent pas concluants (Rylander *et coll.*, 2009). Tout récemment, des agonistes du groupe III, plus

précisement le mGlu4, pourraient avoir des effets bénéfiques pour les LID (Amalric *et coll.*, 2013). Le mGlu4 est pré-synaptique, se retrouve au niveau des synapses corticostriatales (Duty, 2010) et leur stimulation réduit la neurotransmission glutamatergique (Cuomo *et coll.*, 2009). Plus d'études sont nécessaires pour démontrer leur potentiel dans le traitement des LID. Finalement, les données sur les récepteurs métabotropiques dans la PD et les LID proviennent d'études par autoradiographie. Plusieurs questions demeurent en suspens, dont leurs états de phosphorylation et leur distribution membranaire versus intracellulaire. En répondant à ces interrogations, il sera possible de mieux comprendre leur rôle dans la pathophysiologie des LID et ainsi développer de nouvelles avenues thérapeutiques.

Dans cette présente section, nous avons brièvement révisé la pharmacologie des LID selon une perspective dopaminergique et glutamatergique et ce, strictement pour les besoins de cette thèse. Il est tout de même important de souligner que d'autres systèmes de neurotransmission sont impliqués dans la pharmacologie des LID (Huot *et coll.*, 2013). En effet, les systèmes opioïdergiques (Bezard *et coll.*, 2001c, Tamim *et coll.*, 2010), sérotoninergiques (récepteurs et transporteur à la 5-HT) (Huot *et coll.*, 2011), GABAergiques (Calon et Di Paolo, 2002, Calon *et coll.*, 2000b), adénosinergiques (Morelli *et coll.*, 2007), noradrénergiques (Johnston *et coll.*, 2010b, Savola *et coll.*, 2003) et cholinergiques (Quik *et coll.*, 2007, Quik *et coll.*, 2013) ont un rôle à jouer dans l'induction et dans l'expression des LID (Huot *et coll.*, 2013, Samadi *et coll.*, 2007). La pharmacologie des LID est très complexe et certains paramètres qui diffèrent entre les études (technique utilisée, temps d'euthanasie après L-DOPA, modèle animal, état de dénervation, etc.) ne rendent certainement pas la tâche de compréhension plus simple et ne permettent pas encore un consensus.

4.1.4 Effets oxydants de la L-DOPA

Mise à part les effets secondaires cliniques revus prédécemment, la L-DOPA a aussi le potentiel d'accélérer la progression de la PD. En effet, l'ajout de L-DOPA à des cultures de cellules primaires ou à des cultures de neurones dopaminergiques induit une toxicité par des mécanismes de libération de radicaux libres (Graham, 1978, Tse *et coll.*, 1976). D'autre part, rendu dans la cellule, la DA peut s'auto-oxider et produire des radicaux libres par différents processus oxidatif (Fahn et Cohen, 1992). La DA peut aussi être métabolisée par

la MAO et produire du peroxyde d'hydrogène (Adams *et coll.*, 1972). Ce dernier, en présence d'ion de fer, peut produire des radicaux hydroxyl très réactif et oxidant pour la cellule (Fahn et Cohen, 1992). Toutefois, ces effets potentiellement délétères ne se traduisent pas concrètement chez les patients. En effet, il ne fut jamais démontré clairement que la L-DOPA accélérait la progression de la PD (Parkkinen *et coll.*, 2011, Schapira, 2008) ou produisait une perte de neurones dopaminergiques chez des patients non-parkinsoniens (Rajput *et coll.*, 1997).

4.2 Hypothèses de recherche

4.2.1 Hypothèse 1: La subthalamotomie potentialise la réponse antiparkinsonienne de la L-DOPA

La subthalamotomie est offerte aux patients qui présentent des LID importants (Walter et Vitek, 2004). Les bénéfices cliniques de cette chirurgie sont bien connus (voir appendice 1). Suivant cette chirurgie, les patients voient leur médication réduite d'environ 45%. Chez l'humain, la lésion est faite par thermolyse, donc elle est non-spécifique (neurones, cellules gliales, axones) et excède les bordures du STN (Alvarez *et coll.*, 2009, Patel *et coll.*, 2003). Il n'est toutefois pas clair si la réduction de la prise de médication antiparkinsonienne est due à la lésion des fibres pallidothalamiques, à la lésion stricte du STN ou à la combinaison des deux. Nous nous sommes donc penchés sur la lésion stricte du STN par injection unilatérale d'acide iboténique (voir section 4.2.1.2). Le choix du côté de la lésion était fait en fonction de la sévérité de l'atteinte motrice et de la main dominante pour la tâche de préhension. Cette tâche était une mesure objective de la bradykinésie (voir section 5.4). Nous avons donc fait des mesures comportementales (voir section 4.2.1.1) en utilisant trois doses de L-DOPA : une dose optimale (qui représente la plus haute dose de L-DOPA offrant le meilleur bénéfice antiparkinsonien, mais provoquant peu ou pas de LID), une dose sous-optimale (60% de la dose optimale) et une dose induisant des LID (140% de la dose optimale). Chaque concentration de L-DOPA était titrée pour chacun des animaux pour créer un paradigme le plus représentatif de la situation clinique. Nous avons testé ces trois doses ainsi que le véhicule avant et après la lésion.

Notre hypothèse était la suivante :

La lésion stricte des neurones du STN potentialise la réponse antiparkinsonienne de la L-DOPA. Si tel est le cas, les singes MPTP devraient avoir de meilleurs bénéfices antiparkinsoniens avec toutes les doses testées suivant la subthalamotomie.

L'hypothèse nulle était qu'il n'y aurait pas de différence dans la réponse antiparkinsonienne à la L-DOPA suivant la subthalamotomie. Ce qui suggérerait que c'est la lésion des fibres pallidothalamiques qui aurait cet effet potentialisateur.

L'importance de cette réponse réside dans le fait que, malgré que la subthalamotomie fut étudiée chez le primate parkinsonien (Aziz *et coll.*, 1992, Bergman *et coll.*, 1990, Guridi *et coll.*, 1996), aucune étude n'a utilisé de la L-DOPA et que plus d'études sur les lésions dont les fibres de passage sont épargnées (*fiber-sparing lesions*) sont nécessaires pour connaître leur rôle potentiel dans le traitement des LID (Okun et Vitek, 2004).

4.2.1.1 Échelles de mesure comportementale

L'atteinte motrice chez le patient est mesurée par la troisième partie de l'Unified Parkinson's Disease Rating Scale (UPDRS), qui fut développée en 1987 (Fahn *et coll.*, 1987). La participation du patient est exigée lors de l'évaluation en effectuant des tâches. Il est toutefois difficile de demander à un primate d'effectuer de telles tâches pour évaluer son atteinte motrice. Une échelle de parkinsonisme fut alors développée et validée à l'Université Laval (Gomez-Mancilla et Bédard, 1993). Cette échelle mesure l'atteinte motrice et l'atteinte non-motrice chez le primate (voir Appendice 4). Le score maximal est de 16 et plus le score se rapproche du maximum, plus le singe est parkinsonien. D'autre part, les LID furent quantifiées par une échelle dyskinétique (voir Appendice 5). Chacun des membres inférieurs et supérieurs est quantifié individuellement, ainsi que le tronc, le cou et le visage. Le score maximal est de 21 et plus le score se rapproche du maximum, plus le singe est dyskinétique.

4.2.1.2 Procédure chirurgicale

Ventriculographie

L'animal fut pré-anesthésié et mis sous anesthésie générale sous isoflurane 1,5%. Le site chirurgical fut analgésié localement par l'injection de lidocaïne avant la procédure. Une injection intraveineuse de phénytoïne fut administrée avant la ventriculographie pour éviter les convulsions pouvant être induites par l'injection du liquide radio-opaque. Le singe fut placé dans un appareil stéréotaxique de type David Kopf et deux clichés radiographiques furent pris pour s'assurer du bon positionnement de l'animal dans le cadre. Les coordonnées stéréotaxiques utilisées étaient tirées de l'atlas du macaque (Szabo et Cowan, 1984) pour une plus grande précision. Le point visé se trouvait à 22,0 mm antérieurement au point intra-auriculaire et 1,5 mm latéral par rapport à la ligne sagittale. Avant de procéder, une correction s'est fait avec le cliché radiographique latéral. Le point corrigé était la moyenne de la distance entre le clinoïde et la distance théorique de 22,0 mm. Le point d'entrée s'est fait à une angulation de 45 degrés. Un trou de trépan de 3 mm était fait pour permettre le passage de l'aiguille pour la ventriculographie. La présence de liquide céphalo-rachidien confirmait le bon positionnement de l'aiguille dans le ventricule. Un liquide radio-opaque (iohexol) fut injecté avant de prendre une radiographie. Deux clichés aux rayons X, en latéral et en frontal, furent obtenus pour visualiser les commissures antérieure et postérieure. Ceci permit de corriger les coordonnées de l'atlas pour tenir compte de la variabilité morphologique de chaque singe.

Lésion chimique du STN

Avant correction, le point visé se situait 12,1 mm antérieur au point intra-auriculaire, 5 mm latéral à la ligne médiane du plan sagittal et 8,0 mm dorsalement au cadre stéréotaxique. Une fois que les coordonnées du noyau sous-thalamique furent corrigées, une deuxième incision d'une longueur de 2,5 cm fut effectuée à la latéralité du STN dans une angulation entre 25 et 30 degrés. Cette plage d'angles correspond à l'angulation du STN, permettant donc une plus grande distance de couverture dans la structure. D'autre part, les structures importantes, tels que le thalamus et le complexe pallidal, furent épargnées étant donné que la canule passe par les axones. Un trou de trépan de 3 mm fut fait dans le crâne pour permettre le passage de la canule. La canule fut descendue à l'aide du bras stéréotaxique à la profondeur correspondante à la partie dorsolatérale du noyau. Un volume total de 10 µl d'une solution stérile d'acide iboténique (10 µg/µl) fut injecté sur une

durée totale de 10 minutes. Chaque injection d'acide iboténique s'effectua à différents endroits de la trajectoire de la canule, à savoir la cible ± 0,5 mm. Cet acide provient du champignon *Amanita muscaria* (Michelot et Melendez-Howell, 2003) et est hautement excitotoxique. Son avantage principal est qu'il se lie spécifiquement aux récepteurs glutamatergiques. Ces récepteurs sont fortement exprimés dans le STN. De plus, comme c'est un ligand, son utilisation évite d'endommager les axones. Le STN est une petite structure qui est entourée d'axones et ces fibres furent épargnées avec l'injection d'acide iboténique. Après l'injection de l'acide, l'aiguille fut laissée en place pendant 5 minutes, puis retirée lentement pour éviter l'effet de succion. Les incisions furent suturées en couches.

4.2.2 Hypothèse 2: Hypothèse dopaminergique

L'étude comportementale (Chapitre 5) des singes MPTP qui ont reçu une subthalamotomie unilatérale a pu démontrer qu'il y avait une meilleure réponse à la L-DOPA suivant la lésion. Cette potentialisation de réponse serait due à la lésion spécifique des neurones sous-thalamiques, car aucun dommage ne fut observé dans les structures motrices avoisinantes (zona incerta, SNr, thalamus et GPi) et dans les fibres de passage. Suivant la subthalamotomie, les singes avaient une réponse antiparkinsonienne à la L-DOPA similaire à celle obtenue avant la lésion, tandis que la L-DOPA fut réduite de 40%. Cette augmentation de réponse antiparkinsonienne suggère une composante dopaminergique et pourrait correspondre à des changements biochimiques dans la densité des récepteurs de ce système de neurotransmission. Nous avons donc entrepris l'analyse *post-mortem* de la synthèse (ARN messager par hybridation *in situ*) et l'expression (par autoradiographie avec des radioligands spécifiques) des récepteurs D_1 et D_2 sur coupes des cerveaux des singes qui ont reçu la L-DOPA et la subthalamotomie unilatérale. Nous avons aussi mesuré les niveaux d'ARN messagers des neuropeptides associés aux récepteurs D_1 (préprodynorphine, PPD) et D_2 (préproenképhaline, PPE). Le côté opposé à la lésion a servi de contrôle intra-animal. Les résultats furent comparés à des singes contrôles et des singes MPTP qui n'ont pas reçu de L-DOPA.

Notre hypothèse était la suivante :

La potentialisation de réponse à la L-DOPA observée après la subthalamotomie serait due à des changements biochimiques dans la synthèse et l'expression des récepteurs dopaminergiques D_1 et D_2 dans les ganglions de la base, ainsi que dans les neuropeptides PPD et PPE associés.

L'hypothèse nulle était qu'il n'y aurait pas de changement observé dans la synthèse et l'expression des récepteurs dopaminergiques et leurs neuropeptides associés.

Les résultats de cette analyse s'inscrivent dans une perspective plus large que celle de la subthalamotomie. Il est bien connu que la médication dopaminergique est réduite dans le STN-DBS (Krack *et coll.*, 2003). La potentialisation dopaminergique observée dans ces deux chirurgies pourrait partager un mécanisme commun. Une meilleure compréhension des changements induits par la subthamatomie permettrait possiblement l'ajout d'un traitement pharmacologique adjuvant pour mieux traiter les patients parkinsoniens.

4.2.3 Hypothèse 3: Hypothèse glutamatergique

La distribution des récepteurs ionotropiques et métabotropiques au glutamate dans les BG (section 1.4.2) suggère qu'ils pourraient participer dans le contrôle moteur et une dysrégulation de ces récepteurs pourraient entraîner des troubles moteurs. En effet, plusieurs études ont pu démontrer une implication franche de certains récepteurs glutamatergiques dans la pathophysiologie des dyskinésies (Blandini et Armentero, 2012). Le STN est la seule structure intrinsèque aux BG qui possède des projections glutamatergiques. Une lésion de cette structure pour le traitement de la PD et des LID pourrait provoquer des changements dans ces récepteurs au glutamate à cause de la baisse de l'afférence glutamatergique du STN. Nous avons analysé l'expression des récepteurs ionotropiques AMPA et NMDA/NR2B et métabotropiques mGlu2/3 et mGlu5 par autoradiographie avec des radioligands spécifiques sur coupes *post-mortem* de cerveaux des singes qui ont reçu la L-DOPA et la subthalamotomie unilatérale. Le côté opposé à la lésion a servi de contrôle intra-animal. Les résultats furent comparés à des singes contrôles et des singes MPTP qui n'ont pas reçu de L-DOPA.

Notre hypothèse était la suivante :

La subthalamotomie et la L-DOPA induisent des changements dans la densité des récepteurs glutamatergiques dans le striatum et dans le complexe pallidal.

L'hypothèse nulle était qu'il n'y aurait pas de changement observé dans la densité des récepteurs glutamatergiques dans les ganglions de la base suivant la subthalamotomie et le traitement à la L-DOPA.

Les résultats de cette étude pourraient aider à mieux comprendre les mécanismes sous-jacents de la subthalamotomie et ainsi offrir, éventuellement, un meilleur traitement au patient parkinsonien qui présente des LID importantes.

PARTIE II. RÉSULTATS

CHAPITRE 5. POTENTIATION OF RESPONSE TO LOW DOSES OF LEVODOPA IN MPTP-INJECTED MONKEYS BY CHEMICAL UNILATERAL SUBTHALAMOTOMY

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5.1 Résumé

Objet : La subthalamotomie est une chirurgie stéréotaxique pratiquée chez les patients parkinsoniens présentant des dyskinésies débilitantes. Nous avons répliqué cette condition humaine chez le singe MPTP et déterminé si la subthalamotomie permet une réduction de la demande en lévodopa tout en gardant des bénéfices similaires.

Méthodes. Nous avons pratiqué une subthalamotomie unilatérale chez 4 singes parkinsoniens dyskinétiques par injection stéréotaxique d'acide iboténique. Une dose optimale, définie comme étant la plus haute dose de lévodopa améliorant les symptômes moteurs reliés à la PD, tout en induisant peu ou pas de dyskinésies, fut établie chez ces animaux. Chaque singe fut évalué pour les effets antiparkinsonien et dyskinétique de la dose optimale de lévodopa, ainsi que les doses sous-optimale et induisant des dyskinésies (équivalentes à 60% et 140% de la dose optimale) et ces scores furent comparés à ceux du niveau de base avant et après la subthalamotomie. La bradykinésie fut mesurée par une tâche de préhension.

Résultats. La subthalamotomie unilatérale eut des effets positifs sur la réponse antiparkinsonienne pour toutes les doses testées, ainsi que pour le niveau de base. Il n'y avait plus de différences entre la dose sous-optimale après la lésion et la dose optimale pré-lésion en matière de la réponse antiparkinsonienne. Les dyskinésies furent augmentées pour les doses optimales et sous-optimales. Après la chirurgie, la durée de réponse antiparkinsonienne fut augmentée entre 20% et 25% pour la dose sous-optimale, mais resta inchangée pour les doses plus élevées. La bradykinésie fut réduite significativement après la chirurgie seulement à la dose sous-optimale de lévodopa.

Conclusions. La subthalamotomie eut un effet potentialisateur sur la réponse à la dose sous-optimale de lévodopa. Ainsi, la lévodopa peut être réduite de 40% suivant la chirurgie pour une réponse antiparkinsonienne similaire tout en induisant moins de dyskinésies que la dose optimale pré-chirurgicale.

5.2 Abstract

Object. Subthalamotomy is a stereotactic surgery performed in patients with disabling dyskinesias due to Parkinson disease. The authors set out to model this human condition in MPTP monkeys and determine if subthalamotomy allowed a reduction of levodopa for similar benefit.

Methods. The authors performed unilateral subthalamotomy in 4 parkinsonian dyskinetic monkeys by stereotactic injection of ibotenic acid. An optimal dose, defined as the highest dose of levodopa improving parkinsonian motor symptoms while inducing low or no dyskinesias, was established in these animals. Each monkey was scored for the antiparkinsonian and dyskinetic effects of the optimal dose of levodopa, as well as suboptimal and dyskinesia-inducing doses (60% and 140% of the optimal dose, respectively), and these scores were compared with those obtained at baseline before and after subthalamotomy. Bradykinesia was assessed by a prehension task.

Results. Unilateral subthalamotomy had a positive effect on the antiparkinsonian response for all doses of levodopa as well as the baseline. There were no differences in the antiparkinsonian response between the suboptimal dose postsurgery and the optimal dose presurgery. Dyskinesias were increased at the suboptimal and the optimal doses. After surgery, the duration of response to levodopa increased between 20% and 25% in the suboptimal dose, whereas it remained unchanged with higher doses. Bradykinesia was significantly reduced after surgery only at the suboptimal dose.

Conclusions. Subthalamotomy potentiated the response to suboptimal doses of levodopa. Thus, levodopa can be reduced by 40% after surgery for similar beneficial antiparkinsonian response and less dyskinesia than with an optimal dose before surgery.

5.3 Introduction

Parkinson disease affects around 1% of the population older than 65 years old, and this percentage increases with age.[14] The disease is characterized by poverty of motor functions (bradykinesia, tremor, rigidity, gait disturbance, and postural instability) and non-motor features (neuropsychiatric symptoms, autonomic dysfunctions, and sleep disturbances).[66] Levodopa is the most widely used symptomatic drug treatment for patients with PD.[16] Although it has a high efficiency in alleviating parkinsonian symptoms, chronic administration leads to important motor side effects, such as dyskinesias, wearing off, and motor fluctuations, as well as behavioral disorders.[70] Levodopa-induced dyskinesias are aimless choreic or dystonic involuntary movements that appear in 30%–80% of patients after 3 years of levodopa treatment.[48] Although LIDs are quite disabling when severe, patients prefer to take levodopa and have mild dyskinesias than be immobile.[15] There is currently no approved pharmacological treatment for LIDs,[40] but there are good indications for glutamatergic and serotoninergic involvements.[34,58]

The STN glutamatergic neurons are the driving force of the basal ganglia.[49,50] They become hyperactive in PD,[31] where an increase in burst firing is observed.[9,61] This bursting activity is reduced after administration of dopaminergic medications, correlating with improvements in motor functions.[57,72]

Subthalamic nucleus surgery is presently offered for patients in whom levodopa-induced side effects become disabling. Lesioning of the STN, also called subthalamotomy, was first practiced for the relief of parkinsonian symptoms.[33,62] This procedure came to a precipitate decrease with the introduction of levodopa as first treatment.[18] Studies in neurotoxin-induced PD in nonhuman primates[5,8,24] have led to the reintroduction of subthalamotomy for the treatment of PD with good outcome.[1,19] However, none of the previous studies conducted in parkinsonian monkeys have reported the effect of subthalamotomy on levodopa treatment. Although there is a great wealth of literature on this procedure in humans,[2,11,41] its biochemical mechanisms remain unknown. Thus, animal studies are needed.

Animal models, specifically MPTP monkeys, offer a possibility to examine the effects of subthalamotomy and its mechanisms through postmortem analysis. In this study,

we used dyskinetic MPTP monkeys to investigate the effects of unilateral subthalamotomy on parkinsonian symptoms and LIDs, the possibility of reducing the optimal dose of levodopa after surgery, and the effects of unilateral subthalamotomy on bradykinesia. A unilateral lesion was chosen over a bilateral subthalamotomy to allow a comparison between the lesioned and non-lesioned sides in the same animal, thus reducing interindividual variability. Moreover, bilateral lesioning may induce behavioral deficits, enhance LIDs, or even induce hemiballism.[6,41] A portion of this study was reported in abstract form.[35]

5.4 Methods

Animal Preparation

The number of animals used in this study was kept to a minimum for statistically valid analyses. Four ovariectomized female cynomolgus monkeys (Macaca fascicularis) were used for this study (Table 5.1). Ovariectomy was performed to minimize the cyclic variations in estrogen concentrations that might affect brain dopamine levels.[20] The monkeys were first rendered parkinsonian by subcutaneous and intramuscular administration of the neurotoxin MPTP (mean dose 15.3 ± 5.9 mg total, range 6.8–19.3 mg) followed by a period of stabilization (5–6 months) until stable and severe parkinsonian syndrome was obtained. These primates received a chronic treatment of levodopa and benserazide and developed dyskinesias. These primates had also been used in different acute studies testing antidyskinetic drugs, mimicking patients who are candidates for surgery. In addition, the brains of 4 ovarioectomized female monkeys were used for comparisons of dopamine levels. The monkeys were housed separately in individual observation cages in a temperature-controlled room (23 ± 1°C). They were exposed to a 12-hour light/dark cycle (lights on 7:00 a.m.–7:00 p.m.) and fed once daily, during the afternoon (to optimize gastrointestinal absorption of levodopa), with pellets and fruits, and had unrestricted access to water. Housing cages were enriched with auditory and tactile stimuli. The work was performed in accordance with the Canadian Guide for the Care and Use of Laboratory Animals, and the Institutional Animal Care Committee of Laval University approved all surgical and animal care procedures.

Drug Administration

Injectable levodopa (levodopa methyl ester, Sigma) was always administered along with a fixed dose of 50 mg of benserazide. An optimal dose, defined as the highest dose improving parkinsonian motor symptoms while inducing low or no dyskinesias, was established in all 4 animals. Suboptimal and dyskinesia-inducing doses were defined as 60% and 140% of the optimal dose, respectively. Levodopa and benserazide were dissolved in 1 ml of sterile saline, were adjusted to pH 6, and were given subcutaneously at the same time. Each dose was tested 3–4 times at an interval of 2–3 days. Doses were given in a

specific sequence (suboptimal, dyskinesia-inducing, saline, and optimal) to keep the primates primed to levodopa and to avoid a habituation to the doses.

Behavioral Assessments

The MPTP monkeys were placed in observation cages at the beginning of the protocol and were kept in the same cages for the entire duration of the protocol. The animals were filmed during all sessions and were scored for antiparkinsonian and dyskinetic responses a posteriori. Parkinsonian and dyskinetic scores were obtained immediately after levodopa administration, and the monkeys were then continuously observed and scored until the effect of levodopa subsided.

Parkinsonian Score

A disability scale developed in our laboratory was used to evaluate the parkinsonian syndrome in MPTP monkeys.[21,22,26,44] The behaviors were scored every 15 minutes as follows (maximum score of 16): a) posture: normal = 0, flexed intermittent = 1, flexed constant = 2, and crouched = 3; b) mobility: normal = 0, mild reduction = 1, moderate reduction = 2, and severe reduction = 3; c) climbing: present = 0 and absent = 1; d) gait: normal = 0, slow = 1, very slow = 2, and very slow with freezing = 3; e) grooming: present = 0 and absent = 1; f) vocalization: present = 0 and absent = 1; g) social interaction: present = 0 and absent = 1; and h) tremor: absent = 0, mild action tremor = 1, moderate action tremor = 2, and resting tremor = 3.

Dyskinetic Response

Dyskinesias were observed continuously and scored twice every 15 minutes for the duration of the treatments, according to a scale developed in our laboratory.[22,26,44] Both dystonic and choreic dyskinesias were scored. Dyskinesias were rated for the face, neck, trunk, arms, and legs as follows: none = 0; mild (occasional) = 1; moderate (intermittent) = 2; and severe (continuous) = 3. The dyskinetic score obtained was the sum of the scores for all body segments (maximum score of 21).

Prehension Task

Each MPTP monkey was trained in a prehension task, which consisted of retrieving an object (a piece of grape) that was placed 15 cm out of the cage. Both suboptimal and optimal doses of levodopa, as well as the vehicle, were tested. The dyskinesia-inducing dose was not tested since the MPTP monkeys were unable to complete the task because of LIDs. The task was performed twice after each administration of the drugs, first at the onset of response and second at the peak of the response to levodopa. Every session was filmed and was quantified a posteriori. The task was calculated from the onset of the movement to reach the object. A minimum of 10 trials was performed, and only trials that were done with the hand contralateral to the surgically treated side were analyzed.

Surgical Procedure

Animals were preanesthetized with an intramuscular mix of ketamine and glycopyrolate. An intravenous injection of phenytoin was given to prevent seizures. After induction of 1.5% isoflurane anesthesia, the monkeys were placed in a Kopf stereotactic frame for a ventriculography. After trepanation, the radiopaque solution (Omnipac or Iohexol, 0.8 ml of a 65% solution, Nicomed Imaging) was injected through a microsyringe into the ventricle ipsilateral to the STN lesion. A few seconds after the injection, lateral and frontal radiographs of the ventricular system were obtained to precisely localize the baseline formed by the anterior and posterior commissures in each animal.[55] Stereotactic coordinates for the STN were calculated based on the atlas of Szabo and Cowan[65] and were corrected according to the data collected from ventriculography. A 29-gauge cannula, fixed on a stereotactic arm, was lowered through a 3-mm bur hole in the dorsolateral part of the nucleus. Ten injections of 1 µl of a sterile solution of the fiber-sparing ibotenic acid (10 µg/µl diluted in 1× PBS) were given at 1-minute intervals over a 10-minute period. Each dose of ibotenic acid was injected along the track of the cannula, ± 0.5 mm from the target. After injection, the cannula was kept in place for 5 minutes, and it was then slowly retracted to avoid suction of the neurotoxin. Monkeys were given a 2-week period to fully recover from surgery before pursuing behavioral observations. If needed, adjusted low doses of levodopa were given in those 2 weeks for animal comfort. At the end of testing, the monkeys were killed 24 hours after administration of 50/12.5 mg of

levodopa/benserazide orally by an overdose intracardiac injection of sodium pentobarbital (100 mg/kg). The brains were extracted and were quickly flash-frozen in isopentane (-45°C) and stored at -80°C.

Tissue Preparation

The brains were cut into 12-mm-thick coronal sections with a cryostat (-18°C) through the entire rostrocaudal extent of the STN, corresponding approximately to ac-7 to ac-5 mm in the Martin and Bowden atlas.[39] The sections were mounted on Super Frost Plus (Fisher) slides. The frozen sections used for cresyl violet, cytochrome oxidase, and TH immunohistochemical analyses were postfixed for 1 hour in 4% paraformaldehyde at room temperature.

Evaluation of Ibotenic Acid Lesion

To delineate the STN, 7 equally spaced transverse sections per animal, distributed across the entire STN, were stained for cytochrome oxidase according to the histochemical protocol of Wong-Riley.[74] Adjacent sections were stained with cresyl violet to help in delineating the lesion. Briefly, sections were rinsed in 0.1 M PBS, rinsed in distilled water for 30 seconds, and immersed in a 0.1% cresyl violet solution for 25 minutes. They were then dehydrated in graded alcohol, cleared in toluene, and coverslipped with DPX. The volume of the STN and the lesions were estimated using the Cavalieri method and StereoInvestigator software (version 7.00.3, MicroBrightField).

Tyrosine Hydroxylase Immunohistochemistry

Tyrosine hydroxylase immunohistochemistry was adapted from the protocol of Parent and Hazrati.[51] For each monkey, 3 sections taken at regular intervals through the substantia nigra were analyzed. These sections were rinsed 3 times in PBS (pH 7.4) solution and preincubated for 1 hour at room temperature in a PBS solution containing 5% NHS and 0.1% Triton X-100. They were then incubated overnight at 4°C in a PBS solution containing 2% NHS, 0.1% Triton X-100, and the primary antibody directed against TH (dilution 1:500, mouse monoclonal antibody; ImmunoStar). After 3 rinses in PBS, the sections were incubated at room temperature for 2 hours in a PBS solution containing 2%

NHS, 0.1% Triton, and 0.44% biotinylated anti–mouse horse-made immunoglobulin G (secondary antibody, Vector Labs). After 3 additional rinses in PBS, the sections were incubated for 1 hour with an avidin biotin peroxidase complex (dilution 1:500, Vectastain ABC kit; Vector Labs), and washed 2 times in PBS and once in TRIS 0.05 M. The antigen-antibody complexes were revealed by incubating the sections for 8 minutes in a 0.05% solution of 3,3'-diaminobenzidine diluted in TRIS, to which 0.005% H_2O_2 was added. After 2 rinses in TRIS and 2 additional rinses in 0.1% PBS, the sections were counterstained with cresyl violet for 18 minutes, rinsed in distilled water for 30 seconds, dehydrated in graded alcohol, cleared in toluene, and coverslipped with DPX.

High-Performance Liquid Chromatography

The concentrations of dopamine were measured by high-performance liquid chromatography with electrochemical detection, according to previously published procedures.[45] Briefly, small frozen tissue pieces of putamen and caudate were taken from coronal sections and homogenized in 250 ml of 0.1 μM $HClO_4$ at 4°C and centrifuged at 10,000g for 20 minutes to precipitate proteins. The supernatants were kept at -80°C in small polyethylene tubes until assayed, while the pellets were dissolved in 100 ml of 1 μM NaOH for determination of protein content.

Statistical Analysis

A mean parkinsonian score and a mean dyskinetic score (total period) were calculated by averaging all 15-minute scores obtained for the duration of the response. Moreover, for dyskinesias, values for the 1-hour peak period and the maximum dyskinesia scores were computed. All data were analyzed using a 2-way ANOVA mixed with an animal random effect. For the duration of response to levodopa, a semiparametric Cox model was used to take into account the fact that some responses were right censored. Also, a sandwich covariance matrix was used to consider the correlation between measures on the same animal. For the elapsed time before the behavioral response, a Student paired t-test was used. A Z-test for 2 proportions was used to measure the rate of success in the prehension task. In the figures, parkinsonian and dyskinetic scores are illustrated as follows: median (horizontal line), interquartile range (box), and range (bars). Mean values

are presented as the mean ± standard error. A p value ≤ 0.05 was considered significant. Analyses were performed using SAS (version 9.2, SAS Institute, Inc.).

5.5 Results

Extent of Dopaminergic Denervation

Very few TH-immunopositive cells were found in the substantia nigra of monkeys treated with MPTP both contra- and ipsilateral to the STN lesion (Fig. 5.1A). Dopamine concentrations were measured in the caudate nucleus and putamen both ipsi- and contralateral to the STN lesion. Administration of MPTP resulted in a marked depletion of putaminal and caudate dopamine concentrations in all MPTP monkeys with an average decrease of 99.7% compared with intact monkeys (Fig. 6.1B and C). No differences were found between the ipsi- and contralateral sides to the STN lesion (see the smaller graphs in Fig. 5.1B and C). No neuroprotection or neurorestoration of dopaminergic cells was observed, since the striatum contra- and ipsilateral sides to the STN lesion were similarly denervated.

Subthalamic Lesion

Lesions were obvious on the cresyl violet– and cytochrome oxidase–stained sections. The STN could be easily delineated on the cytochrome oxidase–stained sections (Fig. 5.2A and B), and the intensity of the signal was markedly reduced at the lesion site (Fig. 5.2B). Cresyl violet staining of adjacent sections (Fig. 5.2C and D) confirmed the complete neuronal loss in the lesioned area (Fig. 5.2D). Lesions were placed in the dorsolateral part of the STN in all animals, extending to the ventrolateral part in 2 animals (Animals LS-87 and #64). No neuronal loss was observed in other brain areas, including the ipsilateral thalamus, the substantia nigra, and the contralateral STN. The total volume estimated for the STN lesion varied between 4.4% and 25.5% (Table 5.1). The extent of the STN lesion for Animal LS-87 is detailed in Fig. 5.2E.

Effects on the Antiparkinsonian Response

All doses of levodopa had a significant beneficial effect on the parkinsonian score compared with vehicle (Fig. 5.3A–D). There was a significant difference between the suboptimal dose and the optimal dose of levodopa ($F_{1,21}$= 6.13, $p < 0.05$ and $F_{1,21}$= 4.18, $p < 0.01$ for mean total period and 1-hour best-on scores, respectively). Subthalamotomy had a

global and positive effect on all doses of levodopa and vehicle. Improvements were equivalent between all doses. It is noteworthy that parkinsonian scores associated with the postoperative suboptimal dose were not different from the preoperative optimal dose of levodopa. As expected, increasing the levodopa dosage caused an increase in the duration of the antiparkinsonian response ($p < 0.01$). The duration of levodopa antiparkinsonian response increased by 20%–25% for all animals after the lesion for the suboptimal dose of levodopa ($p < 0.05$) but remained unchanged in the optimal and dyskinesia-inducing doses after STN lesioning (Fig. 5.3E and F). It is worth noting that the duration of behavioral response of the postoperative suboptimal dose was not different from the preoperative optimal dose of levodopa. The elapsed time after levodopa administration for the behavioral response was unaffected by the concentration of levodopa ($F_{2,15} = 2.20$, $p = 0.145$) and remained unchanged following surgery for all doses ($F_{1,15} = 2.20$, $p = 0.674$) (Fig. 5.3G and H).

Effects on Dyskinetic Response

All doses of levodopa induced dyskinesias, both pre- and postoperatively. Augmenting the dose had a significant increasing effect on mean dyskinesias scores over the total period compared with the suboptimal dose (Fig. 5.4A and B) as well as on the 1-hour peak dyskinesias (Fig. 5.4C and D). Subthalamotomy modified the mean (total period) and 1-hour peak LID scores. These modifications were not similar between each dose of levodopa ($F_{2,15} = 23.47$, $p < 0.0001$). In fact, they were found to increase in both suboptimal ($p < 0.0001$ for both mean total period and 1-hour peak LID) and optimal doses of levodopa ($p = 0.05$ for both mean and 1-hour peak LID), whereas they remained unchanged in the dyskinesia-inducing dose after surgery ($p > 0.05$ in both mean and 1-hour peak LID). It is noteworthy that, even though lower, the mean (total period) and 1-hour peak dyskinetic scores with the postoperative suboptimal dose were not different from the preoperative optimal dose of levodopa. No dyskinesia or hemiballism was observed at the baseline state.

Prehension Task

Compared with baseline, levodopa significantly decreased the time to execute the task (Fig. 5.5) at both onset and peak of response. A tendency toward reduction in the

execution time was observed with the vehicle after surgery, but it did not reach significance ($p = 0.07$ and $p = 0.15$ for onset and peak of response, respectively). No lesion effect was observed at the onset of response to levodopa, regard- less of the dose of levodopa. A lesion effect was observed at the peak of response to levodopa, with a reduction of time to execute the task (0.70 ± 0.13 seconds preoperatively vs 0.45 ± 0.04 seconds postoperatively) at the suboptimal dose, whereas no lesion effect was observed at the optimal dose of levodopa. In the monkey that had the best behavioral response to levodopa in the prehension task but also the smallest lesion (Animal #34), there was a significant increase in the number of drops of the reward postoperatively. For this animal, the rate of success decreased to 80% in both onset and peak of response with the suboptimal dose of levodopa ($p < 0.01$ and $p < 0.001$, respectively; Z-test). No drops were observed with vehicle pre- and postlesioning in this animal or during all pre- and postsurgery tests in the other animals.

Adverse Events

Although the surgery was well tolerated, a contralateral head rotation was observed in 1 monkey (Animal #64). This rotation disappeared the day after surgery without requiring any levodopa. In the 3 other monkeys, contralateral head and trunk rotations were observed. These animals received low doses of levodopa during the following days postsurgery. For 2 of these monkeys (Animals LS-87 and #34), the rotation disappeared after the first administration of levodopa and did not recur. In the other monkey (Animal NS-02), a 30° head rotation remained after surgery with a gradual and partial recovery at the time of euthanasia (~10° at the time of euthanasia). This rotation disappeared under levodopa until its effect subsided. Moreover, oculomotor signs were observed contralateral to the side of the lesion in this particular monkey, which resolved within the 1st week. No serious adverse events were noted.

5.6 Discussion

The present experiment investigated the effects of subthalamotomy on the response to levodopa in dyskinetic MPTP monkeys. The parkinsonian scores were all reduced after subthalamotomy, regardless of the dose of levodopa. It is interesting to note that the postoperative suboptimal parkinsonian scores were no different from the preoperative optimal and dyskinesia-inducing doses of levodopa (Fig. 5.3A and B). Levodopa-induced dyskinesias were increased after surgery at the suboptimal and optimal doses, but not at the dyskinesia-inducing dose, which remained unchanged, suggesting a ceiling effect. Although the dyskinesias were less severe, postoperative dyskinesias with suboptimal doses were not statistically different from those with the preoperative optimal and dyskinesia-inducing doses of levodopa (Fig. 5.4). Similar results were observed between the postoperative dyskinesias with optimal doses and preoperative dyskinesia-inducing doses. Considering the small number of monkeys used in this study, statistical significance might have been reached by increasing the sample. Furthermore, the duration of antiparkinsonian response to levodopa was increased at the suboptimal dose, whereas it remained unchanged for the 2 higher doses. Finally, the execution time to reach the reward in the prehension task was reduced only at the peak of effect to levodopa at the suboptimal dose, whereas no effect was seen with the optimal dose or with the vehicle. Taken together, results of this study suggest that unilateral subthalamotomy potentiates the response to low doses of levodopa in MPTP monkeys. Interestingly, the size and the location of the lesion within the STN made no difference in the behavioral results obtained, since all monkeys displayed similar improvements after subthalamotomy.

Subthalamotomy has already been investigated in monkeys rendered parkinsonian by MPTP insult or hemiparkinsonian by unilateral intracerebral administration of 6-OHDA.[4,5,8,23,24,28,71,73] However, the effect of the STN lesion on the response to levodopa has never been studied. Levodopa was used in one study and was given postoperatively. In that study, subthalamotomy-induced hemidyskinesias were found to exacerbate with administration of levodopa.[24] In MPTP monkeys, thermolytic lesions covering at least 40% of the STN completely reversed parkinsonian motor symptoms.[4] In another study,

injections of kainic acid resulting in 80%–90% cell loss in the STN showed improvements in all cardinal signs, and these results were similar whether the subthalamotomy was performed before or after MPTP administration.[23] On the other hand, in a more recent study no behavioral improvements were observed after lesioning with kainic acid in monkeys with 50% dopaminergic cell loss, even with 80% destruction of the STN.[71] In the present study, except for one monkey, parkinsonian disabilities were improved after surgery, but the reversal of parkinsonism was not complete. The previous published reports are hard to reconcile with each other as well as with the results of the present study. First of all, the elapsed time between the MPTP insult and the subthalamotomy, when indicated, was reported to be very short,[71] whereas many years separated these 2 events in the present study. In fact, we performed the STN surgeries 10 years or more after monkeys were rendered parkinsonian. Such late STN lesioning after exposure to MPTP reflects more faithfully the clinical conditions. It is known that some monkeys may recover during the first few weeks after exposure to MPTP.[17,46] Therefore, complete or partial reversal of parkinsonism observed after STN lesioning performed rapidly after MPTP exposure could be explained by spontaneous recovery. Moreover, the total quantity of MPTP given varied among studies, thus having an impact on the dopaminergic neuronal loss. Most importantly, the response to levodopa after subthalamotomy in monkeys has never been investigated previously. This is surprising, since subthalamotomy is performed in parkinsonian patients to alleviate their motor symptoms and to reduce the levodopa needs. Finally, the method used to lesion the STN may also account for differences. In our study, we used stereotactic microinjections of ibotenic acid to produce a chemical lesion that spared axons passing around the STN, whereas others have used thermolytic approaches that lesion fibers of passage.[4,13] Although the sizes of thermolytic lesions are well documented, small and precise lesions strictly affecting the STN neurons are more difficult to achieve than with chemical lesions. Taken together, these differences could, at least partially, explain the discrepancies with previous studies.

In the clinic, subthalamotomy can be performed when patients display disabling levodopa-induced complications and deep brain stimulation is contraindicated.[32] In fact, peak-dose and biphasic dyskinesias, as well as motor fluctuations are reduced after uni- and bilateral subthalamotomies.[2,54,67] Those improvements tend to fade over the years, but most

of them are still significant after 2 years. Among parkinsonian symptoms, off-medication tremor is the one that responds the best to STN lesioning,[63] whereas pallidotomy offers variable results.[53] Rigidity, bradykinesia, and drug-induced dyskinesias are reduced in a similar manner in both lesioning procedures.[54] Furthermore, compared with pallidal lesioning, subthalamotomy allows a reduction in the levodopa needs.[2,53,54] Roughly between 40% and 50% of the levodopa daily intake can be reduced. However, this percentage tends to diminish over the years, probably because of the progression of the disease.[2] Interestingly, a study reported an increase in the on-time duration when the medication was maintained following a unilateral subthalamotomy.[1] The percentage of the day passed in "on" condition doubled, almost reaching a complete daytime cycle. In the present study, we also observed an increase in the time to levodopa response but only at the suboptimal dose. When maintaining the optimal or dyskinesia-inducing doses, no increase in the on-time duration was noted. Finally, a 1-year prospective study has shown that there were no differences in the motor scores and levodopa needs between bilateral subthalamotomy and bilateral deep brain stimulation.[41]

Prehension Task

Since some of the monkeys used in this study did not move per se, even with levodopa, and our parkinsonian scale takes the speed of spontaneous mobility into consideration, monkeys were trained in a prehension task that allowed an objective analysis of bradykinesia. Bradykinesia improved with all doses of levodopa tested compared with vehicle. The only improvement from surgery that reached statistical significance was at the peak of levodopa effect at the suboptimal dose (36%). Reduction in the execution of the task was also observed with the vehicle, but this did not reach significance. In patients undergoing unilateral subthalamotomy, off-medication contralateral bradykinesia is reduced, reaching significance only 2 years after surgery, whereas on-medication contralateral bradykinesia is slightly improved during the same period.[54] More recently, both off- and on-medication bradykinesia were shown to significantly reduce over a 3-year period after unilateral subthalamotomy.[2] However, bilateral STN lesions do not appear to further improve bradykinesia.[67] In a previous study in 6-OHDA-lesioned marmosets, Henderson et al.[28] observed a reduction in time in the initiation of a reaching task but not in

the execution after subthalamotomy. In their study, monkeys that became "clumsy" following 6-OHDA injections remained clumsy after subthalamotomy. In our group, only one monkey became clumsy following STN lesioning and only during levodopa response, not at baseline.

Adverse Events

Lesioning the STN in patients has been long avoided due to fears of causing hemiballism,[25] as demonstrated in the pioneering work of Carpenter and Carpenter[13] in which a normal monkey developed this involuntary movement following STN lesioning. However, a recent paper clearly showed that this side effect is not frequent and is transient when present in parkinsonian patients.[2] Furthermore, lesions in the STN are not the sole cause of hemiballism. Hemiballism has many etiologies and may be caused by lesioning other structures of the basal ganglia other than the STN.[68] We did not observe any hemiballism in our MPTP monkeys, regardless of the location and the extent of the lesion in the STN. The small number of animals used could explain the absence of this complication. Some authors showed that unilateral subthalamotomy had discrete cognitive and neuropsychological changes, but there was no demonstration of hippocampal damage.[54] Bickel et al.[10] observed no deterioration following simultaneous bilateral subthalamotomies.

