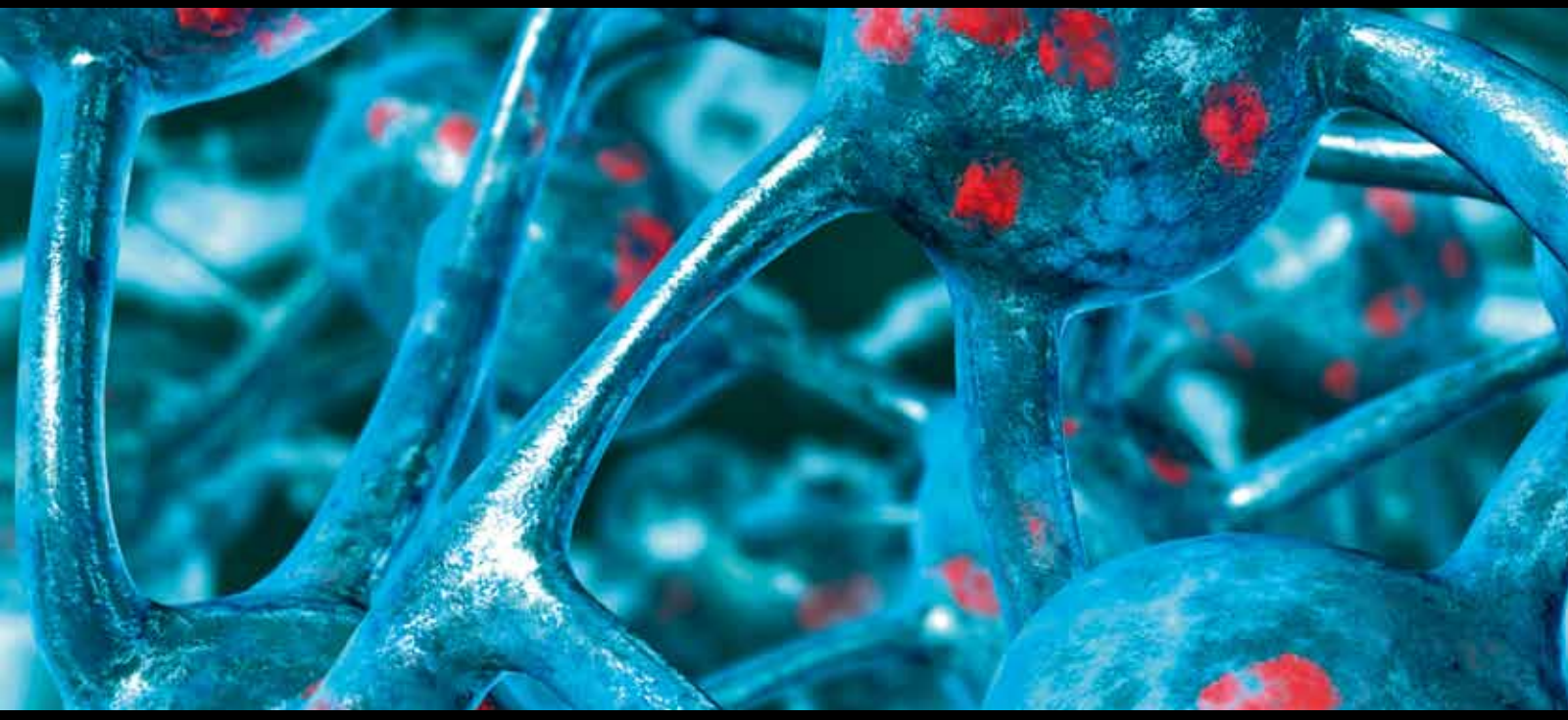
Dyskinesia in Parkinson's Disease Therapy

Guest Editors: Anna Rosa Carta, Andrea Giuffrida, and Gilberto Fisone



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Editorial Board

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Hindawi Publishing Corporation
Parkinson's Disease
Volume 2012, Article ID 639080, 2 pages
doi:10.1155/2012/639080

Editorial

Dyskinesia in Parkinson's Disease Therapy

Anna Rosa Carta,[1] Andrea Giuffrida,[2] and Gilberto Fisone[3]

[1] *Department of Biomedical Sciences, University of Cagliari, Via Ospedale 72, 09124 Cagliari, Italy*
[2] *Department of Pharmacology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229, USA*
[3] *Department of Neuroscience, Karolinska Institutet, Retzius väg 8, 171 77 Stockholm, Sweden*

Correspondence should be addressed to Anna Rosa Carta, acarta@unica.it and Gilberto Fisone, gilberto.fisone@ki.se

Received 19 November 2012; Accepted 19 November 2012

L-DOPA is still regarded as the standard pharmacotherapy for the treatment of the motor symptoms of Parkinson's disease (PD). However, the efficacy of this drug is limited by the emergence of dystonic and choreic involuntary movements, generally referred to as dyskinesia. Current interventions to treat dyskinesia are mainly based on continuous delivery of L-DOPA, administration of glutamatergic drugs (i.e., amantadine), replacement or combined administration of L-DOPA with less dyskinetic, albeit less effective, dopaminergic agonists, and deep-brain stimulation of discrete regions of the basal ganglia.

Preclinical research, on the other hand, is searching for novel approaches to the treatment of L-DOPA-induced dyskinesia, targeting alternative neurotransmitter systems, such as the serotonin, adenosine, and opioid systems, or identifying abnormalities in intracellular signal transduction and synaptic plasticity associated to this condition. This Special Issue discusses recent breakthroughs in this direction and, at the same time, provides an update of the clinical features and management of L-DOPA-induced dyskinesia.

