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Subthalamotomy-induced changes in dopamine receptors in parkinsonian monkeys

Vincent A. Jourdain [a,b], Nicolas Morin [a,b], Marc Morissette [a], Laurent Grégoire [a], Thérèse Di Paolo [a,b,*]

[a] Neuroscience Research Unit, Centre Hospitalier Universitaire de Québec, Quebec, QC, Canada
[b] Faculty of Pharmacy, Laval University, Quebec, QC, Canada

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ABSTRACT

Subthalamotomy allows a reduction of doses of L-DOPA in dyskinetic patients while its antiparkinsonian benefits are preserved. However, the mechanisms of the potentiation of this response to medication remain to be elucidated. Hence, dopamine D_1 and D_2 receptors as well as the dopamine transporter were investigated using receptor binding autoradiography. D_1 and D_2 receptors as well as preproenkephalin and preprodynorphin mRNA levels were measured by in situ hybridization. Four dyskinetic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) parkinsonian monkeys that underwent unilateral subthalamotomy were compared to four controls, four saline-treated and four L-DOPA-treated MPTP monkeys. Dopamine, its metabolites and its transporter were extensively and similarly decreased in all parkinsonian monkeys. D_1 receptor specific binding was decreased in the striatum of all MPTP monkeys. The L-DOPA-induced decrease in D_1 receptor specific binding was reversed in the striatum ipsilateral to subthalamotomy. 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 MPTP monkeys; the STN-lesioned parkinsonian group had significantly lower values than the saline-treated and L-DOPA-treated parkinsonian monkeys in the dorsolateral putamen. Striatal preprodynorphin mRNA levels remained unchanged in MPTP monkeys compared to controls whereas it increased in all monkeys treated with L-DOPA compared to controls; subthalamotomy induced a decrease in the dorsolateral putamen ipsilateral to surgery. The improved motor response to L-DOPA after subthalamotomy 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.

Introduction

Dopaminergic depletion in Parkinson's disease (PD) causes an imbalance in the functional circuitry of the basal ganglia (Montgomery, 2007). The subthalamic nucleus (STN) abnormal activity in PD and during L-DOPA-induced dyskinesia (LID) influences several structures of the basal ganglia, mainly the globus pallidus pars interna (GPi), thus contributing to the already overinhibition of the thalamocortical relay originating from the direct pathway (Obeso et al., 2008).

Lesioning the STN is a surgical option for PD patients with intractable LID (Guridi et al., 2012) and may be preferable over its stimulation in some cases (Hooper et al., 2008). Subthalamotomy abolishes the overactive subthalamopallidal excitatory outflow (Bergman et al., 1994) and that results in motor improvements in PD patients in both "ON-medication" and "OFF-medication" states (Jourdain et al., 2014). Furthermore, PD patients may see their dopaminergic medication reduced by 45% in the first year and 30% after two years (Jourdain et al., 2014). 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). These observations are indicative of a subthalamotomy-induced potentiation of response to L-DOPA and the possible involvement of the dopaminergic system may, at least partially, explain this beneficial effect.

Though the clinical outcome is well documented, little is known about its dopaminergic mechanisms. Striatal content of dopamine (DA) is decreased after subthalamotomy in intact and hemiparkinsonian rats (Walker et al., 2009), as well in normal monkeys (Shimo and

Abbreviations: 6-OHDA, 6-hydroxydopamine; DA, dopamine; DAT, dopamine transporter; DL, dorsolateral; DM, dorsomedial; DOPAC, 3,4-dihydroxyphenylacetic acid; GPe, globus pallidus pars externa; GPi, globus pallidus pars interna; HFS, high-frequency stimulation; HPLC, high-performance liquid chromatography; 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, ventrolateral; VM, ventromedial.

* Corresponding author at: Neuroscience Research Unit, Centre Hospitalier Universitaire de Québec, 2705 Laurier Boulevard, Quebec, QC G1V 4G2, Canada. Fax: +1 418 654 2761.
E-mail address: therese.dipaolo@crchul.ulaval.ca (T. Di Paolo).

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Table 1
Parkinsonian and dyskinetic scores.

Experimental groups of monkeys	Parkinsonian score—baseline	Parkinsonian score on L-DOPA	Dyskinetic score on L-DOPA
Controls	3.2 ± 0.1	NA	NA
Saline-treated MPTP	10.1 ± 1.2	NA	NA
L-DOPA-treated MPTP	9.7 ± 0.8	5.6 ± 0.8	3.0 ± 0.9
STN-lesioned and L-DOPA-treated MPTP	Pre-op: 11.1 ± 0.7 Post-op: 10.8 ± 0.4	Pre-op: 7.6 ± 0.5 Post-op: 7. 2 ± 0.3	Pre-op: 3.1 ± 0.3 Post-op: 2.8 ± 0.6

NA: not applicable; Pre-op: pre STN lesion; Post-op: post-STN lesion.