In our study, head rotations were observed in all monkeys and trunk rotations in 2 monkeys after unilateral subthalamotomy. All these rotations disappeared with levodopa treatment. Such asymmetry was also noted after unilateral subthalamotomy in parkinsonian patients,[38,64] as well as in previous reports of parkinsonian monkeys.[28] Su and colleagues[64] proposed that this postural asymmetry was due to an imbalance between the operated and unoperated hemispheres and suggested that dopamine had more influence on the operated side than on the un- operated side. However, similar observations were made in intact monkeys with a unilateral STN lesion[3,12,27] or at high current during high-frequency stimulation in MPTP monkeys.[7] In primates, the dorsolateral area of the STN receives important glutamatergic input from the motor cortex.[43] This STN region is also known to be involved in orofacial movements and to innervate the substantia nigra pars reticulata.[36,59] Therefore, subthalamotomy might lead to a decrease in glutamatergic input at the substantia

nigra pars reticulata level, resulting in a contralateral head rotation. This hypothesis is supported by the fact that head rotations were observed after substantia nigra pars reticulata lesioning in 6-OHDA monkeys.[29]

Mechanism of Action

The fields of Forel and zona incerta were lesioned to alleviate some parkinsonian symptoms in the 1960s.[47,60] These areas are still targeted nowadays by deep brain stimulation electrodes in parkinsonian patients,[56,69] whereas others stimulate or lesion the dorsolateral part of the STN.[1,30,63] In this case, it is believed that the pallidothalamic fibers that run through the Forel Field H2 located at the dorsal surface of the STN are also affected by these procedures.[42,52] In the present study, only STN neurons were damaged; surrounding fibers were unaffected by the injection of axon-sparing ibotenic acid. Thus, the pallidothalamic axons remained intact, and no pseudo-pallidotomy-like antidyskinetic effect was observed. Moreover, dyskinesias were found to increase after surgery at both suboptimal and optimal doses of levodopa. These observations are in agreement with those of Krack and colleagues,[37] who suggested that reduction in dyskinesias was not due to an alteration in the STN activity but rather due to a reduced levodopa intake.

5.7 Conclusions

Unilateral subthalamotomy in dyskinetic MPTP monkeys is a safe and efficient neurosurgical procedure. This procedure can be used to study the mechanisms of action of STN lesioning and its effects on the response to levodopa. This surgery potentiated the response and the duration of antiparkinsonian response to low doses of levodopa. It also provided a reduction in on-levodopa bradykinesia, as assessed in the prehension task. Medication could be reduced by 40% with similar antiparkinsonian response than those obtained preoperatively with lower levodopa-induced dyskinesias.

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Table 5.1 Description of the four MPTP female cynomolgus monkeys used in the present study

Animal No.	Age (yrs)	Weight (kg)	Side of STN Lesion	Total MPTP Dose (mg)	Optimal Levodopa Dose (mg/kg)	Survival Duration After Op (days)	Extent of Lesion (% vol/vol)
34	21	3.2	rt	16.0	12.5	80	4.4
64	16	2.7	lt	6.8	16.0	74	6.8
LS-87	14	3.8	lt	19.3	24.0	88	25.5
NS-02	14	5.4	rt	19.2	7.5	75	10.6

* % vol/vol = percentage volume of the lesion divided by the total volume of the STN.

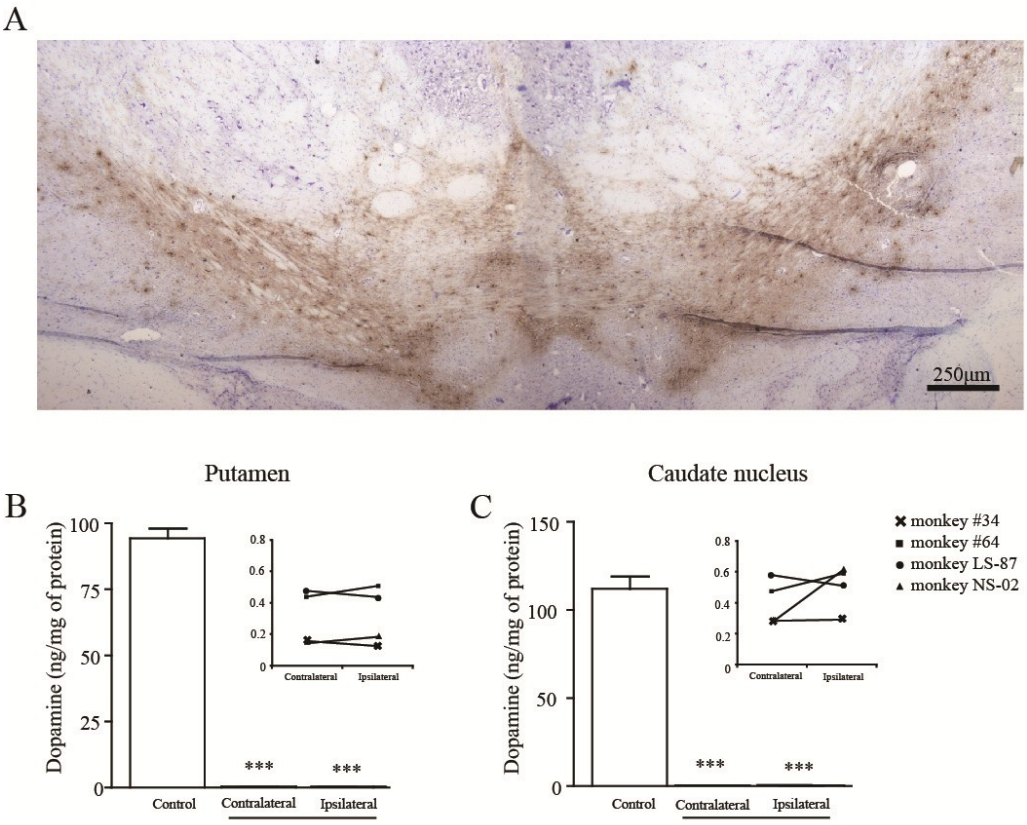

Figure 5.1. Administration of MPTP resulted in an extensive dopaminergic neuronal loss. A: Tyrosine hydroxylase-immunostained transverse section obtained through the substantia nigra of Animal #64 and counterstained with cresyl violet. Very few TH-immunoreactive cells are seen, with no difference between the ipsilateral and contralateral sides of the STN lesion. B and C: Dopamine concentrations were assayed by high-performance liquid chromatography in the putamen (B) and the caudate nucleus (C) ipsi- and contralateral to the lesion and were compared with intact animals ($F_{2,11} = 560.3$, $p < 0.0001$ and $F_{2,11} = 245.4$, $p < 0.0001$, respectively). The bars indicate the mean and the whiskers indicate the SE. *** $p < 0.001$ vs control. Insets: Smaller graphs showing low values of dopamine with an expanded y axis for clarity.

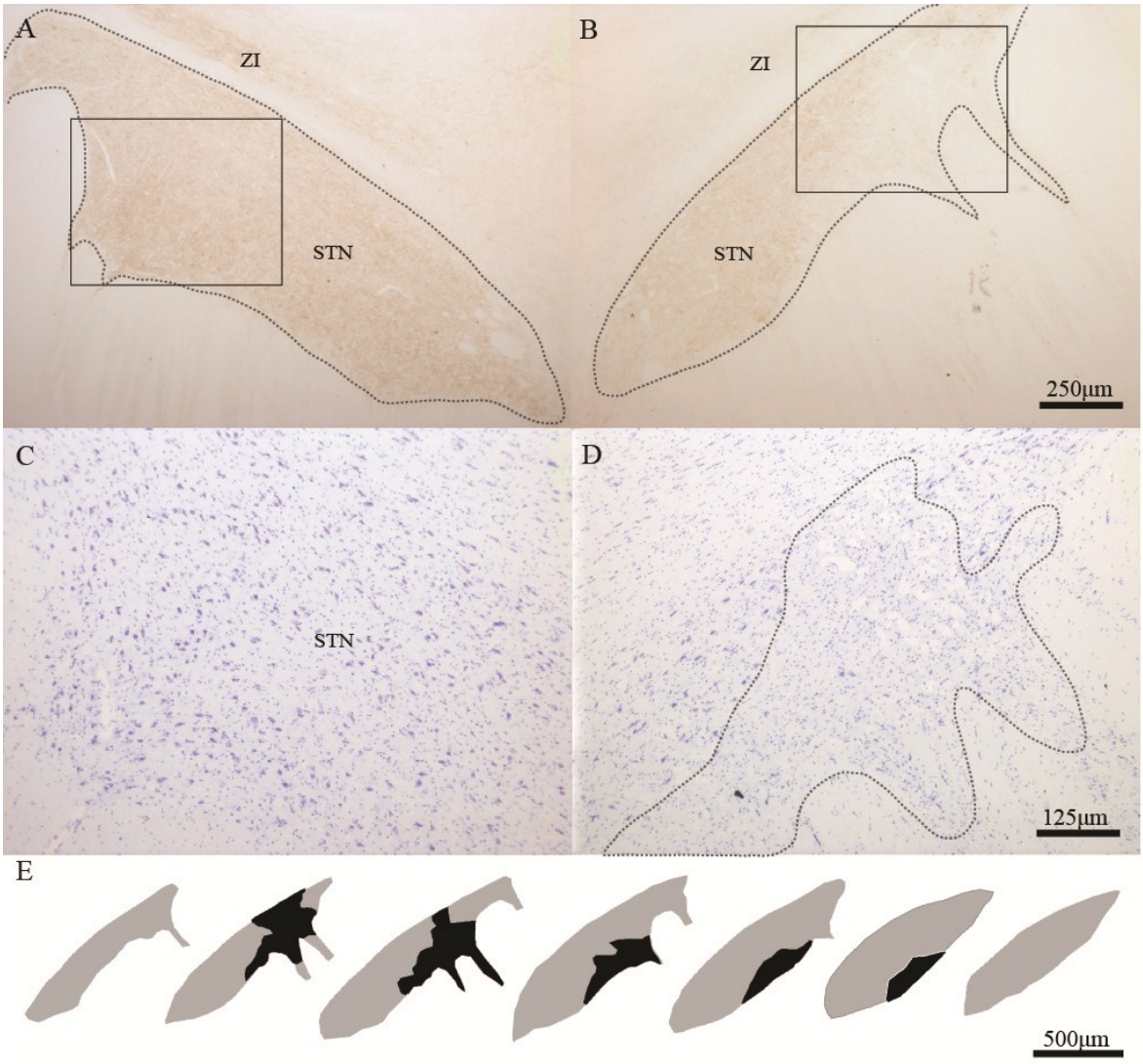

Figure 5.2 Example of ibotenic acid lesioning in the left STN of Animal LS-87 that resulted in significant neuronal loss (26% of the STN volume). **A and B:** The STN could be easily delineated on cytochrome oxidase–stained sections, both on the intact side (A) and on the lesioned side (B). Note the lower reactivity of cytochrome oxidase in the dorsolateral part of the left STN in panel B. **C and D:** Higher magnifications of the frames delineated by rectangles in panels A and B, taken from adjacent sections that were stained with cresyl violet. Note the complete absence of neurons in the delineated area in panel D. **E:** Drawings of 7 equally spaced transverse sections of the lesioned STN depicted in an anteroposterior order. The extent of the ibotenic acid lesion is shown in black. ZI = zona incerta.

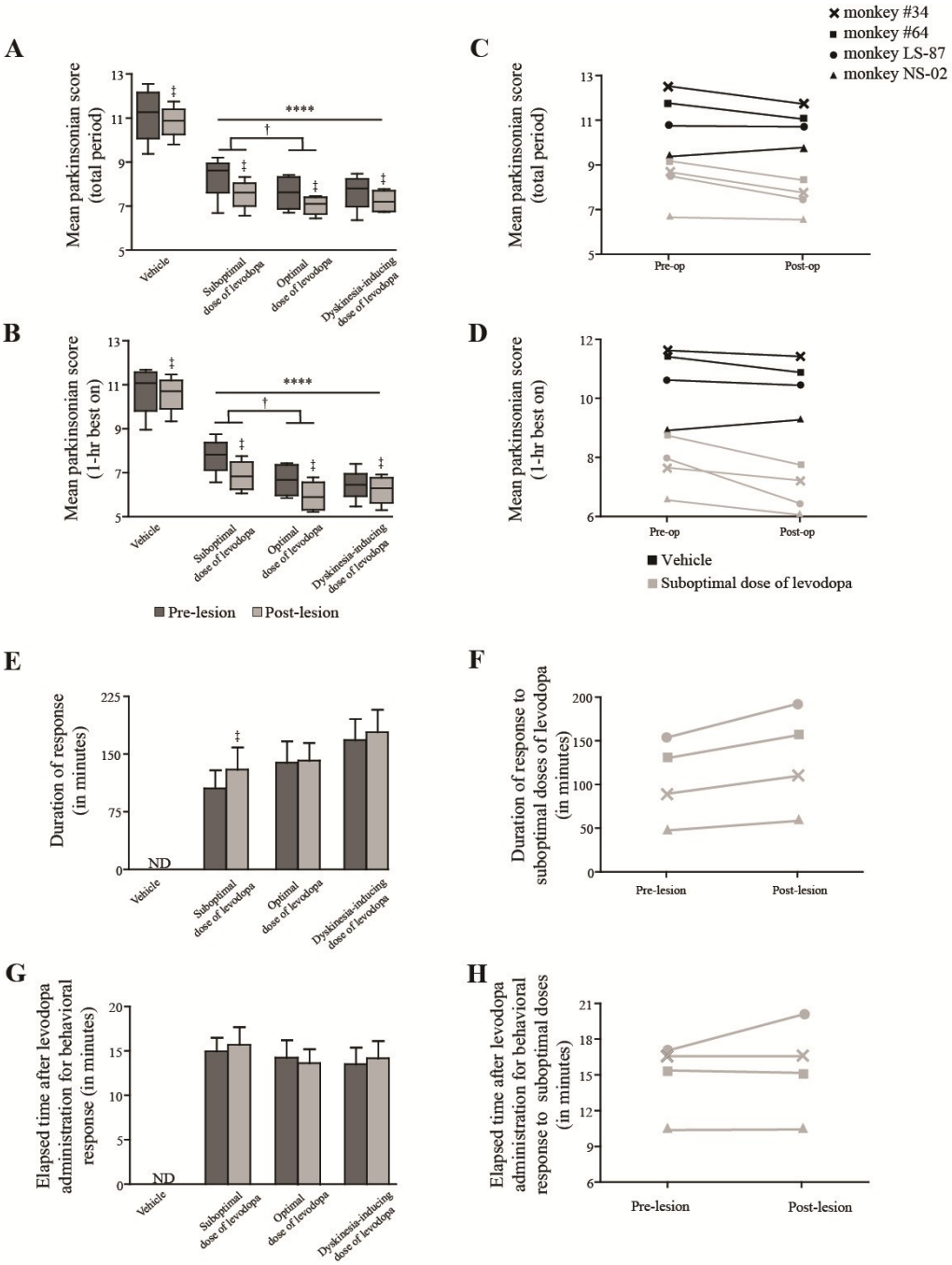

Figure 5.3 Behavioral effect of subthalamotomy in the 4 MPTP monkeys comparing postsurgical and presurgical motor behavior. **A and B:** The parkinsonian scores in the total period (A) and 1-hour best (B) were reduced by administration of levodopa compared with vehicle ($F_{3,21} = 74.7$, $p < 0.0001$ and $F_{3,21} = 77.3$, $p < 0.0001$, respectively). Lesioning of the STN had a global effect by reducing both parkinsonian scores ($F_{1,21} = 6.13$, $p = 0.02$

and $F_{1,21} = 4.18$, $p = 0.05$, respectively), and all doses of levodopa improved similarly, including the vehicle ($F_{3,21} = 0.27$, $p = 0.849$ and $F_{3,21} = 0.62$, $p = 0.610$, respectively). **C and D:** Individual parkinsonian scores with vehicle and the suboptimal dose are represented for both total period and 1-hour best antiparkinsonian behavioral response to levodopa. **E and F:** The mean duration of levodopa antiparkinsonian response (E) increased with higher doses of levodopa ($p = 0.004$, chi-square test). Lesioning of the STN had a beneficial effect on suboptimal dose ($p = 0.012$), with increases between 20% and 25% of the preoperative values (F). **G and H:** Elapsed time after levodopa administration for the behavioral response remained unchanged regardless of the dose of levodopa, both pre- and postlesioning. In A and B the median score is indicated by the horizontal line, the interquartile range by the box, and range by the whiskers. In E and G, the bars indicate the mean and the whiskers indicate the SE. ****$p < 0.0001$ vs vehicle; †$p < 0.05$ vs optimal dose; ‡$p < 0.05$ vs respective preoperative values. ND = no drug (levodopa).

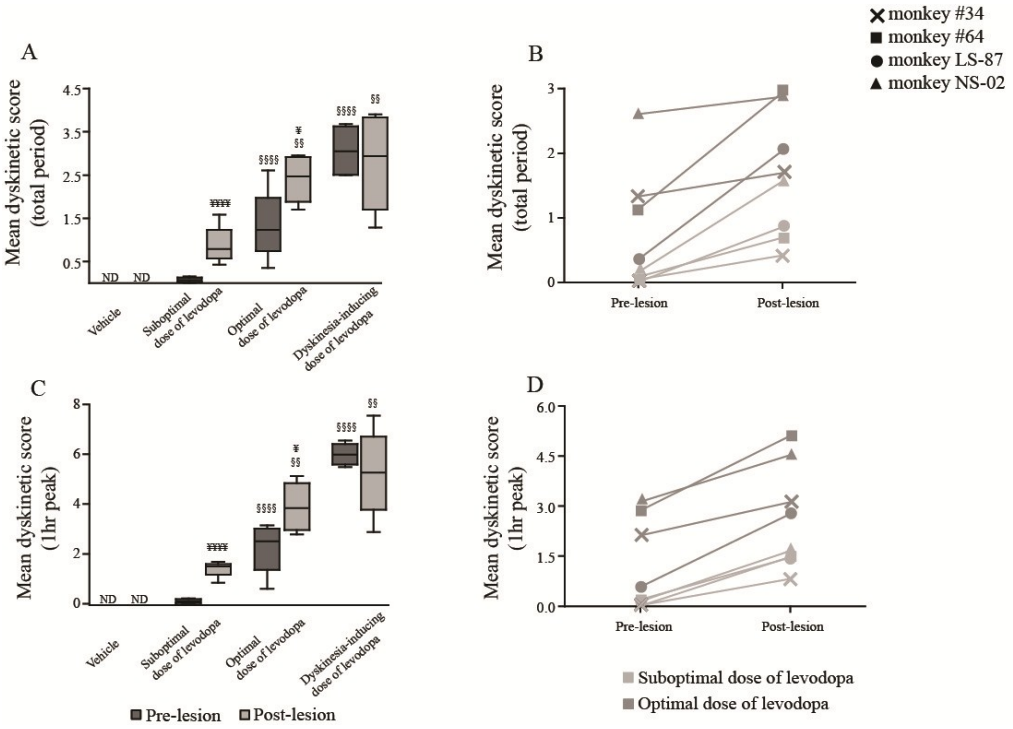

Figure 5.4 Effects of subthalamotomy on LIDs in 4 MPTP monkeys comparing postsurgical and presurgical dyskinetic scores. **A and B:** The total period (A) and 1-hour peak (B) dyskinetic scores were increased by administration of levodopa compared with the suboptimal dose of levodopa ($F_{2,15}$ = 54.0, $p < 0.0001$ and $F_{2,15}$ = 80.9, $p < 0.0001$, respectively). Lesioning of the STN had an increasing effect on both dyskinetic scores ($F_{1,15}$ = 26.6, $p = 0.0001$ and $F_{1,15}$ = 35.3, $p < 0.0001$, respectively). Dyskinesias did not increase similarly between levodopa doses after lesion ($F_{2,15}$ = 23.5, $p < 0.0001$). **C and D:** Individual dyskinetic scores for the suboptimal and optimal doses are shown for total period and 1-hour peak dyskinesias. It is noteworthy that dyskinesias with the suboptimal dose did not reach preoperative dyskinetic scores with the optimal dose. In A and C the median score is indicated by the horizontal line, the interquartile range by the box, and range by the whiskers. ¥$p < 0.05$, ¥¥¥¥$p < 0.0001$ pre- vs postlesion for the same dose; §§$p < 0.01$, §§§§$p < 0.0001$ vs respective suboptimal dose. ND = not detected.

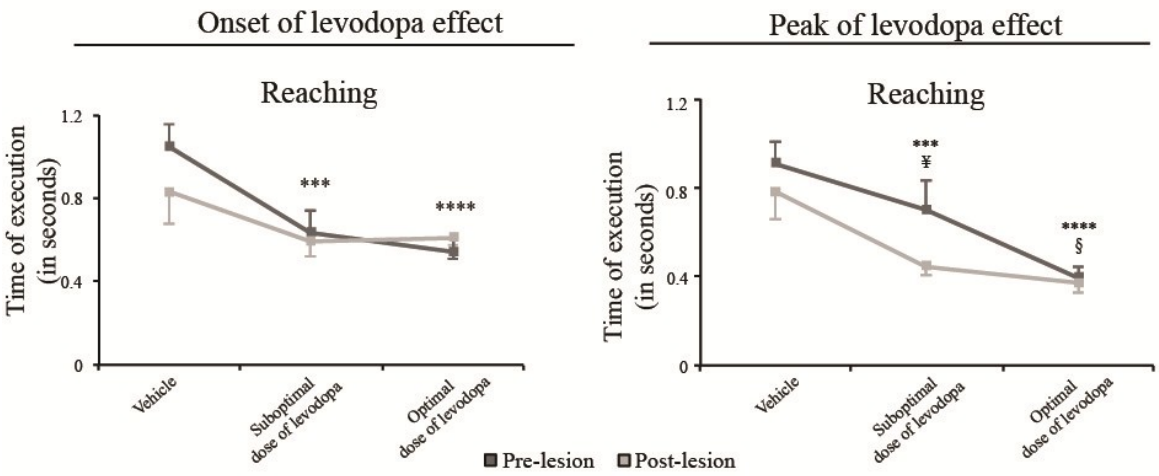

Figure 5.5 Measurements of bradykinesia by a prehension task. Administration of levodopa decreased the time to execute the task at both suboptimal and optimal doses of levodopa compared with baseline ($F_{2,15} = 16.8$, $p = 0.0001$ and $F_{2,15} = 22.1$, $p < 0.0001$ for both, at the onset and at the peak of levodopa effect, respectively). A lesion effect was observed at peak of levodopa effect ($F_{1,15} = 5.24$, $p = 0.037$), whereas no lesion effect was observed at onset of levodopa effect ($F_{1,15} = 1.25$, $p = 0.281$). ***$p < 0.001$, ****$p < 0.0001$ vs vehicle; ¥$p < 0.05$ pre- vs postlesion for the same dose; §$p < 0.05$ vs respective suboptimal dose.

CHAPITRE 6. DOPAMINE RECEPTORS AND SUBTHALAMOTOMY-INDUCED IMPROVED MOTOR RESPONSE IN PARKINSONIAN MONKEYS

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Abbreviations **:** 6-OHDA = 6-hydroxydopamine; DA = dopamine; DARPP-32 = DA- and cAMP-regulated phosphoprotein of 32kDa; DAT = dopamine transporter; DBS = deep brain stimulation; DL = dorsolateral; DM = dorsomedial; DOPAC = 3,4-dihydroxyphenylacetic acid; ERK/1/2 = extracellular signal-regulated kinase 1 and 2; GPe = globus pallidus pars externa; GPi = globus pallidus pars interna; HFS = high frequency stimulation; HVA = homovanillic acid; LID = L-DOPA-induced dyskinesia; L-DOPA = L-3,4-dihydroxyphenylalanine; MPTP = 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine; PPD = preprodynorphin; PPE = preproenkephalin; SNc = substantia nigra pars compacta; STN = subthalamic nucleus; VL = ventromedial; VM = ventromedial

6.1 Résumé

La subthalamotomie permet la réduction de L-DOPA chez les patients dyskinétiques tout en gardant les bénéfices antiparkinsoniens. Malgré que les apports cliniques soient bien connus, les mécanismes sous-jacents le sont beaucoup moins. Nous avons donc investigué les changements biochimiques dans le système dopaminergique et ses neuropeptides associés qui sont impliqués dans les LID par des mesures dans les ganglions de la base de singes. Les niveaux de dopamine et ses métabolites furent quantifés par HPLC. Le transporteur de DA, les récepteurs D_1 et D_2 furent investigués par autoradiographie avec des radioligands spécifiques. L'ARN messager de ces deux récepteurs, ainsi que ceux de la préproenképhaline et préprodynorphine furent quantifiés par hybridation *in situ* chez les singes MPTP qui ont reçu une subthalamotomie unilatérale pour réduire leur LID et comparés à des contrôles et des singes MPTP. La signalisation intracellulaire associée aux récepteur D_1 fut mesurée par immunobuvardage de type Western. Nos résultats démontrent que la DA, ses métabolites et son transporteur sont diminués avec le MPTP et demeurent inchangés avec la subthalamotomie. Les niveaux du récepteur D_1 furent diminués par le MPTP dans le noyau caudé et dans le putamen dorsolatéral. Ces niveaux furent diminués davantage avec la L-DOPA, mais -furent rétablit avec la subthalamotomie. L'ARN messager pour le récepteur D_1 a suivi un patron similaire à la liaison spécifique. La synthèse et l'expression du récepteur D_2 sont demeurés inchangés dans tous les groupes. La préproenképhaline et la préprodynorphine furent respectivement augmentés et réduits par le MPTP et augmentés par la L-DOPA comparativement aux contrôles. La protéine intracellulaire DARPP-32 fut augmentée dans le noyau caudé ipsilatéral à la subthalamotomie comparativement à l'hémisphère non-opéré. La potentialisation de la réponse à la L-DOPA telle qu'observée après une subthalamotomie serait associée à une augmentation dans la synthèse et l'expression des récepteurs D_1 ipsilatérale à la lésion du STN.

6.2 Abstract

Subthalamotomy allows a reduction of doses of L-DOPA in dyskinetic patients while its antiparkinsonian benefits are preserved. This was modeled in parkinsonian monkeys where we showed that a unilateral subthalamotomy improved the antiparkinsonian response to L-DOPA. However, the mechanisms of the potentiation of this response to medication remain to be elucidated.

The objective of the present study was to investigate the biochemical changes in the dopaminergic system and related neuropeptides in the basal ganglia of parkinsoninan monkeys with L-DOPA-induced dyskinesias that received an unilateral subthalamic lesion.

Dopamine D_1 and D_2 receptors as well as the dopamine transporter were investigated using receptor binding autoradiography. D_1 receptor, D_2 receptor, preproenkephalin and preprodynorphin mRNAs levels were measured by *in situ* hybridization. Four dyskinetic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine parkinsonian ovariectomized monkeys that underwent unilateral subthalamotomy were compared to four ovariectomized controls and four saline-treated 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine parkinsonian ovariectomized monkeys. D_1 receptor-mediated intracellular signalling was measured by Western immunoblotting.

Dopamine, its metabolites and its transporter were extensively and similarly decreased in all the parkinsonian monkeys investigated. D_1 receptor specific binding was decreased in the caudate nucleus and in the putamen in 1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine monkeys. Parkinsonian monkeys with a subthalamic lesion also showed an overall striatal decrease of D_1 receptor specific binding whereas in the dorsolateral putamen and in caudate nucleus a correction of the decrease of D_1 receptor specific binding was measured in the ipsilateral side to the lesion. D_1 receptor mRNA levels followed a similar pattern. D_2 receptor specific binding and mRNA levels remained unchanged in all groups. Striatal preproenkephalin mRNA levels were overall increased in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine monkeys and in parkinsonian monkeys with a subthalamic lesion compared to controls; the latter parkinsonian group had significantly lower values than the saline-treated parkinsonian monkeys in the dorsolateral putamen. Striatal preprodynorphin mRNA levels remained unchanged in 1-methyl-4-phenyl-1,2,3,6-

tetrahydropyridine monkeys compared to controls whereas it increased in parkinsonian monkeys with a subthalamic lesion compared to controls; in the latter parkinsonian group the dorsolateral putamen had lower values contralateral to the subthalamic lesion. The DARPP-32 protein increased in the caudate nucleus ipsilateral to subthalamotomy compared to the unoperated hemisphere and no change of ERK1/2 proteins and their phosphorylated state were measured.

In conclusion, the improved motor response to L-DOPA after a subthalamotomy observed in the parkinsonian monkeys investigated may be associated with an increased synthesis and expression of D_1 receptors ipsilateral to STN lesion of the direct pathway.

6.3 Introduction

Parkinson's disease is a hypokinetic disorder resulting from a progressive degeneration of dopaminergic cells in the midbrain area (Toulouse and Sullivan, 2008). Administration of the DA precursor L-DOPA shows tremendous beneficial effects in Parkinson's disease patients. Its chronic intake induces however important motor complications, including dyskinesias. These LID are present in 30% of patients after 2 years of treatment, and this percentage increases dramatically with the duration of L-DOPA treatment (Ahlskog and Muenter, 2001). LID appears in the form of involuntary choreic or dystonic movements and are thought to be the results of both nigral denervation and pulsatile non-physiological stimulation of DA receptors on striatal cells (Jenner, 2008).

DA receptors are G protein-coupled receptors that are divided into 2 groups, namely the D_1-like (D_1 and D_5) and D_2-like (D_2, D_3 and D_4) receptors based on their physiological activities (Missale *et al.*, 1998). Among these five subtypes of DA receptors, D_1 and D_2 subtypes are those mainly related to locomotor activity (Centonze *et al.*, 2003). D_1 receptors are the most widespread DA receptor (Missale *et al.*, 1998) and found exclusively post-synaptically on DA-receptive cells (Bergson *et al.*, 1995; Smiley *et al.*, 1994), whereas the D_2 receptors are more complex since its short form is expressed pre-synaptically and the long form of D_2 is post-synaptic (Usiello *et al.*, 2000). Both D_1 and D_2 receptors are expressed in striatal medium spiny neurons and give rise to two segregated pathways according to the model of functional circuitry in the basal ganglia (Albin *et al.*, 1989). Activation of the so-called direct and indirect pathways would have opposing effects on movements. The direct striatonigral disinhibits the thalamocortical pathway and facilitates motor activity, whereas the indirect striatopallidal promotes inhibition of the thalamocortical neurons and thereby reduces movements. However, such segregation was challenged and it was shown that a significant proportion (≈40%) of striatofugal neurons coexpressed both D_1 and D_2 receptors in primates (Nadjar *et al.*, 2006), as well as their associated neuropeptides, namely dynorphin and enkephalin respectively.

Dopaminergic cell loss in Parkinson's disease induces a supersensivity of D_1- and D_2-receptor subtypes in the striatum (Creese *et al.*, 1977; Lee *et al.*, 1978). Several autoradiographic studies have investigated DA receptor specific binding in parkinsonian and dyskinetic states in primates and in Parkinson's disease patients with no general

consensus. In fact, D_1 receptor binding was found to remain unchanged in L-DOPA-treated and untreated Parkinson's disease patients (Shinotoh *et al.*, 1993a; Shinotoh *et al.*, 1993b) and L-DOPA-naive MPTP monkeys (Alexander *et al.*, 1991; Aubert *et al.*, 2005; Calon *et al.*, 1995; Gagnon *et al.*, 1995; Goulet *et al.*, 1996a; Graham *et al.*, 1993; Guigoni *et al.*, 2005), but increased after L-DOPA treatment in the dorsal striatum of MPTP monkeys (Aubert *et al.*, 2005; Guigoni *et al.*, 2005; Rioux *et al.*, 1997) or remains unchanged (Alexander *et al.*, 1993; Calon *et al.*, 1995; Gagnon *et al.*, 1995). D_1 receptor binding was also negatively correlated with both duration of disease and L-DOPA treatment in Parkinson's disease patients, but failed to correlate with the motor disability (Turjanski *et al.*, 1997). D_1 mRNA levels are reported to be unaffected (Goulet *et al.*, 2000; Goulet *et al.*, 1997; Morissette *et al.*, 1996) or to be reduced after MPTP treatment in monkeys (Aubert *et al.*, 2005; Goulet *et al.*, 1997; Grondin *et al.*, 1999; Morissette *et al.*, 1996), and such decrease was corrected with L-DOPA (Aubert *et al.*, 2005; Morissette *et al.*, 1996).

On the other hand, striatal D_2 receptors show no change (Calon *et al.*, 1995; Gagnon *et al.*, 1995; Gnanalingham *et al.*, 1993; Goulet *et al.*, 1996b; Pifl *et al.*, 1992) or increase in MPTP monkeys (Alexander *et al.*, 1991; Alexander *et al.*, 1993; Aubert *et al.*, 2005; Falardeau *et al.*, 1988; Gagnon *et al.*, 1995; Gomez-Mancilla *et al.*, 1993; Graham *et al.*, 1993; Guigoni *et al.*, 2005; Todd *et al.*, 1996) and in untreated Parkinson's disease patients (Lee *et al.*, 1978; Turjanski *et al.*, 1997). Such elevation in D_2 receptors returned to normal values when treated with L-DOPA (Alexander *et al.*, 1993; Falardeau *et al.*, 1988; Graham *et al.*, 1993; Lee *et al.*, 1978). In other studies, D_2 receptors were decreased in the caudate nucleus of both dyskinetic and non-dyskinetic Parkinson's disease patients compared to controls, but levels of D_2 receptors were unchanged in the putamen (Brooks, 2000). It is worth noting that such changes observed are assumed to be on the long-form variant of D_2 receptors, since the presynaptic short-form of D_2 receptors would be absent with the nigrostriatal degeneration. D_2 receptors and its mRNA levels increased concomitantly in striatum with MPTP (Aubert *et al.*, 2005; Goulet *et al.*, 1997; Herrero *et al.*, 1996; Morissette *et al.*, 1996) and returned at control levels when L-DOPA was administered (Morissette *et al.*, 1996), but remains elevated in dyskinetic monkeys (Aubert *et al.*, 2005).
The STN is currently the target of choice for surgical alteration for patients refractive to medication or with disabling LID (Jourdain and Schechtmann, 2013). STN abnormal

activity in Parkinson's disease and during LID influences several structures of the basal ganglia, mainly the GPi, thus contributing to the already overinhibition of the thalamocortical relay originating from the direct pathway (Obeso *et al.*, 2008). Lesioning the STN is one of the options (Guridi *et al.*, 2012) in order to reestablish the overactive subthalamopallidal excitatory outflow observed in Parkinson's disease models (Bergman *et al.*, 1994).

We recently published results from MPTP monkeys with LID that received a unilateral chemical lesion of the STN (Jourdain *et al.*, 2013); these monkeys presented a better response and had a longer duration of response to low-doses of L-DOPA. These results were similar to those obtained in Parkinson's disease patients receiving a unilateral subthalamotomy (Alvarez *et al.*, 2009). When keeping the same L-DOPA daily dose after subthalamotomy, patients had a better motor response and spent more time "ON-medication", indicative of a beneficial effect on wearing-off (Alvarez *et al.*, 2001). In a two-year follow-up study, patients also had a better motor response to L-DOPA contralateral to surgery, specifically tremor that was almost completely abolished (Patel *et al.*, 2003). This potentiation of response to L-DOPA following subthalamotomy suggests an involvement of a dopaminergic component in this beneficial effect.

The aim of the present study was to investigate the possible changes of dopaminergic systems in the basal ganglia of STN-lesioned MPTP monkeys that we reported previously to have improved motor response to L-DOPA; they were compared to controls and vehicle-treated MPTP monkeys. D1 and D2 receptors as well as the DA transporter were investigated using radioligand receptor autoradiography. D1 and D2 receptor mRNAs levels, as well as the D1- and D2 receptor-associated neuropeptides, PPD and PPE respectively, were measured by *in situ* hybridization. Lastly, phosphorylations of striatal ERK1/2 and DARPP-32 were assayed by Western immunoblotting.

6.4 Material and Methods

Animals and drug treatments

Experiments were carried out using 12 female ovariectomized monkeys (*Macaca fascicularis*) (3.4-5.4 kg) in agreement with the standards of the Canadian Council on Animal Care. The Laval University committee for protection of animals approved this study. Four monkeys served as controls, eight monkeys were treated with systemic MPTP and developed a profound parkinsonian syndrome. All MPTP monkeys displayed similar baseline parkinsonian score. Four of these MPTP monkeys were treated with saline (saline-treated MPTP monkeys). The other four MPTP monkeys were chronically treated with L-DOPA/benserazide, developed LID and underwent unilateral subthalamotomy (STN-lesioned MPTP monkeys) by stereotactic injection of ibotenic acid. The behavioral assessment of these monkeys was previously reported (Jourdain *et al.*, 2013). The STN-lesioned MPTP monkeys were killed 24 h after their last L-DOPA/benserazide treatment.

Tissue preparation

At the end of treatments, all monkeys were killed by an overdose of pentobarbital. Brains were flash-frozen in isopentane (-45°C). Brains were cut into coronal sections of 12 µm on a cryostat (-18°C) at levels corresponding approximately to A15.5, according to the atlas of Szabo and Cowan (Szabo and Cowan, 1984). Sections were mounted onto Super Frost Plus (Fisher, Canada) slides and stored at -80°C until assayed.

High-performance liquid chromatography

The concentration of DA and its metabolites, DOPAC and HVA, were measured by high-performance liquid chromatography with electrochemical detection, according to previously published procedures (Morissette *et al.*, 2006).

Dopamine transporter autoradiography

Dopamine transporter (DAT) specific binding was evaluated with [125I]-RTI-121 (3β-(4-[^{125}I]-iodophenyl)-tropane-2-carboxylic acid isopropylester) (Perkin-Elmer, Boston, MA; 2200 Ci/mmol) according to a previously published procedure (Calon *et al.*, 2001). The slide-mounted tissue sections were exposed to [3H]-sensitive films (BIOMAX MR

Film, Kodak) along with standards ([125I]-microscales, Amersham) for 72 h.

Dopamine receptors specific binding

D_1 and D_2 receptors were labeled using the radioligands [^{3}H]-SCH-23390 (86.0 Ci/mmol; PerkinElmer, Boston, USA) and [^{3}H]-Raclopride (74.4 Ci/mmol; PerkinElmer), respectively (Grondin *et al.*, 1999; Landry *et al.*, 2002). Tissue sections for D_1 receptor specific binding were preincubated 15 minutes in PBS, whereas those for D_2 receptor specific binding were preincubated for 30 min at room temperature in a Tris[hydroxymethyl]aminomethane buffer solution (50 mM Tris-HCl, 120 mM NaCl, 5 mM KCl, 1.5 mM CaCl2, 4 mM $MgCl_2$, pH 7.4). Sections were then incubated for 60 min at room temperature in their respective buffer containing either 1 nM [^{3}H]-SCH 23390 and 50 nM ketanserine (to block 5-HT2A receptors) or 3 nM [^{3}H]-Raclopride. Nonspecific binding was defined in the presence of SKF-38393 1 μM and (+)-butaclamol 1 μM for D_1 and D_2 receptors respectively. After two 5-min washes at room temperature in buffer, sections were then rinsed briefly (10 sec) in ice-cold distilled water. Finally, the slide-mounted tissue sections were dried overnight at room temperature and were exposed to [^{3}H]-sensitive films (BIOMAX MR Film) along with standards ([^{3}H]-microscales, GE Healthcare) for 14 days at room temperature. Films were developed and autoradiograms analyzed by densitometry.

Generation of radioactive probes D_1 receptor, D_2 receptor and PPE

Complementary DNA oligonucleotide probes corresponding to bases 2341-2391, 1517-1564 and 464–511 of the human sequence of cloned D_1 receptors, D_2 receptors and PPE cDNA respectively were labeled at the 3'-end by deoxynucleotidyltransferase with a [^{33}P]-ATP (3000 Ci/mmol; Perkin-Elmer) using a DNA tailing kit (GE Healthcare, Baie d'Urfé, Quebec, Canada). The percentage of homologies between the human and the monkey cDNA sequences used to generate the radioactive probes for D_1 receptor, D_2 receptor, and PPE are 100% (GenBank accession no. NM_000794.3, NM_000795.3 and AF512368, for D_1, D_2 and PPE respectively). The reaction was carried out at 37 °C for 30 min, and the labeled oligonucleotide was purified on a QIAquick Nucleotide removal Kit (QIAGEN Inc., Mississauga, ON, Canada).

Preprodynorphin (PPD)

A 397 bp human dynorphin fragment directed against bases 581–977 of cDNA hPro-DYN was subcloned into pCR II TOPO plasmid and served as template to generate radioactive dynorphin riboprobe. The plasmid containing the dynorphin cDNA insert was linearized with Xho I. Antisens-strand RNA probe was labeled with Uridine 50-[α-^{35}S] thiotriphosphate (PerkinElmer) and prepared by *in vitro* transcription of linearized template with SP6 polymerase using the riboprobe Gemini System II (promega). The percentage of homologies between the human and the monkey cDNA sequences used to generate the radioactive probe PPD was 95% (GenBank accession no. X54466).

In situ hybridization histochemistry

Sections were treated according to a previously published procedure (Tamim *et al.*, 2010). For D_1 receptor, D_2 receptor and PPE *in situ* hybridization, the [33P]-labeled oligonucleotide probe was added in hybridization buffer to reach a concentration of $1x10^7$ cpm/ml, whereas [^{35}S]-labeled RNA probe was added for PPD *in situ* hybridization. Slide-mounted tissue sections were exposed to Kodak BIOMAX MR film for 10, 11, 12 and 14 days (for PPE, D_1, PPD and D_2 receptor mRNAs respectively) at room temperature. Films were developed and autoradiograms analyzed by densitometry.

Western Blotting

Small frozen tissue pieces of coronal sections were treated according to a previously published procedure (Morissette *et al.*, 2010). Antibodies against p44 MAP Kinase (ERK1) and p42 MAP Kinase (ERK2) were obtained from R&D Systems, Inc. (Minneapolis, MN), pERK1/2 and DARPP-32 were obtained from Cell Signaling Technology (Beverly, MA) and βIII-tubulin antibody from Chemicon International, Inc., (Temecula, CA) and was used as a loading control.

After incubation with the primary antibody, membranes were washed with PBS-Tween and incubated with horseradish peroxidase-coupled secondary antibodies (Cell Signaling Technology, Beverley, MA: diluted 1:5000). Immunoreactive bands were detected using an enhanced chemiluminescence system (LumiGLO Reserve, KPL,

Gaithersburg, USA). The exposed membranes were analyzed using an Alpha Innotech FluorChem Q MultiImage III camera. Bands were semi-quantitatively analyzed through scanning with the Alpha Innotech-Alpha View image acquisition and analysis software version 3.1.1.0 (Alpha Innotech Corporation, Copyrights 1993–2009). All individual band densities were normalized with respect to their internal control βIII-tubulin values in order to express arbitrary units of relative kinase abundance. Experiments were repeated 3–4 times. For analysis of results, phosphorylated protein levels were normalized to their respective non-phosphorylated protein form.

Data analysis

Intensity of autoradiographic and hybridization labeling was quantified on X-ray films by a Power Macintosh G4 connected to a video camera (XC-77; Sony) and a constant illumination light table using computerized densitometry (NIH ImageJ 64-bit mode, v.1.46). The signal was measured as the optical density for the caudate nucleus, the putamen and the pallidal complex and corrected for non-specific binding for each experiment. Subsequently, optical gray densities were transformed into nanocuries per mg of tissue equivalent using a standard curve generated with [^{3}H] or [^{125}I]-standards, respectively. Results were then converted into femtomoles per mg of tissue using specific activity of the radioligands. Statistical comparisons of data were performed by a 2-way ANOVA (pharmacological and surgical treatments) mixed model using paired and non-paired values with an animal random effect, followed by post hoc pairwise comparisons of least squares means test. A 2-way ANOVA was used to analyse the interactions between the brain subdivisions and the treatments. A two-tailed paired Student t-test was used for individual comparisons of Western immunoblotting results. Analyses were conducted using SAS software, version 9.3. A p value of ≤ 0.05 was considered significant.

6.5 Results

Changes in motor behaviour

Behavioural measurement of these monkeys receiving a unilateral subthalamotomy was previously reported (Jourdain *et al.*, 2013). Briefly, lesioning the STN lowered the parkinsonian scores of all animals when receiving three different doses of L-DOPA tested (suboptimal, optimal and dyskinesia-inducing doses) as well as when injected with the vehicle. The parkinsonian disability scores were similarly reduced, indicating that the behavioral response to L-DOPA benefited from subthalamotomy at any concentration of L-DOPA. LID were increased following subthalamotomy in the suboptimal and optimal doses of L-DOPA and remained unchanged in the dyskinesia-inducing dose. Although they increased, LID remained not disabling in the suboptimal dose of L-DOPA. The duration of the L-DOPA antiparkinsonian response was also increased (20-25%) after subthalamotomy.