The article by J. Guridi et al. describes the mechanisms underlying the various forms of dyskinesia produced by prolonged administration of L-DOPA. Basic pathophysiological mechanisms and current treatments are presented in detail and critically discussed.

I. Aviles-Olmos et al. focus on the comparison between L-DOPA-induced dyskinesia and graft-induced dyskinesia, an analogous condition observed in response to transplantation of fetal dopaminergic cells in PD patients. This article also provides a timely discussion of the use of gene therapy in PD and of its effects on dyskinesia.

The article by N. Tambasco et al. presents the clinical and epidemiological characteristics of dyskinesia and describes the management of this condition, based on the use of various types of dopaminergic agonists. On the same line, J. C. P. Piedad and A. E. Cavanna discuss more in detail the use of pramipexole, an agonist at dopamine D_2-type receptors, in the treatment of dyskinesia.

A number of signaling components potentially implicated in dyskinesia have been discovered during the last decade. In this regard, V. Ghiglieri et al. provide a comprehensive overview of the mechanisms and the possible pathological consequences of abnormalities affecting various forms of corticostriatal plasticity associated to L-DOPA-induced dyskinesia.

Recently, studies have pointed to the serotonergic system as a key player in the aberrant effects produced by L-DOPA and linked to the emergence of dyskinesia. The article by S. Navailles and P. De Deurwaerdère describes the evidence at the basis of this hypothesis and discusses the use of therapeutic approaches designed to prevent this phenomenon. On the same subject, E. Shin et al. discuss the experimental and clinical evidence implicating the serotonin system in L-DOPA- and graft-induced dyskinesia.

Drugs acting as antagonists at adenosine A_{2A} receptors have attracted considerable interest as antiparkinsonian and antidyskinetic agents. The article by M. Morelli et al. provides a critical appraisal of the potential therapeutic properties of these compounds, as determined in experimental models of PD and L-DOPA-induced dyskinesia.

Finally, G. Frazzitta et al. present an interesting study showing the beneficial effects produced on dyskinesia by

intensive physiotherapeutic rehabilitation. These results are discussed with regard to similar studies performed in animal models of PD.

Acknowledgments

We hope that the reader will find these articles interesting and informative both at the preclinical and clinical level. We are very grateful to the contributors and to all the colleagues involved in the reviewing process.

Anna Rosa Carta
Andrea Giuffrida
Gilberto Fisone

Hindawi Publishing Corporation
Parkinson's Disease
Volume 2012, Article ID 943159, 15 pages
doi:10.1155/2012/943159

Review Article

Clinical Features, Pathophysiology, and Treatment of Levodopa-Induced Dyskinesias in Parkinson's Disease

J. Guridi, R. González-Redondo, and J. A. Obeso

Department of Neurosurgery and Neurology, Clinica Universidad de Navarra, 31008 Pamplona, Spain

Correspondence should be addressed to J. Guridi, jguridi@unav.es

Received 6 May 2012; Accepted 8 August 2012

Academic Editor: Anna Rosa Carta

Dyskinetic disorders are characterized by excess of motor activity that may interfere with normal movement control. In patients with Parkinson's disease, the chronic levodopa treatment induces dyskinetic movements known as levodopa-induced dyskinesias (LID). This paper analyzed the pathophysiology, clinical manifestations, pharmacological treatments, and surgical procedures to treat hyperkinetic disorders. Surgery is currently the only treatment available for Parkinson's disease that may improve both parkinsonian motor syndrome and LID. However, this paper shows the different mechanisms involved are not well understood.

1. Introduction

Hyperkinetic or dyskinetic disorders are characterized by excessive muscular activity that may interfere with normal movement control. Dyskinesias include different types of movement disorders such as chorea-ballism, dystonia, myoclonus, tics, and tremor. In patients with Parkinson's disease (PD), chronic levodopa treatment may induce various dyskinetic movements (levodopa induced dyskinesias (LID)) which are classified according to the phenomenology and also their temporal presentation in relation with the effect of levodopa.

The association between levodopa and the induction of dyskinesias was recognized soon after the introduction of levodopa [1, 2]. In the past, levodopa therapy was associated with the development of motor complications in about 80% of patients within 5 years of treatment [3, 4]. In patients with young onset PD, the incidence of LID was higher and ensued more rapidly [2, 5]. Currently, with the introduction and widespread use of dopaminergic agonists, the overall treatment exposure to levodopa is decreasing, especially in the first years of treatment; nevertheless, progression of the nigrostriatal deficit will facilitate the onset of LID at a later point in time. Thus, LID continues to be a common and important cause of disability in PD and one of the main reasons for recommending surgical treatment.

In this paper we describe the major clinical features, main pathophysiological and pharmacological abnormalities associated with LIDs, and the drug and surgical treatments currently available.

2. Clinical Presentation

LID may be divided into various presentation forms (Figure 1) [6].

(1) "Peak dose" or "on" period dyskinesia related to high plasma levels of levodopa, in parallel with the maximal antiparkinsonian benefit. These are typically choreic in nature and predominantly involve the neck, trunk, and upper limbs, but dystonic movements may also occur.