Wichmann, 2009). In hemiparkinsonian rats, subthalamotomy reversed the L-DOPA-induced increases in the D_2/D_1 receptors ratio (Aristieta et al., 2012). Until recently, none of the studies using monkeys exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) investigated the effects of subthalamotomy on the response to L-DOPA. We published results from MPTP monkeys with LID that received a unilateral chemical lesion of the STN; these monkeys presented a better response and had a longer duration of response to suboptimal doses of L-DOPA (Jourdain et al., 2013). Dyskinesia at the optimal and suboptimal doses of L-DOPA slightly but significantly increased, whereas LID at the highest dose remained unchanged by the subthalamotomy. These results were similar to those obtained in PD patients receiving a subthalamotomy (Jourdain et al., 2014). From a neuroanatomical standpoint, monkeys are more closely related to humans than rodents. For instance, the caudate nucleus and the putamen are two distinct structures, just like humans, whereas they are fused and indistinguishable in rodents (Parent, 1997). Therefore, the use of nonhuman primates in the study of surgical therapies is preferable to rodents as it is more easily translated to humans.

The aim of the present study was thus to investigate possible changes of dopaminergic systems in the basal ganglia of these STN-lesioned MPTP monkeys which may explain the behavioral results. They were compared to controls, saline-treated and L-DOPA-treated MPTP monkeys. D_1 and D_2 receptors as well as the DA transporter were investigated using radioligand receptor autoradiography. D_1 and D_2 receptor mRNA levels, as well as the D_1 receptor- and D_2 receptor-associated neuropeptides, preprodynorphin (PPD) and preproenkephalin (PPE) respectively, were measured by in situ hybridization.

Material and methods

Animals and drug treatments

Experiments were carried out using 16 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 and twelve monkeys were treated with systemic MPTP and

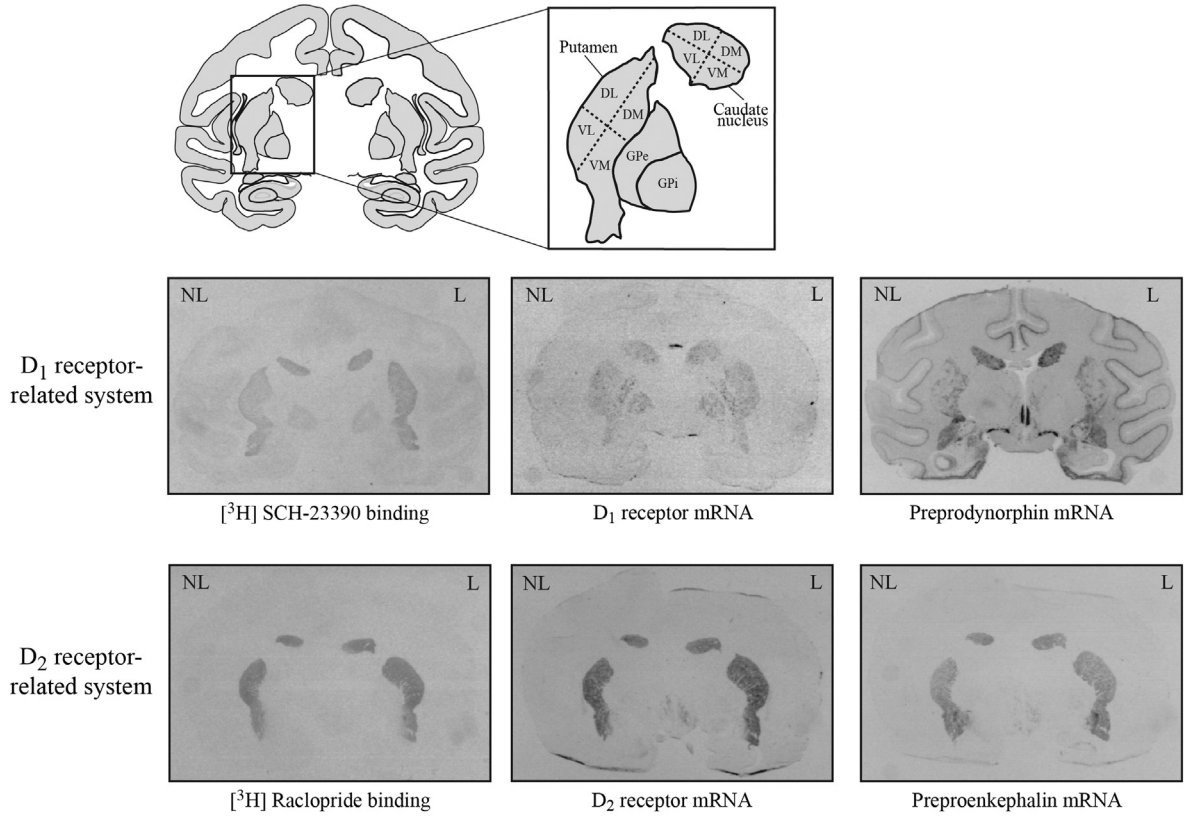

Fig. 1. Representative autoradiograms of coronal brain sections showing D_1 and D_2 receptor binding, as well as D_1 receptor and D_2 receptor, and PPE and PPD mRNA levels in the post-commissural striatum of the MPTP treated monkeys that received a unilateral subthalamotomy to alleviate their LID with 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. L = ipsilateral to STN lesion; NL = contralateral to STN lesion.