Effect of MPTP, L-DOPA and subthalamotomy on DA receptors expression and synthesis

Fig. 1 shows representative autoradiograms of D_1 and D_2 receptors, their respective mRNAs, as well as PPE and PPD mRNAs in the post-commissural striatum of the MPTP monkeys that received a unilateral subthalamotomy to alleviate their LID.

Effect of MPTP, L-DOPA and subthalamotomy on DA and metabolites concentrations and DAT

In the post-commissural striatum, MPTP induced an extensive decrease of [^{125}I] RTI-121 specific binding in the caudate nucleus (average: 90%; $F_{3,12} = 76.2$, $p < 0.0001$) and putamen (average: 93%; $F_{3,12} = 103.2$, $p < 0.0001$) of all MPTP monkeys in comparison to control animals. MPTP lesioning resulted in a marked depletion of putaminal and caudate nucleus DA concentrations in all MPTP monkeys with an average decrease of 99.7% compared to controls (putamen: $F_{3,12} = 557.9$, $p < 0.0001$; caudate nucleus: $F_{3,12} = 245.5$, $p < 0.0001$). The striatal DA metabolites (DOPAC and HVA) were also decreased extensively with an average decrease over 85% (putamen: DOPAC: $F_{3,12} = 362.9$, $p < 0.0001$; HVA: $F_{3,12} = 18.5$, $p = 0.001$; caudate nucleus: DOPAC: $F_{3,12} = 8.15$, $p < 0.01$; HVA: $F_{3,12} = 90.4$, $p < 0.0001$). There was no difference in DAT, DA, its metabolites induced by the

subthalamotomy.

Subthalamotomy increases D_1 receptor binding and mRNA levels

D1 receptor specific binding decreased in all subdivisions of the caudate nucleus (Figure 2A) in saline-treated MPTP monkeys (DL: 21%; DM: 24%; VL: 27%; VM: 33%) compared to controls. Contralateral to subthalamotomy, STN-lesioned MPTP monkeys had generally decreased caudate nucleus D_1 receptor specific binding. On the other hand, this was less or not significant for the ipsilateral caudate nucleus, subthalamotomy correcting the MPTP and L-DOPA-induced decreases.

D_1 receptor specific binding decreased in the putamen (DL: 17%; DM: 27%; VL: 23%; VM: 12%) in vehicle-treated MPTP monkeys compared to controls (Figure 2B). In STN-lesioned MPTP monkeys with LID, contralateral to subthalamotomy a further decrease of the D_1 receptor specific binding was observed in all subdivisions of the putamen compared to controls (DL: 43%; DM: 27%; VL: 34%; VM: 37%) and compared to vehicle-treated MPTP monkeys (DL: 31%; VM: 29%). Subthalamotomy partly corrected the dorsolateral decrease in putaminal D_1 receptor specific binding induced by L-DOPA and MPTP. In the dorsolateral putamen, D_1 receptor specific binding ipsilateral to the STN lesion was higher than its contralateral side.

In the GPe, no D_1 receptor specific binding was detected (Figure 2C), but its mRNA was clearly observed (Figure 1).

Striatal D_1 receptor mRNA levels were unchanged in vehicle-treated MPTP monkeys compared to controls (Figure 2D and E). In the caudate nucleus, D_1 receptor mRNA levels remained unchanged for all experimental groups (Figure 2D). In the ventrolateral putamen of the STN-lesioned MPTP monkeys D_1 receptor mRNA levels were decreased compared to vehicle-treated MPTP monkeys in the contralateral side. Ipsilateral to subthalamotomy, D_1 receptor mRNA levels increased significantly compared to vehicle-treated MPTP monkeys dorsolaterally (47%) in the putamen and compared to the contralateral side of the brain (DL: 56%; DM: 29%; VL: 36%; VM: 23%).

In the GPe, D_1 receptor mRNA was unchanged in vehicle-treated MPTP monkeys compared to controls (Figure 2F) but highly increased in the STN-lesioned MPTP monkeys contralateral to the STN lesion, and further increased ipsilaterally, compared to controls

(100 and 151% for contra- and ipsilateral respectively) and vehicle-treated MPTP monkeys (122 and 178% for contra- and ipsilateral respectively).

In the GPi, D_1 receptor specific binding and its mRNA levels were unchanged in vehicle-treated MPTP monkeys compared to controls (Figure 2C and 2F). In the STN-lesioned MPTP monkeys, D_1 receptor mRNA levels showed an opposite pattern than the corresponding D_1 receptor specific binding. In fact, D_1 receptor specific binding decreased compared to controls (46 and 47% for contra- and ipsilateral respectively) and vehicle-treated MPTP monkeys (40 and 41% for contra- and ipsilateral respectively), whereas its mRNA increased compared to controls (107 and 151% for contra- and ipsilateral respectively) and vehicle-treated MPTP monkeys (115 and 160% for contra- and ipsilateral respectively).

D_2 receptor binding and mRNA levels are unaffected by MPTP, L-DOPA and subthalamotomy

By contrast to D_1 receptors, in all subregions of the caudate nucleus and putamen no significant changes of D_2 receptor specific binding or D_2 receptor mRNA was observed for all the experimental groups analyzed (Figure 3A-D). No [^{3}H]-Raclopride specific binding or D_2 receptor mRNA levels was detected in the globus pallidus.

Effect of MPTP, L-DOPA and subthalamotomy on neuropeptide expression

In vehicle-treated MPTP monkeys, highly increased PPE mRNA levels (Figure 4) were observed in all parts of the caudate nucleus (DL: 73%; DM: 40%; VL: 71%) and putamen (DL: 165%; DM: 85%; VL: 95%) compared to controls, except for the ventromedial striatum. Compared to controls, the STN-lesioned MPTP monkeys also had increased PPE mRNA levels in the lateral caudate nucleus (DL: 58 and 52%; VL: 47 and 48% for contra- and ipsilateral, respectively) and the putamen (DL: 72 and 82%; DM: 58 and 68%; VL: 49 and 59% for contra- and ipsilateral, respectively). When compared to vehicle-treated MPTP monkeys, PPE mRNA levels decreased in the dorsolateral putamen (35 and 31% for contra- and ipsilateral, respectively) and ventrolateral putamen contralateral to subthalamotomy (23%). PPE mRNA was not detected in the GPe or GPi.

Vehicle-treated MPTP monkeys showed no change of PPD mRNA levels in all parts

of the caudate nucleus and of the putamen, compared to controls (Figure 5). On the contrary, STN-lesioned MPTP monkeys had increased PPD mRNA levels compared to controls in the dorsolateral caudate nucleus (DL: 64 and 74% for contra- and ipsilateral, respectively) and dorsal putamen (DL: 43 and 26%; DM: 38 and 31% for contra- and ipsilateral, respectively). When compared to vehicle-treated MPTP monkeys, PPD mRNA levels increased in caudate nucleus (DL: 123 and 136%; DM: 76 and 82%; VL: 115 and 128%; VM: 88 and 81% for contra- and ipsilateral, respectively) and putamen (DL: 78 and 57%; DM: 82 and 73%; VL: 60 and 74%; VM: 52 and 57% for contra- and ipsilateral, respectively). Subthalamotomy induced an ipsilateral decrease in PPD mRNA levels in the dorsolateral putamen compared to the unlesioned contralateral DL putamen.

In the GPe and GPi, no significant change of PPD mRNA levels was observed between the experimental groups (data not shown).

Effect of MPTP, L-DOPA and subthalamotomy on intracellular signalling

In the caudate nucleus and putamen, the levels in the phosphorylated state of ERK1, ERK2 as well as the ratio phosphorylated/non-phosphorylated proteins were similar ipsilateral compared to contralateral to subthalamotomy (data not shown). Unfortunately, quantification of phosphorylated DARPP-32 was not possible in our animals. Levels of DARPP-32 in the caudate nucleus contralateral to subthalamotomy were increased by 19% ($p < 0.05$) and decreased by 7% in the putamen ($p > 0.05$) compared to the non-lesioned side.

6.6 Discussion

The present study used dyskinetic MPTP monkeys to investigate the modulation of basal ganglia DA receptors following a unilateral subthalamotomy. Our data suggest that D_1 receptors participate in the potentiation of response to L-DOPA after subthalamotomy since its striatal dorsolateral expression and synthesis increased ipsilaterally to the STN lesion compared to the contralateral side (present results are summarized in Table 1). On the other hand, D_2 receptors remained unchanged in all groups investigated. Furthermore, we provide evidence that the improvement in motor response to L-DOPA after surgery is not caused by pre-synaptic modifications, since no change in the expression of DAT or in DA and its metabolites was observed. Finally, D_1- and D_2-associated neuropeptides followed the expected pattern after MPTP and L-DOPA treatments. PPD mRNA levels were decreased in the dorsolateral putamen ipsilateral to subthalamotomy. Together, these data suggest that the potentiation of response to L-DOPA after subthalamotomy is post-synaptically D_1-related, most likely occurring in the striatofugal neurons of the direct pathway. To our knowledge, this is the first investigation of DA receptors in primates with a STN lesion.

DA neurotransmission

MPTP decreased extensively striatal DA concentration in all MPTP monkeys used in this study. These results corroborate those previously published, where similar doses of MPTP (<16 mg) resulted in near complete DA depletion (Samadi *et al.*, 2008). Unilateral subthalamotomy, on the other hand, induced no change in ipsilateral baseline DA and its metabolites compared to contralateral side in our MPTP monkeys.

Conclusions on DA neurotransmission from surgical alteration of the STN in animal models of Parkinson's disease are not very consistent. Subthalamotomy increased DA and DOPAC in normal and 6-OHDA hemiparkinsonian rats (Hwang *et al.*, 2006), while others found a decrease in DA and its two metabolites in 6-OHDA rats (Walker *et al.*, 2009). In partially-denervated hemiparkinsonian rats, DA release remained unchanged with STN-HFS (Lacombe *et al.*, 2007) or increased bilaterally (Bruet *et al.*, 2001). On the contrary, DA was decreased whereas DOPAC and HVA were increased by STN-HFS in full hemiparkinsonian rats, suggesting an elevated DA turnover (Meissner *et al.*, 2002). In

hemiparkinsonian MPTP monkey, unilateral subthalamic HFS also increased striatal DA ipsilateral to stimulation, both in short and long-term stimulation (Zhao *et al.*, 2009). On the other hand, no change was observed contralaterally (Zhao *et al.*, 2009). Studies in Parkinson's disease patients however failed to observe any changes in DA release with DBS when measured by PET (Abosch *et al.*, 2003; Hilker *et al.*, 2003; Nimura *et al.*, 2005; Strafella *et al.*, 2003).

DAT

In Parkinson's disease, there is a neuronal loss of the presynaptic cells of the nigrostriatal pathway. DAT is expressed presynaptically in dopaminergic neurons that degenerate in Parkinson's disease. The loss of DAT can be detected before the clinical symptoms (Marek *et al.*, 1996) and its binding is correlated with the severity of the disease (Booij *et al.*, 1997). In the present study, DAT binding was reduced by >90% compared to controls, indicating a severe denervation. Such decreases are similar to those measured previously in our group (Calon *et al.*, 2001), in other groups working with MPTP monkeys (Bezard *et al.*, 2001; Quik *et al.*, 2013), as well as measured in Parkinson's disease patients (Booij *et al.*, 1997). To our knowledge, there are no studies regarding the effect of subthalamotomy on DAT specific binding. Our results show that STN lesion had no effect. This is not surprising since presynaptic cells were exposed to MPTP many years before subthalamotomy and a neuroprotective effect on the SNc cells, as measured by the expression of DAT, is thus hardly conceivable. Two studies in Parkinson's disease patients receiving subthalamic DBS measured DAT by single-photon emission computed tomography (Hesse *et al.*, 2008; Lokkegaard *et al.*, 2007). Both studies observed no difference induced by STN-DBS when compared to an age-matched group of Parkinson's disease controls (Lokkegaard *et al.*, 2007) or to their respective preoperative values (Hesse *et al.*, 2008).

D_1 receptors

D_1 receptors are present in the striatopallidal system forming the direct pathway (Albin *et al.*, 1989). D_1 receptors are reported to remain unchanged after exposure to MPTP in the pre-commissural striatum (Alexander *et al.*, 1991; Aubert *et al.*, 2005; Calon *et al.*,

1995; Gagnon *et al.*, 1995; Goulet *et al.*, 1996a; Graham *et al.*, 1993; Guigoni *et al.*, 2005) and to increase with L-DOPA (Aubert *et al.*, 2005; Guigoni *et al.*, 2005; Rioux *et al.*, 1997). In the present study, we observed significant decreases in the post-commissural D_1 specific binding after MPTP in all subdivisions of the striatum. Consistent with our results, striatal density of D_1-immunoreactive spines was shown to decrease in MPTP-treated monkeys (Villalba *et al.*, 2009). The D_1 receptor specific binding was further decreased in the STN-lesioned MPTP monkeys in the dorsolateral putamen contralateral to subthalamotomy, whereas it remained unchanged compared to D_1 specific binding in vehicle-treated MPTP monkeys in the caudate nucleus. On the other hand, subthalamotomy corrected the MPTP and L-DOPA-induced decreases in the dorsolateral putamen and the decreases in most subdivisions of the caudate nucleus. Such subthalamotomy-induced increases in the D_1 receptor in the dorsolateral putamen were associated with an increase in D_1 receptor mRNA levels. The dorsolateral putamen receives the largest midbrain projections (Haber, 2003; Lynd-Balta and Haber, 1994) and is the most susceptible region to degeneration in the first stages of Parkinson's disease and in monkeys exposed to MPTP (Parent *et al.*, 1995). It is also worth noting the similar pattern of changes between the D_1 receptor binding and D_1 mRNA levels in the putamen and the caudate nucleus.

Both compartments of the globus pallidus are innervated by dopaminergic cells of the SNc (Lavoie *et al.*, 1989) and arise from a distinct population that projects to the striatum (Smith *et al.*, 1989). In the present study, D_1 receptor levels were probably too low to be detected in the GPe by autoradiography, despite the presence of D_1 receptor mRNA measured in this structure. This nigropallidal pathway was unaffected by MPTP in the present study, a sparing previously reported (Parent *et al.*, 1990), and decreased significantly in STN-lesioned MPTP monkeys. The exact role of this nigropallidal pathway has not yet been established, though some data suggest a compensatory role in the early stages of Parkinson's disease (Whone *et al.*, 2003). Whether the decrease in D_1 receptors after L-DOPA is due to rapid desensitization after their stimulation (Blanchet *et al.*, 1996) or it participates in LID remains to be addressed.

D_2 receptors

D_2 receptors are present in the striatofugal system forming the indirect pathway,

comprising the GPe and STN (Albin *et al.*, 1989). Postsynaptic D_2 receptors are elevated in the striatum of MPTP monkeys and untreated Parkinson's disease patients compared to controls when measured by autoradiography (Alexander *et al.*, 1991; Alexander *et al.*, 1993; Aubert *et al.*, 2005; Falardeau *et al.*, 1988; Gagnon *et al.*, 1995; Gomez-Mancilla *et al.*, 1993; Graham *et al.*, 1993; Guigoni *et al.*, 2005; Lee *et al.*, 1978; Todd *et al.*, 1996) or PET (Antonini *et al.*, 1997; Turjanski *et al.*, 1997). Such increases are reversed by the administration of L-DOPA (Alexander *et al.*, 1993; Brooks *et al.*, 1992; Falardeau *et al.*, 1988; Graham *et al.*, 1993; Lee *et al.*, 1978). D_2 receptor mRNA levels follow a pattern closely similar to its receptor protein after MPTP and L-DOPA treatments (Aubert *et al.*, 2005; Goulet *et al.*, 1997; Morissette *et al.*, 1996). We observed no change of D_2 receptor specific binding and mRNA levels in the monkeys of the present study. In patients with disabling LID, the L-DOPA-induced elevation of striatal D_2 receptors, as measured by PET, was corrected by either posteroventral pallidotomy or pallidal DBS, returning to values obtained from healthy volunteers of similar age (Nakajima *et al.*, 2003). Moreover, LID-induced reduction of thalamic D_2 receptors were also corrected by surgery in the GPi (Nakajima *et al.*, 2003). On the other hand, STN-DBS exerted no modifications in striatal D_2 binding in Parkinson's disease patients (Thobois *et al.*, 2003). The results of this study suggest that MPTP, L-DOPA and unilateral subthalamotomy do not impair the D_2 receptors and its mRNA.

Neuropeptides expression in Parkinson's disease and LID

The striatal expression of the neuropeptide enkephalin is altered in Parkinson's disease and correlates with changes in neuronal activity within the indirect pathway. Striatal PPE mRNA levels are increased in monkeys treated with MPTP (Asselin *et al.*, 1994; Augood *et al.*, 1989; Morissette *et al.*, 2006; Morissette *et al.*, 1997; Morissette *et al.*, 1999), as well as in Parkinson's disease patients (Calon *et al.*, 2002; Nisbet *et al.*, 1995). These elevated striatal PPE mRNA levels remain high (Herrero *et al.*, 1995; Jolkkonen *et al.*, 1995; Morissette *et al.*, 1997) or are increased further with the administration of L-DOPA compared to vehicle-treated MPTP monkeys (Morissette *et al.*, 2006; Tamim *et al.*, 2010). In 6-OHDA rats, STN lesions either reversed the increased levels of PPE mRNA levels (Bacci *et al.*, 2004) or had no effect (Delfs *et al.*, 1995). In 6-OHDA rats receiving L-

DOPA, subthalamotomy reversed the overexpression of PPE mRNA levels (Périer *et al.*, 2003) whereas STN-DBS had no effect (Salin *et al.*, 2002). In the present study, we observed elevated levels of striatal PPE mRNA in vehicle-treated MPTP monkeys, as well as the STN-lesioned MPTP monkeys compared to controls. There was a significant bilateral reduction between the vehicle-treated MPTP monkeys and the STN-lesioned MPTP monkeys in the dorsolateral putamen. This decrease in PPE mRNA in the motor putamen may result from subthalamotomy and participate in its bilateral behavioral benefits (Jourdain *et al.*, 2013).

The direct pathway-related neuropeptide dynorphin changes differently than the indirect pathway-related enkephalin (Gerfen *et al.*, 1991) and the overexpression in striatal PPD mRNA levels have been associated with LID (Cenci *et al.*, 1998; Henry *et al.*, 2003). Striatal PPD mRNA levels decreased in MPTP treated monkeys, but increased when L-DOPA is administered (Tamim *et al.*, 2010; Tel *et al.*, 2002). We obtained concordant results in the present study. PPD mRNA levels were reduced in the dorsolateral putamen ipsilateral to subthalamotomy compared to the contralateral unoperated side, but were still higher than controls and vehicle-treated MPTP monkeys. This partial reduction in PPD mRNA levels after subthalamotomy could be associated with the regulation in D_1 receptors ipsilateral to STN lesion. In 6-OHDA rats treated with L-DOPA, the addition of STN-HFS further increased the L-DOPA-inducing elevation of PPD mRNA levels, whereas in L-DOPA–naive hemiparkinsonian rats STN-HFS had no effect (Lacombe *et al.*, 2009; Oueslati *et al.*, 2007). Taken together, the results from neuropeptide studies (PPD and PPE mRNA) provide further evidence that STN lesion and stimulation act through different mechanisms.

Intracellular signalling

Non-canonical ERK1/2 and canonical DARPP-32 signalling cascades are among the marked changes in LID, which are D1-mediated (Aubert *et al.*, 2005; Pavon *et al.*, 2006; Santini *et al.*, 2007). We therefore restricted our measures to their striatal levels in the four dyskinetic animals to compare the effects of subthalamotomy. We found no change in the phosphorylation of ERK1/2 and in their unactivated states. Since the monkeys used in the present study were killed 24 hours after their last dose of L-DOPA, the changes in the

intracellular signalling might have subsided. Indeed, after administration of dopaminergic drugs, phosphorylation of ERK1/2 peaks and returns to baseline values within the hour after administration (Valjent *et al.*, 2000). Therefore, it is not surprising that we did not observe changes in this pathway 24 hours post-L-DOPA. Subthalamotomy re-established the pDARPP-32/DARPP-32 in dyskinetic 6-OHDA rats (Aristieta *et al.*, 2012). Unfortunately, our animal paradigm (with the euthanasia and delays in dissection) did not allow the measurement of the unstable pDARPP-32, thus such prevention in the phosphorylation of DARPP-32 could not be assessed in the present study. However, we found increases in caudate nucleus DARPP-32 levels ipsilateral to STN lesion compared to the unoperated side, but no change was found in the putamen. The role of such caudate nucleus increase in DARPP-32 ipsilateral to surgery remains to be addressed but may participate in the increase in behavioural response to low doses of L-DOPA. Phosphorylation of D_2-mediated intracellular pathways (Akt/GSK3β) were shown be increased in dyskinetic MPTP monkeys (Morissette *et al.*, 2010). Measurements of these pathways were not included in the present study since no change in D_2-related neurotransmission was found.

Proposed mechanism of action

A direct connection from the STN to the dopaminergic cells of the SNc has been demonstrated by both retro- (Kanazawa *et al.*, 1976; Parent and Smith, 1987) and anterograde (Carpenter *et al.*, 1981; Nauta and Cole, 1978; Rinvik and Ottersen, 1993) tracing studies. Such subthalamonigral glutamate-enriched pathway may promote a sustained excitation of dopaminergic cells. Indeed, lesions in the STN reduce significantly the levels of burst firing in the SNc (Shimo and Wichmann, 2009; Smith and Grace, 1992). Such a decrease in dopaminergic activity results in decreased striatal DA in normal monkeys (Shimo and Wichmann, 2009). In DA-depleted basal ganglia, unilateral subthalamotomy would therefore create an imbalance between the contra- and ipsilateral sides of striatal DA-receiving neurons when L-DOPA is administered. In consequence, an upregulation in the expression of excitatory post-synaptic D_1 receptors could re-establish equilibrium between the two hemispheric striatum. Moreover, it is well established that D_1 receptors play an important role in LID (Aubert *et al.*, 2005; Darmopil *et al.*, 2009; Guigoni

et al., 2007). Thus, the increased LID observed after unilateral subthalamotomy in MPTP monkeys (Jourdain *et al.*, 2013) would be the result of a such recruitment in striatal D_1 receptors.

6.7 Conclusion

Unilateral subthalamotomy was reported to potentiate the response to low doses of L-DOPA in dyskinetic MPTP monkeys. DA receptors and neurotransmission were investigated in these dyskinetic MPTP monkeys. As expected, DA neurotransmission was extensively decreased by MPTP and remained unaffected by L-DOPA and subthalamotomy, providing supporting evidence that the changes observed are post-synaptic in the striatum. The increase of D_1 receptors and D_1 receptor mRNA in the dorsolateral putamen may be associated with the potentiation of response to L-DOPA after unilateral subthalamotomy, whereas D_2 receptors that remained unchanged likely were not involved. Though it was unaffected by MPTP, the nigropallidal D_1-pathway was changed with L-DOPA treatment and subthalamotomy, and may participate in LID. Potentiation of response to L-DOPA after subthalamotomy would therefore implicate post-synaptic D_1 receptors and would most likely occur in the striatofugal neurons of the direct pathway.

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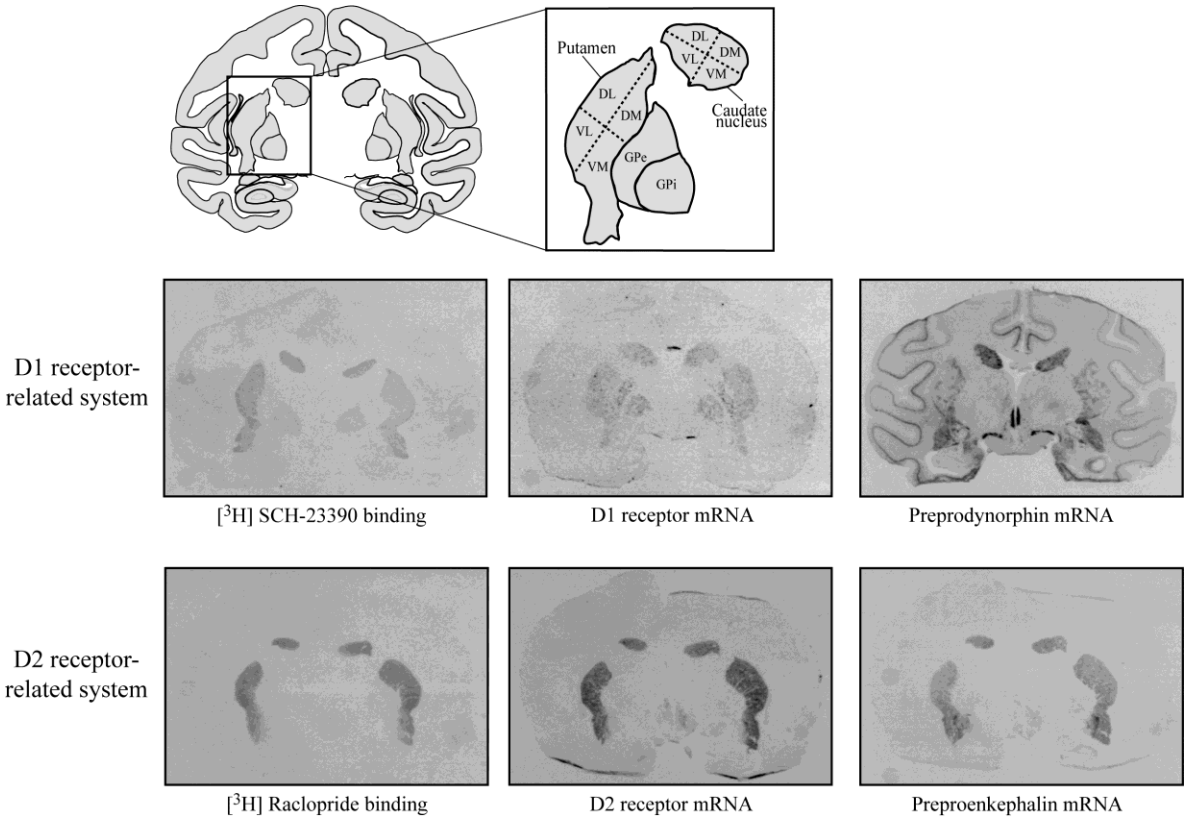

Figure 6.1**:** Representative autoradiograms of coronal brain sections showing D_1 and D_2 receptor binding, as well as D_1 receptor, D_2 receptor, PPE and PPD mRNAs levels in the post-commissural striatum of the MPTP treated monkeys that received a unilateral subthalamotomy to alleviate their LID with the schematic of the monkey brain (adapted from the atlas of (Martin and Bowden, 2000)). Subdivisions of the caudate nucleus and putamen dorsolateral (DL), dorsomedial (DM), ventrolateral (VL) and ventromedial (VM) subregions analyzed are shown.

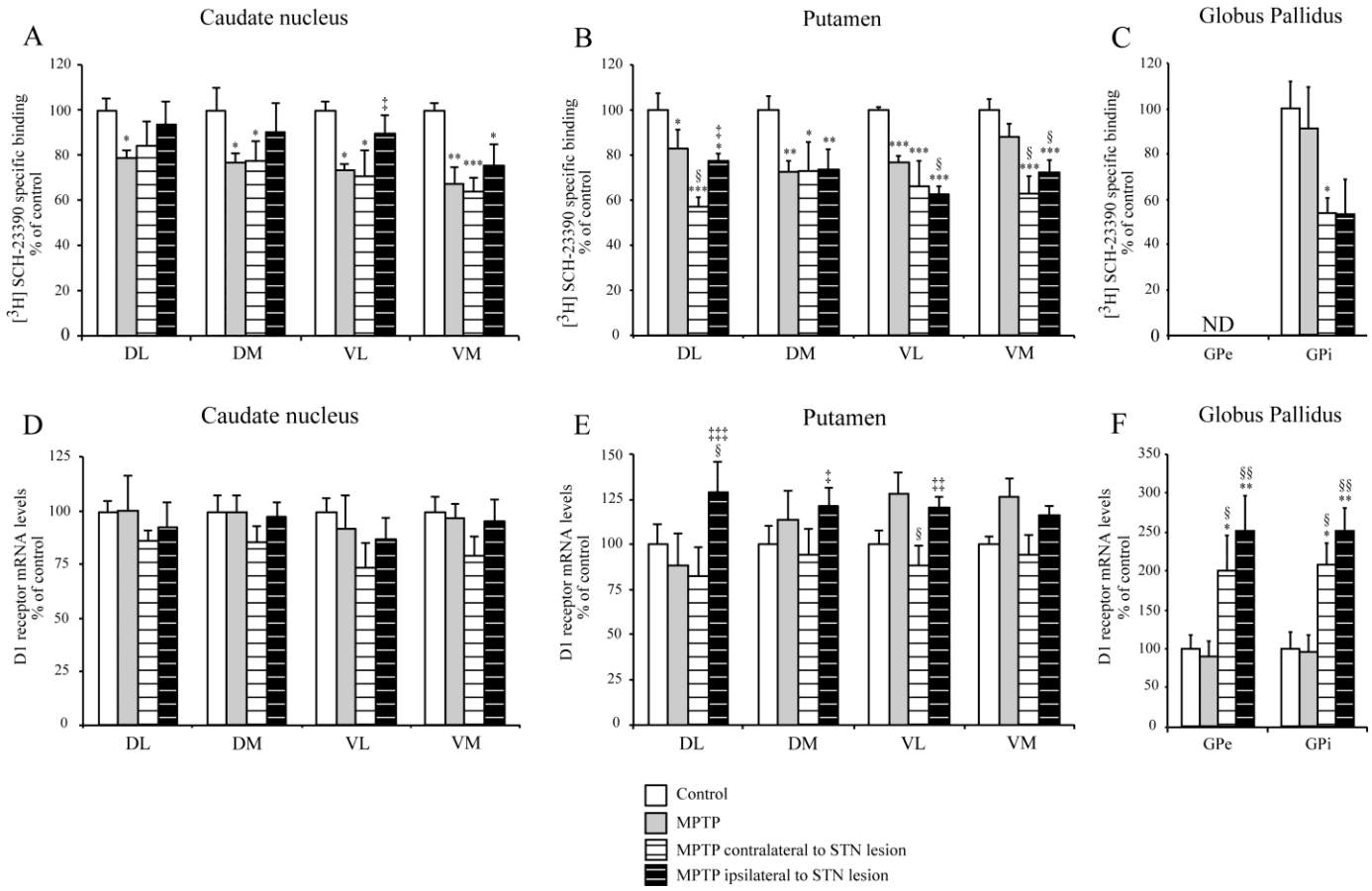

Figure 6.2 Effect of MPTP lesion, L-DOPA treatment and unilateral subthalamotomy on D_1 receptor specific binding in the caudate nucleus (A), putamen (B) and globus pallidus (C), as well as D_1 receptor mRNA levels in the caudate nucleus (D), putamen (E) and globus pallidus (F) of control, vehicle-treated MPTP monkeys and STN-lesioned MPTP monkeys. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs controls; § $p < 0.05$, §§ $p < 0.01$ vs vehicle-treated MPTP monkeys; ‡‡‡ $p < 0.0001$ vs contralateral to STN lesion.

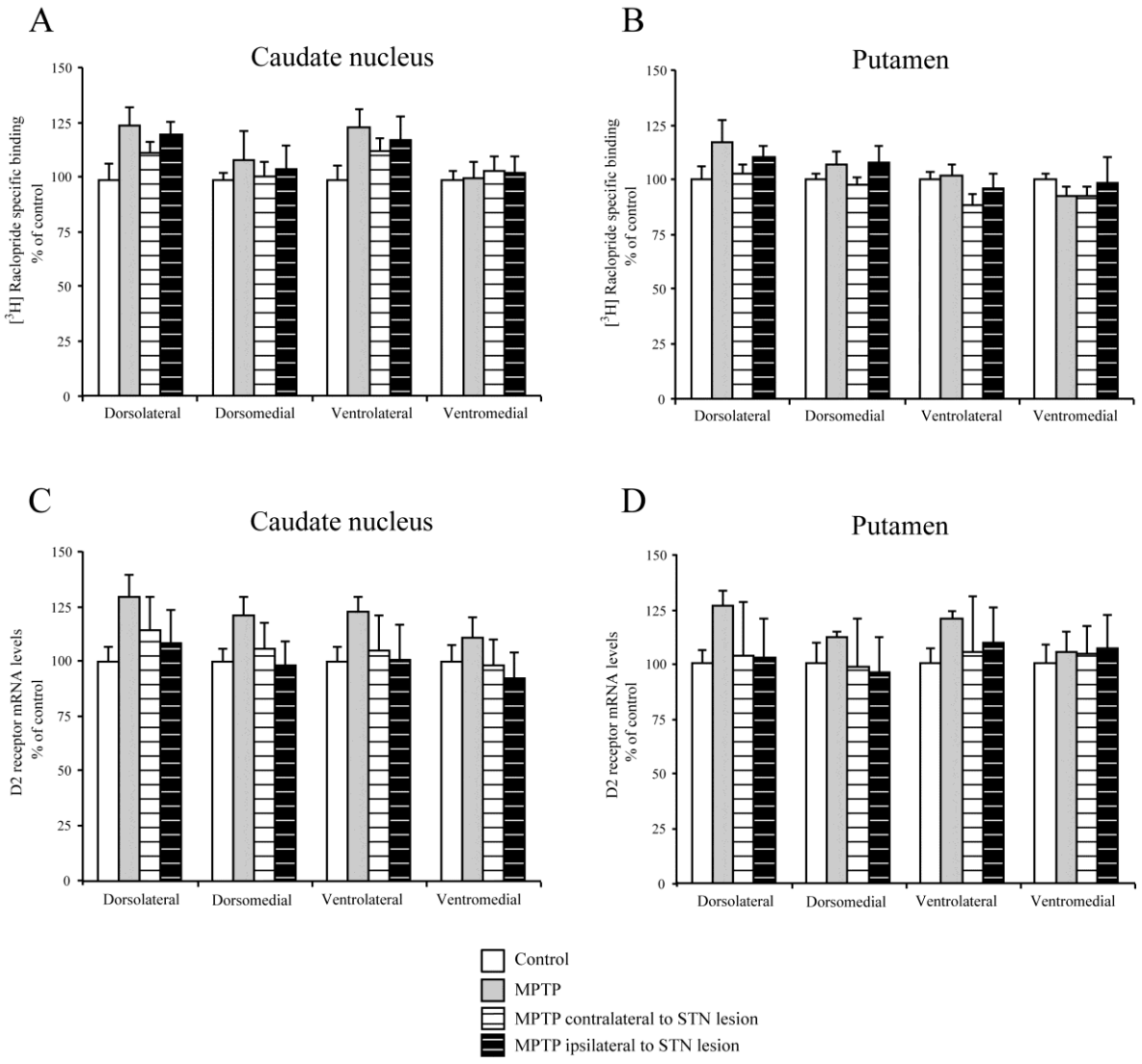

Figure 6.3 Effect of MPTP lesion, L-DOPA treatment and unilateral subthalamotomy on D_2 receptor specific binding in the caudate nucleus (A) and putamen (B), as well as D_2 receptor mRNA levels in the caudate nucleus (C) and putamen (D) of control, vehicle- treated MPTP monkeys and STN-lesioned MPTP monkeys.

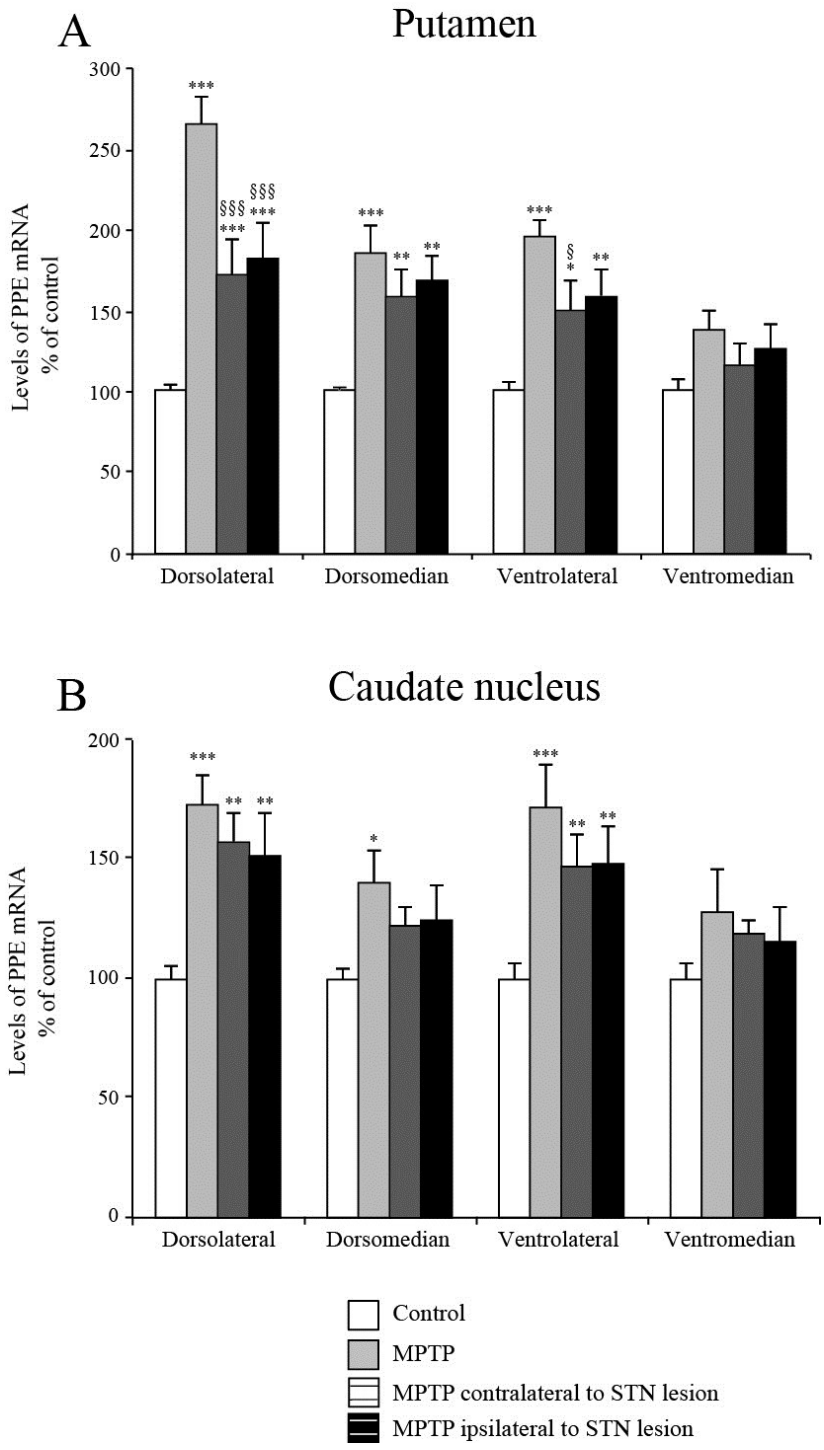

Figure 6.4 Effect of MPTP lesion, L-DOPA treatment and unilateral subthalamotomy on PPE mRNA levels in the caudate nucleus (A) and putamen (B) of control, vehicle-treated MPTP monkeys and STN-lesioned MPTP monkeys. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs controls; § $p < 0.05$, §§§ $p < 0.001$ vs vehicle-treated MPTP monkeys.

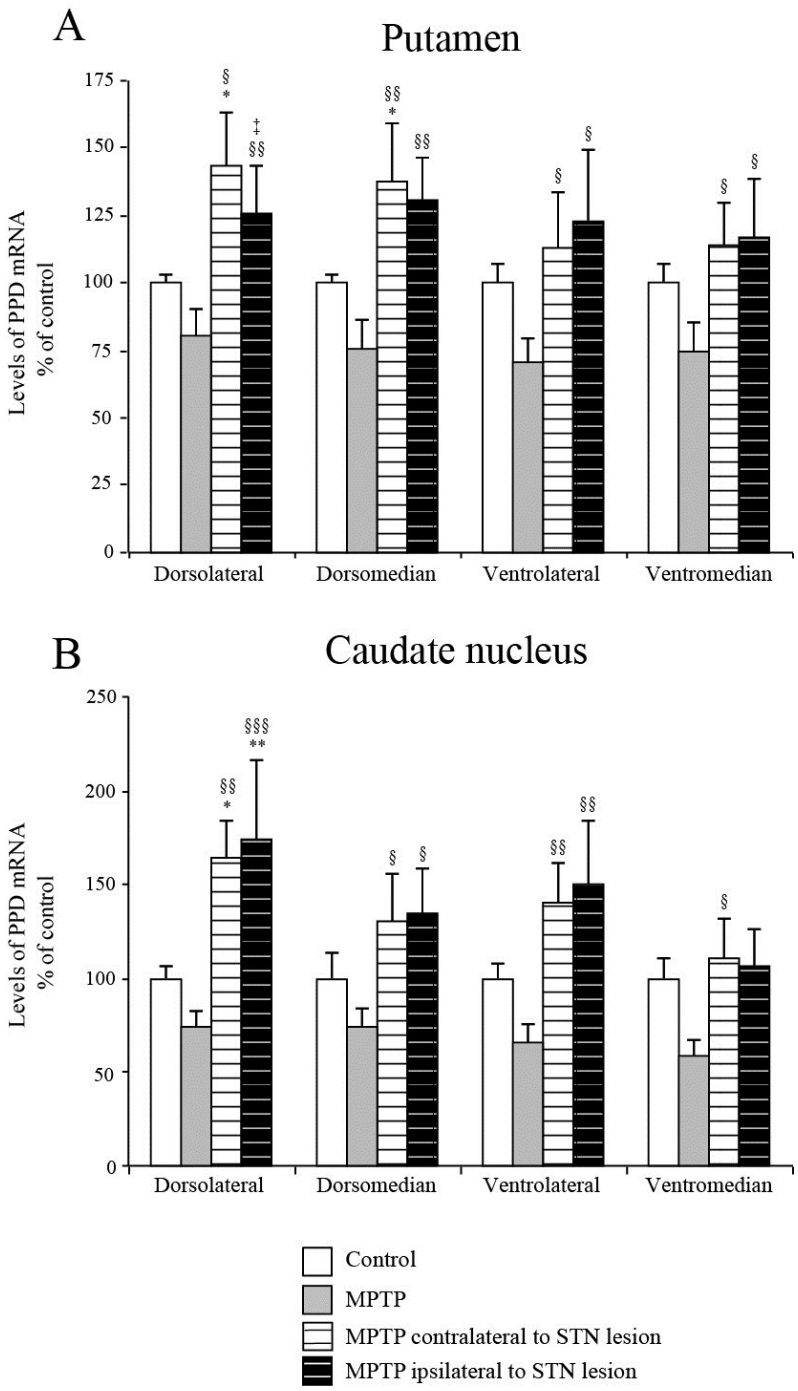

Figure 6.5 Effect of MPTP lesion, L-DOPA treatment and unilateral subthalamotomy on PPD mRNA synthesis in the caudate nucleus (A) and putamen (B) of control, vehicle-treated MPTP monkeys and STN-lesioned MPTP monkeys. * $p < 0.05$ vs controls; § $p < 0.05$, §§ $p < 0.01$, §§§ $p < 0.001$ vs vehicle-treated MPTP monkeys; ‡ $p < 0.05$ vs contralateral to STN lesion.

RECEPTOR/PEPTIDE brain region	TREATMENT					
	MPTP	MPTP + L-DOPA		MPTP + L-DOPA		
		contralateral to subthalamotomy		ipsilateral to subthalamotomy		
D1 receptor	**DL VL**	**DL**	**VL**	**DL**	**VL**	
Caudate nucleus	-	0,•	-,•	0,•, ⇔	0,•,⇑	
Putamen	-	-,↓	-,•	-,•,⇑	-,↓,⇔	
GPi	0	-, •		0,•,⇔		
GPe	ND	ND		ND		
D1 receptor mRNA						
Caudate nucleus	0	0,•		0,•,⇔		
Putamen	0	0,•	0,↓	0, ↑,⇑	0,•, ⇑	
GPi	0	+, ↑		+,↑,⇔		
GPe	0	+, ↑		+,↑,⇔		
D2 receptor						
Caudate nucleus	0	0,•		0,•,⇔		
Putamen	0	0,•		0,•,⇔		
GPi	ND	ND		ND		
GPe	ND	ND		ND		
D2 receptor mRNA						
Caudate nucleus	0	0,•		0,•,⇔		
Putamen	0	0,•		0,•,⇔		
GPi	ND	ND		ND		
GPe	ND	ND		ND		
PPE mRNA						
Caudate nucleus	+	+,•		+,•,⇔		
Putamen	+	+,↓		+,↓,⇔	+,•,⇔	
GPi	ND	ND		ND		
GPe	ND	ND		ND		
PPD mRNA						
Caudate nucleus	0	+,↑	0,↑	+,↑,⇔	0,↑,⇔	
Putamen	0	+,↑	0,↑	0,↑,⇓	0,↑,⇔	
GPi	0	0,•		0,•,⇔		
GPe	0	0,•		0,•,⇔		

0, -, +: No effect, decreased or increased vs. control monkeys;
•, ↓, ↑: no effect, lower or higher values vs. vehicle-treated MPTP monkeys;
⇔, ⇓, ⇑: no effect, lower or higher levels vs. contralateral side to subthalamotomy;
ND: not detected; if the same effect is observed in both subregions it is indicated only once.