(2) Diphasic dyskinesia appears at the onset and offset of the levodopa effect, coinciding with arising and decaying plasma levodopa levels. This is characterized by repetitive and stereotyped repetitive, slow (<4 Hz) movements of the lower limbs often coinciding with 4 Hz tremor in the upper limbs [4], indicating the patient is not fully "on". In severe cases, the movements of the legs may lose the repetitive and stereotypic nature and resemble ballism. In a small proportion of patients, diphasic dyskinesias are very

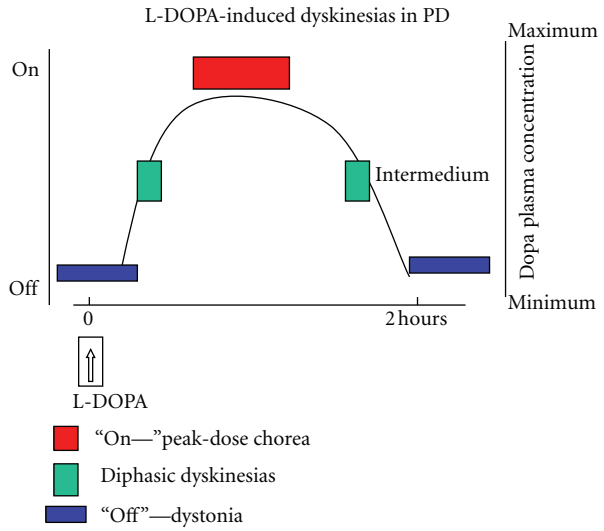

Figure 1: Relationship between LID and DOPA plasma level. "Peak of dose" or "on" period dyskinesia is correlated to high level of levodopa and in parallel with the maximal clinical benefit. Diphasic dyskinesia appears at the onset and offset of the levodopa effect in relationship with increment or decrement of plasma level. "Off" period dystonia is characterized by painful postures in lower extremities and is correlated with the lowest levodopa level. Generally a full spectrum of the three types is present in patients with motor fluctuations.

prominent while walking, drastically interfering with gait, and giving rise to a picturesque pattern [7]. Dystonic posture may also occur, although much less frequently.

(3) "Off" period dystonia, characterized by fixed and painful postures more frequently affecting the feet, but which can be segmental or generalized in distribution.

A combination of any of these 3 types or indeed, all of them, may be observed in some patients throughout the levodopa ("off-on-off") cycle. Until now LID, by definition, were associated with levodopa intake and, to a much lesser extent, with dopamine agonists used in monotherapy. Two more recent situations whereby dyskinesias can be induced in patients with PD despite not being treated with dopaminergic drugs are (1) patients treated with fetal cell transplants [8]; (2) patients treated with deep brain stimulation (DBS) of the subthalamic nucleus (STN) [9]. The former has no practical implications as experimental trials with fetal cell transplants are not a therapeutic option, but STN-DBS is fairly frequently applied. In the latter instance, adjusting the current parameters usually results in control of dyskinesias.

3. Pathophysiology of LID

Levodopa is converted into dopamine (DA) in many brain regions and "a priori" there are several sites where its dyskinesogenic effect could occur. The striatal origin of LIDs was suspected as soon as the problem was recognized in the early 1970's but there were no experimental or clinical proofs. Direct proofs arose unexpectedly when fetal mesencephalic cells transplanted into the striatum in experimental trials for PD were associated with dyskinesias with a similar clinical pattern than LID [10, 11].

Two main factors are involved in the origin of LID. (1) Degree of dopaminergic nigro-striatal depletion, which is related to disease duration and severity. (2) The pharmacokinetics and mechanism of action of levodopa, which delivers a discontinuous or pulsatile stimulation of dopaminergic receptors [3, 12]. Together, degree of nigro-striatal lesion and the action of levodopa interact to induce changes in corticostriatal transmission and plastic synaptic abnormalities in striatal spiny neurons, which ultimately may alter the physiological activity of striatopallidal circuits, leading to abnormal pattern of neuronal activity underlying LID [13, 14]. A direct demonstration of the link between short acting dopaminergic stimulation and changes in basal ganglia output was provided several years ago. It was shown that once or twice a day levodopa or apomorphine administration in parkinsonian monkeys induced dyskinesias which were associated with a reduction in the main firing frequency of globus pallidus internus (GPi) neurons [15, 16]. Similar results have been described in parkinsonian patients who were administered apomorphine during pallidal surgery. Here, the turning from the "off" parkinsonian condition to the "on" mobile state plus LID was associated with a significant reduction in the mean neuronal firing rate of the GPi and STN [17–19]. In addition, STN and GPi activity was decreased when assessed by regional brain uptake of 2-deoxyglucose, which measures afferent synaptic activity, in MPTP monkeys with dyskinesias induced by dopaminergic drugs [20]. Thus, reduced GPi inhibitory output activity to the thalamus leads to disinhibition of the thalamocortical projection, facilitating the abnormal recruitment of cortical motor areas which ultimately give rise to dyskinetic movements. In simple terms therefore, dyskinesias in general and LID in particular may be understood as the reverse of the parkinsonian state, whereby the latter is mainly characterized by overactivity of the STN and GPi output, leading to over-inhibition of the thalamus and decreased thalamocortical activity (Figure 2) [20–24].

The metabolic activity reduction and firing reduction and firing frequency changes in firing pattern of GPi activity to the thalamus are thought to produce an increase in thalamocortical drive leading to dyskinesia.

Which striatopallidal circuits, if any, may be preferentially mediate LID has been a matter of discussion over the years. D_2 mediated activation of the striato-pallidal projections in the "indirect" basal ganglia circuit was favored for a long time. Thus, pharmacological manipulation of the "indirect" circuit induces dyskinesias in monkeys which are similar to LID. For example, this is achieved by injecting bicuculline, a γ-amino butyric acid (GABA) antagonist into the globus pallidus externus (GPe), which results in increased GPe efferent activity and overinhibition of the STN [25] or by blocking STN glutamatergic projection, which provokes GPi neuronal hypoactivity and involuntary movements in the monkey [26, 27]. Moreover, it is well known that STN lesion

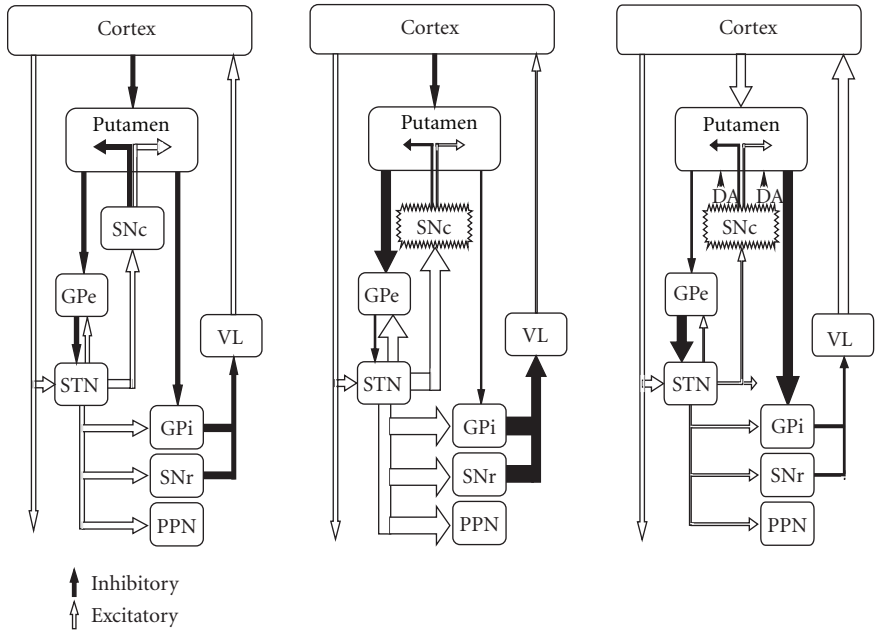

Figure 2: Classic model of basal ganglia in normal condition, parkinsonian, and dyskinetic conditions. During LID the different population of striatal cells from direct and indirect circuit are opposite to parkinsonian state. LID would result from a decrease in the inhibitory pathway by striatal neurons in the indirect pathway to the GPe, leading to an inhibitory increment over the STN and consequently reducing STN and GPi/SNr activity. This is facilitated by the increase in the inhibitory striatal activity of GPi by the direct pathway from striatum.

induces hemichorea-ballism, and both deep brain stimulation (DBS) and subthalamotomy in PD patients may induce dyskinesias that are identical to those triggered by levodopa. On the other hand, more recently molecular changes in the striatum and the effects of some dopaminergic drugs have suggested, that LID are mediated by D_1 receptor activation in the "direct" circuit [28, 29]. Thus, increased activity in the signaling by activation of D_1 receptors has been encountered both in animal models and PD patients with LID [30–33]. D_1 receptor is abnormally abundant at the plasma membrane of striatal neurons and it seems to be dysregulated in LID by alterations in intraneuronal trafficking [34]. In addition, some interesting findings have suggested a relevant role for D_3 receptor in the pathophysiology of LID [35, 36].

It is also important to consider the changes related to glutamatergic striatal input. The striatum receives massive cortical and thalamic glutamatergic inputs, which are increased in the parkinsonian state [37]. This has been suggested as the mechanism mediating loss of spines in medium spiny neurons [38], which in turn could render the striatum vulnerable to large changes in dopamine availability following levodopa treatment in PD. Recent evidence suggests that the expression, proportion and location of striatal NMDA glutamate receptors may play a paramount role in the molecular mechanisms mediating LID. In the 6-hydroxydopamine (OHDA) rat model it has been shown that the ratio of NR_{2b}/NR_{2a} is increased and there is a shift to the extra-synaptic space of the NR_{2b} receptor subunit in dyskinetic rats [39].

Recently, optogenetics was applied to selectively block the protein DARPP-32 in medium spiny neurons of the "direct" striatonigral projection, resulting in marked LID reduction in the rat model, whereas blockade of striatopallidal neurons giving rise to the "indirect circuit" produced a robust increase in locomotors activity and reduced cataleptic response to haloperidol [40].

Finally, dopaminergic drugs act not only in the striatum but also on other basal ganglia nuclei, the thalamus and cortex, all of which are dopamine depleted in variable extent in PD. The possible action of levodopa and other dopaminergic drugs modulating firing activity of the GPe, GPi and STN should not be underestimated and is still pending definitive studies.

Altogether, there is increasing evidence that overlapping mechanisms underlie the appearance of LID. They seem to converge in alterations of the striatal synaptic function in response to the loss of dopaminergic input and to subsequent replacement of dopamine by pharmacological means [29]. This concept, defined as striatal plasticity, occurs through functional processes such as long term potentiation, long term depression, or a maladaptive form of plasticity invoked as depotentiation [33, 41]. In the presence of exogenous levodopa, distinct patterns of synaptic aberrant plasticity developed in both the direct and indirect pathways, and so a new perspective is open whereby LID in PD could be considered as a network disorder [42]. Indeed, two recent studies comparing LID versus non-LID groups of patients found an increase in the structural signal of the gray-matter focused on the inferior frontal gyrus (IFG) particularly in the right hemisphere, whereas a functional MRI study pointed to an increased task-related activity in the supplementary motor area and reduced activity in the right IFG. These data

suggest that changes in the right IFG reflect neuroplasticity following from years of increased use of executive control to override involuntary movements in LID [43].