Table 6.1 Summary of changes of dopamine receptors, their respective mRNAs and peptides mRNAs in the dorsolateral (DL) and ventrolateral (VL) motor striatum, external (GPe) and internal (GPi) globus pallidus of vehicle-treated MPTP monkeys and STN-lesioned MPTP monkeys with LID.

CHAPITRE 7. MODULATION OF GLUTAMATE RECEPTORS IN DYSKINETIC MPTP MONKEYS RECEIVING A UNILATERAL SUBTHALAMOTOMY

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Keywords: Subthalamotomy, levodopa-induced dyskinesia, MPTP monkey, Parkinson's disease, L-DOPA, glutamate receptors

7.1 Résumé

La subthalamotomie unilatérale est une option chirurgicale pour alléger les dyskinésies induites à la L-DOPA (LID) chez les patients parkinsoniens dont les mécanismes sont largement inconnus. Les mécanismes impliqués demeurent largement inconnus. Le noyau sous-thalamique est la seule structure glutamatergique dans les ganglions de la base et sa lésion exercerait des changements dans l'expression des récepteurs glutamatergiques. Dans cette étude, nous avons investigué les changements biochimiques au niveau des récepteurs glutamatergiques qui sont connus pour être impliqués dans les LID dans un modèle de singes parkinsoniens qui présentent des dyskinésies qui ont reçu une subthalamotomie unilatérale. Les récepteurs glutamatergiques ionotropiques (AMPA et NMDA contenant les sous-unités NR1/NR2B) et métabotropiques (mGlu2/3 et mGlu5) furent investigués par autoradiographie avec des radioligands spécifiques. Un total de 12 singes furent utilisés dans cette étude, dont 4 singes contrôles, 4 singes ayant reçu du MPTP pour les rendre parkinsoniens et 4 singes MPTP ayant développé des LID suivant un traitement chronique de L-DOPA et une subthalamotomie unilatérale. Les augmentations induites par le MPTP de la liaison spécifique au récepteur AMPA dans le putamen dorsal et le caudé ventrolatéral furent prévenues avec le traitement à la L-DOPA. Les récepteurs mGlu2/3 furent réduits dans le striatum et le globus pallidus chez les singes MPTP qui ont reçu de la L-DOPA et la subthalamotomie comparativement aux contrôles et les singes MPTP. Le récepteur mGlu5 a présenté un profil opposé en ayant augmenté dans ces mêmes régions. Les changements des récepteurs NMDA, mGlu2/3 et mGlu5 ont correlé avec les changements des scores parkinsoniens et dyskinétiques chez les singes MPTP qui ont reçu de la L-DOPA et la subthalamotomie. Ces changements dans les récepteurs pourraient participer à la réduction des symptômes parkinsoniens et des LID après cette chirurgie.

7.2 Abstract

Unilateral subthalamotomy is a surgical option to alleviate disabling L-DOPA-induced dyskinesias (LID) in parkinsonian patients. The mechanisms implicated remain largely unknown. The subthalamic nucleus (STN) is the sole glutamatergic nucleus within the basal ganglia and its lesion may exert changes in the expression of glutamate receptors. The present study investigated the biochemical changes in glutamate receptors known to be involved in LID in the basal ganglia of STN-lesioned monkeys. Ionotropic (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) containing NR1/NR2B) and metabotropic (mGlu2/3 and mGlu5) glutamate receptors were investigated using receptor binding autoradiography in four 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-monkeys with LID that underwent unilateral subthalamotomy. These monkeys responded to lower doses of L-DOPA after their STN lesion and were compared to four controls and four saline-treated MPTP-monkeys. MPTP monkeys showed increases in AMPA receptors in the dorsal putamen and ventrolateral caudate nucleus compared to controls whereas striatal binding was at control values in the STN-lesioned MPTP monkeys. NMDA receptors were reduced in the ventrolateral putamen of MPTP monkeys and the STN-lesioned MPTP monkeys compared to controls. Striatal and pallidal mGlu2/3 receptors were highly decreased in the STN-lesioned MPTP monkeys compared to controls and saline-treated MPTP-monkeys whereas mGlu5 receptors increased in these brain regions. Subthalamotomy-induced changes in parkinsonian and dyskinetic scores correlated with striatal and pallidal differences in NMDA, mGlu2/3 and mGlu5 receptors specific binding between the lesioned versus the unlesioned side. Hence, these results support the implication of glutamate receptors in the beneficial motor effects of a unilateral subthalamotomy.

7.3 Introduction

Dyskinesias are the most common and the most disabling side effects of chronic administration of L-DOPA in parkinsonian patients (Fabbrini et al., 2007). In fact, 55% of the patients will display L-DOPA-induced dyskinesias (LID) after 5 years of treatment (Hely et al., 1994) and this percentage will rise up to 95% after 15 years (Hely et al., 2005). The clinical appearance of LID involves limb, truncal and facial choreic and dystonic movements (Nutt, 1990) and each patient will display its own pattern (Luquin et al., 1992). Despite the recent advances in understanding the underlying pathophysiology of LID, there are still no approved antidyskinetic agents available.

There is strong evidence for an altered glutamatergic neurotransmission in Parkinson's disease (PD), as well as in the development and expression of LID (Blandini and Armentero, 2012; Nevalainen et al., 2013). Glutamate accounts for approximately 70% of the synaptic transmission in the central nervous system, thus being the most abundant excitatory neurotransmitter (Platt, 2007). Reduction of glutamate overactivity by the non-selective N-methyl-D-aspartate (NMDA) antagonist amantadine, was reported as clinically effective and useful in the reduction of LID in both PD humans and parkinsonian primates (Grégoire et al., 2013; Wolf et al., 2010), but at the expense of a shortened duration of L-DOPA antiparkinsonian activity (Blanchet et al., 1998; Rylander et al., 2010) and significant cognitive side effects, thus limiting its use (Stocchi et al., 2008). Other ionotropic glutamate antagonist compounds targeting NMDA or ⟨-amino-3- hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) have been developed and tested in parkinsonian primates as add-on antidyskinetic agents to L-DOPA (Konitsiotis et al., 2000; Papa and Chase, 1996; Zuddas et al., 1992).

In addition to ionotropic glutamate receptors (AMPA and NMDA), the actions of glutamate are mediated via G-protein coupled metabotropic glutamate (mGlu) receptors. Eight mGlu receptors have been isolated and divided into three groups (I-III) based on their molecular structure, pharmacological profile and associated second messenger (Cartmell and Schoepp, 2000). Metabotropic receptors from group I (mGlu1 and mGlu5), particularly the mGlu5 receptor, have drawn much interests based on their distribution within the basal ganglia, mainly the striatum (Testa et al., 1994). The latter receptor is located preferentially post-synaptically on striatal medium spiny neurons and cholinergic interneurons (Smith et

al., 2000) and they are rarely expressed pre-synaptically in thalamostriatal and corticostriatal afferents (Paquet and Smith, 2003). mGlu5 receptor density was shown to increase significantly in the basal ganglia with L-DOPA treatment in both 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkeys (Ouattara et al., 2010a; Ouattara et al., 2011; Samadi et al., 2008b) and patients presenting motor complications (Ouattara et al., 2011). Moreover, the use of mGlu5 receptor negative allosteric modulators was reported for the treatment of LID in animal models (Grégoire et al., 2011; Johnston et al., 2010; Morin et al., 2010; Morin et al., 2013a; Rylander et al., 2010) and in PD patients (Berg et al., 2011; Stocchi et al., 2013).

Group II metabotropic receptors (mGlu2/3) are located pre-synaptically on corticostriatal neurons and on subthalamonigral terminals (Phillips et al., 2000). Their expression in both compartments of the pallidal complex, namely the internal and external segments (GPi and GPe respectively) suggests a localization in subthalamopallidal neurons, but this has not yet been demonstrated. Activation of mGlu2/3 receptors exerts an inhibitory action upon glutamate release (Lovinger and McCool, 1995). Their specific role in motor control remains unclear since administration of either agonist or antagonist exerts antiparkinsonian-like effects in rodent models of PD (Konieczny et al., 1998; O'Neill et al., 2003). Moreover, no clear changes of mGlu2/3 receptors were observed in post-mortem tissues from MPTP monkeys and PD patients (Samadi et al., 2008a; Samadi et al., 2009) whereas a recent study observed a decrease with LID (Morin et al., 2013b). Lastly, receptors from group III (mGlu4 and mGlu6, 7 and 8) are the least studied for the pathophysiology of PD and LID, but recent investigations of mGlu4 receptor show promising results (Amalric et al., 2013). The evidence mentioned above clearly suggest an hyperactivity of glutamatergic pathways in PD and LID and therapies oriented on modifying glutamate neurotransmission may provide benefits to parkinsonian patients.

The primate basal ganglia receive massive glutamate afferences from several cortical areas (Künzle, 1975; Künzle, 1977), the centromedian/parafascicular thalamic nuclei (Sadikot et al., 1992; Smith et al., 2009), as well as the subthalamic nucleus (STN) (Carpenter et al., 1981). The STN is currently the target of choice for surgical alteration for patients refractive to medication or with disabling LID (Abosch et al., 2012; Jourdain and Schechtmann, 2012). We recently demonstrated that unilateral subthalamotomy in MPTP

monkeys with LID had beneficial effects bilaterally on the parkinsonian scores both when monkeys received saline (baseline) or different doses of L-DOPA (Jourdain et al., 2013). A reduction of STN glutamatergic activity had thus beneficial effects on PD symptoms, as predicted by the direct and indirect pathways model of the basal ganglia (DeLong, 1990). Given the glutamatergic nature of the STN, subthalamotomy is hypothesized to induce changes in levels of glutamate receptors in the basal ganglia. In the present study, ionotropic (AMPA and NMDA) and metabotropic (mGlu2/3 and mGlu5) receptors, which are known to be modulated in PD and LID, were investigated using receptor binding autoradiography in STN-lesioned MPTP monkeys with LID as compared to controls and saline-treated MPTP monkeys.

7.4 Material and Methods

Animals and drug treatments

The number of animals used in this study was kept to a minimum for statistically valid analyses. Experiments were carried out using 12 female ovariectomized monkeys (*Macaca fascicularis*) (3.4-5.4 kg) in agreement with the standards of the Canadian Council on Animal Care. The Laval University committee for protection of animals approved this study. Four monkeys served as controls, eight monkeys were treated with systemic MPTP and developed a profound parkinsonian syndrome. MPTP insult resulted in depletion of DA concentration in both caudate nucleus and putamen to a similar extent in all MPTP monkeys with an average loss of 99% compared to intact monkeys (data not shown). Four of these MPTP monkeys were treated with saline (saline-treated MPTP monkeys). The other four MPTP monkeys were chronically treated with L-DOPA, developed LID and underwent unilateral subthalamotomy by stereotactic injection of ibotenic acid (Jourdain et al., 2013). All MPTP monkeys of the present study displayed similar baseline parkinsonian score (saline-treated MPTP monkeys: 10.13 ± 1.1 and MPTP monkeys with LID and subthalamotomy: 11.1 ± 0.7). The detailed behavioral assessment of these MPTP monkeys with a unilateral subthalamotomy was previously reported (Jourdain et al., 2013). Briefly, subthalamotomy improved the antiparkinsonian response after vehicle and for all doses of L-DODA tested (suboptimal, optimal and LID-inducing doses).

Tissue preparation

At the end of the experiments, all monkeys were killed by an overdose of pentobarbital. The STN lesioned MPTP monkeys were killed in their "off" state that is at least 24 h after L-DOPA/benserazide treatment. Brains were flash-frozen in isopentane (-45°C). Brains were cut into coronal sections of 12 μm on a cryostat (-18°C) at levels corresponding approximately to A18-A22, according to the atlas of Szabo and Cowan (Szabo and Cowan, 1984). Sections were mounted onto Super Frost Plus (Fisher, Canada) slides and stored at -80°C until use for assays.

AMPA receptors autoradiography

Tissue sections for AMPA receptor binding were preincubated for 20 min in a 50 mM

TRIS-HCl buffer solution pH 7.4, then were incubated for 60 min at 4 °C in the same buffer, supplemented with 5 nM [^{3}H]-Ro 48-8587 (52.0 Ci/mmol; Novartis, Basel, Switzerland). Non-specific binding was determined in a set of adjacent slides through incubation in the presence of 50 μM of the AMPA antagonist (1,4-dihydro-6-(1H-imidazol-1-yl)-7-nitro-2,3-quinoxalinedione hydrochloride, YM90K, (Tocris Biosciences, USA)). After incubation, washing of the labeled sections consisted of two 30 s washes in an ice-cold buffer followed by a brief dipping in bi-distilled water (4 °C) (Ouattara et al., 2010b). Finally, the slide-mounted tissue sections were dried overnight at room temperature and were exposed to [^{3}H]-sensitive films (BIOMAX MR Film, Kodak) for 4 weeks along with standards (^{3}H-microscales, GE Healthcare).

NMDA/NR2B receptors autoradiography

Tissue sections for NMDA (containing NR1/NR2B) receptor binding were preincubated twice for 10 min at room temperature in a 50 mM Tris-HCl/10 mM EDTA buffer solution, pH 7.4. Sections were then incubated for 90 min at room temperature in the same buffer containing 5 nM [^{3}H]-Ro 25-6981 (25.7 Ci/mmol; F. Hoffman-Laroche, Basel, Switzerland). Non-specific binding was defined in the presence of the NMDA antagonist Ro 04-5595 10 μM (Hoffmann-La Roche, Basel, Switzerland). After two 5 min washes and one 15 min wash at 4 °C in the TRIS/EDTA buffer, sections were then rinsed briefly (10 sec) in ice-cold distilled water (Ouattara et al., 2008). Finally, the slide-mounted tissue sections were dried overnight at room temperature and were exposed to [^{3}H]-sensitive films (BIOMAX MR Film, Sigma, USA) for 4 weeks along with standards (^{3}H-microscales).

mGlu2/3 receptors autoradiography

Tissue sections for mGlu2/3 receptors binding were preincubated for 30 min at 4 °C in a phosphate buffer solution (8.66 mM K_2HPO_4; 1.34 mM KH_2PO_4; 100 mM KBr), pH 7.6. Sections were then incubated for 90 min at room temperature in the same buffer containing 5 nM [^{3}H]-LY341495 (40.0 Ci/mmol; American Radiolabeled Chemicals, St-Louis, USA). Non-specific binding was defined in the presence of glutamate 20 mM. After two 30 s washes at 4 °C in the phosphate buffer, sections were then rinsed (30 s) in ice-cold distilled water (Samadi et al., 2009). Finally, the slide-mounted tissue sections were dried

overnight at room temperature and were exposed to [^{3}H]-sensitive films (BIOMAX MR Film) for 2 weeks along with standards (^{3}H-microscales).

mGlu5 receptors autoradiography

Tissue sections for mGlu5 receptor binding were preincubated for 30 min at room temperature in a Krebs-Ringer Hepes (KRH) buffer solution (20 mM HEPES, 118 mM NaCl, 4.8 mM KCl, 2.5 mM $CaCl_2$, 1.2 mM $MgSO_4$, 10 mM NaOH), pH 7.4. Sections were then incubated for 15 min at room temperature in the KRH buffer containing 5 nM [^{3}H]-ABP688 (81.6 Ci/mmol; Novartis, Basel, Switzerland) added with 0.05 mg/ml bovine serum albumin (BSA). Non-specific binding was defined in the presence of MPEP (Tocris, Ellisville, Missouri, USA) 10 μM. After three 20 min washes at 4 °C in the KRH buffer, sections were then rinsed briefly (5 s) in ice-cold distilled water (Ouattara et al., 2011). Finally, the slide-mounted tissue sections were dried overnight at room temperature and were exposed to [^{3}H]-sensitive films (BIOMAX MR Film, Kodak) for 4 weeks along with standards (^{3}H-microscales).

Data analysis

For each brain regions investigated, we used 3 to 6 brain slices for each animal for autoradiographic analyses. Intensity of autoradiographic labeling was quantified on X-ray films by a Power Macintosh G4 connected to a video camera (XC-77; Sony) and a constant illumination light table using computerized densitometry (NIH ImageJ 64-bit mode, v.1.46). The signal was measured as the optical density for the caudate nucleus, the putamen and the pallidal complex and corrected for non-specific binding for each experiment. Subsequently, optical gray densities were transformed into nanocuries per mg of tissue equivalent using a standard curve generated with [^{3}H]-standards (^{3}H-microscales, GE Healthcare). Results were then converted into femtomoles per mg of tissue using specific activity of the radioligands. Figures show the means and standard error of the mean. Statistical comparisons of data were performed by a 2-way ANOVA (pharmacological and surgical treatments) mixed model using paired and non-paired values with an animal random effect, followed by post hoc pairwise comparisons of least squares means test. A 2-way ANOVA was used to analyse the interactions between the brain

subdivisions and the treatments. A Pearson *R* correlation test was used to measure the correlation between parkinsonian or dyskinetic scores and changes in receptors specific binding. Analyses were conducted using SAS software (version 9.3, SAS Institute, Inc.). A p value of ≤ 0.05 was considered significant.

7.5 Results

Effect of MPTP denervation and treatments on glutamate receptors expression

Fig. 1 shows representative autoradiograms of AMPA, NMDA/NR2B, mGlu2/3 and mGlu5 receptors in the posterior striatum of the present MPTP monkeys that received a unilateral subthalamotomy to alleviate their LID, as well as an example of the subdivisions of the caudate nucleus and putamen.

AMPA receptors

[^{3}H]-Ro 48-8587 specific binding in the putamen (Fig. 2) was overall more intense in the ventral compared to its dorsal part ($F_{3,27} = 18.39$, $p < 0.0001$) and the caudate nucleus showed binding of [^{3}H]-Ro 48-8587 higher in the medial compared to the ventral part ($F_{3,27} = 6.05$, $p < 0.001$). Non-specific binding was low (<10% of total binding). AMPA receptor specific binding was unchanged in all subregions of the caudate nucleus after MPTP treatment except for an increase in the ventrolateral caudate nucleus (+15%). Compared to saline-treated MPTP monkeys, AMPA receptor specific binding was reduced in the ventral caudate nucleus of the STN-lesioned MPTP and ipsilateral to the STN lesion in the dorsolateral caudate nucleus (-17%). In the putamen, specific binding of [3H]-Ro 48-8587 was increased in saline-treated MPTP monkeys, reaching statistical significance in the dorsal putamen (dorsolateral (DL): +13%; dorsomedial (DM): +21%). In the STN-lesioned MPTP monkeys, levels of AMPA receptors were at control levels in the dorsal putamen for ipsilateral and contralateral to STN lesion and were reduced compared to controls in ventral putamen whereas AMPA receptors were reduced significantly in all subdivisions compared to saline-treated MPTP monkeys (DL: -15 and -16%; DM: -25 and -24%; ventrolateral (VL): -19 and -25%; ventromedial (VM): -21 and -26% for contra- and ipsilateral respectively). No specific binding of [^{3}H]-Ro 48-8587 was measured in the GPi and GPe in all groups.

NMDA/NR2B receptors

The [^{3}H]-Ro 25-6981 specific binding (Fig. 3) was overall more intense in the ventral putamen compared to its dorsal part ($F_{3,27} = 50.09$, $p < 0.0001$). Its distribution was also not uniform in the caudate nucleus, with a lower binding in the lateral subdivision ($F_{3,27} =$

15.98, $p < 0.0001$). The GPe and GPi also showed difference in the receptor specific binding with lower values in the pars externa ($F_{3,27} = 17.20$, $p < 0.01$). Non-specific binding was low (<10% of total binding). No change was observed in any subregions of the caudate nucleus in all groups ($F_{3,12} = 0.69$, $p = 0.53$). [^{3}H]-Ro 25-6981 specific binding was decreased in the ventrolateral putamen of both saline-treated MPTP monkeys (-16%) and STN-lesioned MPTP monkeys (-23 and -24% for contra- and ipsilateral respectively). A similar pattern was observed in the ventromedial putamen, but reached significance only for the STN-lesioned MPTP monkeys ipsilateral to STN lesion. The GPe and GPi showed weaker binding of [^{3}H]-Ro 25-6981 compared to the striatum in all groups and showed no difference between experimental groups.

mGlu2/3 receptors

The [^{3}H]-LY341495 specific binding (Fig. 4) was more intense in the ventral putamen compared to its dorsal part ($F_{3,27} = 32.28$, $p <0.0001$). The caudate nucleus showed binding of [^{3}H]-LY341495 uniformly distributed in its subregions in controls but not in the other groups ($F_{3,27} = 15.32$, $p <0.0001$) and the intensity of binding was similar to the ventral putamen. Non-specific binding was low (<10% of total binding). Striatal and pallidal [^{3}H]-LY341495 specific binding increased in the dorso- and ventromedial part of the caudate nucleus (DM: +29%; VM: +27%) of saline-treated MPTP monkeys and remained unchanged in the other subregions. In the caudate nucleus, mGlu2/3 receptor specific binding were highly decreased in the STN-lesioned MPTP monkeys compared to controls (DL: -28 and -26%; DM: -28 and -22%; VL: -40 and -37%; VM: - 33 and -28% for contra- and ipsilateral respectively) and compared to saline-treated MPTP monkeys (DL: -36 and -34%; DM: -41 and -36%; VL: -40 and -36%; VM: -42 and -37% for contra- and ipsilateral respectively). A similar pattern was observed in the putamen of STN-lesioned MPTP monkeys where [^{3}H]-LY341495 specific binding was lower compared to controls (DL: -39 and -38%; DM: -43 and -41%; VL: -48 and -49%; VM: -44 and -49% for contra- and ipsilateral respectively) and saline-treated MPTP monkeys (DL: -37 and -36%; DM: -43 and -40%; VL: -40 and -38%; VM: -45 and -42% for contra- and ipsilateral respectively).

The GPe and GPi showed lower [^{3}H]-LY341495 specific binding compared to the

striatum in all groups, with lowest values in the GPi. An extensive decrease of pallidal [^{3}H]-LY341495 specific binding was seen in the STN-lesioned MPTP monkeys compared to controls (GPe: -72 and -69%; GPi: -70 and -72% for contra- and ipsilateral respectively) and saline-treated MPTP monkeys (GPe: -76 and -73%; GPi: -76 and -77% for contra- and ipsilateral respectively).

mGlu5 receptors

Similar to all the other glutatame receptors investigated, [^{3}H]-ABP688 specific binding (Fig. 5) was overall more intense in the ventral putamen compared to its dorsal part ($F_{3,27} = 191.43$, $p < 0.0001$). The lateral caudate nucleus was less labelled compared to the medial caudate ($F_{3,27} = 29.14$, $p < 0.0001$). The caudate nucleus was more labelled than the putamen ($p < 0.0001$). Non-specific binding was low (<10% of total binding). In the caudate nucleus, [^{3}H]-ABP688 specific binding was similar in saline-treated MPTP compared to control monkeys in all its subregions whereas it was significanlty higher in the STN-lesioned MPTP monkeys compared to controls (DL: +62 and +64%; DM: +45 and +50%; VL: +41 and +49%; VM: +31 and +31% for contra- and ipsilateral respectively) and to the saline-treated MPTP monkeys (DL: +40 and +41%; VL: +25 and +30%; DM: +26 and +33%; VM: +23 and +23% for contra- and ipsilateral respectively). Similarly in the putamen, [^{3}H]-ABP688 specific binding was similar in saline-treated MPTP compared to control monkeys, but was higher in the STN-lesioned MPTP monkeys compared to controls (DL: +57 and +51%; DM: +52 and +60%; VL: +22 and +19% for contra- and ipsilateral respectively; VM ipsilateral: +20%) and to the saline- treated MPTP monkeys (DL: +31 and +26%; DM: +32 and +39%; VL: +17 and +14% for contra- and ipsilateral respectively; VM ipsilateral: +17%).

The GPe and GPi showed lower [^{3}H]-ABP688 specific binding compared to the striatum in all groups, with similar binding intensity between the two parts. The binding levels of [^{3}H]-ABP688 were not affected by MPTP compared to controls in the GPe and in the GPi. In the STN-lesioned MPTP monkeys, mGlu5 receptor specific binding was significantly higher compared to controls (GPe: +47 and +60%; GPi: +56 and +53% for contra- and ipsilateral respectively) and to saline-treated MPTP monkeys (GPe: +37 and +49%; GPi: +67 and +64% for contra- and ipsilateral respectively).

Correlations between autoradiography and clinical outcomes

To investigate more closely the effect of the STN lesion, we correlated for individual STN-lesioned MPTP monkey the STN-lesion induced difference in PD scores and dyskinesias scores (previously reported in (Jourdain et al., 2013)) versus the difference in receptor binding between the STN lesioned to the unlesionded side. The total caudate nucleus, putamen, GPe and GPi were correlated and the following significant correlations were obtained. In the caudate nucleus, there was a positive correlation between the differences in NMDA/NR2B receptor binding and the increase in dyskinesias induced by low-doses of L-DOPA (Figure 6A). A similar correlation was observed between the increase in dyskinesias induced by low-doses of L-DOPA and the increase in mGlu5 receptors specific binding in the caudate nucleus (Figure 6B). A negative correlation was observed between the increase in putaminal NMDA/NR2B receptor specific binding and the change in parkinsonian score at low-dose of L-DOPA (Figure 6C).

In the GPe, there was a positive correlation between the changes in baseline parkinsonian scores and the increase in mGlu2/3 receptor specific binding (Figure 7A). A positive correlation was also observed between the changes in the dyskinetic score and the increase in the mGlu2/3 receptors in the GPe (Figure 7B) and the GPi (Figure 7C).

7.6 Discussion

The STN is the only excitatory structure intrinsic to basal ganglia and its lesion is hypothesized to induce modifications in glutamate receptors. Therefore, changes in glutamate receptors known to be involved in LID were investigated in monkeys after MPTP and L-DOPA treatments and unilateral subthalamotomy and summarized in Table 1. A STN lesion was shown to increase striatal glutamate in normal rats (Walker et al., 2009) and decrease the 6-OHDA-induced elevation of glutamate (Centonze et al., 2005; Walker et al., 2009). It was also previously shown that STN ablation in normal primates decreased pallidal 2-deoxyglucose uptake (Mitchell et al., 1985) and GAD67 mRNA expression (Guridi et al., 1996), indicative of a decreased cellular activity in STN efferent structures. To our knowledge, this is the first investigations on glutamate receptors in primates with a STN lesion.

AMPA receptors

AMPA receptors are postsynaptic glutamate-gated ion channel receptors involved in many brain function, including neurologic disorders (Ashby et al., 2008). The MPTP-induced increases in AMPA receptors by MPTP were limited to the ventrolateral caudate nucleus and the dorsal putamen. In the STN-lesioned MPTP monkeys, this binding was at control levels in all subregions of the caudate nucleus and the dorsal putamen except for the ipsilateral ventral putamen which was reduced compared to controls. Previous studies in monkeys showed few or no changes in caudate nucleus and putamen after MPTP or L-DOPA treatment compared to control animals (Ouattara et al., 2010b; Silverdale et al., 2002), others showed striatal increases in dyskinetic monkeys (Calon et al., 2002; Morin et al., 2013b). An autoradiographic study demonstrated an increase of AMPA receptor specific binding in the lateral putamen of PD patients with motor complications (both wearing-off and dyskinesias) compared to those without motor (Calon et al., 2003). Consistent with this observation, blockade of AMPA receptors was shown to reduce the induction and expression of LID as measured in rats and primates (Kobylecki et al., 2010; Konitsiotis et al., 2000; Silverdale et al., 2005). However, administration of the AMPA antagonist perampanel did not succeed in reducing wearing-off (Lees et al., 2011). On the other hand, blockade of AMPA receptors by the antagonist NBQX had a potent effect on

the antiparkinsonian response of L-DOPA in MPTP- monkeys, measured with an increase of activity and reduction in bradykinesia (Klockgether et al., 1991), whereas it remained unaffected by topiramate, another AMPA antagonist (Silverdale et al., 2005).

Rather than AMPA receptor density increases, trafficking of its subunits between the vesicular and postsynaptic membrane may be associated with overactive AMPA receptor activty in PD and LID (Silverdale et al., 2010). An increase in the Glu2/3 subunit in the postsynaptic fraction of AMPA receptors may render striatal neurons more sensitive to glutamate (Silverdale et al., 2010). In the present study, lesioning the STN decreased striatal AMPA receptors to control levels. One study reported no change of AMPA receptor levels in basal ganglia after surgical ablation of the STN (Blandini et al., 1995), while another found an 11% increase in the substantia nigra *pars reticulata* (SNr) (Price et al., 1993). A recent electrophysiological study showed that the effects of STN high-frequency stimulation (HFS) were not mediated via AMPA receptors (Ledonne et al., 2012). The above evidence suggests that AMPA receptors participate in the expression of LID, probably through membrane/vesicular subunits trafficking, but not in the clinical effects of lesional or stimulation procedures for PD.

NMDA/NR2B receptors

NMDA receptor is the other major ionotropic postsynaptic glutamate receptor in the brain. Administration of the NMDA non-competitive antagonist amantadine in 6- OHDA rats (Dekundy et al., 2007; Lundblad et al., 2002), MPTP monkeys (Bibbiani et al., 2005; Blanchet et al., 1998; Grégoire et al., 2013) and PD patients (Metman et al., 1999; Wolf et al., 2010) was shown to be beneficial in reducing LID. Functional NMDA receptors contain the subunit NR1 and one of the NR2 or NR3 subunits (Petralia and Wenthold, 2008). Among the two latters, the NR2B subunit has been proposed to be involved in the development of LID since its binding sites increase in dyskinetic patients and MPTP monkeys (Calon et al., 2003; Hurley et al., 2005; Morin et al., 2013b; Ouattara et al., 2008). However, the development of NR2B-selective antagonists, brought conflicting results. The compound CP-101-606 was found to reduce peak-dose LID in a small cohort of PD patients (Nutt et al., 2008), but increased LID in MPTP-marmosets (Nash et al., 2004). CP-101-606 had antiparkinsonian actions in monkeys (Steece-Collier et al., 2000), but such

activity failed to appear in PD patients (Nutt et al., 2008). While pharmacological blockage of NR2B with some agents (CI-1041 and Co 101244) has antidyskinetic activity in primate models of PD (Blanchet et al., 1999; Hadj Tahar et al., 2004), other compounds (Ro 25-6981 and Ro 63-1908) failed to reproduce such activity in 6-OHDA rats (Rylander et al., 2009).

In the present study, the NMDA/NR2B specific binding was decreased significantly only in one subregion of the putamen compared to controls and is in agreement with our previous findings in MPTP monkeys showing a regionally limited decrease (Calon et al., 2003; Hurley et al., 2005; Ouattara et al., 2008) and PD patients without motor complications (Calon et al., 2003). This decrease was also observed in the STN-lesioned MPTP monkeys in the ventral putamen. By contrast, an increase of NMDA/NR2B specific binding in the putamen was observed in MPTP monkeys with LID and PD patients with motor complications (Calon et al., 2003; Hurley et al., 2005; Morin et al., 2013b; Ouattara et al., 2008). This difference in the present findings in MPTP monkeys with LID and our previous reports may be due to the STN lesion that opposed the L-DOPA-induced increase of NMDA receptors.

No change was also seen in both compartments of the globus pallidus, but there was a tendency towards increases in the vehicle–treated MPTP monkeys and ipsilateral to STN compared to the controls. Considering the small number of monkeys used in this study, statistical significance might have been reached by increasing the sample size. NMDA receptor binding was found to decrease in the globus pallidus (equivalent of the GPi in primate) and SNr ipsilateral to STN lesion in normal rats (Blandini et al., 1995; Price et al., 1993). In normal rats receiving STN-HFS at sub- or suprathreshold-triggering forelimb dyskinesia, NR2B and its phosphorylated form were increased in the ipsilateral STN (Quintana et al., 2010). Upregulation of the phosphorylated NR2B was seen in the lateral striatum of dyskinetic rats, but no change was observed in phopsphorylated NR2B and NR2B in the SNr by both amplitude of stimulation (Quintana et al., 2010). When rats are exposed to 6-OHDA, dyskinesiogenic STN-HFS or high doses of L-DOPA will increase phosphorylated NR2B ipsilaterally in the STN and bilaterally in the entopeduncular nucleus (equivalent of the primate GPe). In the SNr, the 6-OHDA treatment increased phophorylated NR2B and remained increased with STN-HFS or L-DOPA. The non-

phosphorylated form of NR2B was only increased by L-DOPA treatment in the STN, it remained unaffected in the entopeduncular nucleus and SNr (Quintana et al., 2012). These observations add evidence that the activated form of NR2B plays a more important role in dyskinesias than the non-phosphorylated NR2B, and that lesion and stimulation of the STN affected NMDA/NR2B throught different mechanisms. Furthermore, treatments received (6-OHDA vs MPTP, vehicle vs L-DOPA, lesion vs stimulation), species and age of the animals used are other factors to consider.

mGlu2/3 receptors

The specific role of the mGlu2/3 receptors in the basal ganglia remains to be elucidated. They closely interact with the dopamine system, pre- and postsynaptically in the dopamine circuitry (Adewale et al., 2006; Bauzo et al., 2009; Kronthaler and Schmidt, 2000; Morishima et al., 2005). Administration of mGlu2/3 receptors agonists post-exposure to 6-OHDA in rats or pre-MPTP injection in mice have shown interesting neuroprotective results (Battaglia et al., 2003; Chan et al., 2010; Murray et al., 2002) and its blockade amplified the MPTP-insult (Battaglia et al., 2003).

An autoradiographic study in monkeys observed no change in the mGlu2/3 receptor specific binding in the striatum after MPTP (Morin et al., 2013b; Samadi et al., 2008a). Similarly here we found no change in the putamen and the lateral caudate nucleus but an increase in the medial caudate nucleus. No change of mGlu2/3 receptors has been observed in the striatum of PD patients displaying LID or not (Samadi et al., 2009).

In the striatum of MPTP monkeys no change (Samadi et al., 2008a) or more recently a decrease of mGlu2/3 receptor specific binding was reported with LID (Morin et al., 2013b). In the present study, the striatal and pallidal levels of mGlu2/3 receptors were highly decreased in the STN-lesioned MPTP compared to controls and vehicle- treated MPTP monkeys. This could be the result of aging process considering the age of the monkeys that underwent subthalamotomy (age ranging from 14 to 21 years) (Jourdain et al., 2013) compared to controls and vehicle-treated MPTP monkeys of the present study (age ranging from 4 to 7 years). However, it was recently shown in rats that striatal and cortical mGlu2/3 receptor expression increases with age (Simonyi et al., 2005). The decreases observed in the basal ganglia are also unlikely due to dopaminergic denervation,

since levels of mGlu2/3 remained unchanged in PD patients and MPTP monkeys (Morin et al., 2013b; Samadi et al., 2008a; Samadi et al., 2009) but likley to the L-DOPA treatment as recently observed (Morin et al., 2013b) and the STN lesion.

There is yet no demonstration of the presence of the mGlu2/3 receptors on subthalamopallidal afferents, but it is reasonable to postulate that their expression in the globus pallidus might be from presynaptic STN terminals. If so, a subthalamotomy would consequently reduce mGlu2/3 receptors in the GPi and the GPe since they both receive afferent glutamatergic fibres from the STN (Smith et al., 1990). The same observation could also apply to the reduction in the striatum, since the STN also projects to the striatum (Kita and Kitai, 1987; Smith et al., 1990). That does not exclude a reduction on the corticostriatal efferences, which are assumed to express the mGlu2/3 receptors presynaptically (Testa et al., 1998). To our knowledge, there is no other report exploring the effects of surgical alleviation of LID on the expression of mGlu2/3 receptors, thus more studies are warranted to fully address the mechanisms implicated in the effect of lesions and deep brain stimulation of the STN.

mGlu5 receptors

mGlu5 receptors are preferentially located post-synaptically on striatal projection neurons and interneurons (Gubellini et al., 2004) and are expressed by few cortico- and thalamostriatal presynaptic terminals (Paquet and Smith, 2003). Their wide distribution in the basal ganglia has drawn interests as a potential therapeutic target for PD and LID (Smith et al., 2012). Lesion of the nigrostriatal pathway by MPTP is reported to increase the mGlu5 receptors specific binding in the striatum as measured by autoradiography (Morin et al., 2013a; Ouattara et al., 2011; Samadi et al., 2008b) whereas other studies (Ouattara et al., 2010a) including the present one showed no significant increase.

The most striking change of mGlu5 receptors is observed in MPTP monkeys following chronic L-DOPA treatment. Motor complications induced by L-DOPA are associated to and correlated with an increase of mGlu5 receptors in the posterior striatum (Morin et al., 2013a; Ouattara et al., 2010a; Ouattara et al., 2011; Samadi et al., 2008b). Blocking the mGlu5 receptors with a negative allosteric modulator prevented these L-DOPA-induced increases of mGlu5 receptor levels (Morin et al., 2013a). In the present

study, striatal and pallidal levels of mGlu5 receptors were increased in the STN-lesioned MPTP monkeys, consistent with the current literature of an increase of this receptor in MPTP monkeys with LID and with the fact that these monkeys remained dyskinetic with the STN lesion. These increases in mGlu5 receptors in STN-lesioned MPTP monkeys could not be the result of an aging process since age was reported not to influence the expression of these receptors (Simonyi et al., 2005). One report compared the systemic administration of an mGlu5 receptor antagonist and subthalamic lesion in dyskinetic 6- OHDA rats. The authors concluded that the negative allosteric modulator MPEP reduced better LID than subthalamotomy and that was correlated with a stronger reduction in the number of cells immunoreactive to the LID-associated marker deltaFosB/FosB (Levandis et al., 2008). There are currently no studies on deep brain stimulation and mGlu5 receptors and there is not enough evidence with subthalamotomy to draw solid conclusions. More studies are needed to fully assess the interactions between surgical procedures and mGlu5 receptor, especially since mGlu5 receptors are located postsynaptically in the STN (Awad et al., 2000) and perisynaptic in the GPi (Smith et al., 2000), both structures being the main targets in PD surgery (Jourdain and Schechtmann, 2012).

Correlations between autoradiography and parkinsonian/dyskinetic scores

In order to further assess the biochemal correlates of the behavioral effect of the STN lesion, correlations between the change in parkinsonian or dyskinetic scores (post-subthalamotomy values subtracted from pre-subthalamotomy) and the difference in specific binding (ipsilateral subtracted from contralateral to subthalamotomy) were undertaken in the MPTP monkeys that received L-DOPA and a unilateral subthalamotomy. No correlation was found with AMPA receptors. There were opposite correlations between the increase in NMDA/NR2B receptors and the changes in the parkinsonian and dyskinetic scores. Thus, the increase in the difference between the ipsi minus the contralateral NMDA/NR2B receptors had beneficial effects on the antiparkinsonian response to L-DOPA (low dose), but at the expense of increased LID. This result is consistent with the observation that blocking the NMDA receptor with amantadine reduces LID (Blanchet et al., 1998).

We also found correlations with the mGlu2/3 receptors in the globus pallidus. An

increase in GPe difference between the ipsi minus the contralateral mGlu2/3 receptors was correlated with an increase (worsening) in the baseline parkinsonian disability after subthalamotomy. On the other hand, an increase in pallidal difference between the ipsi minus the contralateral mGlu2/3 receptors correlated with increased in LID (low dose of L-DOPA). mGlu2/3 receptors are assumed to be located pre-synaptically in the globus pallidus and to regulate the release of glutamate (Lovinger and McCool, 1995). Thus, an increase in mGlu2/3 receptors would exert a decrease of glutamate release in the pallidum and result in a reduced excitatory activity. The results of the present study seem to be at variance with the model of the basal ganglia, since hypokinetic disorders would be the consequence of excessive glutamate in the pallidum (DeLong, 1990). However, we observed a better baseline parkinsonian score when there was a decrease in mGlu2/3 receptors in the GPe, suggesting that there would be higher glutamate levels in the GPe. The GPe is known to send GABA to its homologue, the GPi (Hazrati et al., 1990; Smith et al., 1994) and an activation of this pallidopallidal pathway could explain the improvement in the baseline parkinsonian score. Though the importance of this pallidopallidal connection remains to be elucidated, it seems reasonable to postulate it may participate in the behavioral effects of the subthalamotomy.

mGlu5 receptors modulate post-synaptic striatal neurons (Saugstad and Ingram, 2008). It was previously shown that mGlu5 receptors increased in dyskinetic MPTP monkeys, but remained unchanged in non-dyskinetic monkeys (Samadi et al., 2008b). Furthermore, its increase correlated with higher dyskinesia in MPTP monkeys (Morin et al., 2013a). In accordance with the previous studies, increases in caudate mGlu5 receptors were highly correlated with increasing LID (low-doses of L-DOPA). Such observations further support the evidence that mGlu5 receptors are involved in the expression of LID and their antagonism is a potential pharmacotherapy to treat LID.

7.7 Conclusion

The MPTP treatment increased AMPA and mGlu2/3 receptors in some subdivisions of the striatum, whereas it had no effect on glutamate receptors in both compartments of the globus pallidus. Subthalamotomy in MPTP monkeys with LID reestablished the levels of AMPA receptors after MPTP and kept NMDA receptors low. On the other hand, density of metabotropic receptors were clearly affected in the MPTP monkeys with LID despite their subthalamotomy where mGlu5 receptors increased in all subdivisions of the caudate nucleus and putamen, as well as in the GPi and GPe. mGlu2/3 receptors displayed an opposite pattern where their density was downregulated in the striatum and the globus pallidus of STN lesioned MPTP monkeys with LID. Differences in NMDA, mGlu2/3 and mGlu5 receptors bewteen the lesioned and unlesionded STN side of the brain correlated with changes in parkinsonian and dyskinetic scores. Considering the presynaptic nature of mGlu2/3 receptors, their decrease in the globus pallidus and in the striatum may be the result of the subthalamic lesion and a reduction of the corticostriatal and/or subthalamostriatal efferent connections respectively. This decrease could participate in the alleviation of parkinsonian symptoms and LID after subthalamotomy.