In conclusion, the dopaminergic system controls the excitability of the striatum and other basal ganglia nuclei leading to modulation of neuronal firing rates and patterns. LID may originate in striatal spiny neurons, mainly in the putamen leading to reduced mean discharge rate, abnormal firing pattern, and pathological oscillatory activity that are transmitted throughout striatopallidal projection to the thalamocortical projection.

4. LID Pharmacological Treatments

Three main therapeutic strategies have been used to treat LID in PD.

(1) Prevention of LID development by early use of dopamine agonist drugs and reduced levodopa dose intake at the beginning of treatment.

(2) Symptomatic treatment, once LID developed, with putative antidyskinetic interventions.

(3) Reverting dyskinesias by continuous dopaminergic stimulation to achieve a wider therapeutic window, reducing "off" hours while improving dyskinesias.

4.1. Prevention of LID. The use of neuroprotective drugs to slow disease progression has been extensively explored. L-deprenyl(selegiline), in an extension of the DATATOP study, failed to produce a significant reduction in the incidence of dyskinesias [44].

The only group that has demonstrated to some extent a reduction in the risk of developing dyskinesias is the dopamine agonists. Several placebo-controlled studies compared the evolution of patients initiated with a dopamine agonist (ropinirol, pramipexol, and cabergoline) and standard levodopa. Rascol et al. in a comprehensive, double-blind parallel study, compared the efficacy of ropinirol and levodopa over a period of 5 years in 268 patients with early PD [5]. The analysis of the time to onset of dyskinesia showed a significant difference in favor of ropinirol. The cumulative incidence of dyskinesia at fifth year, regardless of levodopa supplementation, was 20% in the ropinirol group and 45% in the levodopa group. The mean daily dose of ropinirol was 15 mg but the majority of the patients enrolled in that group required supplementary treatment with levodopa [5]. When patients receiving ropinirole monotherapy required the addition of levodopa, the risk of developing dyskinesias increased, and eventually, during followup, did not differ significantly from that associated with levodopa alone [45]. The use of ropinirole as monotherapy with only later addition of levodopa over 10-year follow-up delayed the onset of dyskinesias by up to 3 years [46]. Moreover, the prolonged-release form of ropinirole recently demonstrated a delay in the onset of dyskinesias compared with increasing doses of levodopa [47]. These clinical observations under control conditions confirmed experimental data in the MPTP monkey showing that ropinirol alone or in combination with low-dose levodopa delayed dyskinesia onset while improving motor performance [48].

The CALM-PD was a randomized controlled trial that evaluated the risk of developing dyskinesias in patients with early PD treated initially with either pramipexole or levodopa, followed by a maintenance phase during which open-label levodopa-carbidopa was permitted as needed [49]. After 24 months, pramipexole-treated patients were receiving a mean daily dose of 2.78 mg pramipexole plus 264 mg levodopa, compared with 509 mg levodopa for those receiving only this agent. There were fewer pramipexole-treated patients that reached the primary endpoint of time to first occurrence of wearing off, dyskinesias, or on-off motor fluctuations (27.8% versus 50.7%). Patients in the pramipexole group also had a significantly lower incidence of dyskinesias (9.9% versus 30.7%) [49]. After a mean 6-year follow-up, over 90% of patients ended up receiving levodopa therapy regardless of their initial treatment assignment. Compared to those taking pramipexole, patients initially treated with levodopa had significantly more dyskinesias (20.4% versus 36.8%), but there was no difference in the incidence of disabling or painful dyskinesias [50].

The ergot derivativecabergoline holdsa long half-life ($\approx$72 hours) and therefore may be administered once daily. In a double-blind multicenter trial on 419 patients naive to treatment, comparing cabergoline and levodopa as initial therapy for PD, motor complications were significantly delayed and occurred less frequently in cabergoline-treated patients compared to levodopa-treated patients [51].

An evidence-based review compared the results of studies published on early treatment of PD with dopamine agonists with similar studies using levodopa [52]. Cabergoline, pramipexole, and ropinirol were similarly effective in reducing the risk of LID, although reduction was slightly greater for pramipexole and ropinirol than for cabergoline. The latter is no longer used widely because of the associated risk of cardiac valvulopathy [53].

A concern encountered in the three studies was that, whereas treatment with a dopamine agonist reduced the risk of dyskinesia, this was associated with less antiparkinsonian benefit. Currently, three dopamine agonists provide longer stimulation of DA receptors, by delay-release per oral route (for pramipexol and ropinirole) and transdermal application (rotigotine). The efficacy of these new dopamine agonists formulations on LID has not been specifically assessed yet. It remains also open to future analysis to determine whether the initial benefit on LID of treatment with a dopamine agonist is carried forward over the long-term evolution once levodopa is added to the regimen. In addition, several issues related to the design of the studies have been raised by critical voices. Our own view, which is generally shared by most movement disorder neurologists, is that the severity of LID observed in clinical practice has been considerably reduced over the last decade, coinciding with the earlier use of dopamine agonists and the associated possibility of reducing levodopa daily dose. Thus, while more definitive data are being compiled, we favor the prevailing concept of starting therapy with a dopamine agonist, particularly in patients who are 65 years old or younger at the time of diagnosis.

This approach has been tempered by the more recent realization of a variety of impulse control disorders (ICD) associated with the use of dopamine agonists. Whether or not pathological impulsivity in PD patients will be also reduced by the use of long-acting dopamine agonists, it is too early to tell. We hope this will be the case by the analogy and shared pathophysiological mechanisms of LID and ICD [54].

4.2. LID as a Clinical Management Problem: Symptomatic Treatments. This is the commonest clinical scenario. Patients have already developed LID and the clinician has to attempt to control the abnormal movements by adjusting antiparkinsonian drugs or adding agents capable of reducing LID without increasing motor disability. The difficulty in achieving therapeutic efficacy is directly related to the severity and complexity of PD in each individual subject. Thus, LID are relatively easy to control when they are mild and occur in patients with a wide therapeutic window, but may be difficult or impossible to treat pharmacologically in advanced patients who exhibit all forms of LID and fall into severe "off" episodes when they are not dyskinetic. We shall review here the different individual pharmacological approaches available to treat LID but commonly, in many instances of clinical practice one needs to combine several options aiming to control both fluctuations and dyskinesias.

4.2.1. Dopamine Agonists. Any one of the above mentioned dopamine agonists may be added with the intention of reducing levodopa dose and avoiding peak of dose on-dyskinesias associated with high levodopa plasma levels while controlling the severity of "off" motor state. Belanger et al. first examined the possibility of reducing LID by using a small dose of cabergoline [55]. During treatment, they found LID in the levodopa group but not in the levodopa + cabergoline group, which suggests that a small dose of a long-acting D_2 agonist combined with low doses of levodopa could reduce the incidence of LID in patients with PD. This study supports a commonly applied clinical strategy. The practical problem in many instances arises when the reduction in levodopa doses precludes achieving a sufficiently good anti-parkinsonian response, a situation poorly tolerated by most patients.

A partial D_2 receptor agonist may represent an interesting alternative for the treatment of PD and dyskinesias. These drugs, characterized by having lower intrinsic activity at the receptor level than full agonists, act as either functional agonist or antagonist, depending on the levels of endogenous dopamine. Preclamol has a selective dopamine mixed agonist-antagonist profile for both pre and postsynaptic receptors. Its action in patients with disabling "on-off" fluctuations was compared against placebo and subcutaneous apomorphine [56], showing a mild but significant antiakinetic effect which was of lesser magnitude than that achieved with subcutaneous apomorphine but caused less dyskinesia. Aripiprazole is an antipsychotic drug showing partial agonist activity for D_2 and $5HT_{2A}$, and antagonist for $5HT_{2A}$ receptors. Lieberman postulated that this drug may be able to reduce dyskinesias without enhancing parkinsonism [57], and a small pilot study was positive, [58]. However further studies are required to investigate its antidyskinetic capacity.

4.2.2. Dopamine Antagonists. The use of drugs that block the dopaminergic system has been a classical approach for the treatment of dyskinesias in general. D_2 antagonists, like haloperidol, olanzapine, tiapride, and sulpiride, and presynaptic dopamine-depleting drugs, like reserpine and tetrabenazine, have all proven useful in the management of hemichorea-ballism, tardive dyskinesias, and tics. These same drugs are also effective in reducing or suppressing LID in PD, but this is invariably associated with marked motor worsening after a variable period (ranging from hours to weeks). In clinical practice, therefore, they are neither useful nor recommended.

Recent observations increasingly suggest that atypical neuroleptic drugs, which are able to block D_3 receptors preferentially, can be beneficial for patients with movement disorders. Oh et al. evaluated the effects of an atypical antipsychotic drug which is antagonistic of $5HT_{2A/C}$ and $D_{2/3}$ receptors, quetiapine, on motor behavior in the OHDA lesioned rat, and in MPTP treated monkeys [59]. In unilaterally lesioned rats, quetiapine reversed the shortening of the motor response to levodopa challenge produced by treatment during 3 weeks with levodopa twice daily. Quetiapine also normalized the short-duration response to acute injection of agonists either for D_1 receptor (SKF38392) or D_2(quinpirole) in rats that had received levodopa in chronic administration. Quetiapine had no effect on parkinsonian manifestations when given alone to OHDA lesioned rats or MPTP monkeys, but did substantially reduce LID when administered together with levodopa. Katzenschlager et al. assessed the effect of quetiapine on dyskinesias in a double-blind cross-over study in 9 patients with PD, receiving different doses of quetiapine or placebo at night [60]. On 50 mg/day quetiapine, a slight reduction in LID severity was observed on a visual analog scale but this improvement was not reflected in the patients' overall impression of treatment effect. Durif et al. investigated the efficacy of clozapine in the treatment of LID in 50 patients during a 10-week, double-blind, placebo-controlled, multicenter trial. During a levodopa challenge the maximal LID score was significantly decreased in the clozapine group (mean dose $\approx$40 mg/day), which led to the conclusion that clozapine is effective in the treatment of LID in severe PD [61].

4.2.3. Glutamatergic Antagonists. The N-methyl-D aspartate (NMDA) receptor is thought to mediate excitotoxicity in the basal ganglia, but the use of NMDA antagonists in humans has generally been limited because of adverse effects associated with a non-selective blockade. Metman et al., in a double-blind cross-over study, showed that 3 weeks' treatment with dextrometorphan was able to reduce dyskinesias by 30–40% while maintaining the response to levodopa. In recent years amantadine, which is believed to increase dopamine release from presynaptic uptake sites, has become popular as an antidyskinetic drug based on its putative anti-NMDA action [62]. Del Dotto et al. evaluated the effect of a 2-hour intravenous amantadine or placebo infusion

against LID in 9 PD patients with motor fluctuations and severely disabling peak-dose dyskinesias [63]. Intravenous amantadine acutely improved LID by 50%, without losing the antiparkinsonian benefit of levodopa along the 5-week, double-blind cross-over trial. In another study, Luginger et al. assessed LID severity by self-scoring diaries after oral levodopa challenges and found them to be reduced by approximately 50% after amantadine treatment compared with baseline or placebo control [64]. Further studies also found a positive effect for amantadine on LID [65, 66]. Moreover, in a recent trial in advanced PD patients receiving amantadine continuously over 1 year, a withdrawal of amantadine led to a significant increase of dyskinesias in those patients when double-blind switched to placebo, while no change occurred in those maintained on amantadine. This supports the notion of a sustained antidyskinetic effect of amantadine beyond one year of therapy. Our own view is that, on an individual basis, amantadine may result in a drastic amelioration of LID and is therefore worth trying in the absence of contraindications. The antidyskinetic effect is probably exerted at the level of the STN as amantadine failed to control dyskinesias evoked by subthalamotomy in patients who had previously responded markedly well [67].