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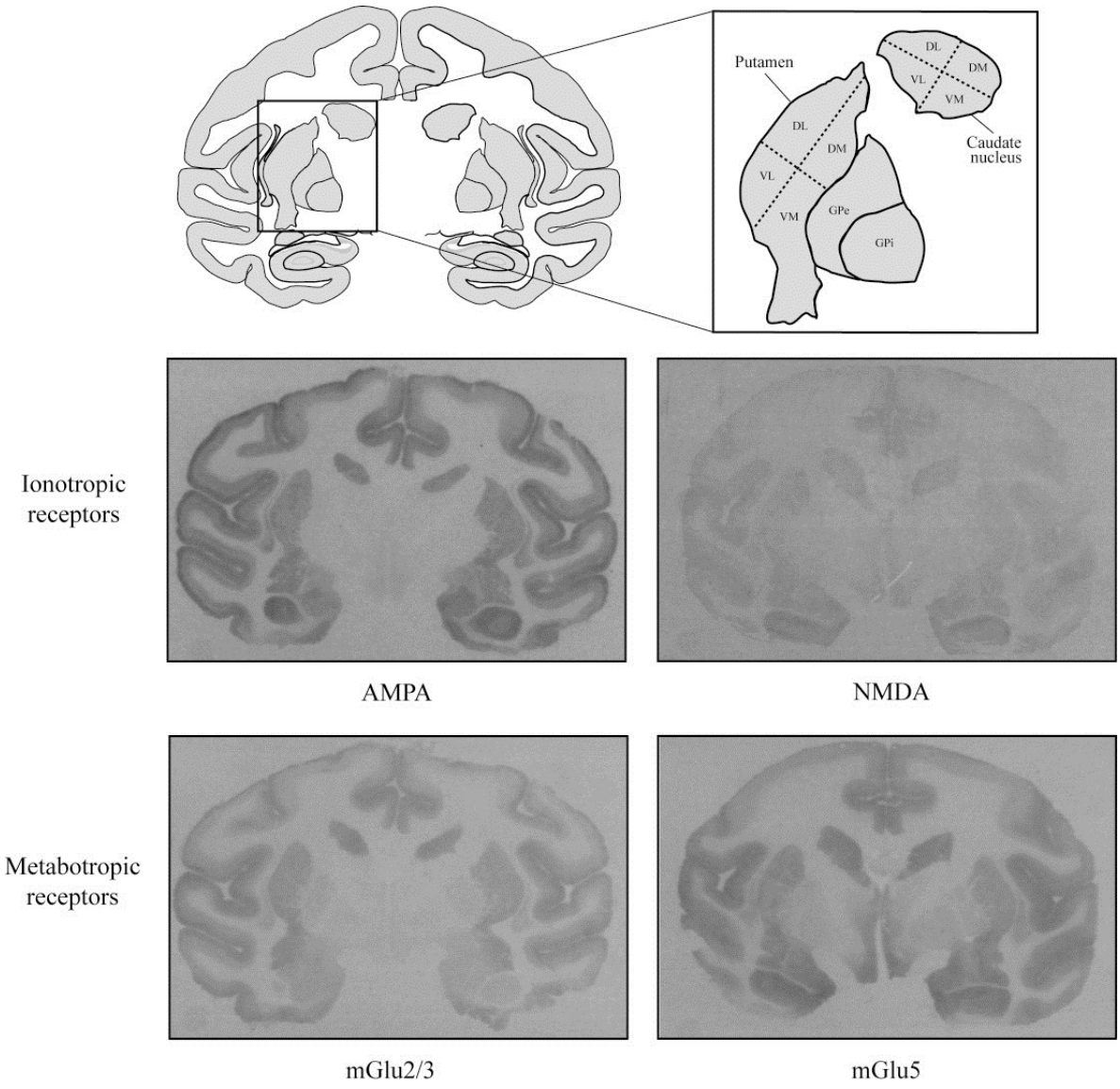

Figure 7.1 Representative autoradiograms of coronal brain sections showing AMPA, NMDA/NR2B, mGlu2/3 and mGlu5 receptor binding in the posterior striatum of the MPTP monkeys that received a unilateral subthalamotomy to alleviate their LID as compared to the schematic of the monkey brain (adapted from the atlas of (Martin and Bowden, 2000)). Subdivisions of the caudate nucleus and putamen dorsolateral (DL), dorsomedial (DM), ventrolateral (VL) and ventromedial (VM) subregions, as well as the globus pallidus *pars externa* (GPe) and globus pallidus *pars interna* (GPi) analyzed are shown.

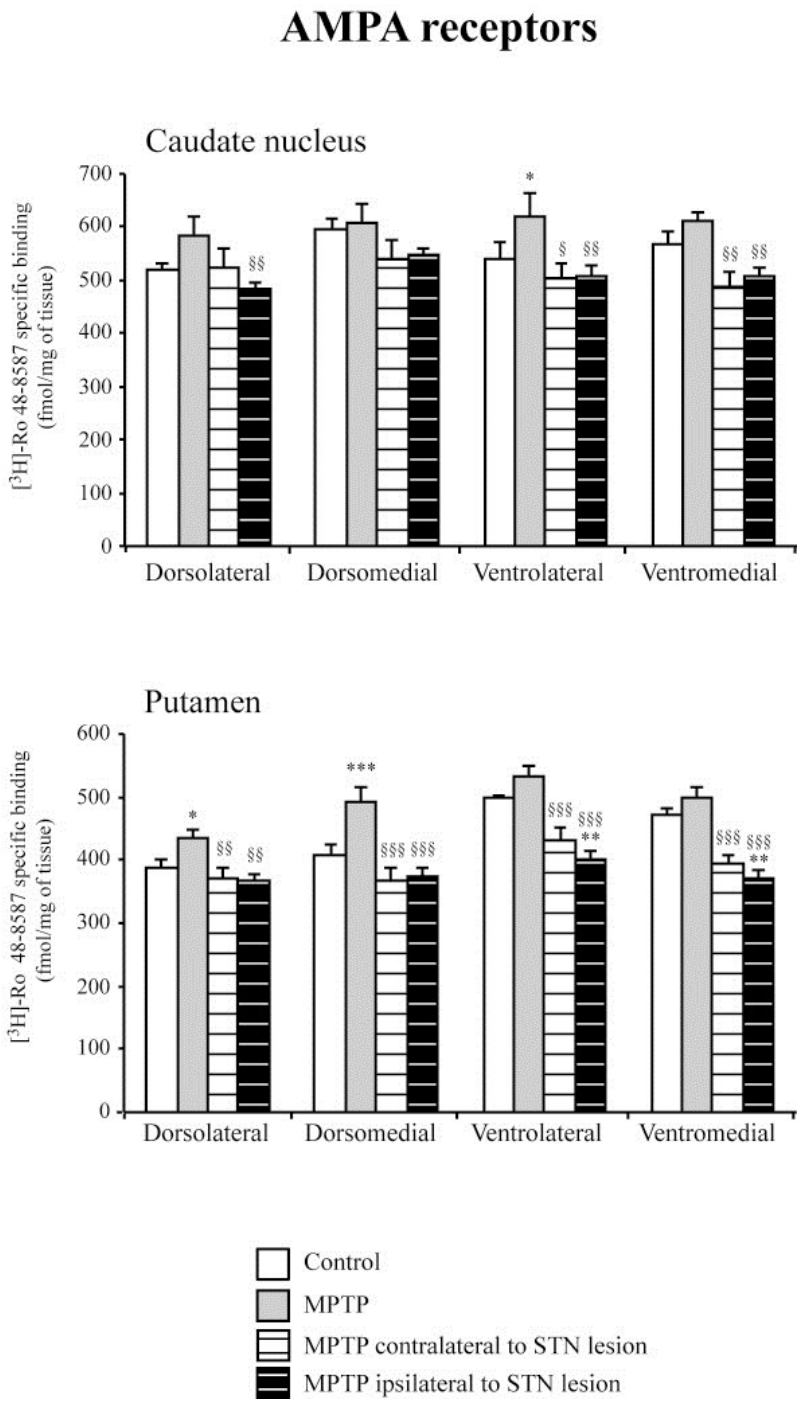

Figure 7.2 AMPA receptor specific binding in the caudate nucleus and putamen of control, saline-treated MPTP monkeys (MPTP) and STN-lesioned MPTP monkeys with LID showing binding contralateral and ipsilateral to the STN lesion. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs controls; § $p < 0.05$, §§ $p < 0.01$, §§§ $p < 0.001$ vs saline-treated MPTP monkeys.

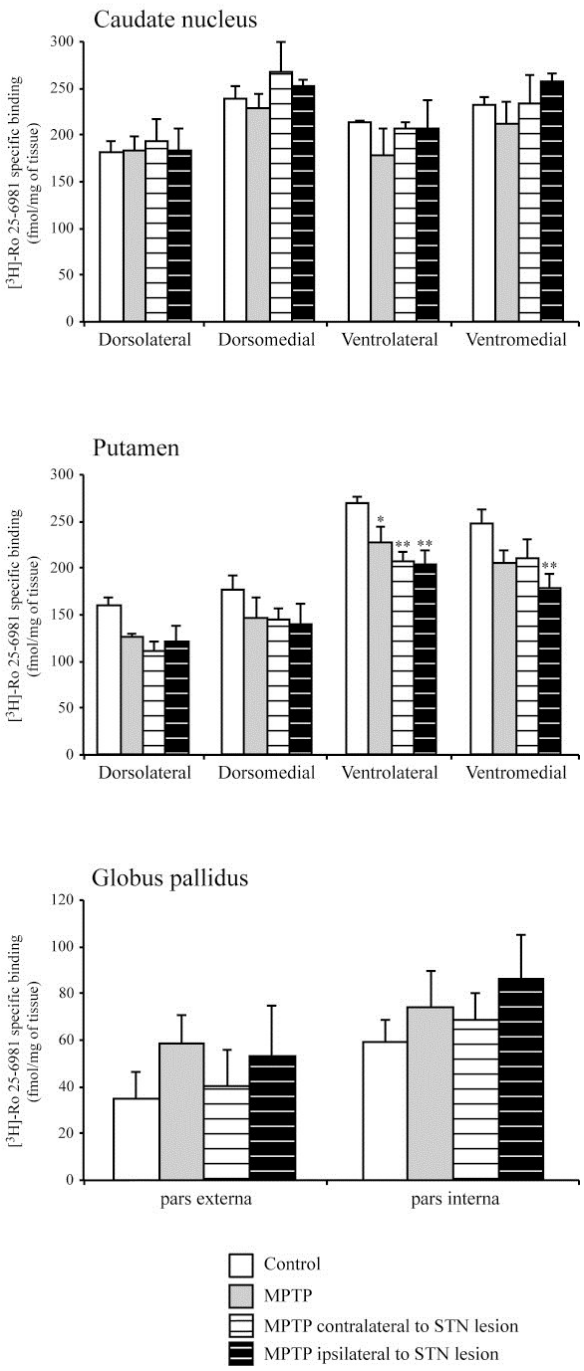

Figure 7.3 NMDA/NR2B receptor specific binding in the caudate nucleus, putamen and globus pallidus of control, saline-treated MPTP monkeys (MPTP) and STN-lesioned MPTP monkeys with LID showing binding contralateral and ipsilateral to the STN lesion. * $p < 0.05$, ** $p < 0.01$ vs controls.

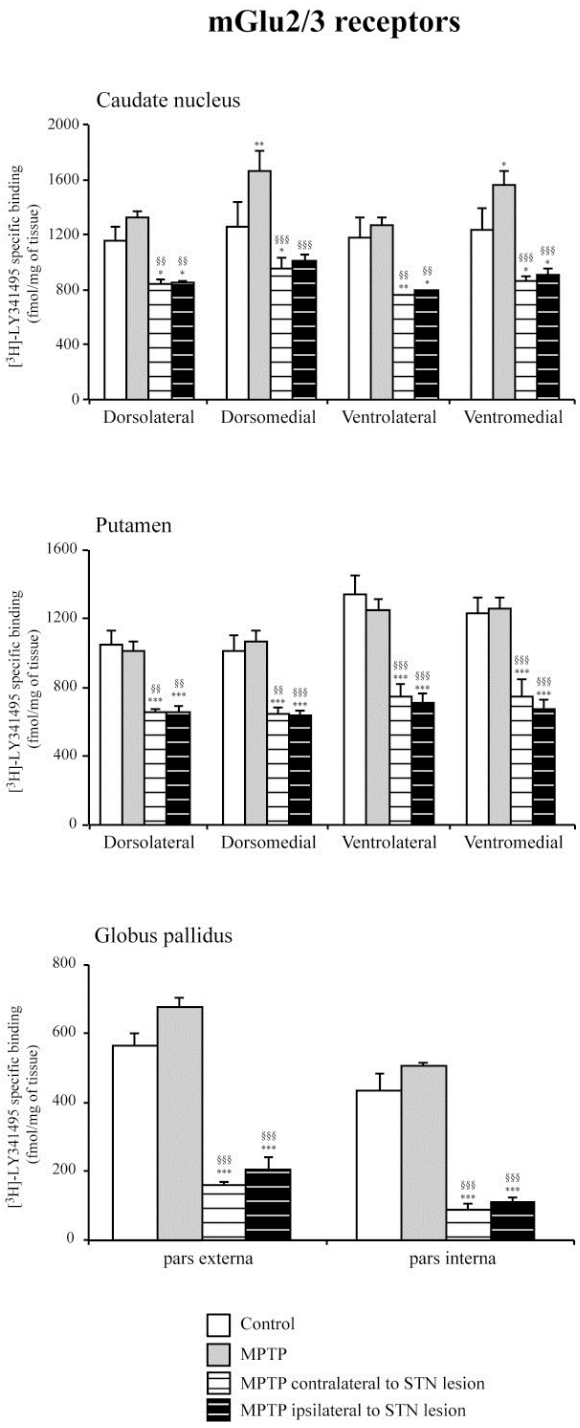

Figure 7.4 mGlu2/3 receptor specific binding in the caudate nucleus, putamen and globus pallidus of control, saline-treated MPTP monkeys (MPTP) and STN-lesioned MPTP monkeys with LID showing contralateral and ipsilateral to the STN lesion. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs controls; §§ $p < 0.01$, §§§ $p < 0.001$ vs saline-treated MPTP monkeys.

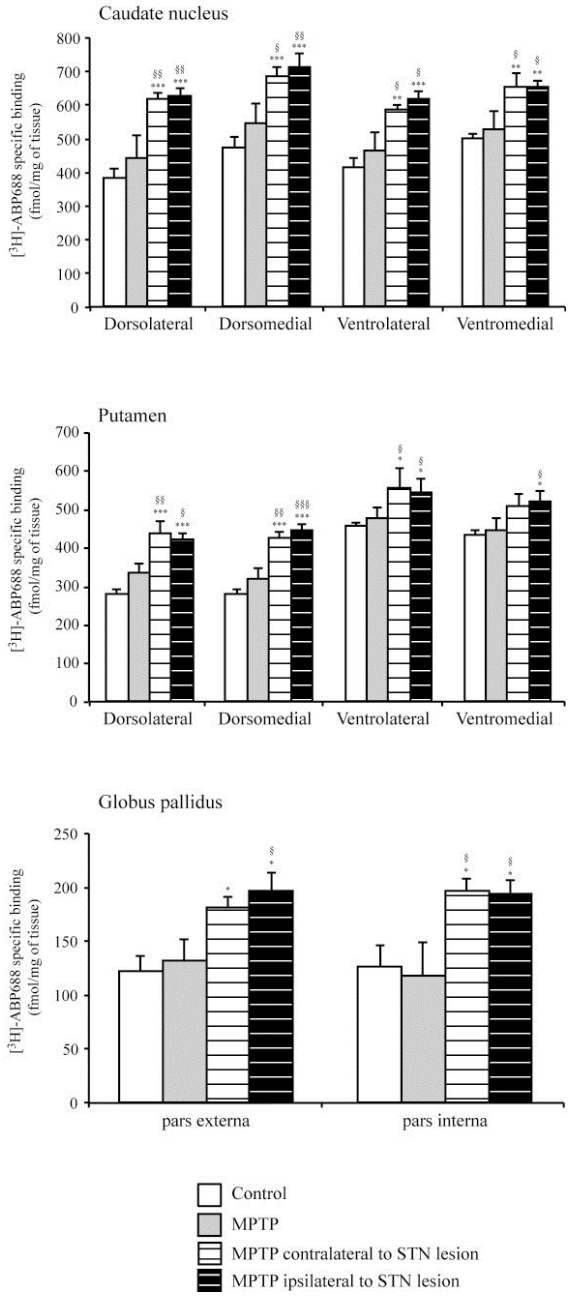

Figure 7.5 mGlu5 receptor specific binding in the caudate nucleus, putamen and globus pallidus of control, saline-treated MPTP monkeys (MPTP) and STN-lesioned MPTP monkeys with LID showing binding contralateral and ipsilateral to the STN lesion. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs controls; § $p < 0.05$, §§ $p < 0.01$, §§§ $p < 0.001$ vs saline-treated MPTP monkeys.

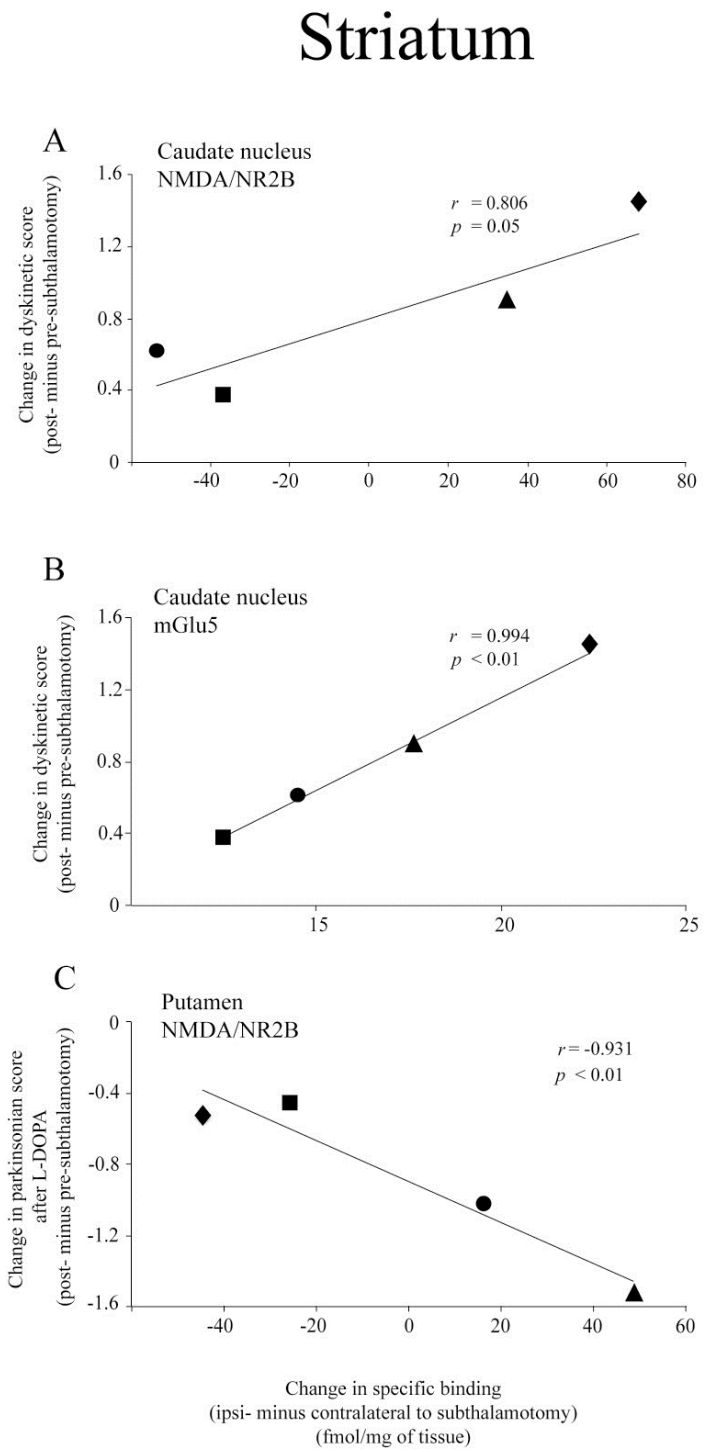

Figure 7.6 **A:** Correlation between the change in dyskinetic score (low dose of L-DOPA from (Jourdain et al., 2013)) induced by subthalamotomy and the difference between the ipsi- and contralateral to STN lesion [3H]-Ro 25-6981 specific binding in the caudate nucleus. **B:** Similar correlations with [3H]ABP688 specific binding in the caudate nucleus and **C:** Similar correlations with [3H]-Ro 25-6981 specific binding in the putamen.

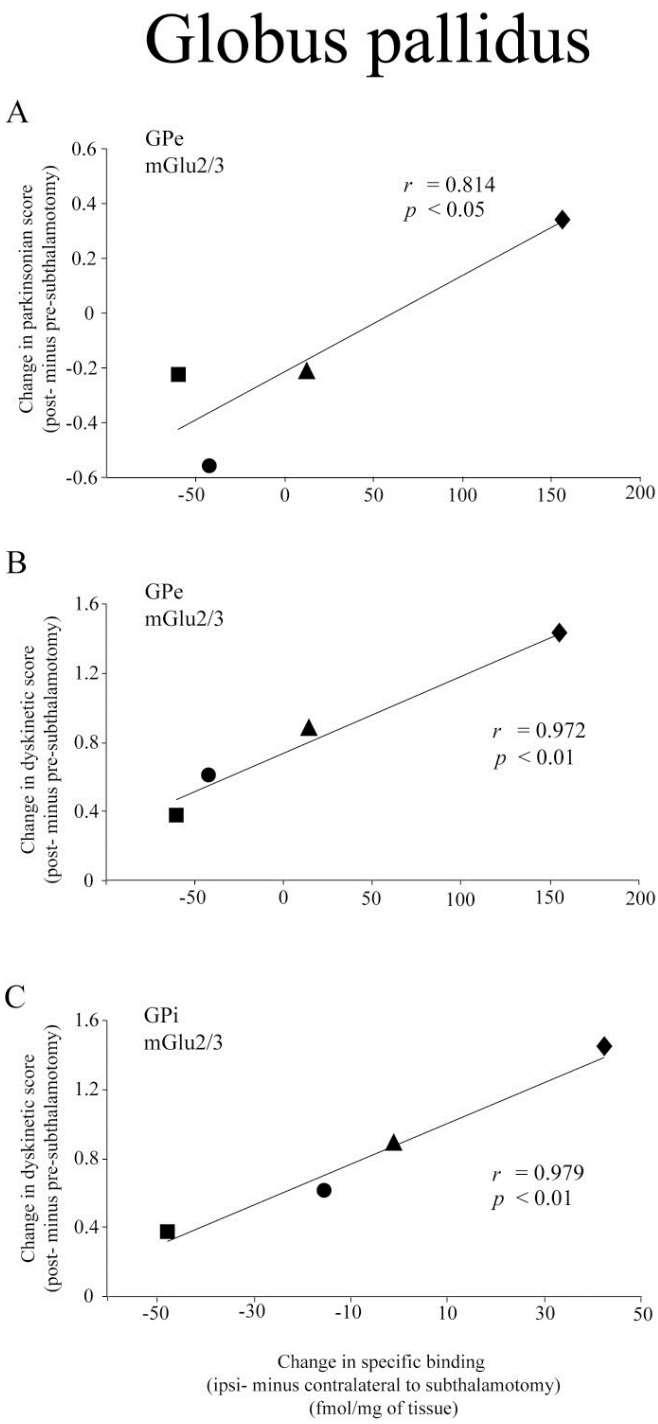

Figure 7.7 **A:** Correlation between the change induced by subthalamotomy in baseline parkinsonian score (from (Jourdain et al., 2013)) and the difference between the ipsi- and contralateral to STN lesion [^{3}H]LY341495 specific binding in the GPe. Correlations between the change in dyskinetic score (low dose of L-DOPA from (Jourdain et al., 2013)) induced by subthalamotomy and the difference in the [^{3}H]LY341495 specific binding in **B:** the GPe and **C:** the GPi.

RECEPTOR and brain region	STN-lesioned MPTP monkeys with LID	Correlation
AMPA		
Caudate nucleus	0, !	None
Putamen	0, !	None
GPe	ND	N/A
GPi	ND	N/A
NMDA		
Caudate nucleus	0, □	Positive with LIDS
Putamen	-, □	Negative with PDS
GPe	0, □	None
GPi	0, □	None
mGlu2/3		
Caudate nucleus	-, !	None
Putamen	-, !	None
GPe	-, !	Positive with PDS Positive with LIDS
GPi	-, !	Positive with LIDS
mGlu5		
Caudate nucleus	+, ″	Positive with LIDS
Putamen	+, ″	None
GPe	+, ″	None
GPi	+, ″	None

0, -, +: No effect, decreased or increased receptor specific binding vs. control monkeys;
□, ! , ″ : no effect, lower or higher receptor specific binding vs. vehicle-treated MPTP monkeys;
LIDS: L-DOPA-induced dyskinesia score;
N/A: not applicable; ND: no specific binding detected;
PDS: parkinsonian score.

Table 7.1 Summary of glutamate receptors results in the basal ganglia of MPTP monkeys with LID that underwent a unilateral subthalamotomy.

PARTIE III. DISCUSSIONS ET CONCLUSION

Cette thèse s'est penchée sur l'étude de la subthalamotomie comme traitement des LID chez le primate parkinsonien. Les résultats obtenus ont été discutés dans les sections de discussion des articles respectifs dans les chapitres 5 à 7. Dans le présent chapitre, nous tenterons de circonscrire les éléments les plus importants qui ressortent des résultats présentés et de proposer une hypothèse générale qui combine les différents éléments explorés. De plus, nous nous pencherons sur quels autres systèmes neurochimiques qui seraient à investiguer dans la subthalamotomie, mais aussi dans les autres chirurgies offertes aux patients pour le traitement des dyskinésies, soient la pallidotomie et la stimulation cérébrale profonde.

8.1 Discussion générale

Les LID sont des effets secondaires débilitants pour le patient parkinsonien. Elles seraient le résultat d'une stimulation pulsatile non-physiologique des récepteurs dopaminergiques dans un système nigrostriatal largement déplété ainsi qu'une mauvaise régulation glutamatergique dans les BG, principalement le striatum (Jenner, 2008). La L-DOPA nouvellement administrée chez le parkinsonien est transformée en DA et est utilisée rapidement par les cellules dopaminergiques restantes de la SNc. La stimulation pulsatile des récepteurs dopaminergiques D_1 et D_2 sont intrinsèquement associés aux LID. De plus, il est bien connu qu'il y a une augmentation de l'activité excitatrice corticostriatale (Ghiglieri *et coll.*, 2012). Cette altération dans la transmission glutamatergique a probablement des conséquences sur les récepteurs au glutamate NMDA et AMPA, qui interagissent avec les récepteurs dopaminergiques (Johnson *et coll.*, 2009, Wang *et coll.*, 2012). Les récepteurs au glutamate métabotropiques mGlu2/3 et mGlu5 sont aussi connus pour interagir avec les récepteurs dopaminergiques (Johnson *et coll.*, 2009). Donc, une administration discontinue de L-DOPA et une augmentation de glutamate thalamo- et corticostriatale génèrent des changements biochimiques dans les structures impliquées. Ceux-ci se traduisent fonctionnellement sous forme de LID. Ces changements biochimiques conséquents furent souvent révisés (Bezard *et coll.*, 2001a, Brotchie, 2000, Brotchie *et coll.*, 2005, Calon *et coll.*, 2000a, Huot *et coll.*, 2013, Jenner, 2008).

Les chirurgies lésionnelles (section 3.2), qui sont aujourd'hui offertes aux patients présentant des LID importantes ou étant réfractaires à la médication dopaminergique, ont

une longue histoire derrière elles, étant introduites avant la L-DOPA (Gildenberg, 2006). N'ayant pas les connaissances neuroanatomiques dont nous avons accès aujourd'hui, le site de lésion variait selon le chirurgien et son expérience personnelle (Gildenberg, 2006). Les bénéfices cliniques de la pallidotomie et de la subthalamotomie sont bien connus (voir section 3.2, appendice 1 et (Hariz, 2009, Obeso *et coll.*, 2009)). Malgré tout, très peu est connu des mécanismes sous-jacents de ces deux chirurgies. Dans le cas de la subthalamotomie, les effets pro-dopaminergiques de cette lésion et la nature glutamatergique de cette structure nous ont amené à nous pencher sur ces deux systèmes de neurotransmission, déjà connus pour être impliqués dans les LID.

8.2 Hypothèse dopaminergique

Le chapitre 5 de cette thèse s'est penché, entre autres, sur la faisabilité de reproduire une lésion du STN chez le singe MPTP présentant des LID (Jourdain *et coll.*, 2013). En utilisant trois doses de L-DOPA (pour définition, voir section 4.2.1), nos résultats ont démontré que la subthalamotomie unilatérale provoquait une potentialisation de la réponse à la L-DOPA. En effet, toutes les doses de L-DOPA testées, ainsi que le véhicule, induisaient une meilleure réponse motrice suivant la lésion. Plus spécifiquement, la dose sous-optimale avait des bénéfices antiparkinsoniens similaires à ceux observés à une dose optimale avant la lésion du STN, mais avec une réduction 40% de L-DOPA. Les LID furent aussi augmentées aux doses optimale et sous-optimale de L-DOPA. De plus, la bradykinésie, telle que mesurée par une tâche de préhension, fut améliorée à la faible dose de L-DOPA après la subthalamotomie. Donc, ces éléments pointent tous vers une potentialisation de la réponse à la L-DOPA induite par la lésion du STN, plus précisement à une faible dose.

Nous avons aussi pu démontrer que ces effets pro-dopaminergiques étaient conséquents d'une lésion restreinte aux neurones du STN. À notre connaissance, ceci était la première démonstration que ce type de lésion était une des causes permettant la réduction de la médication antiparkinsonienne. Les lésions pratiquées dans les études chez les patients sont de type thermolyse/électrocoagulation, lésant du même coup les fibres pallidothalamiques et possiblement la zona incerta (Alvarez *et coll.*, 2009, Patel *et coll.*,

2003). Il est donc difficile de discerner, dans leur cas, les effets de la lésion du STN de ceux de la lésion du H_2 et de la zona incerta (pour discussion voir ci-bas, section 8.4.2.1).

Par après, nous avons investigué les changements dans la neurotransmission dopaminergique. Nos résultats ont démontré que la voie directe striatonigrale serait probablement responsable de cette potentialisation de réponse. En effet, nous avons observé des augmentations significatives dans la synthèse et la densité des récepteurs D_1 dans le striatum dorsolatéral ipsilatéral à la lésion. D'un autre côté, les récepteurs D_2, associés à la voie indirecte striatopallidale du modèle des BG, sont demeurés inchangés par la lésion.

Cette hausse dans les récepteurs D_1 pourrait être conséquente de la baisse de l'afférence excitatrice subthalamonigrale (Carpenter *et coll.*, 1981b, Nauta et Cole, 1978) par la subthalamotomie. Il fut récemment démontré que la lésion du STN diminuait les niveaux de DA striatal ipsilatéral à la lésion chez le singe normal (Shimo et Wichmann, 2009), confirmant l'importance de cette voie subthalamonigrale. Une hausse dans la densité des récepteurs D_1 dans le striatum favoriserait la voie directe striatonigrale, qui est connue pour être facilitatrice ou, en d'autres termes, « pro-mouvement » (DeLong, 1990). De plus, les récepteurs D_1 sont fortement associés à l'expression des LID (Aubert *et coll.*, 2005, Guigoni *et coll.*, 2007). Ce qui pourrait expliquer pourquoi nous avons observé une augmentation des LID après la chirurgie, tout en maintenant les mêmes doses de L-DOPA. Cette dernière observation fut précédemment démontrée chez les patients parkinsoniens après une subthalamotomie unilatérale (Alvarez *et coll.*, 2001). Nos résultats sur le système dopaminergique démontrent des aspects intéressants, qui devront être confirmés sur des tissus humains de patients ayant reçu cette chirurgie et/ou par PET (Laihinen *et coll.*, 1994).

8.3 Hypothèse glutamatergique

Parmi les changements biochimiques dans les LID (Huot *et coll.*, 2013), le glutamate est bien reconnu pour son implication (section 4.1.3.3). Le STN est la seule structure glutamatergique intrinsèque aux BG (Smith et Parent, 1988) et son activité neuronale est modifiée dans un modèle de PD (Bergman *et coll.*, 1994). En effet, son activité électrique augmente en termes de fréquence, d'activité oscillatoire et de décharges par bouffée (*burst firing*) (Bergman *et coll.*, 1994). Sa lésion aurait pour effet de réduire les dysrégulations afférentes vers ses structures de projection et ainsi rétablir un équilibre

(Bergman *et coll.*, 1990). Dans le chapitre 7 de cette thèse, nous avons mesuré la densité des récepteurs ionotropiques et métabotropiques impliqués dans la PD et les LID chez les singes MPTP dyskinétiques qui ont reçu une subthalamotomie unilatérale et avons comparé ces données à celles obtenues chez des contrôles et des singes MPTP. Il fut précédemment observé que le traitement à la L-DOPA induisait des hausses de la liaison spécifique pour les récepteurs AMPA dans le striatum (Ouattara *et coll.*, 2010b). Nous avons observé que les récepteurs AMPA dans les parties motrices du striatum n'étaient pas différents des contrôles et des singes MPTP. Cette absence d'augmentation chez les singes MPTP avec le STN lésé pourrait s'expliquer par cette lésion du STN. De plus, l'état de phosphorylation de ces récepteurs, qui n'est pas mesurable par autoradiographie, pourrait participer à l'efficacité des antagonistes AMPA (Konitsiotis *et coll.*, 2000) et non pas seulement la densité. L'administration de l'antagoniste NMDA amantadine réduit les LID (Blanchet *et coll.*, 1998), mais au coût d'une réduction de l'efficacité antiparkinsonienne de la L-DOPA (Grégoire *et coll.*, 2013, Rylander *et coll.*, 2010). Nous n'avons pas observé de changements chez les singes MPTP ayant reçu une subthalamotomie en termes de densité des récepteurs NMDA. Il fut précédemment observé que le traitement à la L-DOPA induisait des hausses de la liaison spécifique pour les récepteurs NMDA dans le striatum (Ouattara *et coll.*, 2008). Cette correction de hausse pourrait être attribuable à la lésion du STN. Tout comme son homologue ionotropique AMPA, l'état de phosphorylation et la localisation des récepteurs NMDA pourraient aussi jouer un rôle important (Hallett *et coll.*, 2005) dans les LID. D'un autre côté, les récepteurs métabotropiques mGlu2/3 étaient fortement réduits (70 à 80%) dans le striatum et le pallidum chez les singes MPTP qui ont reçu une subthalamotomie unilatérale pour le traitement de leur LID. Ces baisses furent bilatérales et ne semblent pas dues à un traitement à la L-DOPA, car ils demeurent inchangés avec un traitement chronique chez le singe MPTP (Samadi *et coll.*, 2008a). Les améliorations motrices bilatérales de la subthalamotomie pourraient être expliquées par cette baisse bilatérale de mGlu2/3. Ces récepteurs au glutamate sont exprimés par les neurones pré-synaptiques du STN (Testa *et coll.*, 1998). Quoique leur origine dans le pallidum est encore inconnue (Conn *et coll.*, 2005), il est raisonnable de postuler que la présence des récepteurs mGlu2/3 dans le GPi et le GPe proviennent des afférences subthalamiques, car ni le thalamus ni le cortex projettent au pallidum chez le primate

(Carpenter, 1989, Naito et Kita, 1994). Le rôle exact des récepteurs mGlu2/3 dans les ganglions de la base reste à être élucidé, mais son interaction avec le système dopaminergique (Bauzo *et coll.*, 2009, Kronthaler et Schmidt, 2000) soulève des pistes intéressantes à explorer. Dans cette investigation glutamatergique, les récepteurs mGlu5 ont suivi un patron qui est bien connu, qui est une légère augmentation avec le MPTP et une augmentation significative avec l'administration de L-DOPA (Ouattara *et coll.*, 2010a). Aucun changement ne fut observé sur la liaison spécifique au mGlu5 induit par la subthalamotomie. Finalement, de fortes corrélations furent observées entre les changements de densité des récepteurs NMDA, mGlu2/3 et mGlu5 (côté lésé versus côté non-lésé) et les changements dans les scores parkinsoniens et scores dyskinétiques (pré- versus post-subthalamotomie). Ces corrélations mettent en valeur l'impact des changements de récepteurs sur le comportement parkinsoniens, qui ne ressortirait pas nécessairement si l'on ne se fie qu'à l'analyse simple par autoradiographie. Elle démontre que des petits changements dans la liaison spécifique des récepteurs peuvent avoir des conséquences tangibles sur les aspects fonctionnels.

8.4 Perspectives futures

La prochaine section parcoure quelques unes des prochaines étapes à poursuivre dans ce projet de recherche. Elle se veut un peu exploratrice où toutes hypothèses de recherche présentées pourraient faire l'objet d'investigations futures sur la subthalamotomie.

8.4.1 Exploration des autres systèmes

Tel que démontré dans la section sur la neurochimie des ganglions de la base (section 1.2), les structures qui composent les BG reçoivent des afférences GABAergiques, cholinergiques et sérotoninergiques. Ces systèmes de neurotransmission ne furent pas couverts dans cette présente thèse. Il serait toutefois fort intéressant qu'ils soient explorés pour bien discerner tous les changements induits par la subthalamotomie. Le GABA est le neurotransmetteur le plus utilisé dans les BG (Samadi *et coll.*, 2007), dont les deux voies principales de sortie du STN : le GPi et le GPe. La baisse des afférences excitatrices du STN pourrait réduire l'activité enzymatique (GAD65 et GAD67) pour la synthèse de

GABA (Pinal et Tobin, 1998). Conséquemment, les structures qui reçoivent des afférences pallidales pourraient présenter des changements dans la densité des récepteurs GABAergiques. La lésion du GPi (voir ci-bas, section 8.4.2.2) provoque une augmentation des récepteurs $GABA_A$ dans le noyau thalamique recevant ses afférences (Ambardekar *et coll.*, 2003). Il est donc raisonnable de postuler que la subthalamotomie pourrait avoir des effets GABAergiques au second degré.

Dans le même ordre d'idée, la majorité de la 5-HT dans les BG origine du noyau raphé dorsal et innerve toutes les structures de la BG et le thalamus à différents degrés (Lavoie et Parent, 1990, 1991b, Parent *et coll.*, 2011, Wallman *et coll.*, 2011). De plus, la 5-HT a un effet modulateur sur les structures recevant une telle innervation (Huot *et coll.*, 2011). Aucune étude neuroanatomique n'a pu démontré une projection du STN vers le noyau raphé dorsal (Carpenter *et coll.*, 1981b, Nauta et Cole, 1978). Toutefois, une étude récente a démontré que la stimulation à hautes fréquences du STN inhibait les neurones sérotoninergiques du noyau raphé dorsal (Tan *et coll.*, 2011). Cette inhibition pourrait expliquer les baisses de 5-HT dans le cortex préfrontal et dans l'hippocampe chez le rat 6-OHDA avec une stimulation similaire du STN (Navailles *et coll.*, 2010). Ces deux études démontrent qu'une altération chirurgicale du STN provoque des changements dans l'activité sérotoninergique. La subthalamotomie pourrait donc avoir des influences, ce qui pourrait se réfléter sur la densité des récepteurs sérotoninergiques et les taux de 5-HT dans les structures recevant ce type d'innervation.

Le troisième et dernier grand système de neurotransmission qui pourrait être affecté par une subthalamotomie est le système cholinergique. La vaste majorité des connexions cholinergiques des BG et au thalamus proviennent des afférences pédunculopontines (Lavoie et Parent, 1994b, c, Pahapill et Lozano, 2000). Le STN et le PPN sont intimement interconnectés chez le rat (Granata et Kitai, 1989, Inglis et Winn, 1995, Jackson et Crossman, 1981b); la voie subthalamo-pédunculopontine reste à être démontrée chez le primate. Si une telle connexion existait, elle serait fort probablement affectée par la lésion du STN. Tout d'abord, son activité fonctionnelle serait diminuée étant donné la nature excitatrice du STN (Smith et Parent, 1988). En retour, le GPi, la SNc et le thalamus recevraient moins d'afférences cholinergiques et/ou glutamatergiques (Lavoie et Parent, 1994a, c). D'un autre côté, des études neuropathologiques ont clairement démontré une

dégénérescence d'environ 40% des cellules du PPN dans la PD (Jellinger, 1991, Zweig *et coll.*, 1989a). Est-ce que le STN pourrait participer à cette perte cellulaire par excitotoxicité (Henchcliffe et Beal, 2007)? Dans la positive, la subthalamotomie aurait un effet bénéfique si pratiquée précocement dans la PD, ce qui n'est pas présentement le cas (Alvarez *et coll.*, 2009, Patel *et coll.*, 2003).

8.4.2 Explorations des approches chirurgicales

Cette sous-section de discussion se veut exploratoire des approches chirurgicales offertes aux patients pour le traitement de leurs LID. Nous allons tout d'abord voir quelles sont les autres approches de recherche sur la subthalamotomie qui permettraient de mieux comprendre cette chirurgie. Cette présente thèse n'a que commencé à l'étudier; il reste d'autres paradigmes à considérer. Ceux-ci seront exposés dans la présente sous-section. Toujours dans une perspective d'exploration, nous ferons une ouverture sur la pallidotomie et la stimulation cérébrale profonde. Finalement, quelques-unes des questions qui restent en suspens seront exposées.

8.4.2.1 Subthalamotomie

Les résultats de cette thèse furent basés sur une lésion partielle du STN. En effet, la lésion la plus importante en terme de volume fut de 25% du volume total du STN. Toutes les lésions étaient produites dans la portion sensorimotrice du STN pour représenter le plus fidèlement les subthalamotomies dans un cadre clinique. Malheureusement, les pourcentages de STN lésé sont rarement publiés dans la littérature clinique. D'un autre côté, la plupart des études produites chez le rat considèrent seulement les animaux dont le STN est complètement lésé (Blandini et Greenamyre, 1995, Centonze *et coll.*, 2005, Périer *et coll.*, 2003, Price *et coll.*, 1993). La situation est similaire dans les études chez le primate dont plus de 80% du STN est lésé (Guridi *et coll.*, 1996, Wallace *et coll.*, 2007). Il serait donc intéressant de se pencher sur les différences entre les lésions partielles et totales du STN. De plus, nous avons procédé à une lésion unilatérale, représentant la majorité des études dans ce domaine (voir appendice 1). La subthalamotomie bilatérale est aussi pratiquée (Alvarez *et coll.*, 2005, Tseng *et coll.*, 2007). Dans une autre série d'études, les changements induits par les lésions uni- versus bilatérales pourraient être comparées.

D'autre part, nous avons utilisé l'acide iboténique, qui se lie aux récepteurs glutamatergiques, provoque une mort cellulaire par excitotoxicité et épargne les fibres de passage (Schwarcz *et coll.*, 1979). Alors, les axones de la voie pallidothalamique furent épargnés de la lésion, ce qui diffère de la thermolyse/radiofréquence utilisé en clinique (Patel *et coll.*, 2003). Dans une autre série d'études, il serait intéressant de comparer ces deux types d'approches lésionnelles. En effet, nous avons démontré dans le chapitre 5 que la réduction de la médication était possible avec la lésion restreinte aux neurones du STN sans toucher aux fibres pallidothalamiques. Est-ce qu'un effet similaire est possible avec la destruction de ces fibres sans toucher les neurones sous-thalamiques? Si oui, est-ce qu'on obtient une meilleure réponse pro-dopaminergique avec des lésions qui affectent le STN et les fibres H_2? D'autre part, nous avons observé une potentialisation de la réponse à la L-DOPA avec un volume lésé de 25% ou moins. On pourrait se demander s'il y a une corrélation entre l'étendue de la lésion et la potentialisation de la réponse. Dans notre étude, nous n'avons vu aucune corrélation, car les quatre singes ont obtenu une potentialisation de réponse similaire. Il n'empêche que les lésions produites furent partielles; une lésion complète pourrait avoir de plus amples bénéfices. La réponse à cette question est importante. Y a-t-il un volume optimal de lésion? Est-ce que le patient retire des bénéfices supplémentaires si le volume du STN lésé est majeur? Si l'on se fie à la pallidotomie (Gross *et coll.*, 1999), il y existe une corrélation négative entre le volume lésé et le score parkinsonien sans médication. Par contre, il y a une corrélation positive entre le volume lésé et la réduction des LID. De plus, les risques d'effets secondaires deviennent-ils importants à partir d'un seuil de lésion? Le STN demeure une petite structure et il y a peu de marge de manœuvre en termes de contrôle de lésion par thermolyse, encore moins par irradiation (gamma knife), d'où l'importance d'approfondir nos connaissances sur les lésions chimiques (Okun et Vitek, 2004). Il reste encore beaucoup de questions sans réponse à propos de la subthalamotomie, laissant la place à d'autres recherches fascinantes.

8.4.2.2 Pallidotomie

Quoiqu'elle n'est pas la plus fréquente parmi les chirurgies lésionnelles pour la PD (Jourdain et Schechtmann, 2013), la subthalamotomie offre des avantages comparativement aux autres lésions (voir appendice 1). La subthalamotomie est, en quelque sorte, une pseudo-pallidotomie, car on réduit la suractivation des neurones du GPi indirectement par

une baisse de l'afférence excitatrice du STN. Cliniquement, la pallidotomie réduit les LID d'environ 60%, mais la médication reste inchangée (Hariz, 2009). Il serait donc intéressant d'explorer les mécanismes de la lésion du GPi, car ils diffèrent nécessairement de la subthalamotomie. Cette structure est GABAergique et projette principalement vers les noyaux VA et VL du thalamus moteur, ainsi que vers le PPN (voir section 1.2.2.1). L'implication du système GABAergique fut déjà explorée chez le singe et l'humain parkinsonien présentant des dyskinésies (Calon *et coll.*, 2000b, Calon *et coll.*, 2003a). Il fut démontré que les récepteurs $GABA_A$ et $GABA_B$ augmentent dans le GPi après le traitement au MPTP (Calon *et coll.*, 2000b, Zeng *et coll.*, 2004), d'autres auteurs n'ont pas vu de différence dans le $GABA_A$ (Robertson *et coll.*, 1990). Dans les noyaux thalamiques recevant de l'afférence pallidale, le $GABA_B$ demeure inchangé avec le MPTP et des agonistes dopaminergiques (Calon *et coll.*, 2000b). Une lésion du GPi unilatérale provoque une augmentation des récepteurs $GABA_A$ dans le VAL comparativement au côté non-lésé chez le macaque normal (Ambardekar *et coll.*, 2003). Aucune différence fut toutefois observée chez le chat normal après une pallidotomie (Kultas-Ilinsky *et coll.*, 1990). L'augmentation thalamique de $GABA_A$ est fort probablement due à une compensation pour la baisse de l'afférence GABAergique pallidothalamique. À notre connaissance, de telles mesures n'ont pas encore été faites chez le singe MPTP. Il serait donc fort intéressant d'investiguer les récepteurs $GABA_A$ chez le singe parkinsonien et/ou dyskinétique dans le thalamus ventral après pallidotomie. Selon les données évoquées précédemment, le récepteur $GABA_B$ ne semble pas être influencé dans un cadre parkinsonien (Calon *et coll.*, 2000b). Il serait donc raisonnable d'écarter l'hypothèse que ce récepteur serait modifié après une pallidotomie.