Merello et al. evaluated the efficacy of memantine on the pharmacological response to levodopa and the induction of LID [68]. In 12 patients, in opposition to recent findings with amantadine, no effect on LID was observed. Nevertheless, several reports described a benefit of memantine in PD patients with cognitive impairment and LID with regard to dyskinesia control [69, 70]. No effect was found for riluzole on LID [71, 72]. In general, the high expectations that were raised with the potential therapeutic impact of antiglutamatergic drugs for PD have so far been disappointed.

4.2.4. Drugs Acting on the Serotoninergic System. The serotoninergic system projects quite profusely to the striatum and also to other key basal ganglia nuclei (i.e., STN, GPe, GPi), exerting an inhibitory effect on dopamine striatal transmission. Durif et al. found a 47% improvement in LID severity induced by apomorphine in 7 patients with PD treated with fluoxetine [73], out of any reduction in antiparkinsonian benefits. Buspirone has a complex mechanism of action, which aside from its $5HT_{1A}$ properties includes partial dopamine agonism and mild opiate and noradrenergic antagonism [74]. Bonifati et al. in a double-blind, placebo-controlled, cross-over study, found that buspirone significantly lessened the severity of LID in 5 out of 7 patients [75]. Meco et al., in an open-label study including 20 parkinsonian patients, found that mirtazapine, an α_2 antagonist, $5HT_{1A}$ agonist, and $5HT_2$ antagonist, may be effective in reducing LID [76].

4.2.5. Drugs Acting on the Opioid System. The opioid striatal neurons may play a role in the induction of dyskinesias. In MPTP monkeys Samadi et al. investigated the effect of different doses of naloxone and naltrexone (opioid receptor antagonists) on the dyskinetic response to the D_1 agonist SKF-82958, the D_2 agonist quinpirole and levodopa [77]. They found that joint administration of naloxone or naltrexone together with dopaminergic agents led to a significant reduction in the severity of dyskinesias without reducing antiparkinsonian efficacy. Recently, the selective μ opioid antagonist ADL5510 provided almost complete alleviation of LID without compromising reversal of parkinsonian disability in the MPTP lesioned macaque model of PD [78]. In PD patients, Carroll et al. conducted a placebo-controlled, double-blind, cross-over trial to examine the potential effect of cannabis on LID in PD [79]. Seventeen patients completed the trial and cannabis was well tolerated with no pro- or anti-parkinsonian action, but there was no evidence of a treatment effect on LID. Thus, despite many experimental suggestions, there is no drug currently employed clinically to manipulate the opioid system for the treatment of LID.

4.2.6. Noradrenergic Drugs. The close relationship between the dopaminergic, adrenergic and noradrenergic systems has led to the assessment of a possible antidyskinetic effect of a few drugs acting on those systems. Carpentier et al. found a significant 40% improvement in dyskinesia scores in PD patients treated with a low dose of propranolol [80]. Other studies have shown how the α_2 adrenoreceptor antagonist idazoxan can significantly reduce LID in monkey and rat models as well as in advanced PD patients [81, 82]. Rascol et al. reported improvement of LID without reappearance of parkinsonian symptoms in 18 patients treated with idazoxan [83]. Another α_2 antagonist, fipamezole, reduced the severity of LID by 23% and 31% at 60 mg, and 90 mg respectively, without affecting antiparkinsonian response. Currently, further trials are being carried out [84].

4.2.7. Adenosine A_{2A} Antagonists. Adenosine A_{2A} receptors are found in the striatum and thalamus and colocalize with dopamine D_2 receptors. Adenosine A_{2A} antagonists regulate dopamine and glutamate release in the brain, and they may improve motor symptoms as novel compensatory mode for loss of dopamine signaling with associated NMDA antagonism [85]. The trials target symptoms associated with dopamine replacement and therapy of dyskinesia, such as istradefylline [86, 87]. However, recent trial outcomes showed that istradefylline did not improve motor behavior or "off" times in PD patients compared with earlier results [88–92]. Preladenant showed, in a phase II placebo-controlled dose-ranging trial of 253 PD patients receiving stable dopaminergic therapy, an increase in awake time spent in the on-state of 1.4 h/day compared to 0.2 h/day in the placebo group, without overall worsening of dyskinesias [93]. The long-term antidyskinetic effect of preladenant needs ascertainment.