L'afférence principale du GPi serait le PPN (voir section 1.2.7 (Pahapill et Lozano, 2000)). En retour, le PPNc et PPNd innervent profusément le GPi et légèrement le VL et le VA (Lavoie et Parent, 1994c). La désinhibition du PPN par une pallidotomie pourrait avoir pour conséquence une augmentation de l'afférence au thalamus. Toutefois, il n'est pas connu si cette afférence est cholinergique et/ou glutamatergique (Lavoie et Parent, 1994b). La présence de récepteurs nicotiniques (Kulak et Schneider, 2004, Pauly *et coll.*, 1991, Perry *et coll.*, 2002) et muscariniques (Warren *et coll.*, 2007) dans les noyaux moteurs du thalamus (VA, VL, CM/Pf) suggère une afférence au moins cholinergique. La

quantification de la densité des récepteurs cholinergiques et glutamatergiques (sans négliger l'afférence de la voie corticothalamique (Catsman-Berrevoets et Kuypers, 1978)) pourrait entre autre éclairer sur l'apport de cette voie dans la PD, les LID et l'effet de la pallidotomie.

8.4.2.3 Stimulation cérébrale profonde

La stimulation cérébrale profonde du STN et du GPi offre des résultats cliniques similaires sinon meilleurs que ceux obtenus par leurs lésions respectives (Guridi *et coll.*, 2008). Il fut longtemps cru que le DBS répliquait les effets inhibiteurs de la lésion sur les cellules et les axones (Montgomery et Baker, 2000). Il est maintenant reconnu que le corps cellulaire des neurones sont inhibés par la stimulation électrique mais que leurs axones sont activés (Lozano et Lipsman, 2013). Donc, la lésion et la stimulation ont des effets opposés sur les fibres de passage, mais les bénéfices cliniques sont similaires. Tels que proposés pour les chirurgies lésionnelles, il serait fort intéressant d'investiguer les changements biochimiques suivant une stimulation chronique du STN ou du GPi. De plus, pour ajouter à la complexité du DBS, les paramètres de stimulation (amplitude de stimulation, durée d'impulsion et la fréquence) sont indépendants et peuvent être variés selon les besoins cliniques (Andrade *et coll.*, 2009). La variation de ces paramètres peut induire des changements importants dans l'activation cellulaire. Par exemple, une stimulation à hautes fréquences et à haute amplitude du STN induit une phosphorylation de la sous-unité NMDA/NR2B similaire à celle obtenue avec la L-DOPA chez le rat (Quintana *et coll.*, 2012). D'autre part, la stimulation du STN provoque la relâche de glutamate dans le GPi et la SNr (Windels *et coll.*, 2003), une relâche intrinsèque de GABA dans la SNr (Windels *et coll.*, 2003, Windels *et coll.*, 2005) et de DA dans le striatum (Lee *et coll.*, 2006). Si l'on considère la complexité de la neurochimie des BG (voir section 1.4), il reste encore beaucoup à explorer dans un cadre parkinsonien et dyskinétique.

Plus récemment, le DBS à courant constant, comparativement au courant variable présentement utilisé et approuvé (Cheung et Tagliati, 2010), fut testé avec des résultats intéressants pour la PD (Okun *et coll.*, 2012). La stimulation à courant constant considère les différences dans l'impédance du tissu environnant, ce que le DBS classique à courant variable ne considère pas (Lempka *et coll.*, 2010). Alors, ces deux types de stimulation ont fort probablement des mécanismes d'action différents au niveau cellulaire, ce qui laisse

place à beaucoup d'explorations. À notre connaissance, aucune étude sur le DBS ne s'est fait sur le primate parkinsonien dyskinétique. Les coûts reliés au DBS et les limites physiques et éthiques de ce modèle animal peuvent entre autre expliquer l'absence d'investigations jusqu'à présent.

8.4.3 Autres questions en suspens

Le but principal de léser le STN est de réduire les dyskinésies chez le patient. Nous avons démontré que les singes ayant reçu une subthalamotomie avait une potentialisation de la réponse antiparkinsonienne de la L-DOPA, soit 1- par une augmentation des bénéfices moteurs due à la médication, 2- par une augmentation des dyskinésies à faible dose et à dose optimale de L-DOPA, 3- par augmentation de la durée de la réponse antiparkinsonienne à faible dose de L-DOPA et 4- par une réduction de la bradykinésie à faible dose de L-DOPA mesurée par une tâche de préhension. Ces effets pro-dopaminergiques sont similaires à ceux mesurés chez le patient après une subthalamotomie. En effet, les patients voient leurs dyskinésies réduites entre 40 et 80%. Une des facettes les plus importantes est la constance de cette réduction de LID dans le temps. La revue de littérature présenté en appendice 1 démontre que les LID sont abaissées de 65% six mois après la subthalamotomie et ce pourcentage reste le même après un et deux ans. Un autre avantage de la subthalamotomie, comparativement à la pallidotomie, est la réduction de la médication. Après un an, la médication est réduite d'environ 45% et de 30% à la deuxième année. Cette divergence entre dyskinésie et prise de médication nous amène à se poser d'autres facettes encore aujourd'hui inexplorées. Par exemple, quelles sont les conséquences biochimiques de réduire la médication suivant un traitement chronique de L-DOPA? Il fut déjà proposé de réduire ou même cesser temporairement la L-DOPA pour réduire le *wearing-off* et les LID (Direnfeld *et coll.*, 1978, Mayeux *et coll.*, 1985), mais cela fut peu concluant cliniquement chez l'humain. Dans le cas de chirurgie, ces réductions de médication ne sont pas transitoires mais bien chroniques. Selon nos connaissances, cette stratégie ne fut pas encore explorée mais elle est d'une importance capitale si l'on veut bien comprendre les effets biochimiques et faire le pont avec les améliorations fonctionnelles du patient.

Une des pistes pourrait résider dans la voie pallidothalamique. La pallidotomie réduit l'afférence GABAergique vers le thalamus ventral, tout comme la subthalamotomie produite en clinique (il est important de se rappeler que la subthalamotomie chez le patient est souvent pratiquée par thermolyse ou radiofréquence et lèse aussi les fibres pallidothalamiques). Par conséquent, on pourrait mesurer une réduction de GABA dans le thalamus ventral, soit par HPLC, par liaison spécifique avec des radioligands ou par microdialyse. L'enregistrement neuronale des structures motrices du thalamus pré-, per- et post-opératoire pourrait aussi éclairer les changements de l'activité des neurones. D'autre part, le thalamus ventral reçoit des afférences sous-thalamiques, telles que démontrées chez le primate (Rico *et coll.*, 2010). Considérant que cette connexion subthalamo-thalamique serait intacte dans la pallidotomie, elle pourrait jouer un rôle dans la réduction de L-DOPA avec la subthalamotomie.

Le CM/Pf projette vers le STN (Sadikot *et coll.*, 1992b), mais il semblerait qu'il est le seul noyau thalamique à innerver le STN (Parent et Hazrati, 1995b). Entre 30 et 40% cellules du CM/Pf dégénèrent dans la PD (Henderson *et coll.*, 2000a, b). Chez le singe MPTP, environ 60% des cellules du thalamus intralaminaires dégénèrent et ce, que les animaux présentent des symptômes parkinsoniens ou non (Villalba *et coll.*, 2013). La déplétion dopaminergique induit une hausse de l'activité du STN (Bergman *et coll.*, 1994) et cette suractivité est corrigée par une lésion du CM/Pf chez le rat (Bacci *et coll.*, 2004). Toutefois, la lésion du CM ne rétablit pas les fonctions motrices, ni réduit les LID chez le primate parkinsonien (Lanciego *et coll.*, 2008). Ces observations semblent contradictoires, mais l'importance de cette voie thalamo-subthalamique pourrait varier selon les espèces. Par contre, chez les sujets parkinsoniens, une stimulation du CM/Pf a des effets bénéfiques sur les LID (Stefani *et coll.*, 2009). En terminant, l'apport important du PPN est aussi à considérer dans le STN et le CM/Pf (Lavoie et Parent, 1994c). En somme, il reste beaucoup à explorer dans la circuitrie des BG et les structures associées, dans la PD, les LID et les chirurgies lésionnelles et de stimulation.

8.5 Conclusion générale

Quelques éléments peuvent être soulevés de la présente thèse et nous permettre de formuler une conclusion générale. Nos résultats comportementaux et *post-mortem* nous permettent de dire que :

La subthalamotomie unilatérale par injection d'acide iboténique peut être reproduite chez le primate MPTP dyskinétique. Cette lésion a permis la réduction de 40% la médication dopaminergique. Ces données expérimentales sont similaires à celles observées chez les patients parkinsoniens qui reçoivent une subthalamotomie unilatérale. Ces effets suggèrent une potentialisation de la réponse à faibles doses de L-DOPA par la subthalamotomie. De plus, elles démontrent aussi que le singe MPTP demeure un excellent modèle pour l'étude des LID, mais aussi pour l'étude des chirurgies.

Nos données démontrent aussi qu'une lésion stricte des neurones STN, tout en épargnant les fibres pallidothalamiques, est suffisante pour avoir des effets bénéfiques bilatéralement. De plus, c'est la réduction de l'activité subthalamique, ici par destruction de portion motrice dorsolatérale, qui permet la réduction de L-DOPA.

Cette lésion du STN provoque des changements biochimiques dans la neurotransmission dopaminergique qui compose la voie directe striatonigrale du modèle des BG. La voie directe striatonigrale est reconnue pour être « pro-mouvement » et une hausse dans son activité serait associée à la potentialisation de la réponse dopaminergique suivant la subthalamotomie unilatérale.

La lésion du STN, la seule structure glutamatergique des BG, provoque des changements dans la densité des récepteurs au glutamate. Nos observations s'ajoutent aux évidences que 1- il existe des altérations glutamatergiques dans la PD et les LID et 2- que les changements dans la neurotransmission glutamatergique induits par la lésion du STN se traduisent par des améliorations motrices.

Les travaux présentés dans cette thèse sont les premiers de ce genre dans l'étude de la subthalamotomie. Ils démontrent que la lésion du STN induit des changements chroniques, sinon permanents, dans les ganglions de la base. D'autres études sont nécessaires pour confirmer ces résultats, mais aussi pour continuer à explorer cette chirurgie. Bien évidemment les éléments souvelés dans les perspectives futures ne sont fondées que sur des connaissances neuroanatomiques et demeurent spéculatives. Les

nouveaux outils de recherche dont le DBS et l'isolation de voies neuroanatomiques par optogénétique (Galvan *et coll.*, 2012) pourront éventuellement répondre à plusieurs de ces questions. La neurochirurgie stéréotaxique est en pleine expansion, pas seulement pour les troubles du mouvement, mais aussi pour des troubles neurologiques et psychiatriques (Benabid, 2007). Les patients atteints de maladies neurologiques peuvent maintenant voir leur avenir et leur qualité de vie de manière plus optimiste.

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PARTIE V. APPENDICES

APPENDICE 1

SUBTHALAMOTOMY IN THE TREATMENT OF PARKINSON'S DISEASE: CLINICAL ASPECTS AND MECHANISMS OF ACTION

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Résumé

La maladie de Parkinson (PD) est une contidion neurodégénérative qui peut être traitée pharmacologiquement avec la L-DOPA. Sa prise chronique génère toutefois des symptômes moteurs et non-moteurs importants. Le noyau sous-thalamique (STN) est connu pour son implication dans la pathophysiologie de la PD et contribue aux complications induites par la L-DOPA. Les traitements chirurgicaux sont offerts aux patients réfractaires à la pharmacothérapie par la L-DOPA et à ceux qui présentent des dyskinésies sévères. La stimulation cérébrale profonde du STN est présentement la chirurgie de l'heure pour le traitement de la PD, mais les lésions sont encore pratiquées dans le monde. La lésion du STN, aussi appelée subthalamotomie, est l'une des options chirurgicales lésionnelles pour les patients avec des dyskinésies induites à la L-DOPA. Ce chapitre est une revue de littérature qui couvre les aspects cliniques et les complications de la subthalamotomie. De plus, les mécanismes possiblement impliqués dans ses effets fonctionnels sont discutés.

Abstract

Parkinson's disease (PD) is a neurodegenerative condition that can be pharmacologically treated with L-DOPA. However, important motor and non-motor symptoms appear with long-term use. The subthalamic nucleus (STN) is known to be involved in the pathophysiology of PD and to contribute to L-DOPA-induced complications. Surgical therapy is considered in advanced PD patients, who are refractive to pharmacotherapy and who display disabling dyskinesia. Deep brain stimulation (DBS) of the STN is currently the main surgical procedure in PD, but lesions are still performed. This review covers the clinical aspects and complications of subthalamotomy as one of the lesion-based options for PD patients with L-DOPA-induced dyskinesias. Moreover, the possible mechanisms involved in the effect subthalamic lesions have are discussed.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease and its frequency is expected to increase as populations age. L-DOPA tremendously improves the cardinal symptoms of PD.[52] However, its chronic administration leads to major motor complications, where patients may encounter motor fluctuations, wearing-off, and dyskinesias.[178] Dyskinesia describes aimless, involuntary movements for which no pharmacological treatments are currently approved.[107] Around 40% of patients will develop L-DOPA-induced dyskinesias (LID) after 4-6 years of treatment, and this percentage increases to 90% after 9 to 15 years.[3] This information led clinicians and surgeons to explore new ways to reduce these severe motor complications without affecting the beneficial effects of L-DOPA. The subthalamic nucleus (STN) is considered to have a pivotal role in the pathophysiology of PD and LID. The co-occurrence of PD patients presenting hemorrhagic lesions in the STN is coincidental, but some patients saw their parkinsonian symptoms alleviated following the infarct.[147,174,190] Subthalamic lesions (subthalamotomy) done on parkinsonian monkeys demonstrated promising results.[17,18,23,64] Nowadays, the STN is one of the major targets of stereotactic lesions and deep brain stimulation (DBS) for the treatment of movement disorders.[53] Despite surgical interest in the STN, there are few reviews covering subthalamotomy as a treatment of PD.[59,65,121] The present study reviews the clinical aspects and complications of subthalamotomy in the treatment of PD. Subthalamotomy is compared to other surgical treatments and a discussion is provided on the possible mechanisms involved in the beneficial motor effects of subthalamic lesions.

History of subthalamotomy

Historically, lesioning the STN has been avoided for fear of inducing hemiballism (HB). In fact, it has been known since the end of the 19th century that STN lesions provoked HB as observed in PD with stroke.[34] It was demonstrated that lesions confined to the STN had high risks of HB in normal monkeys,[35,184] and destruction of 20% of its volume was enough to provoke this involuntary movement.[35] The development of HB was confirmed in non-parkinsonian patients following lesions restricted to the STN.[46,104,108,118] Nevertheless, several authors performed so-called subthalamotomies for PD, giving rise to a great wealth of publications in the 1960's and 1970's.[13,74,102,146] During the lesioning era, the target for subthalamotomy was not the STN as it is today. In fact, authors performed their lesions on the Zona incerta (Zi),[14,112,113] the sub-ventrolateral thalamus,[116] the posterior subthalamic area and the Raprl [24,75,82,173] or H_2 Fields of Forel,[14,76,77,106,113,154,155] all under the term "subthalamotomy", while others coined the term "campotomy".[152] However, none of them targeted the STN itself. Instead, lesions were made in the subthalamic area, mainly in the fiber bundles. As pointed out by Spiegel *et al.*,[152] the advantage of targeting the pallidothalamic fibers is that a smaller lesion is needed to obtain clinical results as compared to pallidal lesions. On the other hand, since precise imaging and electrophysiological data were scarce, if not completely lacking at that time, it is difficult to compare these publications with current subthalamotomy knowledge. In the 1960's and 1970's, lesions in the subthalamic area were not restricted to PD treatment, but were also applied as treatment of tremor,[82,173] cerebral palsy,[82,94] and hyperkinetic movements,[116] including dystonia,[155] intractable spasms,[82,155] athetosis,[119,155] hemiballism,[11,12] and dyskinesia.[183]

Clinical outcome of subthalamotomy

Parkinsonian symptoms

The last two decades have been filled with many studies addressing the motor [5,16,20,47,57,58,99,109,120,129,168,176] and cognitive[7,25,105] effects of subthalamotomy for PD (see Table 1) and several case reports.[38,45,72,87,122] A recollection of studies indicates that subthalamotomies have beneficial effects on the motor symptoms in both "off" and "on"-medication states with better results from bilateral lesions. The surgery significantly reduces contralateral cardinal symptoms (tremor, bradykinesia and rigidity).[8,130] The improvements obtained with unilateral lesions appear to increase in the first 12 months and to decrease in the second year after surgery (see the averages in Table 1). Small benefits were also observed ipsilateral to STN lesions but did not sustain for more than one year.[8,130,161]

Effects on L-DOPA needs and LID

Dyskinesias, assessed by UPDRS part IV, are highly improved by both unilateral and bilateral STN lesions (Table 1). A striking feature is the consistency of LID improvement over the first two years, where a steady 65% reduction is observed (see the averages in Table 1). Contralateral diphasic dyskinesias and "off" dystonia seem to respond best to subthalamotomy, whereas peak-dose dyskinesias remain unchanged.[8] Furthermore, ipsilateral LIDs are unresponsive to STN lesions.[8] It is usually assumed that the reduction of LIDs is the result of reduced L-DOPA equivalency daily doses (LEDD) after altering STN activity.[91] One and two years after subthalamotomy, LEDD was reduced by approximately 45% and 30%, respectively. The progression of the disease may, in part, explain the diminishing improvements in motor and L-DOPA needs.[8] Nevertheless, the reduction of LEDD cannot be the sole explanation of the improvements in LIDs for two main reasons. First, the mean reduction of LIDs remained constant despite LEDD changes over a 2-year period. Second, ipsilateral LIDs continued to increase even if L-DOPA was greatly reduced. Another interesting feature of subthalamotomy is the potentiation of response to L-DOPA. It was reported that the on-time duration without significant

dyskinesia increased 4-fold when the medication was halved.[130] Daily OFF-periods were reduced from 50% to near abolition in the first year.[6,68,130,160]

Lesions created by the insertion of microelectrode probes or DBS electrodes were found to have positive effects on parkinsonian symptoms per- and post-operatively.[100,101,135,152,189] This observation had evidence to the knowledge that small and confined STN inactivation can be sufficient to produce an improvement of PD, as replicated in animal models.[21] These so-called microlesions appear to have similar effects on the metabolic activity of the globus pallidus, the striatum, the thalamus, and the cortex as those measured after subthalamotomy, but to a lesser extent.[135,157,168]

Cognitive outcome

Surgical procedures in the basal ganglia can potentially induce neuropsychological impairments, as observed after bilateral pallidotomy or subthalamic DBS.[43,156] Contrarily, subthalamotomy has not been shown to cause major cognitive impairment.[105, 130] In fact, no studies using a cognitive test (mini-mental state examination, or MMSE) observed a decline after unilateral or bilateral lesions.[7,8,25,110,170] Slight improvements in verbal fluency, as well as decreases in dementia, apathy and depression were seen in patients.[7,8] A recent study demonstrated decreased attention, inhibition and verbal learning in up to 30% of the patients, but these did not affect patients globally.[105] Finally, executive functions and memory remained unaffected by STN lesions.[41,105]

Subthalamotomy versus other surgical treatments

According to the recent review of evidence-based medicine for the treatment of the motor symptoms of PD by the Movement Disorders Society,[54] unilateral pallidotomy and bilateral GPi or STN-DBS were found effective for motor complications of PD. Unilateral posteroventral pallidotomy is known to result in 20% to 35% improvement in "off-medication" motor symptoms during the first two years following surgery.[69] In a randomized controlled trial (RCT) comparing unilateral pallidotomy to medical therapy, contralateral dyskinesias were reduced by 75% and 78% at 6 and 24 months respectively post-pallidotomy, and remained unchanged with medical therapy.[177] In the same study by Vitek et al., ipsilateral dyskinesias were also improved significantly. However, L-DOPA needs remained the same after 6 months (0.4% decrease in pallidotomy and 7.1% increase with the medical therapy only).

Bilateral subthalamic DBS is assumed to be the most widely used surgical procedure for PD treatment.[1,85,145] In a recent 6-month RCT, bilateral STN-DBS was compared to the best medical therapy.[182] It was demonstrated that "off-medication" motor symptoms were improved by 28.6%, and remained unchanged with medical therapy. Similar results were obtained on motor complications (36.9% vs. 5.4% for STN-DBS and medical therapy, respectively). L-DOPA equivalencies were reduced by 23.1% after 6 months of STN-DBS, where it increased insignificantly (1.1%) with the best medical therapy.

Subthalamotomy is still regarded as an experimental procedure for PD.[54,165] Paradoxically, a recent study demonstrated that neurosurgeons performed subthalamotomies as often as pallidotomies or thalamotomies in most or all of their cases.[85,145] It was shown that lesions were more often offered to patients in countries with lower economical development or when patients financed their own surgeries. Subthalamotomy was not included in the recommended procedures for motor complications because of insufficient evidence. Two studies[41,110] met Level I criteria, depicted by at least one high quality RCT, but neither study was included in the review due

to their small sample sizes. In the first study,[41] unilateral subthalamotomy was compared to unilateral pallidotomy and bilateral STN-DBS. The authors concluded that both procedures offered major motor improvement and that these two surgeries were equally effective for the motor treatment of PD. Also, they observed that unilateral subthalamotomy had the advantage of reducing L-DOPA needs, whereas it remained unchanged with unilateral pallidotomy.[41] In the second RCT comparing bilateral subthalamotomy and bilateral STN-DBS, the two surgical procedures had similar benefits on the motor symptomatology of PD patients and were comparable to previous literature.[110] Though these two RCTs provide evidence on the positive effects of STN lesions, larger RCTs are warranted to fully assess the cost-effectiveness and the role of subthalamotomy in the treatment of PD.

The tremendous improvements and low complications profile observed in patients treated with DBS are obvious reasons for its vast use worldwide.[22] However, STN lesions may be an alternative when DBS is not a possible treatment for certain reasons, such as access to care and health status.[73] Lesion therapies are much less expensive compared to DBS.[50] In fact, the direct and indirect costs of a DBS system[153] outrun lesion-based costs. Moreover, patients have shorter hospital stays following lesions compared to those who receive DBS implants.[50] Subthalamotomy also presents advantages that are not seen in other lesion treatments. Patients undergoing unilateral subthalamotomy seem to respond as well as those receiving a unilateral pallidotomy when considering motor and dyskinesia improvements.[41] Bilateral subthalamotomy does not seem to induce severe cognitive decline as seen in bilateral pallidotomy.[55] STN lesions allow for a reduction in L-DOPA, whereas L-DOPA remains practically unchanged after pallidotomy.[88] This advantage is valuable when patients have L-DOPA-induced hallucinations. Although there are no studies on this matter, STN-DBS was recently shown to reduce hallucinations after medication adjustments[172] and could be achieved with STN lesions.

Cellular and biochemical effects of subthalamotomy

Neuroprotection

There is evidence suggesting that DAergic cells are sensitive to excitatory glutamatergic input implicated in neurotoxicity in PD.[62] Dopaminergic cells present both NMDA and non-NMDA glutamate receptors,[125] and antagonizing the former receptor was shown to protect SNc cells against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity.[31,192] The STN is the main excitatory structure of the basal ganglia[151] and has efferences in the SNc.[150] It was originally hypothesized that STN overactivity in PD could contribute to progression of the disease[4,150] and its inactivation may slow or prevent it. In rats, most of the studies failed to demonstrate a neuroprotective effect of previous STN lesions before large exposure to the neurotoxin 6-hydroxydopamine (6-OHDA) on dopaminergic cells survival.[115,131,140] It was, however, shown that the phenotype, measured by tyrosine hydroxylase (TH) immunohistochemistry, the rate- limiting enzyme in the production of DA synthesis, was preserved in the surviving cells in the first weeks following exposure to 6-OHDA.[36,131,187] On the contrary, some authors observed neuroprotection in rats with small DA depletion,[133] but its effectiveness decreased in a time-dependent manner and was no longer detected after one week.[40]

In primates, a recent study has shown the neuroprotective effects of dopaminergic cells, when subthalamotomy is performed two weeks before or one week after MPTP insult.[181] More recently, we observed no changes in TH-positive immunohistochemistry, nor in DA or its metabolite concentrations following unilateral subthalamotomy.[86] This discrepancy might be explained by the same three main factors seen in rodents: the extent of DA depletion, the extent of STN lesion and the time between the two insults. The dopaminergic denervation was much more profound in our monkeys than it was in the study by Wallace and colleagues.[181] Monkeys in the latter study had 50% DAergic loss in the SNc, whereas monkeys in our study had a near complete loss. Neuroprotective effects of STN alteration are inversely proportional to the extent of the MPTP insult. A study in MPTP-injected monkeys failed to show neuroprotection with 85% of DAergic loss.[98] The survival time between MPTP administration and subthalamotomy is also likely to explain the difference. In the study by Wallace et al., monkeys that received a subthalamotomy

only 6 days after MPTP and were killed roughly 14 days after the lesion,[181] whereas the monkeys in our previous study were rendered parkinsonian many years before the STN ablation and were killed several weeks after surgery. Lastly, the STN is not the only glutamatergic source to the SNc. In fact, the latter receives excitatory input from the PPN and the cortex,[93,95] and may also contribute to the glutamate-mediated excitotoxicity.[164]

Clinically, PD cardinal symptoms appear after 80% of striatal DAergic loss,[167] and PD patients are operated when they become pharmacologically refractive to L-DOPA or when LIDs are disabling.[8] Thus, neuroprotective studies do not reflect surgical practices in a clinical perspective and clearly cannot be applied in a clinical context.

Neurophysiology

STN activity in PD is known to increase in frequency and to increase burst firing.[137] In humans and primates, similar changes were observed in the STN output nuclei, that is the GPi and SNr. GPi neuronal activity increases from 60-70Hz in the normal state[163,186] to 70-85 Hz in PD[78,97] and from 60Hz to 70Hz in the SNr.[79,186] The administration of L-DOPA not only reverses these increases, but also tends to further reduce the structures' basal activity.[30,60,70,78,97,124] Subthalamotomy exerts comparable effects by restoring normal electrophysiological activity. STN lesions decreased the GPi firing rate in normal monkeys[66] and reversed the increased GPi neuronal activity induced by 6-OHDA in rats.[117] Some authors observed only that the GPi firing pattern returned to normal, resulting mainly in reduced burst firing without any change in firing rate.[144] However, the MPTP-induced GPi oscillations persisted in parkinsonian monkeys.[185] Similarly, SNr electrical activity was also decreased following subthalamotomy in normal[191] and 6-OHDA rats[32,127,144] with reduced burst firing.[114,171] Moreover, the 6-OHDA-induced increase in the PPN firing rate was prevented with STN lesions in rats, but no change was observed in normal rats following STN destruction.[84] On the contrary, subthalamotomy in normal rats increased the number of PPN neurons that displayed bursting activity by more than 30%, whereas 6-OHDA lesions with or without STN lesions increased the number by only 8 to 12%.[84] These last two observations indicate that the changes in PPN activity following STN lesions are not due to a direct subthalamo-pedunculopontine connection. Lastly, SNc neurons were also observed to reduce their firing rate and their burst activity after STN

lesions,[26,148,149] but those findings were not replicated by others.[191] Thus, it is generally agreed that subthalamotomy decreases neuronal activities in GPi, SNr and SNc, which is consistent with the fact that STN exerts an excitatory input on these structures.

Neurochemistry

The consequences of these physiological changes in STN outputs transpose into measurable biochemical modifications (Table 2). Reductions in cytochrome oxidase and succinate hydrogenase, both markers of cellular activities, were found in GPi and SNr following STN lesions in normal and 6-OHDA rats,[27,28,132] corroborating the decrease in firing rates and patterns. Messenger RNA of enzyme glutamic acid decarboxylase (GAD67), which is needed for the conversion of glutamate to GABA present in GPe, GPi and SNr, also decreases with subthalamotomy in MPTP-monkeys and 6-OHDA rats.[44,132] This indicates that these cells are less active and consume less energy following subthalamotomy.[111] However, increases in GAD67 levels were observed in the GPi and GPe of normal monkeys after STN lesions.[10] As for the changes in the SNc electrophysiology, some studies reported increased striatal DA and TH+,[10,80] and others reported a reduction.[148]

Subthalamotomy complications

Hemiballism (HB)

STN lesions have been known to induce HB, which is the violent, irregular and involuntary movement of one half of the body.[134] HB is usually observed contralateral to STN lesions in PD patients (Table 3), but ipsilateral HB was also described in non-parkinsonian patients secondary to STN infarct or hemorrhage.[42,92,138] HB has many etiologies and may be caused by lesions in the STN, but also in other structures of the basal ganglia.[46,56,61,139,174] In PD patients undergoing subthalamotomy, transient HB (less than a year) was observed in 13.2% (40 out of 303 patients enrolled in studies or case reports) with spontaneous recovery or with successful pharmacological treatment, whereas it remained permanent in 9.9% (includes 2 patients receiving ipsilateral thalamotomy during the same surgical procedure since they presented hemiballism/hemichorea by the end of STN surgery[175,176]). It has been suggested that smaller lesions would allow for compensatory mechanisms within the basal ganglia, tending to re-establish equilibrium and cease hemiballism. Conversely, in larger STN lesions, a persistent decrease in GPi and SNr activities were observed.[169] Recently, two cases were described where transient hemiballism was the result of a small hemorrhage or an infarct in the STN.[118] Both cases recovered within four weeks after the symptoms appeared, without any pharmacological or surgical treatment, supporting this hypothesis. Other authors have suggested that lesions confined to the nucleus were more prone to induce hemiballism and lesions extending its boundaries could prevent the development of hemiballism by reducing pallidothalamic outflow.[39,49] This hypothesis is supported by the fact that pallidotomies can completely abolish hemiballism in PD patients.[162] Finally, HB is not strictly caused by STN lesions. It was also observed in PD patients following thalamotomy[48] and subthalamic DBS.[90,123] Though these two hypotheses (size and location of the lesion) neither exclude nor invalidate one another,[184] the underlying mechanisms of HB following subthalamotomy have yet to be clarified.

Postural disturbance

PD patients may present postural abnormalities such as neck flexion and camptocormia.[83] Patients with postural asymmetry show lateral curvature of the spine with an inclination of the trunk towards the ipsilateral side that is most depleted in dopamine. This instability of posture responds poorly to L-DOPA.[103] Similar postural asymmetry was observed following STN lesions in non-parkinsonian[104] and in PD patients.[102,159] These patients displayed a body tilt contralateral to the lesion accompanied with head rotation. Head rotations were seen in normal and parkinsonian monkeys in which the STN was lesioned.[10,33,67,71] It was proposed that an imbalance of the dopaminergic influence between the lesioned and non-lesioned hemispheres[159] and/or the glutamatergic imbalance between the STN and the SNr may occur.[86] Finally, transient postural disturbance was also reported after unilateral and bilateral subthalamotomy.[110,175]

Other complications

In the series by Alvarez and colleagues[8] consisting of 89 patients undergoing unilateral subthalamotomy, some patients presented transient dysarthria, infection of the scalp, asymptomatic bleeding and seizures. All of these complications were observed in less than 5% of patients. Speech and dysarthria complications were seen in three patients undergoing bilateral STN lesions. Two of these patients also displayed trunk and gait ataxia.[8] Ataxia was associated with larger lesions in those patients.[7] STN lesions were also shown to induce blepharospasm or ptosis in normal individuals,[163] as well as in PD[126] or dystonic patients[89] undergoing subthalamotomy to alleviate their symptoms. Finally, neuropsychiatric side effects were also associated with STN alterations, such as hyperphagia,[51] hypersexuality[2] and impulse behavior.[2,126]

Conclusion

The STN plays a pivotal role in the basal ganglia, since it is connected to many other structures within the basal ganglia, and to nuclei outside of it. It is widely accepted that its overactivity in PD patients is one of the pathophysiological causes underlying the cardinal symptoms of PD and dyskinesias. Despite the fact that the STN is the main target for DBS in PD patients, subthalamotomy remains an alternative surgical option for patients refractive to pharmacological treatment or unable to receive DBS implants due to medical reasons or access limitations. Several studies demonstrated the effectiveness of subthalamotomy in the treatment of PD. It reduces daily L-DOPA needs and was associated with few, mainly transient, complications. Nevertheless, more clinical evidence is needed to warrant its use as a treatment option for PD.

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Table A1.1. Review of published literature on motor and dyskinesia evaluations, and on L-DOPA equivalency daily doses after subthalamotomy

Authors	Total number of operated patients	Follow-up in months (n of patients followed)[a]	% improvement UPDRS-III « off-med »	% improvement UPDRS-III « on-med »	% improvement UPDRS-IV	% LEDD
Unilateral lesions						
Alvarez (2001)[6]	11	12 (n=10)	50	39	N/A	59 (n=5, >12 months)
Alvarez (2009)[8]	89	12 (n=68)	50	60[b]	N/A	45
		24 (n=36)	30	39[b]	N/A	36
		36 (n=25)	18	15[b]	N/A	28
Coban (2009)[41]	5	6	25	23	50[c]	27
Hanagasi (2011)[68]	11	14	49	43	40	23
Parkin (2001)[128]	11	5.4 (n=8)	8	24	N/A	N/A
Patel (2003)[130]	26	6 (n=16)	19	9	58[d]	47
		12 (n=15)	13	5	52[d]	45
		24 (n=18)	15	-6 (deterioration)	64[d]	34
Rodriguez-Oroz (1998)[142]	11	12 (n=7)	60	N/A	N/A	N/A
Su (2002)[158,160]	13	6 (n=12)	30	33	82[d]	49
		12 (n=12)	32	30	85[d]	43
Vilela Filho (2002)[175]	23	13.5 (n=21)	N/A	N/A	74	43
Witjas (2009)[188]	3	12 (n=2)	N/A	N/A	100	40
Bilateral lesions						
Alvarez (2005)[7]	7 staged	> 48	50	38	50[e]	40
	11 simultaneous	> 36	49	33		53
Alvarez (2009)[9 f]	32	36	47	N/A	N/A	N/A
Merello (2008)[110]	5	6	47	N/A	27[g]	79
		12	52	N/A	91[g]	76
Tseng (2007)[170]	10	3	44	54	96[d]	34
		12	52	66	97[d]	38
		24	42	49	67[d]	28
		36	40	42	67[d]	29
Average[h]		6 months	20.8 (3.4)	20.4 (3.0)	65.5 (14.9)	44.7 (10.9)
		12 months	44.2 (9.1)	46.4 (12.0)	65.5 (9.4)	43.7 (7.0)
		24 months	16.7 (3.0)	6.3 (7.9)	64 (N/A)	30.5 (1.5)

[a] If the number of patients differs from the total patients operated
[b] Calculated based on the cardinal scores
[c] UPDRS IV items 32-33
[d] UPDRS IV items 32-35
[e] Dyskinesia rating scale
[f] Some of the patients may have been presented in Alvarez (2005) [7]

[g] UPDRS IV items 32-39
[h] Average calculated by the number of patient at each follow-up for unilateral lesions only

Table A1.2. Neurochemical changes after unilateral subthalamotomy in normal and parkinsonian animals

Authors	Treatment	% DA denervation	% STN lesion	Effect of STN lesion
Studies in rats				
Blandini (1995)[29]	normal	none	Near complete	↓ mitochondrial complex I activity in EN and SNr ↓ SNr NMDA receptor binding No effect on AMPA receptor binding
Blandini (1995)[28]	normal	none	Near complete	↓ SDH and CO mitochondrial activities in striatum, SNc and GP
Price (1993)[136]	normal	none	Complete lesion	↓ AMPA and kainate receptor binding in ipsilateral SNr ↓ NMDA receptor binding in ipsilateral GP
Aristieta (2012)[15]	6-OHDA	Complete loss	≈60%	↑striatal FosB/ΔFosB ipsilateral to STN lesion in 6-OHDA rats treated with L-DOPA ↑striatal pDARPP32/DARPP32 Reverses the increased D2/D1 ratio in 6-OHDA rats treated with L-DOPA
Bacci (2004)[19]	6-OHDA	Complete loss	Near complete	Reverses the increased striatal enkephalin mRNA levels in 6-OHDA rats Reverses the increased GAD_{67} mRNA levels in 6-OHDA rats in the EN and SNr No effect on the decreased levels of substance P mRNA in 6-OHDA rats
Blandini (1997)[27]	6-OHDA	Complete loss	Partial (20% to 70%) Complete lesion	Partial lesion: ↓ CO in EN & SDH in GP, EN Complete lesion: ↓ CO and SDH in EN, GP Both partial and complete STN lesions prevented the increase in CO & SDH in SNr
Centonze (2005)[37]	6-OHDA	Complete loss	Near complete	Reverses the 6-OHDA-induced overactive frequency and amplitude of striatal glutamate-mediated spontaneous excitatory postsynaptic currents
Delfs (1995)[44]	6-OHDA	>90% loss of DA uptake	Near complete	↓ the increase in GAD67 mRNA in the GP induced by 6-OHDA No effect in ipsilateral EN No effect on enkephalin and substance P
Hwang (2006)[80]	6-OHDA	66% loss of striatal DA 50% loss of GPe DA	N/A	↑ striatal and pallidal content of DA & HVA in normal and 6-OHDA rats
Levandis (2008)[96]	6-OHDA	>97% loss of striatal DA >93% loss of SNc DA	>50% loss	↑striatal FosB/ΔFosB ipsilateral to STN lesion in 6-OHDA rats treated with L-DOPA
Périer (2003)[132]	6-OHDA	98% loss of DAT	Near complete	↓ the increase in CO subunit I and GAD_{67} mRNA in the striatum induced by 6-OHDA when combined to L-DOPA
Touchon (2004)[166]	6-OHDA	80-85% loss of striatal TH	N/A	↓ striatal glutamate in 6-OHDA, STN lesion or the combination of both lesions associated with an increase in glutamate immunolabeling in nerve terminals
Walker (2009)[180]	6-OHDA	90% loss of SNc TH	>50% loss	↑ striatal glutamate in normal rats ↓ the striatal increase of glutamate in 6-OHDA rats
Walker (2009)[179]	6-OHDA	90% loss of SNc TH	>50% loss	↓ striatal DA and DA metabolites, ↑in the HVA/DA ratio in normal rats ↓ striatal DA, ↑DA metabolites, DA metabolites/DA ratio unchanged in 6-OHDA rats
Studies in primates				
Andrén (1995)[10]	normal	none	N/A	↑ GAD in bilateral caudate nucleus, GPi, GPe, VA/VL and ipsilateral putamen ↑ GABA in CM/Pf ↑ DA in dorsal contralateral putamen

Guridi (1996)[63]	MPTP	Near complete	80-90% loss	↑ TH in bilateral GPi and contralateral striatum ↓ GAD67 mRNA in GPi, GPe, SNr ↑ GAD67 mRNA in reticular thalamic nucleus
Mitchell (1985)[111]	normal	none	Bicuculline injection	↓ in 2-deoxyglucose activity in GPe and GPi
Shimo (2009)[148]	normal	none	>50% loss	↓ striatal dopamine

Abbreviations: 6-OHDA: 6-hydroxydopamine; CM/Pf: centromedian and parafascicular thalamic nuclei; CO: cytochrome oxidase; DA: dopamine; DAT: dopamine transporter; EN: entopeduncular nucleus, rat homologue of the primate GPe; GAD: glutamic acid decarboxylase; GP: rat globus pallidus, homologue of the primate GPi; HVA: homovanillic acid; SDH: succinate dehydrogenase; SNc: substantia nigra pars compacta; SNr: substantia nigra pars reticulata; STN: subthalamic nucleus; VA/VL: ventroanterior and ventrolateral thalamic nuclei

Table A1.3. Hemiballism following subthalamotomy or STN lesion in PD patients

Author	Total and Patients with Hemiballism	Location of the lesion	Onset	Persistence	Treatment
Unilateral lesions					
Alvarez (2009)[8]	14 (89)	N/A	Immediately (n=13) 7 days (n=1)	Persistent	Pallidotomy
Barlas (2001)[20]	1 (9)	STN	Immediately	2 weeks	Valproate
Chen (2002)[39]	2 (2)	1 STN 1 STN + Zi	Immediately 3 days	Persistent 2 months	Unsuccessful pharmacological treatment Haloperidol & clonazepam
Coban (2009)[41]	1 (4)	N/A	3 days	1 month	Valproate
Doshi (2002)[49]	3 (3)	N/A	N/A	Transient	None
Inzelberg (1994)[81]	1 (1)	N/A	1 year (hemorrhage)	Persistent	Unsuccessful pharmacological treatment
Mamo (1965)[102]	16 (50)	9 posterior STN, Zi, Raprl 3 posterior STN, Zi, Raprl + Thalamus 4 Thalamus	Immediately	Up to 10 days	None
Merello (2006)[109]	3 (3)	N/A	Immediately	1 month	None
Obeso (1997)[120]	1 (5)	N/A	7 days	N/A	N/A
Patel (2003)[130]	2 (26)	STN	Immediately	Persistent	Zi DBS
Rodriguez-Oroz (1998)[141]	1 (7)	Subthalamic region	5 days	N/A	N/A
Su (2003)[161]	3 (13)	1 STN + Zi 1 lateral & anterior STN 1 medial & lateral STN	3 days 3 days 35 days	4 weeks 2 months 5 months (deceased)	None
Tseng (2003)[169]	1 (1)	STN + Zi + H_2	35 days	3 weeks (deceased)	N/A
Vilela Filho (2002)[175]	2 (23)	STN + Zi	Immediately	N/A	Thalamotomy
Bilateral lesions					
Alvarez (2005)[7]	16 (18)	Extending dorsally, medially and caudally to the STN	Within 48 hours	Up to 3 months (n=7) Up to 1 year (n=5) Persistent (n=4)	N/A
Merello (2008)[110]	1 (5)	N/A	Immediately	Persistent	Pallidotomy
Tseng (2007)[170]	2 (10)[a]	STN + Zi + H_2	3 weeks	2 months	None

[a] One of these two patients was presented in Su et al. [203]

APPENDICE 2

MODELING DYSKINESIA IN ANIMAL MODELS OF PARKINSON DISEASE

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Résumé

Le traitement des symptômes moteurs de la PD avec le précurseur de la dopamine, la L-3,4-dihydroxyphénylalanine (L-DOPA), introduit il y a 50 ans demeure encore aujourd'hui un traitement pharmacologique très efficace. Toutefois, des mouvements involontaires, appelés dyskinésies induites à la L-DOPA (LID), surviennent chez la vaste majorité des patients parkinsoniens avec son traitement chronique et deviennent débilitants. Une fois que ces LID apparaissent, un arrêt temporaire de la médication durant plusieurs semaines n'est pas suffisant pour les faire disparaître, ce qui suggère que la L-DOPA a modifié la neurotransmission dopaminergique à long-terme, si non de façon permanente. Les LID sont difficiles à traiter et il n'existe pas encore de traitements pharmacologiques pour leur traitement, mise à part les bénéfices modestes de l'amantadine. De nouveaux médicaments qui n'induisent pas de LID sont nécessaires pour le traitement de la PD. Des modèles animaux ont été développés pour l'étude des mécanismes des LID et les nouvelles cibles thérapeutiques. Le 1-méthyl-4-phényl-1,2,3,6-tétrahydropyridine (MPTP), administré chez la souris et le singe, est depuis près de 30 ans le meilleur modèle neurotoxique animal pour l'étude de la PD et des LID, s'ajoutant au modèle classique du rat rendu hémiparkinsonien avec une lésion induite par la 6-hydroxydopamine. Cette revue de littérature couvre les modèles animaux chez les rongeurs et les primates non-humains qui reproduisent les complications motrices induites par la thérapie pharmacologique classique. De plus, les changements biochimiques importants dans les tissus *post-mortem* de cerveaux de patients parkinsoniens présentant des LID seront comparés à ceux observés chez les modèles animaux. En dernier lieu, les valeurs translationnelles des médications pour le traitement des LID chez les modèles animaux seront comparées à leurs activités cliniques.

Abstract

The treatment of motor symptoms of Parkinson disease (PD) with the dopamine (DA) precursor, L-3,4-dihydroxyphenylalanine (L-DOPA) introduced 50 years ago still remains a very effective medication. However, involuntary movements termed L-DOPA-induced dyskinesias (LID) appear in the vast majority of PD patients after chronic treatment and may become disabling. Once they appeared, the first dose after a several-weeks drug holiday will trigger them again, showing that L-DOPA has permanently or persistently modified the brain response to DA. LID are very difficult to manage and no drug is yet approved for dyskinesias, aside from a modest benefit with amantadine. New drugs are needed for PD to alleviate parkinsonian symptoms without inducing dyskinesias. Hence, animal models have been developed to seek the mechanisms involved in LID and new drug targets. The neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was discovered as a contamination of a derivative of heroin taken by drug users and produced similar motor symptoms as idiopathic PD. Since then, MPTP is used extensively to model PD and LID in non-human primates and mice in addition to the classical PD model in rats with a 6-hydroxydopamine (6-OHDA) lesion. This article reviews rodent and non-human primate models of PD that reproduce motor complications induced by DA replacement therapy. Moreover, key biochemical changes in the brain of post-mortem PD patients with LID will be compared to those observed in animal models. Finally, the translational usefulness of drugs found to treat LID in animal models will be compared to their clinical activities.

Introduction

Parkinson disease (PD) is the most common neurodegenerative movement disorder and is likely to increase due to the aging population (Siderowf and Stern, 2003). PD involves principally the death of dopamine (DA) neurons in the substantia nigra pars compacta (SNc) but other neurotransmitters and neuromodulators are also affected.

Gene mutations in familial PD are reported but the cause for the majority of PD cases remains unknown (Olanow et al., 2009). There is currently no cure for PD. Neuroprotection or disease modification defined as an intervention that would protect or rescue vulnerable neurons, thereby slowing, stopping, or reversing disease progression, is not yet available for PD but laboratory studies are finding promising agents (Olanow et al., 2009).

Restoring deficient DA with its precursor L-3,4-dihydroxyphenylalanine (L-DOPA) is the most effective PD treatment, but remains a symptomatic treatment. Moreover, a majority of patients develop hard-to-manage abnormal involuntary movements called dyskinesias within the first 10 years of treatment (Mones et al., 1971; Olanow and Koller, 1998). Motor fluctuations such as "wearing-off" are also common. Wearing-off is defined as a reduced duration of benefit from an individual L-DOPA dose and a recurrence of parkinsonian symptoms before the next normal dose of L-DOPA (Fahn et al., 2004). Once dyskinesias appear, even if treatment is stopped for several weeks, the first dose will trigger them again, showing that L-DOPA has permanently or persistently modified the brain response to DA. Dopaminergic agonists have less potential to induce motor complications compared to L-DOPA but their symptomatic efficacy is generally inferior to L-DOPA (Olanow, 2004). Hence, most PD patients initiated with DA agonist monotherapy will eventually require L-DOPA as disease progresses and after 10-15 years their motor complications appear similar as they would have if started initially on L-DOPA therapy (Parkinson Study Group, 2009; Katzenschlager et al., 2008). This suggests that disease progression plays the major role in the onset of dyskinesia rather than the type of dopaminergic drug treatment used.

No drug is yet available for dyskinesias, aside from a modest benefit with amantadine in some PD patients (Olanow et al., 2009). Though investigated in numerous studies, the mechanisms involved in the occurrence of dyskinesias are still unknown. Moreover while L-DOPA and DA agonists, currently used in the pharmacological treatments of PD, are effective at reversing the motor symptoms of the disease little they do to combat the progressive underlying degeneration of DA neurons in the SNc.

Much emphasis has therefore been placed on finding alternative non-dopaminergic drugs that could circumvent some or all these problems. The design of novel agents to prevent dyskinesias requires elucidation of the adaptive changes produced in the parkinsonian brain by repeated administration of L-DOPA. An attractive strategy to treat L-DOPA-induced dyskinesias (LID) is to use adjunct drugs to modulate basal ganglia DA neurotransmission (Blanchet et al., 1999; Brotchie, 1998; Brotchie, 2003; Calon and Di Paolo, 2002; Grondin et al., 1999; Henry et al., 2001).

LID are typically observed at the peak of the effect of L-DOPA in PD patients. There is also diphasic dyskinesia at the beginning and at the end of the L-DOPA dosing cycle appearing with the rise and fall of DA levels in the brain (Luquin et al., 1992), and off-dystonia (Marsden et al., 1982). LID occur in 30-80% of PD patients treated with L-DOPA (Barbeau, 1980; Nutt, 1990). Two conditions are necessary for their appearance: 1) the loss of DA in the nigrostriatal pathway and 2) treatment with L-DOPA or DA agonists. Development of dyskinesias in man usually requires daily treatment for 3-5 years in idiopathic PD (Klawans et al., 1977) and for parkinsonism induced in man by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), it occurs after only weeks or months of treatment (Ballard et al., 1985). The same applies to MPTP monkeys where only weeks of L-DOPA therapy are enough before dyskinesias appear (Bedard et al., 1986; Falardeau et al., 1988). MPTP primates respond to DA therapies in a similar manner than idiopathic PD patients (Jenner, 2003a; Jenner, 2003b) and are currently the best model for studying LID.

The rodent basal ganglia show some anatomical differences compared to the human and non-human primates. For instance, the caudate nucleus and putamen are the components of the striatum which are fused in rodents and undistinguishable, whereas they are separated by the internal capsule in primates (Martin and Bowden, 2000; Paxinos and Watson, 2007). Other structures of the basal ganglia also show species differences with an internal (GPi) and external (GPe) globus pallidus in primates compared to the structures termed entopeduncular nucleus and globus pallidus, respectively in rodents (Parent and Hazrati, 1995). Moreover, the segregation of the so-called direct (D1 receptor-related) and indirect (D2 receptor-related) pathways of the basal ganglia is well documented in rodents but their separation is less clear in primates (Parent et al., 2001). Hence, in primates both D1 and D2 receptor agonists can induce dyskinesias (Blanchet et al., 2004) whereas in rodents the contribution of the direct pathway with D1 receptors has been more associated with dyskinesias (Cenci et al., 2009). Nevertheless, the use of rodent models of PD and LID has clear advantages mainly their time- and cost-effectiveness.

Much remains to be learned from rodents and primates models of PD about the biochemical processes that underlie the development of dyskinesias, how dopaminergic and non-dopaminergic drugs can be used to avoid the initiation of dyskinesias in early PD, to prevent or inhibit their expression in later stages of the disease and to reverse the priming process through a normalization of the basal ganglia function. This review will present the current PD rodent and primate models to study dyskinesias with the associated behavioral and biochemical correlates. The translational values of the animal models will be discussed with salient examples of clinical results.

Rodent models of L-DOPA-induced dyskinesias (LID)

The 6-OHDA lesioned rat model

6-hydroxydopamine (6-OHDA) is the oldest and the most widely used toxin animal model for PD and can induce degeneration of central monoamine neurons (Sachs and Jonsson, 1975; Ungerstedt, 1968). 6-OHDA has to be injected stereotactically in the brain since, unlike MPTP, it fails to cross the blood-brain barrier. This toxin can be delivered in

various regions along the nigrostriatal tract, including the medial forebrain bundle (MFB), directly in the SNc or in the striatum resulting in an important decrease in DA in the ipsilateral striatum (Cenci et al., 2002; Schwarting and Huston, 1996; Ungerstedt, 1968; Winkler et al., 2002). When administered in the striatum, the 6-OHDA reveals a progressive and a partially lesioned model, whereas when injected in the SNc, it induces a more severe and rapid lesion. 6-OHDA has a similar chemical structure as DA, is uptaken into the catecholaminergic neurons by the DA transporter, retrogradely transported and promotes neurodegeneration through a combination of mechanisms such as oxidative stress and mitochondrial respiratory dysfunction leading to cell death (Glinka et al., 1997; Kunikowska and Jenner, 2001; Mazzio et al., 2004). The toxin is not specific and selective to the dopaminergic system. Due to its high affinity for the noradrenaline and the serotonin transporters, 6-OHDA may damage serotonin and noradrenergic neurons when injected in the MFB (Luthman et al., 1989). Specificity to the dopaminergic system can be achieved by sparing the noradrenergic neurons with inhibitors of the noradrenaline transporter, such as desipramine, imipramine and mirtazapine, administered before injections of 6-OHDA (Breese and Traylor, 1970; Jacks et al., 1972).

The toxin 6-OHDA is usually injected unilaterally and rats will show a characteristic contralateral turning behavior when the supersensitive receptors in the lesioned side of the brain are activated with L-DOPA or dopaminergic agonists such as apomorphine (Ungerstedt, 1971). Other drugs such as amphetamine produce an ipsilateral turning behavior. Severe bilateral lesions lead to high rates of death, high level of akinesia and disabling feeding issues such as adipsia and aphagia, which require postoperative healthcare treatments (Ungerstedt, 1971). Over the past years, several mechanisms have been proposed to explain the contralateral turning behavior, such as supersensitivity of postsynaptic striatal DA receptors ipsilateral to denervation (Deumens et al., 2002; Ungerstedt, 1971). Despite the fact that the exact mechanism of 6-OHDA toxic effects on striatal neurons and the pathophysiology of the turning behaviors are still unknown, the 6-OHDA-induced hemiparkinsonian rat model provides a good tool for preclinical drug studies for abnormal involuntary movements (AIMs) and neuroprotection. As observed in PD, the development of LID in rats is directly related to the level of striatal dopaminergic

denervation, the dose of L-DOPA administered and the elapsed time since the onset of treatment (Lindgren et al., 2007; Nadjar et al., 2009; Paille et al., 2007). Moreover, the induction of the turning behavior requires a higher dose of L-DOPA than to induce LID (Lindgren et al., 2007). Thus the turning behavior does not interfere the evaluation of LID and better reflects the clinical situation with similar doses used for PD patients.

The popularity of the hemiparkinsonian rat model is related to the fact that it is less expensive and simpler than the use of primates. Moreover, lesions obtained by the unilateral 6-OHDA injections are highly reproducible among animals and administration of dopaminergic drug-inducing turning behaviors provides an easy, accurate and objective tool to measure motor behaviors and drug efficacy. Unilateral lesions also offer the advantage that the non-lesioned brain hemisphere or side of the body can be used as a control relative for biochemical and behavioral evaluations (Lundblad et al., 2002; Sachs and Jonsson, 1975). In spite of its usefulness, the hemiparkinsonian rat model shows limits. For instance, only some motor deficits are reproduced despite the fact that the 6-OHDA toxin has a relatively high specificity for the dopaminergic system and has also the ability to destroy the serotoninergic and noradrenergic fibres when injected in the MFB. Therefore, the model cannot mimic all stages of PD (Papa et al., 1994). Another weakness of the model is that the unilateral, as well as the bilateral 6-OHDA lesions do not induce any obvious parkinsonian symptoms or other similar motor dysfunctions as observed in non-human MPTP primate model. A dopaminergic therapy is needed in order to induce the turning behavior and dopaminergic priming is required to obtain a full antiparkinsonian effect (Di Chiara et al., 1992; Henry et al., 1998). Lastly, unilateral lesions affect only one side of the brain, whereas both hemispheres are depleted in striatal DA in PD.

The 6-OHDA lesioned-rat models do not display the same dyskinesias as those observed in primates and PD patients following a chronic dopaminergic treatment. For a long time, the only method used to study the motor effects of dopaminergic treatment was restricted to the turning behavior and it was generally considered that the animals did not display LID. Therefore, the behavioral assessment was considered to correlate with the antiparkinsonian activity of the drug tested (Fenu et al., 1997; Ungerstedt, 1976). More

recently, the 6-OHDA-lesioned rat treated with L-DOPA was reported to display LID, such as movements with dystonic or hyperkinetic features, which were observed in axial and orofacial muscles (Andersson et al., 1999; Cenci et al., 1998). Hence, this new concept was accepted since these L-DOPA-induced abnormal movements interfered with the animal normal behavior and these were reduced with antidyskinetic drugs already used in non-human primates and in PD (Dekundy et al., 2007; Lundblad et al., 2002). The rotational response was suggested to be an equivalent of LID in rats (Papa et al., 1994) and a rating scale was created to evaluate and quantify the AIMs in parkinsonian rats, gradually replacing the contralateral rotation evaluations (Cenci et al., 1998). In fact, the rotational behavior did not always correlate with the development of dyskinesia in both rat and mouse models (Henry et al., 1998; Papa et al., 1994). A recent behavioral study demonstrated that the rotational behavior did not represent a complete antiparkinsonian response and that would probably be related to the L-DOPA-induced motor response complication syndrome (Konitsiotis and Tsironis, 2006). Moreover, it has been shown that some antiparkinsonian drugs with weak dyskinesiogenic potential, such as ropinirole and bromocriptine, can increase contralateral turning (Carta et al., 2008; Lindgren et al., 2009), while other antidyskinetic drugs that are well known for reducing LID and AIMs, such as amantadine and clozapine, did not prevent the contralateral turning behavior (Lundblad et al., 2002).

The AIMs rating scale is constituted of three main sections each representing a topographical area of the body: 1) Limb dyskinesia characterized by repetitive and rhythmic movements or dystonic posturing of the forelimb on the side contralateral to the lesion; 2) axial dyskinesia characterized by lateral flexion and axial rotation/torsion affecting the neck and the upper trunk toward the side contralateral to the lesion; and (3) orolingual dyskinesia affecting the orofacial musculature including chewing movements, tongue protrusions and jaw tremor (Cenci et al., 2002; Winkler et al., 2002). The AIMs scale is useful, valid and provides a precise evaluation of the intensity of LID for each animal (Dekundy et al., 2007). The 6-OHDA rat model for the study of LID in acute, sub-chronic or chronic study designs, has been largely used over the years for the validation of new pharmacological compounds. Many antidyskinetic treatments used in PD patients and non-human primates have been first tested in the 6-OHDA rat model and showed to reduce

the AIMs score and to improve motor behavior (Bordia et al., 2012; Dekundy et al., 2007; Eskow et al., 2007; Kobylecki et al., 2010; Kobylecki et al., 2011; Munoz et al., 2008; Quik et al., 2007; Rylander et al., 2010).

The 6-OHDA lesioned mouse model

The 6-OHDA lesioned mouse model is a recent model and LID have been reported for the first time in 2004 where the authors reported similar AIMs as those observed in rats (Lundblad et al., 2004). The toxin 6-OHDA can be administered by intracerebral injection to mice, but the rat model remains more practical to perform the lesion and to evaluate the motor behavior (Francardo et al., 2011; Nicholas, 2007; Smith et al., 2012). Compared to the MPTP-lesioned mouse model, the 6-OHDA mouse model is more convenient since the AIMs are easier to evaluate; the animals develop better dyskinesia with less inter-individual variability and biochemical variations (Sedelis et al., 2000). Unilateral 6-OHDA lesions in mice lead to a stable and reproducible damage along the nigrostriatal tract similar to those observed with the 6-OHDA rat model. Moreover, like in the rat model, it is possible to mimic different stages of PD by using different doses and different administration sites. The rating scales used for the motor behavioral evaluation and for detecting dyskinesia in mice is based on the rating scale used for the 6-OHDA rats. The scale used to evaluate the AIMs in mice also includes the frequency, the duration and the intensity of topographical limb, axial and orolingual dyskinesias (Francardo et al., 2011; Smith et al., 2012). Although the 6-OHDA mouse model has been used for pharmacological validation against LID such as amantadine (Bido et al., 2011), the rat model is still more often used for all its advantages.

Other mouse models

Over the past 15 years, many knockout and transgenic mouse models of PD have been developed to study genetic causes of PD, molecular pathways and targets for new pharmacological compounds (Dawson et al., 2010). The principal limitation of these models is that they do not reproduce the dopaminergic degeneration as observed in PD. Therefore, mouse models that have been developed to study overexpression of the genes implicated in some familial PD forms, such as □-synuclein (Chesselet, 2008) and leucine-

rich repeat kinase 2 (Li et al., 2010; Xu et al., 2012), do not develop LID following L-DOPA treatment since there is no dopaminergic cell loss. However, a recent genetic model of PD, the aphakia mouse, showed AIMs after L-DOPA or dopaminergic agonist administrations (Ding et al., 2007). Following an amantadine treatment, the development of LID was reduced and some markers of LID were expressed similarly as those observed in 6-OHDA models such as the abnormal activation of extracellular signal-regulated kinase 1/2 (ERK1/2) and the increased FosB-expression in the dorsal striatum (Ding et al., 2007; Ding et al., 2011).

Non-human primate models of LID

Similar etiology and functions of a particular human disease are the two must-have characteristics to model a disease. In order to avoid confounding and misleading results, the model has to replicate as many characteristics of the pathology as possible. The neurotoxin MPTP closely mimics both behavioral changes and cellular loss as seen in PD (Albanese et al., 1993). In fact, administration of MPTP in primates induces remarkable resemblance to the primary motor features of PD, including rigidity, bradykinesia and tremor. MPTP targets specifically cells expressing the DA transporter and induces neuronal death of dopaminergic cells through a cascade of intracellular reactions (Smeyne and Jackson-Lewis, 2005) and for more information, see corresponding article in the current issue). Moreover, MPTP-treated monkeys also display cognitive (Schneider, 1990) and gastro-intestinal impairments similar to PD patients (Chaumette et al., 2009) and see corresponding articles in the current issue).

Prior to MPTP, lesions of the ventromedian mesencephalic tegmentum were performed in primates to induce tremor (Poirier, 1960) and administration of L-DOPA in these monkeys induced oro-facial dyskinesias similar to LID (Battista et al., 1971). MPTP was first used in monkeys (Burns et al., 1983) following the demonstration of its irreversible parkinsonian effects when taken by drug users as a contaminant of a derivative of heroin (Davis et al., 1979; Langston et al., 1983). Since then, it has been used extensively in rhesus and cynomolgus macaques (macaca mulatta and macaca fascicularis

respectively), but is also used in African green monkeys (Wichmann et al., 1999), squirrel monkeys (Langston et al., 1984) and common marmosets for the study of PD (Jenner et al., 1984). Considering the above facts, MPTP-treated primates remains after nearly 30 years the gold standard for the study of PD and LID, as well as to test compounds for their treatment.

Experimental paradigms

Two experimental approaches are reported to test new drugs as potential antiparkinsonian and/or antidyskinetic pharmacological agents. In the first experimental approach, animals are rendered parkinsonian and then chronically treated with L-DOPA for several weeks or months until they express stable and well-established LID. Then, acute (few doses) or chronic (generally protocols lasting less than a month) effects of new compounds are tested with the co-administration of L-DOPA (Bezard et al., 2004; Grégoire et al., 2011; Grégoire et al., 2009). This model is probably the most widely used since it allows rapid testing of new compounds and its tolerability, and animals may be used for several studies. In a second experimental approach, two or more groups of de novo animals are rendered parkinsonian and then treated with L-DOPA alone or in combination with the new agent. The advantages of the latter paradigm are to allow the study of the specific effects of the test compound on the development of LID and to assess if the effects diminish with long-term use, also called “wearing-off” (Grégoire et al., 2008; Hadj Tahar et al., 2004; Morin et al., 2012; Rylander et al., 2010; Samadi et al., 2006). Furthermore, measurements of biochemical changes are made possible if the animals are killed at the end of the protocol (Morin et al., 2012; Ouattara et al., 2010a; Samadi et al., 2008). However, such experiments are relatively expensive and the animals are not used in subsequent de novo studies since the test drug may have influenced permanently the development and expression of LID.

L-DOPA can be administered through several routes and may play a critical role in the behavioral assessment. Stereotaxic L-DOPA installation was tried in PD patients and seemed successful when infused in the caudate nucleus (Velasco Suárez and Escobedo, 1970). However, leaking L-DOPA into the ventricles failed to achieve improvements in

tremor and rigidity, induced dizziness and nausea, and was no longer investigated. Intraventricular administration of DA or DA agonists using implantable infusion pumps has been investigated in monkeys (de Yebenes et al., 1988; de Yebenes et al., 1987). Hardware-related complications (mainly disconnection of the pump) and the poor stability and solubility of DA in water might explain why this technique was not replicated in other groups. Nowadays, there are two main routes of L- DOPA administration, namely orally or injected systemically. In the former case, L-DOPA is delivered by nasogastric gavage using human formulations of L-DOPA (per os route). In such protocols, all animals receive the same amount of L-DOPA. This route gives a shorter but stronger response compared to injected forms, allowing higher dyskinesias. It comes handy in studies focusing mainly on peak-dose LID (Hadj Tahar et al., 2004). In the systemic administration route, L-DOPA is given intravenously in primates, as sometimes performed in patients for research purpose (Richard et al., 2005; Stocchi et al., 1992), but is seldom used in primates for handling and restraining reasons. Subcutaneous (s.c.) injection of L-DOPA in its methylester form offers more stable and reproducible plasma levels since it avoids first-pass metabolism from the liver (Cooper et al., 1984). Subcutaneous injection of L-DOPA with oral administration of the investigational drugs also allows minimizing possible pharmacokinetic interactions between these drugs. Moreover, dyskinetic responses may vary less among the animals when s.c. doses are titrated. Subcutaneous L-DOPA methyl ester may, on the other hand, accumulate in the fat tissues. Consequently, peak dose LID may be lower than those obtained with per os administration, but will last longer with a smoother response.

The dose of L-DOPA may need to be adjusted according to the drug under investigation. For antidyskinetic drugs, L-DOPA should be administered at doses that offers the greatest improvement of the parkinsonian disability (optimal) or higher to elicit LID. For medications with potential antiparkinsonian activity, partial alleviation of parkinsonian symptoms by suboptimal doses of L-DOPA that elicit low dyskinesia may be needed to fully assess the new agent's effects. If the dose of L-DOPA is kept too high, subtle effects may not be observed or missed and some monkeys may display stereotypies (Graybiel et al., 2000). Similar stereotyped behaviors are observed in PD humans with high doses of L-DOPA (Evans et al., 2004; Fernandez and Friedman, 1999). In the latter case,

when monkeys enter in a stereotypical state, they usually do not display dyskinesia and may have increased or decreased locomotor activity (Mones, 1973; Sassin, 1975). If not corrected, parkinsonian and dyskinetic scores may be interpreted as misleading results. Finally, adjusting the L-DOPA dose for each animal reflects better the clinical situation since each patient has its medication titrated for the best response. Therefore, L-DOPA titration for each animal allows a better assessment of the investigational drugs before moving to clinical trials.

Monkey models and LID

Squirrel monkeys and common marmosets are used for their small sizes and their convenience in handling and housing. Both species show sensitivity to MPTP and will develop PD symptoms. Squirrel monkeys have not been studied thoroughly since significant LID can be elicited in normal squirrel monkeys (Quik et al., 2002; Togasaki et al., 2001) at relatively low-doses of L- DOPA (15 mg/kg for a 2-day period). The underlying reason of this sensitivity of squirrel monkeys to L-DOPA without dopaminergic denervation remains to be addressed but questions its validity as an animal model for the study of LID. MPTP-treated marmosets will display behaviors similar to dyskinesia after 6 to 10 days of L-DOPA administration (Pearce et al., 1995). Under the influence of L-DOPA, marmosets will exhibit dyskinetic movements, including chorea-like (i.e. random flicking movements), dystonic-like (i.e. sustained postures) and repetitive aimless movements, but also tend to be very active and restless. However, choreic and dystonic components of LID in marmosets may be difficult to assess and to distinguish considering the pronounced hyperkinesia in these animals (Fox and Brotchie, 2010). Hemiparkinsonism can also be achieved in marmoset by unilateral injection of 6-OHDA, but was used only in few studies (Pirker et al., 2001; Svenningsson et al., 2000). Bilateral parkinsonism by 2-stage injections of intracerebral 6-OHDA was developed in marmosets, but has not been used to study LID (Mitchell and Carroll, 1997; Mitchell et al., 1995). MPTP marmosets are good models for testing new antiparkinsonian drugs to be used as monotherapy or as adjunct treatments to L-DOPA in order to reduce non-specifically LID and/or to increase its antiparkinsonian response. On the other hand, drugs aiming to reduce more specific

dyskinetic behaviors should be tested in other animal models considering the limited spectrum of dyskinesias in MPTP marmosets.

In contrast to marmosets, rhesus and cynomolgus macaques may show choreic-like, dystonic- like dyskinesias or the combination of both (Grégoire et al., 2011). As in PD patients (Rajput et al., 2009), each macaque will display its own pattern of parkinsonian symptoms. Dyskinesia involves one or more parts of the body and each of them should therefore be quantified separately (Hadj Tahar et al., 2000). Several scales are currently available to measure and quantify dyskinesia and were recently reviewed (Fox et al., 2012). Objective measures of bradykinesia with specific motor tasks are also important to separate the antidyskinetic from antiparkinsonian activity of compounds or surgeries (Jourdain et al., 2013). Moreover, MPTP monkeys display neuronal activity very similar to PD patients in the main targets for stereotactic surgery, that are the subthalamic nucleus (STN) and the GPi both "off-medication" (STN: (Bergman et al., 1994; Tachibana et al., 2011; Weinberger et al., 2006) and GPi: (Lee et al., 2007; Levy et al., 2001; Tachibana et al., 2011)) and "on-medication" (STN: (Gilmour et al., 2011; Levy et al., 2001) and GPi: (Heimer et al., 2002; Hutchison et al., 1997; Levy et al., 2001)). Finally, monkeys will tend to exhibit a worsening of motor symptoms before and after an acute L-DOPA challenge (Kuoppamäki et al., 2002), as seen in some PD patients (Evans et al., 2012). The evidence mentioned above demonstrate the efficacy of monkeys to replicate PD conditions and underlines their usefulness in the study of its treatment.

Despite the fact that animals are equally denervated (Guigoni et al., 2005), individual titration of L-DOPA is often needed to elicit the same amount of LID among the animals (Grégoire et al., 2011; Johnston et al., 2010), but it is generally accepted that there is a positive correlation between L-DOPA dose and the duration and the severity of LID (Kuoppamäki et al., 2007). One of the most interesting features of dyskinetic macaques is that administration of L-DOPA after drug holiday lasting few weeks will trigger the same LID as measured before. The same observation was made in PD patients in whom L-DOPA was stopped (Goetz et al., 1982; Mayeux et al., 1985). This observation supports the feasibility of many acute studies with the same animals therefore keeping the number

needed (and consequently the costs) to a minimum. Furthermore, the reappearance of LID after a withdrawal indicates that permanent, or at least long-term changes are happening in the brain and these changes may be studied in post-mortem brain tissues. One of the other motor side effects of chronic L-DOPA is wearing-off, described as shortening in the duration of response to L-DOPA with gradual reappearance of parkinsonian symptoms. Patients usually experience such end-of-dose deterioration after several months or years of treatment (Pahwa and Lyons, 2009). Wearing-off is also modeled in de novo MPTP monkeys with a shortening of the antiparkinsonian effect of L-DOPA as reported after two weeks of treatment (Morin et al., 2012). This observation strongly suggests that this phenomenon is not due to a loss of presynaptic storage capacity for L-DOPA as the disease progresses.

Dopaminergic denervation and LID

Dopaminergic cell loss is generally required in order to elicit LID. Except for very high doses, chronic administration of L-DOPA does not seem to induce LID in non-PD humans (Rajput et al., 1997). Similar earlier results were observed in normal monkeys where acute administrations of high doses of L-DOPA alone (100 to 400 mg/kg) did not induce LID (Mones, 1973), but rather displayed stereotyped behaviors (Sassin, 1975). More recently, L-DOPA doses of 80 mg/kg given for a three-month period induced LID in normal monkeys, whereas doses of 20 and 40 mg/kg did not (Pearce et al., 2001). LID generally appear rapidly in PD patients diagnosed in late stage (Varanese et al., 2011), young onset PD patients highly-denervated at diagnosis (Schrag et al., 1998) and MPTP exposed humans (Ballard et al., 1985). These observations indicate that a near complete DA depletion is needed to develop LID. This was further confirmed in primates where controlled dopaminergic lesions showed a correlation between the extent of DA denervation, the occurrence and severity of LID (Di Monte et al., 2000; Schneider, 1989). However, dopaminergic cell loss cannot be the sole explanation. For instance, some monkeys will never display LID independently of the nigral denervation (Aubert et al., 2005; Guigoni et al., 2005). A functional imaging study performed in PD patients came to similar conclusions (Linazasoro et al., 2009). A recent study showed that strictly unilateral hemiparkinsonian monkeys treated chronically with L- DOPA did not develop LID,

suggesting compensatory mechanisms through interhemispheric crossover dopaminergic fibers (Lieu et al., 2011). Other individual factors (sex, weight, genetics) may contribute the occurrence or the absence of LID in patients and monkeys.

Limits of MPTP models for LID

There are also experimental disadvantages of using MPTP primates for the study of LID. There is inter-animal variability of PD signs and LID. Parkinsonian symptoms as well as dystonic/choreic patterns of movement will differ for each animal, independently of the dose of MPTP and L-DOPA received (Boyce et al., 1990a). Moreover, a small portion of primates will not develop LID even with chronic L-DOPA (Aubert et al., 2005; Guigoni et al., 2005). These two characteristics may be difficult to interpret in a strict experimental frame, but model the clinical situation since not all patients will develop LID over time (Ahlskog and Muenter, 2001).

Monophasic, or peak dose, dyskinesias are LID with the highest occurrence in MPTP-treated monkeys and normally appear when plasma levels of L-DOPA are at their peak (Clarke et al., 1987; Crossman et al., 1987). PD patients treated with chronic L-DOPA will develop peak dose dyskinesia but may also display dystonia and "onset and end-of-dose" dyskinesias, also called biphasic dyskinesias (Vidailhet et al., 1999). The latter may appear consequently to the rise and fall of plasma levels of L-DOPA, but such diphasic dyskinesia and peak dose dystonia are seldom observed in parkinsonian primates (Boyce et al., 1990b). Lastly, LID in PD humans tend to develop after many years of L-DOPA administration (Ahlskog and Muenter, 2001) and increase in severity and duration (Fox and Brotchie, 2010). This result is multifactorial, including the cumulative dose of L-DOPA and the increase in L-DOPA needs as the disease progresses (Nutt, 1990). The development of LID in monkeys does not follow the same pattern as in humans. In fact, LID appear within the first days or weeks of exposure to L-DOPA (Boyce et al., 1990a; Grégoire et al., 2008) and stabilize at a given dose (Pearce et al., 1995). Lastly, it is generally assumed that systemic exposure to low doses of MPTP leads to neurodegeneration of dopaminergic cells and comes to a stop after exposure to MPTP is discontinued (Fox and Brotchie, 2010). However, some authors recently described a deterioration of parkinsonian symptoms in

monkeys treated with MPTP many years after being rendered parkinsonian (Redmond, 2012). With such recent observations, time-modifying increases or modifications of LID in MPTP-monkeys remain to be addressed.

Biochemical correlates of LID

Denervation-induced supersensitivity of DA receptors is generally recognized as a plausible mechanism of LID. Post-mortem studies have shown that striatal DA receptors particularly of the D2 subtype were increased in PD patients (Bokobza et al., 1984; Guttman et al., 1986; Lee et al., 1978), while both D1 and D2 DA receptor subtypes were increased in MPTP-lesioned monkeys (Bedard et al., 1986; Falardeau et al., 1988; Gagnon et al., 1990; Graham et al., 1993). L-DOPA reverses this increase in humans (Guttman et al., 1986; Lee et al., 1978) and monkeys (Berretta et al., 1997; Falardeau et al., 1988; Gagnon et al., 1990). In MPTP monkeys D3 receptors are decreased; this is corrected with dopaminergic treatments (Morissette et al., 1998; Quik et al., 2000). D3 receptors were reported to be either decreased (Ryoo et al., 1998) or unchanged in PD patients (Hurley et al., 1996). Dyskinesias are clearly more complex than hypersensitivity due to a simple increase in the density of striatal DA receptors. Hence, changes were sought in the signaling pathways activated by DA receptors. DA receptors regulate cAMP-protein kinase A through G-protein mediated signaling (Beaulieu et al., 2007). The D1 class of receptors (D1 and D5) stimulates production of cAMP and activity of protein kinase A while the D2 class (D2, D3 and D4) regulates production of cAMP negatively and modulates intracellular Ca2+ levels (Greengard, 2001; Missale et al., 1998). ERK, a well-known player in the MAP kinase cascade signaling, is an important mediator of cAMP signaling involved in responses to DA drugs (Beaulieu et al., 2006; Valjent et al., 2006; Valjent et al., 2005). DA receptors also exert their effect through Akt/GSK3 signaling (Beaulieu et al., 2007). Akt can phosphorylate GSK3β at Ser9 (pGSK3β (Chong et al., 2005). GSK3 is at the crossroads of several pathways (Pelech and Charest, 1995; Salinas, 1999; Shaw et al., 1998). Prolonged stimulation of D2 receptors in rodents leads to specific dephosphorylation/inactivation of striatal Akt on Thr308 (pAkt(Thr308)), Ser473 (pAkt(Ser473)) remaining unaffected (Beaulieu et al., 2005). A significant positive

correlation between LID AIMs scores in mice and extent of ERK1/2 phosphorylation was reported (Santini et al., 2007) but not in monkeys (Santini et al., 2010). L-DOPA-treated MPTP monkeys with dyskinesias display a positive correlation between dyskinesia scores and pAkt(Ser473) and pGSK3β(Ser9) levels in putamem (Morissette et al., 2010). Moreover, the metabotropic glutamate (mGlu) receptor 5 antagonist MTEP acutely inhibits LID and opposes L-DOPA-induced elevation of striatal pERK1/2 in the 6-OHDA lesioned rat model of PD (Rylander et al. 2009).

Glutamate is the most abundant excitatory neurotransmitter, mediating as much as 70% of brain synaptic transmission (Klockgether and Turski, 1993). The striatum receives two major inputs: massive excitatory glutamatergic projections from the cerebral cortex and the thalamus, as well as a dopaminergic projection from the SNc (Samadi et al., 2007). In PD, loss of striatal DA is associated with loss of the inhibitory DA control of corticostriatal glutamatergic drive with consequent increased glutamate release (Garcia et al., 2010). Glutamate activity is increased in the basal ganglia in PD (Klockgether and Turski, 1993) and is also believed to be involved in LID (Calon et al., 2003; Chase and Oh, 2000). Changes in ionotropic and metabotropic glutamate receptors are reported in the brain of PD patients with dyskinesias and dyskinetic MPTP monkeys (Calon et al., 2002; Calon et al., 2003; Carlsson, 1993; Ouattara et al., 2009; Ouattara et al., 2010a; Ouattara et al., 2010b). GABA is the most abundant inhibitory neurotransmitter and its receptors are also changed in the brains of dyskinetic human and non-human primates (Calon and Di Paolo, 2002). Serotonin receptors (Huot et al., 2010), serotonin transporters (Rylander et al. 2010b), adenosine A2a receptors (Calon et al., 2004) are also affected in LID, as well as the neuropeptides preproenkephalin and preprodynorphin (Tamim et al., 2010). Significant work has been published over the last few years on the role of serotonergic neurons in the appearance of LID both in rodents and primates and several compounds that increase brain extracellular serotonin levels have shown antidyskinetic efficacy in these models (Durif et al., 1995; Gomez- Mancilla and Bedard, 1993; Iravani et al., 2003). The mechanisms underlying the antidyskinetic effects of serotoninergic compounds remains unknown; but it is probably related to the activation of presynaptic 5-HT1A receptors, which reduces the synaptic release of glutamate (Barnes and Sharp, 1999; Meltzer et al., 2003) as seen with

the 5-HT1A agonists sarizotan (Bara-Jimenez et al., 2005; Bibbiani et al., 2001; Grégoire et al., 2009; Olanow et al., 2004) and buspirone (Bonifati et al., 1994; Kleedorfer et al., 1991). Moreover, it has been shown that the agonists of the 5-HT1A receptors were able to prevent the increase of extracellular DA levels in the striatum after the administration of L-DOPA (Kannari et al., 2001), which can also explain the reduction of LID. Furthermore, the blockade of the postsynaptic 5-HT2-type receptors can also alleviate the severity of LID (Baron and Dalton, 2003; Oh et al., 2002), probably related to the ability of 5- HT2 antagonists to boost dopaminergic cellular responses in striatal neurons (Svenningsson et al., 2002). The serotonin transporter (SERT) and other serotonin receptor subtypes are also implicated in PD and in the development of LID (for review, see (Huot et al., 2011)). Hence, the mechanisms involved in the occurrence of LID are complex and involve numerous neurotransmitters.

LID models and surgical treatment

Lesion studies

Surgical therapy is one of the options offered to patients with disabling LID. STN deep brain stimulation (DBS) is currently the mainstream surgery, but other structures are also targets for stimulation, including the GPi and the ventralis intermedius nucleus of the thalamus (Fasano et al., 2012; Walter and Vitek, 2004). These three nuclei may also be lesioned and provide a reasonable alternative when DBS is unavailable or contraindicated (Hooper et al., 2008). Despite the tremendous effects of these surgical treatments, few studies have been conducted on the interactions of L-DOPA and surgeries. Behavioral studies in rats showed that unilateral STN lesion, also called subthalamotomy reduced AIMs when performed ipsilateral to 6-OHDA-lesioned side (Aristieta et al., 2012; Levandis et al., 2008). On the contrary, some authors observed no changes in AIMs with ipsilateral subthalamotomy, but contralateral or bilateral STN lesions induced repetitive flexo-extensive movements of the upper members and repetitive movements of the head (Marin et al., 2004). Surprisingly, STN lesions made contralateral to 6-OHDA or bilaterally corrected the wearing-off phenomenon, whereas no such change was seen with ipsilateral lesions (Marin et al., 2004). On the cellular level, unilateral subthalamotomy was shown to

correct the L-DOPA-induced increase in FosB/ΔFosB and pDARPP32/DARPP32 protein expression in the striatum (Aristieta et al., 2012; Levandis et al., 2008), as well as reduce the 6-OHDA-induced increases in striatal GAD67, preproenkephalin and cytochrome oxidase mRNAs (Périer et al., 2003). These neurochemical observations suggest attenuation in the molecular changes associated with LID and a return to normal striatal activity. Recently, the first study on the response to L-DOPA after subthalamic lesion was conducted in MPTP-treated monkeys (Jourdain et al., 2013). The authors demonstrated that subthalamotomy had potentiation effects on suboptimal doses of L-DOPA and its doses could be reduced by 40% after STN lesion to have the same beneficial antiparkinsonian response to the medication as with optimal doses pre-surgery. Subthalamotomy also increased LID when the dose of L-DOPA was maintained. These results closely resemble those obtained in patients undergoing unilateral subthalamotomy (Alvarez et al., 2001; Alvarez et al., 2009; Su et al., 2002). Unilateral lesion of the GPi, also called pallidotomy was performed in dyskinetic marmosets and showed a lesion-size-dependency reduction of LID, with better improvement in dystonia compared to chorea (Iravani et al., 2005). Lesions in the ventrolateral pars oralis nucleus of the thalamus were also shown to reduce L- DOPA-induced chorea in MPTP-treated monkeys, where dystonia remained unchanged (Page et al., 1993). This particular thalamic nucleus receives pallidal efference and its lesion would therefore mimic an indirect pallidotomy. Lesions in ventrolateral thalamus (but no longer used) and pallidotomies are also performed in patients with disabling LID or hemiballism (Hariz, 2009; Narabayashi and Kubota, 1966; Suarez et al., 1997). Overall, these studies in monkeys not only show that stereotactic lesions can be replicated in animals, but they also add to the evidence that MPTP-treated monkeys are definitively the best model currently available for the study of PD, LID and their respective treatments.

High frequency stimulation studies

High frequency stimulation (HFS) via an implantable electrode is the closest model of DBS for animal models (Quintana et al., 2012). When applied in rats, STN-HFS reverses the striatal hyperactivity observed in 6-OHDA rats treated with saline or L-DOPA in both 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors as measured by patch clamp (Gubellini et al., 2006). This

reduction in glutamatergic transmission from the corticostriatal pathway paralleled with an improvement in akinesia (Gubellini et al., 2006). In partially DA-denervated rats, ipsilateral STN-HFS elevated striatal concentration of DA and its metabolite DOPAC compared to parkinsonian rats receiving L-DOPA only during a one-hour stimulation and remained significantly higher 2.5 hours post-stimulation (Lacombe et al., 2007). This latter increase in DA may explain in part the effects on the time spent "off" in patients with STN DBS (Deuschl et al., 2006), but also the decrease in L-DOPA requirements in PD patients (Follett et al., 2010). More recently, L-DOPA alone or STN-HFS alone decreased similarly serotonin levels in the prefrontal cortex and hippocampus compared to 6-OHDA rats receiving vehicle and sham stimulation, but no synergic effects were observed when L-DOPA and STN-HFS were combined (Navailles et al., 2010). On the other hand, DA levels were increased in these structures when L-DOPA was administered and further increased when STN-HFS was applied (Navailles et al., 2010). Finally, addition of STN-HFS to L-DOPA potentiated the L-DOPA-induced striatal increases in FosB/ΔFosB, glial glutamate transporter type 1, as well as levels of preproenkephalin and preprodynorphin mRNAs (Oueslati et al., 2007). The latter findings contrast with those obtained with unilateral subthalamotomy (Aristieta et al., 2012; Levandis et al., 2008; Périer et al., 2003) and suggests that although clinical outcomes are similar (Merello et al., 2008), lesions and DBS have different cellular mechanisms. To our knowledge, no studies using DBS have been conducted in dyskinetic primates yet. The high costs related to DBS implants (McIntosh, 2011) and feasibility in dyskinetic MPTP-primates may explain partially the absence of such studies. Nevertheless, interactions between surgery and LID animal models are only beginning to be explored and open new and fascinating fields of research on the pathophysiology of LID and their treatments.

Translational values of animal models

The rodent and non-human primate models of PD reproduce well the responsiveness of the motor symptoms to dopaminergic medications known to be effective in PD (Duty and Jenner, 2011; Jenner, 2009). Dissociating antidyskinetic from an antiparkinsonian activity is not an easy task. Much recent research emphasis has been placed on finding non-

dopaminergic drugs to treat dyskinesias while maintaining the antiparkinsonian activity of the dopaminergic drugs. This may require additional complexities from the animal models to reproduce more closely the non- dopaminergic pathological changes in PD in the search for non-dopaminergic targets to treat dyskinesias.

As described in the previous section glutamate is an important neurotransmitter in PD and LID and is therefore a primary target for antidyskinetic drug development. Amantadine, a weak non-competitive antagonist of the ionotropic NMDA glutamate receptor has antidyskinetic activity in rat (Dekundy et al., 2007; Kobylecki et al., 2011), mouse (Lundblad et al., 2005) and monkey (Blanchet et al., 1998) models of PD. These results in animal models translate well in PD patients. Amantadine is currently the only available efficacious medication for the pharmacological management of LID as add-on to L-DOPA in patients with PD (Fox et al., 2011), although the duration of benefit is reportedly to be short (Thomas et al., 2004).

Compounds targeting mGlu receptors are presently the objects of intense research for dyskinesias. The mGlu5 receptor subtype shows relatively selective distribution in the brain with high density in the striatum (Ouattara et al., 2011). Several mGlu5 receptor negative allosteric modulators (more commonly called antagonists) are shown to reduce the severity of dyskinesias in rats (Levandis et al., 2008; Marin et al., 2011; Mela et al., 2007; Rylander et al., 2009) and macaques (Johnston et al., 2010; Morin et al., 2010; Morin et al., 2012; Rylander et al., 2010). More specifically the translational value of the models for testing mGlu5 receptor antagonists is well demonstrated with AFQ056 (mavoglurant), an mGlu5 receptor antagonist, that is shown to reduce LID in MPTP monkeys (Grégoire et al., 2011) and also in PD patients (Berg et al., 2011).

Sarizotan, a serotonergic 5-HT1A agonist was tested in MPTP primates (Grégoire et al., 2009) and was shown at low doses to reduce dyskinesias while maintaining the antiparkinsonian efficacy of L-DOPA whereas at higher doses it reduced the L-DOPA-induced locomotor response. An other study in 6-OHDA rats showed that LID were improved acutely by sarizotan 2.5 mg/kg and in MPTP monkeys at 2 mg/kg (Bibbiani et

al., 2001). In PD patients, sarizotan was shown to reduce the duration and severity of dyskinesias (UPDRS Items 32 + 33) at 2 mg/kg with a trend at 10 mg/kg but not on diary-based measures of dyskinesia or the Abnormal Involuntary Movement Scale (Goetz et al., 2007). At higher doses, sarizotan's dopaminergic antagonist property appears causing a deterioration of the antiparkinsonian response and could partly explain the inconsistent results obtained. Dyskinesias are highly sensitive to placebo effect and in a large double-bind placebo controlled clinical trial all effects in the sarizotan group were statistically explained by the placebo-effect regression model (Goetz et al., 2008).

The present models in rodents and primate were designed to reproduce the nigrostriatal pathology and the main dopaminergic loss and do not reflect the overall pathological picture occurring in PD. These models have been very useful to investigate motor complications in PD. Dyskinesias in MPTP primates model closely this motor symptom in humans but monkeys with severe dyskinesias may alter their pattern of movement to prevent the appearance of involuntary movements. Monkeys are observed to gasp bars of their cage to avoid bucco-lingual dyskinesias or sit on their hand to avoid limb dyskinesias (personal observations). In addition, pharmacological agents can induce hypotension, muscle relaxation or sedation that reduce movement.

It is increasingly recognized that nonmotor symptoms are common in PD and have yet to be modeled properly in animals and require future attention. Nonmotor symptoms are of neuropsychiatric nature such as anxiety, depression, hallucinations, impulse control disorders, and cognitive impairment, as well as autonomic, such as gastrointestinal, urinary, and sexual disturbances (Lyons and Pahwa, 2011). Excessive sweating, orthostatic hypotension, and sleep disturbances are also nonmotor symptoms observed in PD (Lyons and Pahwa, 2011). Do the antidyskinetic drugs presently under development improve non-motor symptoms of PD? This has yet to be fully investigated. Animal models combining MPTP-induced loss of nigrostriatal DA neurons with other toxins to mimic more closely the PD pathological condition would be beneficial to widen the applicability of the models and find better drug treatments.

In conclusion, the MPTP lesioned monkey continues to be the best to model of dyskinesias in humans and has brought significant advances for the treatment of dyskinesias and will continue to do so. With the rodent models that are less expensive, initial screening of numerous compounds can be performed. Moreover, the mouse models of PD and dyskinesias can be developed with genetically modified animals that will provide additional tools to understand the mechanisms involved in the development of dyskinesias.

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Table A2.1 : Animal models of PD and LID

Animal model	Advantage	Inconvenient	Translational value
Rodent			
6-OHDA rat model	Inexpensive Time- and cost-effective Widely used toxin animal model Easily reproducible Excellent for preclinical drug validation Different stage of PD can be produced Turning behavior provides an objective evaluation tool for LID More recently an AIMs scale is available to measure LID	Fused components of the striatum Segregation in the indirect and direct DA pathways 6-OHDA toxin is not specific/selective to DA system Unilateral lesion Does not mimic all PD stages and is not progressive Dopaminergic priming is required for antiparkinsonian effect Displays different dyskinesia compared to human and non-human primates Turning behavior may interfere with dyskinesia	Excellent initial step for preclinical drug validation
6-OHDA mouse model	Inexpensive Time- and cost-effectiveness Develops better LID than MPTP mouse/easier to evaluate	Model less well-known compared to rat and less suited to study fine motor behavior	Weak for LID
Genetic mouse model	Most of these mice model PD The aphakia mouse models PD and LID	Most of these models do not reproduce DA degeneration hence no LID	Weak for LID
MPTP mouse model	Models PD	Requires large dose of L-DOPA to induced AIMs	Weak for LID
Non-human primate			
MPTP cymologus and rhesus macaque	Currently the best model to study LID Similar response to DA therapies as idiopathic PD Basal ganglia structures similar to humans Bilateral lesion (if systemic) as observed in PD Antiparkinsonian response at first dose of L-DOPA MPTP reproduces cognitive and gastro-intestinal impairments like in PD Allows to measure wearing-off Reappearance of LID after drug holiday Abundance of literature on PD and LID pathophysiology	Expensive Requires experienced personnel to handle and specialized infrastructure Interindividual biochemical variations Stereotyped behavior and hypotension at high doses of L-DOPA Different pattern of LID between animals Dose of L-DOPA may need to be titrated	Excellent to test both antiparkinsonian and antidyskinetic drugs both in acute and *de novo* studies Final step before undergoing clinical studies Excellent to test surgical therapies
MPTP marmoset	Small size Easy handling and housing Tends to be very active under L-DOPA Good literature on PD pathophysiology Displays LID	Dystonic- and choreic-like movements are difficult to distinguish due to hyperkinesia Limited literature on LID pathophysiology	Excellent to test antiparkinsonian drugs both in acute and *de novo* studies Good to test surgical treatments Weak to test antidyskinetic drugs
6-OHDA marmoset	Small size Easy handling and housing Tends to be very active under L-DOPA Strong literature on PD pathophysiology	Mainly unilateral lesions Limited literature on LID pathophysiology	Good to test antiparkinsonian drugs both in acute and *de novo* studies More studies are needed to validate the model
MPTP squirrel monkey	Small size Easy handling and housing Displays LID	Can display LID under normal (unlesioned) conditions Limited literature on PD and LID pathophysiology	No translational values

APPENDICE 3

DOPAMINE RECEPTORS AND LID

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Résumé

Ce chapitre couvre les études cliniques et pré-cliniques qui ont investigué le rôle et la distribution des sous-types de récepteurs à la dopamine (DA) dans la pathophysiologie des dyskinésies induites (LID) à la L-3,4-dihydroxyphénylalanine (L-DOPA) chez les patients parkinsoniens et les modèles animaux de la maladie de Parkinson. La neurotransmission dopaminergique est altérée dans les ganglions de la base lors de LID. Deux conditions sont nécessaires pour leur apparition: 1) une perte de dopamine dans la voie nigrostriée et 2) un traitement à la L-DOPA ou des agonistes dopaminergiques comme thérapie de remplacement. Les LID sont beaucoup plus complexes que le principe d'hypersensibilité due à la simple augmentation de la densité des récepteurs dopaminergiques dans le striatum. Le développement et l'expression des LID sont reliés à l'augmentation des activités des récepteurs D1, D2 et D3, tandis que la contribution des récepteurs D4 et D5 demeure peu explorée. Dans les études cliniques chez des patients parkinsoniens, certains facteurs ont été identifiés pour l'augmentation du risque de développer des LID, tels que des traitements à hautes doses de L-DOPA ou agonistes dopaminergiques, une stimulation anormale et pulsatile des récepteurs dopaminergiques, l'activation spécifique de sous-types de récepteurs dopaminergiques (D1 vs. D2/D3) et certains polymorphismes de sous-types de récepteurs à la dopamine (D1 et D2). Les récepteurs à la dopamine interagissent aussi avec les récepteurs provenant d'autres systèems de neurotransmission. L'implication de ces interactions dans le développement et l'expression des LID chez les patients et les modèles animaux présentent des voies intéressantes à investiguer pour développer de nouvelles avenues thérapeutiques.

Abstract

This chapter reviews preclinical and relevant clinical studies investigating the role and contribution of dopamine (DA) receptor subtypes in pathophysiology of L-3,4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesias (LID) in parkinsonian patients and animal models. Altered dopaminergic neurotransmission in the basal ganglia are observed in LID. Two conditions are necessary for their appearance: 1) loss of DA in nigrostriatal pathway and 2) treatment with L-DOPA or DA agonists, the basis of replacement therapy. LID are clearly more complex than hypersensitivity due to a simple increase in the density of striatal DA receptors. The development and expression of LID are related with increases in the activity of D_1, D_2 and D_3 receptors, while the contribution of the activity of D_4 and D_5 receptors remains unexplored. In clinical trials with PD patients, some factors have been identified to increase the risk of developing LID such as high doses of L-DOPA or DA agonist treatment, abnormal and pulsatile stimulation of DA receptors, activation of a specific DA receptor subtype (D_1 vs. D_2/D_3) and polymorphisms of the DA receptor subtypes (D_1, D_2). DA receptors interact with receptors of several other neurotransmitters. The implication of these interactions in the development and expression of LID in PD patients and animal models need further investigation to find novel drug targets.

Introduction

Parkinson's disease (PD) is the most common neurodegenerative movement disorder and is likely to increase due to the aging of populations [1, 2]. PD involves principally the death of dopamine (DA) neurons in the substantia nigra *pars compacta* (SNc) but other neurotransmitters and neuromodulators are also affected [3].

The treatment of motor symptoms of PD with the DA precursor, L-3,4-dihydroxyphenylalanine (L-DOPA) introduced 50 years ago still remains a very effective medication. However, various complications including motor fluctuations and abnormal involuntary movements, such as L-DOPA-induced dyskinesias (LID), limit the quality of life in PD patients and can be very difficult to manage [4-6]. LID are irreversible, or at least persistent, and this suggests that dopaminergic drugs can permanently or persistently modify the brain response to DA. Indeed, once LID have appeared and L-DOPA treatment is withdrawn, the first dose after several weeks of drug holiday will trigger them again [7]. No drug is yet approved for dyskinesias, aside from a modest benefit with amantadine in some PD patients [8]. Selective D_2/D_3 DA agonists have less potential to induce motor complications compared to L-DOPA [9, 10]. However, even if such DA agonists exert an antiparkinsonian effect, they are less potent than L-DOPA to control motor symptoms of PD [11]. Hence, as disease progresses, parkinsonian patients initiated with DA agonist monotherapy will eventually require L-DOPA and after 10-15 years, their motor complications appear similar as they would have been if started initially on L-DOPA therapy [12, 13]. These observations suggest that disease progression plays a major role in the onset and the development of LID rather than the type of dopaminergic drug treatment used.

The mechanisms involved in the occurrence of LID are complex and have been investigated in numerous studies using animal models and parkinsonian patients. The loss of DA in the nigrostriatal pathway and the chronic administration of L-DOPA, or DA agonists, are two necessary conditions for their appearance. However, LID are clearly more complex than hypersensitivity due to a simple increase in the density of striatal DA receptors. Moreover, L-DOPA can induce a sensitization to dopaminergic response. Hence, multiple changes in DA receptors located in the basal ganglia and in their respective

signaling pathways have been observed, including but not restricted to the modulation of the expression and the activity of subtypes of DA receptors, G proteins, effectors, protein kinases, transcription factors, etc. The development of LID seems to be related to increases in the activity of D_1, D_2 and D_3 receptor subtypes, while the contribution of the activity of D_4 and D_5 receptors remains unexplored.

Much information has been gained from animal models, especially from the 6-hydroxydopamine (6-OHDA)-lesioned rat and the 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (MPTP) non-human primate models [14]. However, differences in the basal ganglia dopaminergic system between animal models and human brain are observed. Hence, the rodent basal ganglia show anatomical differences compared to the human and non-human primates. For instance, the caudate nucleus and putamen are components of the striatum which are fused in rodents, whereas they are separated by the internal capsule in primates [15, 16]. Moreover, the segregation of the so-called direct (D_1 receptor-related) and indirect (D_2 receptor-related) pathways of the basal ganglia is well documented in rodents but their separation is not as clear in primates [17]. Hence, in primates both D_1 and D_2 receptor agonists can induce dyskinesias [18], whereas in rodents the contribution of the direct pathway with an increased activity of D_1 receptors has been more associated with LID [19]. Moreover, most striatal output neurons in rodent and primate brains can extensively collateralize and send collateral projections to every striatal output target [20-22]. Thus, DA transmission in the basal ganglia is more complex than the simplistic model of a complete segregation between D_1 and D_2 DA receptors.

Much remains to be learned from dopaminergic systems and biochemical processes that underlie the development of LID, how dopaminergic and non-dopaminergic drugs can be used to avoid the initiation of LID in early PD, to prevent or inhibit their expression in later stages of the disease and to reverse the priming process through a normalization of the basal ganglia function. This chapter presents preclinical and relevant clinical studies reviewing the role and contribution of DA receptor subtypes and their signaling in the pathophysiology of LID. The translational values of the animal models will be discussed with salient examples of clinical results.

Classification of dopamine receptors and their distribution in the basal ganglia

DA binds to one of the five different subtypes of G protein-coupled DA receptors, D_{1-5} [23]. DA receptors regulate cAMP-protein kinase A through G-protein mediated signaling [24]. The D_1 class of receptors (D_1 and D_5) couples mostly to Gαs/Gαolf and stimulates production of cAMP and activity of protein kinase A [25, 26]. In contrast, the D_2 class (D_2, D_3 and D_4) couples Gαi/Gαo, regulates production of cAMP negatively and modulates intracellular Ca^{2+} levels [27, 28].

Both D_1 and D_2 receptors are highly expressed by striatal medium spiny neurons (MSN) and are the most studied in PD and LID as compared to the other subtypes [29, 30]. D_1 and D_2 receptors are present at lower levels in the cortex as compared to the striatum [31]. D_1 receptors are expressed in striatofugal neurons containing substance P and dynorphin that project to the substantia nigra *pars reticulata* and to the internal globus pallidus, which constitute the direct striatal output pathway [32]. By contrast, D_2 receptors are predominantly localized in striatofugal neurons expressing enkephalin, which project to the external globus pallidus, constituting the indirect pathway [33, 34]. As compared to the postsynaptic D_1 receptors, D_2 receptors are also localized on presynaptic nigrostriatal dopaminergic terminals, on the SNc neurons and on presynaptic corticostriatal terminals where they can inhibit striatal glutamate release [29, 35, 36]. In humans and non-human primates, D_3 receptors are mostly found in the nucleus accumbens and in the striatum and are also localized in the internal globus pallidus, anterior thalamus, amygdala, hippocampus and cortex [37-39]. In the human striatum there is approximately one D_3 receptor for two D_2 receptors and D_3 receptor can co localize with both D_1 and D_2 receptors [38, 40]. The distribution of D_3 receptors in rodents is not similar to the pattern observed in human and non-human primate brains [40, 41]. This receptor is undetectable in the internal globus pallidus of rodents [40]. Moreover, a lower D_3/D_2 ratio (approximately 1/20) is found in the rodent's striatum as compared to human and non-human primate brains [38, 40]. The D_4 receptor is found in extrastriatal areas namely the septum, cortex, hippocampus and thalamus [31, 42]. The D_5 receptor is localized in the neck of dendritic spines in striatal medium spiny neurons and cholinergic interneurons [43]. The D_5 receptor is also found in

the cortex, hippocampus, substantia nigra, cerebellum and thalamus [42, 44].

Contribution of dopamine receptors in L-DOPA-induced dyskinesias

Dopamine receptors supersensivity and dopamine sensitization

Denervation-induced supersensitivity of DA receptors was initially recognized as a plausible mechanism of LID. Numerous studies evaluated the density of D_1, D_2 and D_3 receptors by autoradiography in the brain of human and animal models (summarized in Tables 9-1 and 9-2). LID were found to be clearly more complex than an hypersensitivity due to a simple increase in the density of striatal DA receptors. If hypersensitivity of DA receptors was present in untreated PD patients and were the cause of LID, LID would appear with the first dose of L-DOPA. However, LID usually do not emerge at first exposure to L-DOPA, but rather develop gradually over years of treatment.

D_1-like family of dopamine receptors

Early studies using dopaminergic drugs showed that D_1 receptor agonists were as effective as D_2 receptor agonists in improving parkinsonian symptoms in primates while inducing less dyskinesia [45-47]. More recently, use of D_1 receptor agonists in 6-OHDA rats demonstrated their dyskinesiogenic effects and pharmacological blockade of D_1 receptor is more effective than with D_2 receptor antagonists in reducing LID [48-50]. However, this concept was already known for some time. In fact, it has been shown several years before that dyskinesia could develop in drug-naive MPTP primates by a chronic administration of a full D_1 receptor agonist [51]. Furthermore, genetic knockout of D_1 receptors completely blocks LID in parkinsonian mice, whereas D_2 receptor knockout mice develop LID similar to wild-type mice [52].

Several autoradiographic investigations of D_1 receptors were performed *in vivo* and on *postmortem* tissues of animal models (Table 1) and in PD humans (Table 2), but no general consensus emerges [53]. These differences maybe due to various experimental assays and the sub-region of the striatum measured. In primates, striatal D_1 receptors specific binding remains unchanged [54-63] or increases [58, 64-68] after MPTP lesion. L-DOPA treatment in MPTP monkeys induces increases [56, 62, 68] or no change in D_1 receptors [55, 57, 58]. Administration of D_1 receptor agonists in monkeys increases D_1

receptors binding [56, 57, 59, 69], whereas D_1 receptors specific binding returns to control values with D_2 receptor agonists or the combination of D_1 and D_2 receptor agonists [58, 70]. In humans, D_1 receptors are unaffected whether PD patients are treated or not with L-DOPA [71, 72] or decreased by 20% with long-term L-DOPA treatment as measured by PET [73]. D_1 receptor mRNA is reported to remain unchanged [67, 74, 75] or decrease after exposure to MPTP [56, 67, 69, 74, 75]. This decrease is reversed with the administration of L-DOPA [56, 75] or with pulsatile administration of D_1 receptor agonists in the caudal striatum [69]. On the other hand, D_2 receptor agonists exert no change on MPTP-induced decrease of D_1 receptor mRNA [67, 74].

Although the association between the expression of D_1 receptors and LID is unclear, the sensitivity of D_1 receptors as measured by GTPγS binding is reported to be linearly related to the severity of LID [56]. L-DOPA induces a decrease of D_1 receptor sensitivity in non-dyskinetic MPTP monkeys, whereas its sensitivity is strongly increased in dyskinetic animals [56]. Such change in sensitivity of D_1 receptors in LID may depend on its sub cellular distribution. Indeed, in non-dyskinetic animals killed at the peak of L-DOPA plasma levels (1 hour), D_1 receptors are located at the synaptic membrane, while, by contrast, they are present at both synaptic and cytoplasmic membranes of striatofugal neurons in dyskinetic monkeys [76]. Activation of D_1 receptors by exogenous L-DOPA produces a proteasome chymotrypsin-like catalytic hypoactivity, which, in turn, leads to a D_1 receptor abnormal trafficking in striatal neurons by an impairment of receptor degradation [77]. Lentiviral overexpression of striatal G protein-coupled receptor kinase 6 leads to an internalization of D_1 receptors and decreases in primates with established LID [78]. On the other hand, in 6-OHDA rats killed 45 minutes after a single dose of L-DOPA, D_1 receptors were internalized in the cytoplasm compared to normal rats treated with L-DOPA [79]. Similar findings were found in PD patients, with a preferential cytoplasmatic localization of D_1 receptors after chronic L-DOPA when compared to healthy controls [80]. Though the subcellular distribution of D_1 receptors is altered with L-DOPA, it is not clear what is the consequence of this distribution in the development, priming process and expression of LID.

Stimulation of D_1 receptors activates the phosphorylation of the DA and cAMP-regulated phosphoprotein 32kDa (DARPP-32) [81]. DARPP-32 is unaffected by L-DOPA

treatment in normal mice, but L-DOPA produces increases in its phosphorylation in a DA-depleted state [82]. Long-term potentiation (LTP) and long-term depression (LTD) are two types of synaptic plasticity that modify neurotransmission efficacy in striatofugal neurons [83]. LTP is lost in parkinsonian animals [84] and L-DOPA treatment restores corticostriatal LTP, but not in those displaying LID [85]. Activation of the D_1 receptor/DARPP-32 pathway is important in the induction of LTP and LTD since both are lost in mice lacking DARPP-32 [86].

D_1 receptors interact with the ionotropic glutamate receptors NMDA at the postsynaptic striatal level and may form hetero-oligomeric complexes [87]. This interaction influences trafficking, signaling and desensitization of both receptors [88, 89], and such complexes are lost in 6-OHDA rats displaying abnormal involuntary movements (AIMs) [90]. The extracellular signal-regulated kinase (ERK) is an important intracellular protein involved in LTP [91] and thought to be associated with the LID priming process [92]. Interestingly, ERK signaling is part of the intracellular pathways of both NMDA and D_1 receptors [93] and its dephosphorylation is regulated by the protein phosphatase 1 [94]. Activation of D_1 receptors induces phosphorylation of ERK in normal [95] and in DA-depleted rodents' brains [96], and there is a correlation between phosphorylated ERK and LID [50, 52, 82, 97]. Phosphorylation of ERK is, at least, dependent of abnormal activation of DARPP-32; its phosphorylated state being greatly reduced in mice lacking DARPP-32 receiving L-DOPA [82]. In addition, LID are reduced with pharmacological inhibition of ERK intracellular signaling [98, 99]. Lastly, Ras-GRF1 is a neuronal specific activator of ERK signaling [93, 100]. Its genetic deletion abolishes D_1 receptor-induced phosphorylation of ERK [100] and reverts LID in mice and monkeys [101], but at the cost of reduced locomotor activity [101]. It remains however important to consider that ERK is not restricted to LID, but is also involved in many other functions [102].

The family of transcription factors *fos/jun* has been extensively studied [103]. Dopaminomimetic agents induce the expression of c-jun, c-fos, ΔFosB and FosB in striatal neurons in normal animals [104, 105], hemiparkinsonian animals [106] and require, at least, the activation of D_1 but not D_2 receptors [105]. In monkeys, ΔFosB is increased with MPTP and remains elevated for several months after exposure to MPTP [107]. Pulsatile administration of the short-acting D_1 receptor agonist SKF-82958 upregulated further

ΔFosB in MPTP monkeys and was associated with the development of LID, thus indicating an involvement of D_1 receptors in the priming process leading to their expression [107]. On the other hand, SKF-82958 administered continuously through a minipump or chronic treatment with a D_2 receptor agonist did not induce LID and no change in ΔFosB [108]. Such dopaminergic-induced elevation in ΔFosB remains upregulated several weeks after treatment discontinuation [109]. In addition, there is a positive correlation between the number of cells immunoreactive to FosB/ΔFosB and the severity of AIMs in 6-OHDA rats [110]. Genetic overexpression of ΔFosB in normal rats leads to involuntary movements similar to L-DOPA-induced AIMs observed in 6-OHDA rats [111]. Genetic overexpression of JunD, a dominant negative inhibitor of ΔFosB, reduces LID in MPTP primates [112]. Moreover, the D_1 antagonist SCH-23390, as well as antidyskinetic agents, is associated with a decreased FosB/ΔFosB expression in dyskinetic animals [50, 113]. The long-term increase in ΔFosB [109], and possibly the activation of ERK pathway, may contribute to the "memory for LID" [114] and could explain partially why L-DOPA drug-holiday has few or no effect on LID in patients [7]. More information on D_1 receptor-mediated abnormal transmission in LID can be found in [115].

D_1 and adenosine A_1 receptors are known to form functionally interacting complexes in cortical neurons and basal ganglia [116, 117]. Simultaneous pretreatment with A_1 and D_1 receptors agonists in D_1/A_1 cells was shown to decrease D_1 receptor adenylyl cyclase signaling [118]. The adenosinergic involvement in LID is discussed in another chapter of the present textbook. Concerning the other DA receptor in the D_1-like subfamily, namely the D_5 receptor, there is to our knowledge, no study on its involvement in PD and LID.

D_2-like family of dopamine receptors

Though D_1 receptors have been classically thought as being responsible for priming and expression of LID and have thus received more attention [115, 119, 120], D_2 receptors also contribute to LID. In fact, once primed to express LID, D_2 agonists will trigger AIMs in 6-OHDA rats [121, 122] as well as LID in MPTP monkeys [101, 123] and PD patients [124]. Moreover, a comparison of several D_1 and D_2 agonists in MPTP monkeys with established LID demonstrated that D_2 agonists produce higher dyskinesia than their D_1 counterparts [45]. Furthermore, administration of the D_2/D_3 agonist (+)-PHNO may also

lead rapidly to the development of LID in MPTP monkeys [125]. Once primed, these monkeys displayed LID that were unaffected by the addition of the D_1 antagonist SCH-23390 to (+)-PHNO [125, 126]. Once primed with (+)-PHNO, MPTP monkeys will display LID, as severe as those elicited with (+)-PHNO, when administered with the D_1 agonist CY-208243 [126].

Compared to D_1 receptors, autoradiography studies on D_2 receptors show more consistent results (Table 9-1). Nevertheless, here also differences among studies are reported and maybe due to the experimental assay and the sub-region of the striatum investigated. Levels of D_2 receptors in the striatum remain unchanged [57-59, 65, 127-132] or were increased with MPTP lesion in monkeys [54, 55, 58, 60-64, 66, 133-136] and in untreated PD patients [137-152]. Such DA denervation-induced increases in the expression of D_2 receptors are reversed with the administration of L-DOPA [55, 61, 64, 134, 153, 154] or were not affected [57, 62]. Administration of D_2 receptor agonists reduces the MPTP-induced upregulation of D_2 receptors [58, 66], but not as efficiently as L-DOPA, whereas D_1 receptor agonists have no effects on D_2 receptors or can produce an increase [59]. Similar observations were made in *de novo* PD patients as measured by PET scan [148, 155]. In PD patients for whom dopaminergic treatment was discontinued after subthalamic deep brain stimulation, the L-DOPA-induced down-regulation of D_2 receptors was reversed [150]. D_2 receptor mRNA increases in the posterior striatum after exposure to MPTP [56, 74, 75, 156] or remains unchanged [67, 136]. The MPTP-induced upregulation of striatal D_2 receptor mRNA is completely reversed by L-DOPA treatment in monkeys [75] or unaffected [56, 156], whereas administration of D_2 receptor agonists will either decrease (pulsatile) or reverse (continuous) the upregulation [74]. To our knowledge, D_2 receptor trafficking alterations in PD and LID has not yet been established.

The regulator of G-protein signaling (RSG) 9-2 is known to inhibit D_2 adenylyl cyclase-dependent intracellular signaling in the basal ganglia [157]. Its genetic deletion in mice causes greater locomotor responses to the D_1/D_2 agonist apomorphine [157]. Overexpression of RSG9-2 in MPTP monkeys diminishes LID, as well as D_2 agonist-induced dyskinesia, but at the cost of decreased antiparkinsonian activity [158]. On the other hand, the striatal D_2-receptor regulated Akt/GSK3 signaling cascade, which is independent from adenylyl cyclase, contributes to neurodegenerative disease including PD

[159]. It was recently shown in MPTP monkeys that L-DOPA treatment with or without antidyskinetic drugs induced a prolonged phosphorylation of both Akt and GSK3 [160].

Furthermore, severity of LID was correlated with their respective levels of phosphorylation in the posterior putamen [160]. As demonstrated for D_1 receptors, intracellular signaling pathways in D_2 receptor expressing neurons are also impaired in LID and may represent other targets for pharmacological treatments.

D_2 and adenosine A_{2A} receptors are known to form functional hetero-oligomers [117, 161]. Long-term administration of A_{2A} or D_2 agonists induces an internalization and desensitization of the D_2/A_{2A} complex [161], whereas D_2 antagonists trigger an increase in D_2/A_{2A} complex immunoreactivity [162]. Moreover, A_{2A} and the glutamate metabotropic mGlu5 receptors are also known to interact [163].

Compared to D_1 and D_2 receptors, striatal D_3 receptor is much less abundant [164] and is unaffected by DA denervation in rats [165]. D_3 receptor specific binding decreases in MPTP monkeys [37, 62, 166, 167] and PD patients [168-170]. However, its expression highly increases with L-DOPA treatment or D_1-like agonists and suggests an involvement of D_3 receptors in sensitization to L-DOPA [37, 62, 166, 167, 171]. Furthermore, administration of a D_3 receptor agonist potentiates the behavioral response to D_1 receptor stimulation in 6-OHDA rats [172]. On the other hand, no change in D_3 specific binding and mRNA was observed after MPTP and L-DOPA in common marmosets [173] and in humans [174], indicating species differences. Nevertheless, administration of a selective D_3 receptor agonist in L-DOPA-primed MPTP monkeys elicited LID comparable to those induced by apomorphine [175]. Antagonizing D_3 receptors may help in reducing the development of LID but not those already established, as demonstrated in MPTP marmosets [176]. In MPTP macaques, the D_3 antagonist nafadotride reduced established LID, but at the cost of decreased antiparkinsonian benefits of L-DOPA [37]. D_3 receptors seem to be involved in LID, but further studies are needed to establish its role in the development, priming and expression of LID.

To our knowledge, no investigation of D_4 receptors has yet been done on *postmortem* tissues of PD patients or MPTP monkeys. However, the addition of the selective and potent D_4 receptor antagonist L-745,870 to L-DOPA was recently associated with a reduced severity of LID and an increased on-time without disabling LID in MPTP monkeys [177].

Though its antidyskinetic effects remain to be elucidated, the relative abundance of D_4 receptors on GABAergic neurons of the pallidum compared to the striatum [178] suggests an involvement of the nigropallidal pathway, the latter being relatively spared in MPTP monkeys [179]. It also remains unknown if D_4 receptors are involved in the priming process.

Dopamine-dopamine receptor hetero-oligomers

The so-called direct D_1 receptor-related and the indirect D_2 receptor-related pathways (subject covered in the previous chapter) have opposite effects [180] and may be an important factor to consider in LID. In rodents, it has long been thought that both pathways were well segregated [181]. It was however shown that most [182] if not virtually all DA neurons express both D_1 and D_2 receptors in rodents [183]. It is noteworthy that a significant proportion of MSN co express both D_1 and D_2 receptor proteins in monkeys [21]. On the other hand, roughly 25% of neurons in rats [184] and up to 5% in primates [33] coexpress both receptor mRNAs. Such co expression of D_1 and D_2 receptors suggest a functional crosstalk between these two receptors. Indeed, administration of D_2 agonists potentiates the effects of immediate early genes upon D_1 receptors stimulation [185]. Moreover, D_1 and D_2 receptors can form functional hetero-oligomers and may account for the D_1-D_2 receptor synergetic effects [186]. In fact, the D_1/D_2 hetero-oligomer produces a functional unit for calcium generation, which is not observed with stimulation of D_1 or D_2 receptor homo-oligomer [187]. A rapid desensitization of such D_1/D_2 hetero-oligomer may occur with the stimulation of D_1 receptors with the specific agonist SKF 83822 or a pretreatment with the D_1/D_2 hetero-oligomer agonist SKF 83959 [188]. D_1 and D_3 receptors are coexpressed in several striatal neurons in rats [189] and may also physically interact and form functional hetero-oligomers [190]. Hetero-oligomerization between the D_1 and D_3 receptors abolishes the D_1 agonist-induced cytoplasmatic sequestration [191]. Behavioral and locomotor implications of D_1/D_3 hetero-oligomer have been reviewed [192] and deserve more attention. The D_1/D_2 and D_1/D_3 hetero-oligomers offer a new exploratory path of research for LID and more studies are needed to fully understand their possible involvement in LID.

Although most of the binding, *in situ* hybridization and PET studies described in the

present section did not show a clear correlation between DA receptor supersensitivity and LID (Tables 9-1 and 9-2), it should be considered that receptor supersensitivity may not be strictly related to changes in receptor protein or mRNA levels [193, 194]. Changes in DA-related intracellular pathways are to be taken into account in the development, priming process and expression of LID. Furthermore, DA receptor subtypes interact with one another and with receptors from other neurotransmitters. Hence, LID are by far more complex than one would expect from classical biochemical concepts.

Relevant clinical studies in parkinsonian patients on dopamine receptors

The implications of the DA receptor subtypes in the pathophysiology of PD and LID have been investigated in major clinical studies in PD patients. Studies verified if the use of higher doses of L-DOPA or DA agonist, where DA receptors are probably more stimulated, provide a better antiparkinsonian response but may increase the risk of developing LID. In the Deprenyl and Tocopherol Antioxidant Therapy of Parkinsonism (DATATOP) controlled and multicenter trial, a mean daily L-DOPA dose of 338 mg was not associated with LID in parkinsonian patients, while at higher dose (mean of 387 mg), LID were observed at the same follow- up time [195]. Moreover, the Earlier vs. Later L-DOPA Therapy in PD (ELLDOPA) study, a prospective, double-blind and placebo-controlled trial, was assessed to address the efficacy and the safety of different doses of L-DOPA in 317 previously untreated PD patients (<14 days of dopaminergic drugs) for 40 weeks [196]. While providing a better antiparkinsonian effect, higher doses of L- DOPA were associated with a dose-dependent effect on LID [196]. Moreover, a community- based study, where 87 PD patients were treated with L-DOPA with a >10-year follow-up, showed that the development of LID was increased with disease duration and severity, but LID were also related to the duration and the dose of L-DOPA treatment [197]. In normal brains, striatal DA concentrations are constant, there is a continuous stimulation of MSN and the activity of the basal ganglia are normalized. However, L-DOPA is not able to maintain constant both synaptic and extrasynaptic DA concentrations in PD. Hence, DA receptors are not constantly exposed to DA. L-DOPA, which already promotes fluctuations in brain DA concentration levels, is not able to completely normalize basal ganglia activity. It has been showed in a [11C]-Raclopride PET study that patients with peak-dose LID had larger 1-h

increases in synaptic DA levels than non-dyskinetic PD patients [198]. Inversely, diphasic dyskinesia, which are different from the peak-dose LID (which are associated with high L-DOPA doses) can occur with low doses of L-DOPA and can be attenuated by increasing L-DOPA doses [199]. These studies suggest a relation between L-DOPA doses (level of stimulation of DA receptors) and the risk of developing LID.

The development of LID is also probably due to an abnormal and pulsatile stimulation of DA receptors. This has been verified with dopaminergic drugs that are able to stimulate more continuously DA receptors consequently decreasing the risk of developing LID [8, 200-202]. Hence, long-acting DA agonists and continuous infusion of L-DOPA can reduce already established LID or reduce the development of LID as compared to L-DOPA-treated PD patients. The ergot derivatives (bromocriptine, pergolide and cabergoline), long acting D_2 receptor agonists, were the first DA agonists approved and they reduce dyskinesia when combined to L- DOPA or used as monotherapy [203-209]. Similar results were also obtained with nonergot DA agonists such as pramipexole and ropinirole where these agonists improved parkinsonian disability and reduce established LID in advanced PD state [210, 211]. Interestingly, many prospective double-blind randomized-control trials evaluated the risk of developing LID in previously untreated early PD patients when treated chronically with L-DOPA or DA agonists. In a five-year study including 268 PD patients, ropirinole reduced the development of LID as compared to the L-DOPA group (45% vs. 20%) [10]. Similarly, in the prospective randomized multicenter and double-blind CALM-PD (Comparison of the agonist pramipexole with L-DOPA on motor complications of Parkinson's disease) study, pramipexole reduced the risk of developing LID as compared to L-DOPA (31% vs. 10%) after 2 years of treatment [9]. The authors of this same study obtained similar results at 6-year follow-up (54% with L-DOPA vs. 24% with pramipexole) [212]. However, a later subanalysis of the ropirinole study and CALM- PD showed that delaying the introduction of L-DOPA did not prevent the development of LID [213, 214]. Thus, the use of a long-acting DA agonist may mask LID but does not prevent the development of LID once L-DOPA treatment is started.

Another strategy to avoid fluctuating DA concentrations in the basal ganglia and reducing already established LID is to add catechol-O-methyltransferase (COMT) inhibitors to L-DOPA treatment [215-218]. The COMT inhibitor entacapone was shown to

inhibit the expression of LID in monkeys [219] while in the multicenter and double-blind clinical trial Stalevo Reduction in Dyskinesia Evaluation (STRIDE-PD), an increase of LID was observed with entacapone [220]. The increase of LID observed might be related to the choice of a non-appropriate 3.5 h interval between Stalevo administrations [220]. Concerning the monoamine oxidase B (MAO-B) inhibitors, in PRESTO and LARGO clinical studies, the use of rasagiline 1 mg/d and rasagiline 1 mg/d + entacapone 200 mg respectively in adjunct to L-DOPA was associated with increases in LID [221, 222]. Thus, DA brain levels were probably too high, enhancing global dopaminergic activity and increasing the risk of developing LID. It has also been hypothesized that development of LID might be related to activation a specific DA receptor subtype. In rodent models, the contribution of the direct pathway with an increased activity of D_1 receptors has been associated with AIMs [19]. It was also initially thought that stimulation of D_2 rather than D_1 receptors with a specific agonist could reduce or prevent the development of LID. However, in humans and non-human primates, the use of short-acting and specific agonists of D_1, D_2 and D_3 receptor subtypes seems to be implicated in the development of LID [37, 45, 51, 223, 224]. For instance, the selective D_1 agonist prodrug, ABT-431 was administered as monotherapy in advanced PD patients with fluctuating response to L-DOPA and induced similar antiparkinsonian benefits and dyskinesia as L-DOPA [224]. Hence, this study shows that D_1 receptor agonists are as likely to produce dyskinesias as L-DOPA.

Moreover, genetic variations in DA receptors have been identified to play a role in the occurrence of peak-dose LID. A case-control study comparing sporadic PD patients and control subjects was conducted to evaluate three polymorphisms involving the D_1 receptor gene and one intronic short tandem repeat polymorphism of the D_2 receptor gene [225]. Polymorphisms of the D_1 receptor gene were not associated with the risk of developing PD or peak-dose LID while the 15 allele of the polymorphism of the D_2 receptor gene was more frequent in parkinsonian than in control subjects [225]. The frequency of both the 13 allele and the 14 allele of the D_2 receptor gene polymorphism was higher in non-dyskinetic than in the dyskinetic PD subjects while the risk reduction of developing peak-dose LID for PD subjects carrying at least 1 of the 13 or 14 alleles was 72% with respect to the PD subjects who did not carry these alleles [225]. In another cohort study, genetic factors

related to the D_2 receptor polymorphic status were found to have a protective effect in the development of LID in men, but not in women [226]. Moreover, more recent studies also suggest that gene polymorphisms in DA receptor subtypes might be implicated in the development of LID [227, 228].

Conclusion

Studies of LID in parkinsonian patients and animal models show multiple changes in the basal ganglia dopaminergic systems in the activity and the modulation of DA receptors and their signaling pathways. The mechanisms involved in the occurrence of PD, DA depletion and LID are complex and involve numerous neurotransmitters. LID are by far more complex than one would expect from classical biochemical concepts. DA receptor supersensitivity may not be strictly related to changes in receptor protein or mRNA levels. Moreover, LID may not be associated with a specific DA receptor subtype but are generated less by dopaminergic drugs with long half-life. It is important to continue to identify which proteins are up- or downregulated in direct and indirect output pathways of the basal ganglia implicated in LID. More studies with PD patients and animal models are needed to better understand the implication of DA receptors subtypes and their interactions with other neurotransmitters and their receptors in the development of LID to improve the effectiveness of present treatments or to develop new therapies against the LID.

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Table A3-1. Changes in striatal dopamine (DA) receptors and intracellular pathways associated to MPTP lesion and L-DOPA treatment inducing dyskinesias in non-human primates.

DA markers	Effect of lesion and treatment by technique			References
D_1 receptor	***Autoradiography & homogenate binding***			
	MPTP:	No change		[54-57, 59-63]
			Posterior	[58]
		Increase		[64-68]
			Anterior	[58]
		Decrease*		[58]
	MPTP + L-DOPA:			
		No change		[55, 58]
		Increase		[56, 62, 68]
		Decrease		[64]
	In situ hybridization			
	MPTP:	No change	Anterior	[67]
			Posterior	[74, 75]
		Decrease	Anterior	[56, 69, 74, 75]
			Posterior	[67, 69]
	MPTP + L-DOPA:	No change	Anterior	[56]†
			Posterior	[75]
		Increase	Anterior	[56]†
		Decrease	Anterior	[75]
D_2 receptor	***Autoradiography & homogenate binding***			
	MPTP:	No change		[57, 59, 65,
			Posterior	127]
		Increase		[58]
				[54, 55, 60-64,
			Anterior	66, 133-136]
	MPTP + L-DOPA:			[58]
		No change		
		Decrease		[57, 62]
				[55, 61, 64,
				134]

	In situ hybridization		
	MPTP:	No change	[67, 136]
		Increase	[56, 74, 75, 156]
	MPTP + L-DOPA:	No change	
		Decrease	[56, 156] [75]
D_3 receptor	***Autoradiography***		
	MPTP:	No change	[173]
		Posterior	[166]
		Decrease	[37, 62, 167]
		Anterior	[166]
	MPTP + L-DOPA:		
		No change	[173]
		Increase	[37, 62, 167]
	In situ hybridization		
	MPTP:	Increase (early)	[136]
Akt/GSK3	***Western blot***		
	MPTP:	Decrease phosphorylation	[160]
	MPTP + L-DOPA:	Increase phosphorylation	[160]
ERK1/2	***Western blot***		
	MPTP:	No change	[92]
		Increase phosphorylation	[229]
	MPTP + L-DOPA:	Increase phosphorylation	[92]
		Decrease phosphorylation	[229]
DARPP-32	***Immunohistochemistry***		
	MPTP:	Decrease	[230]
	Western blot		
	MPTP:	No change	[56, 92]
	MPTP + L-DOPA:	Increase phosphorylation	[56, 92]
ΔFosB	***Western blot***		
	MPTP:	Increase	[107, 112]
	MPTP + L-DOPA:	Increase	[112]

* An agonist radioligand was used for this particular autoradiography, whereas antagonists were used for the others listed.

† Non-dyskinetic animals showed no change whereas dyskinetic animals showed increases.

Table A3-2. Changes in striatal dopamine (DA) receptors and intracellular pathways associated with Parkinson's disease and L-DOPA treatment inducing dyskinesias.

DA markers	Technique	Effect of disease compared to controls	Effect of L-DOPA compared to controls	References
D_1 receptor	***Homogenate binding and autoradiography***			
	[^{3}H]SCH23390	Increase	No change	[231]
			No change	[140, 143, 145-147, 153]
			Caudate: decrease Putamen: no change	[232]
			Increase	[169]
	PET			
	[^{11}C]SCH23390	No change		[233]
		No change	No change	[71, 72]
			No change	[151]
D_2 receptor	***Homogenate binding and autoradiography***			
	[^{3}H]haloperidol	Increase	No change	[144]
			Caudate: No change Putamen: Increase	[138, 143]
	[^{3}H]spiperone	Increase	No change	[141]
			No change	[140, 142, 145-147]
		No change	No change	[130, 131]
			Caudate: decrease Putamen: no change	[232]
	[^{3}H]raclopride		Increase	[169]
	[^{125}I]epidepride		Increase	[170]
	[^{3}H]CV205-502		No change	[153]
	PET			
	[^{11}C]raclopride	Increase		[148, 149]

		Increase	No change	[137, 150]
		Increase	Caudate: decrease Putamen: no change	[139, 151]
		No change		[129]
	[^{11}C]methylspiperone		No change	[154]
		No change		[129]
	[^{123}I]IBZM	No change		[132]
		No change	Decrease	[128]
			Increase	[234]
		Increase		[152]
D_3 receptors	***Homogenate binding and autoradiography***			
	[^{3}H]7-OH-DPAT		Decrease	[169]
			No change	[174]
	[^{125}I]trans-7-OH-PIPAT		Decrease	[170]
	mRNA			
			No change	[174]
	PET			
	[^{11}C]-(+)-PHNO	Decrease		[168]
Akt and pAkt(Ser473)	***Western blot***			
			Decrease	[235]
DARPP-32	***Western blot***			
			Decrease	[140, 236]

PET: Positron emission tomography

APPENDICE 4

ÉCHELLE PARKINSONIENNE

LAVAL UNIVERSITY DISABILITY SCALE FOR MPTP MONKEYS

Date / Time	00:15	00:30	00:45	01:00	01:15	01:30	01:45	02:00	02:15	02:30	02:45	03:00	03:15	03:30	03:45	04:00
Posture																
Mobility																
Climbing																
Gait																
Grooming																
Voicing																
Socialising																
Tremor																
Total																
Remarks																

a) Posture: normal=0, Flexed intermittent=1, flexed constant=2, crouched=3 b) Mobility: normal=0, mild reduction=1, moderate reduction=2, severe reduction=3 c) Gait: normal=0, slow=1, very slow=2, very slow with freezing=3 d) Tremor: absent=0, mild acting tremor=1, moderate acting tremor=2, resting tremor=3 e) Climbing: present=0, absent=1; f) Grooming: present=0, absent=1; g) Socialising: present=0, absent=1; h) Voicing: present=0, absent=1.

APPENDICE 5

ÉCHELLE DYSKINÉTIQUE

LAVAL UNIVERSITY DYSKINESIA SCALE FOR MPTP MONKEYS

Date Time AIM	00:15	00:30	00:45	01:00	01:15	01:30	01:45	02:00	02:15	02:30	02:45	03:00	03:15	03:30	03:45	04:00
Rue																
Lue																
Neck																
Trunk																
Face																
Rle																
Lle																
TOTAL																

Other observations

Comments				

Score of 0-3 for each segment of the body. Maximum total/15 minutes= 21

Abbreviations: AIM, abnormal involuntary movements; Rue, right upper extremity; Lue, left upper extremity; Rle, right lower extremity; Lle: left lower extremity