4.2.8. Other Drug Treatments. Levetiracetam, an antiepileptic drug, has been evaluated against LID with mixed results in several open-label studies [94–98]. The most promising data come from a study of 9 patients experiencing LID for at least 25% of waking hours [98]. After 60 days treatment with a mean of 625 mg of levetiracetam, patients experienced a 42% increase in the "on" time without LID or with nontroublesome dyskinesia in absence of significant change in the "off" time. Pardoprunox is a mixed dopamine agonist/antagonist D_2 and D_3, and a full agonist

at $5HT_{1a}$ receptors. It also binds with lower affinity to D_4, α_1 adrenergic, and $5HT_7$ receptors [99, 100]. Due to its unique pharmacologic profile, pardoprunox might have a lower tendency than other dopaminergic therapies to cause dyskinesias or neuropsychiatric side effects [93, 99–101]. Safinamide is an antiparkinsonian agent that is also in advace state of development to reach clinical practice. It has a dual mechanism of action, as it is a MAO_B inhibitor and also reduces overactivity of glutamatergic signaling by inhibiting glutamate release [102, 103]. On this prospection, AFQ056 recently achieved a significant and relevant antidyskinetic clinical effect without reducing the antiparkinsonian benefits of dopaminergic therapy [104]. Recently, low-frequency transcranial magnetic stimulation has also been applied to the treatment of LID, showing transient experimental improvements in preliminary study [105].

4.2.9. Practical Considerations. There appear to be many drugs that are capable of reducing LID severity. In occasional patients the therapeutic impact of any one of the treatments summarized above may be strikingly positive, but in the majority of patients it is limited to mild and short-lasting improvement. Nevertheless, these treatments are generally well tolerated and worth trying, when available, in patients in whom other therapeutic measurements cannot be afforded. In our experience, the degree of symptomatic control of LID mainly depends upon the complexity of dyskinesias and severity of "off" periods. This may be schematically summarized as follows: (1) in patients with mild but bothersome peak-dose dyskinesias, readjust the levodopa schedule, and consider adding a dopamine agonist. If this approach fails, any one of the drugs discussed above may be tried out; (2) for patients with intense peak-dose dyskinesias, consider switching treatment to provide continuous dopaminergic stimulation; (3) patients with severe peak-dose dyskinesias and diphasic dyskinesias probably require surgical treatment (Table 1).

4.3. Continuous Dopaminergic Stimulation. Since the introduction of the concept of continuous dopaminergic stimulation in the 1980s [3, 106–108], it has been realized that constant delivery of dopaminergic drugs is associated with a reduction in LID severity. Over the past decade, further evidence has accumulated to support the notion that continuous stimulation of dopamine receptors may even reverse some of the changes induced by chronic pulsatile levodopa administration. The antidyskinetic response to this approach is not immediate and it may take several weeks of continuous infusion before becoming apparent. The initial pivotal study using continuous delivery was published by Mouradian et al., who used levodopa intravenously for 7–12 days to a small group ($n = 12$) of patients with advanced PD [109]. They found a progressive attenuation of LID and improvement of the "on–off" fluctuations. Levodopa is too acid to be delivered intravenously or subcutaneously in practice, a problem by and large resolved with the development of duodenal levodopa infusion. This has been used with clear benefit to improve motor complications and quality of life despite the obvious practical limitations [110–113]. Very recently, the first double-blind, placebo controlled study assessing the effect of duodenal levodopa carried out in North America has been disclosed. However, the technique is complex, expensive, and potential long-term adverse effects are under debate, such as axonal polyneuropathy and vitamin B complex deficiency [114, 115]. The infusion of the duodenal levodopa gel, which also contains the dopa-decarboxylase inhibitor carbidopa, is currently available only in certain countries.

Further alternative strategies of oral intake were also tested, such as controlled release levodopa/carbidopa formulations, but they did not delay the onset of motor complications [116]. The STRIDE-PD study, initiating levodopa with entacapone, failed to reduce the frequency or delay the onset of LID [117]; an inadequate dosing schedule perturbing the putative continuous stimulation expected to be achieved with this treatment and a bias in the treatment group toward more severe disease have been suggested as potential confounders [118]. IPX066 might be soon available and it may be used to attain and maintain therapeutic levodopa plasma concentrations with a potential antidyskinetic efficacy [119].

In line with continuous delivery procedures, dopamine agonists that operate via the subcutaneous route, such as lisuride and apomorphine, are associated with a reduction in LID. The majority of trials used infusions during the daytime but stopped at night to reduce the risk of severe psychiatric complications. Stocchi et al. compared the long-term incidence of dyskinesias in patients treated with subcutaneous infusion of lisuride (plus supplementary oral levodopa as needed) versus patients treated with standard levodopa orally, and showed that patients receiving lisuride infusions experienced a reduction in the incidence of dyskinesia and motor fluctuations, compared with patients receiving standard therapies [120]. The benefit lasted over the 4 years of follow-up and this study also endorsed earlier results indicating that continuous lisuride infusion can be fairly well tolerated and beneficial for patients' motor complications, provided they have not previously developed severe psychiatric complications [121, 122].

Similarly, Manson et al. reviewed their experience in 64 patients treated with subcutaneous apomorphine infusions [123]. Forty-five patients were successfully converted to monotherapy and discontinued all other dopaminergic drugs during the daytime infusion. LID were reduced by 64% in the monotherapy group compared to 30% in those on polytherapy. Another retrospective evaluation over a 5-year period of 82 patients receiving apomorphine obtained a similar outcome [124], with average follow-up of $\approx$20 months, 5 mg/h dose, and 14 hours/day duration. Patients improved in severity of dyskinesia by 31% as assessed by the UPDRS dyskinesia evaluation, injection-site adverse events being the main reason for discontinuation of treatment. These results confirmed that monotherapy with infusions of apomorphine may reset peak-dose dyskinesia threshold in patients treated with levodopa, while further reducing off-period disability. Katzenschlager et al. prospectively assessed the antidyskinetic effect of continuous subcutaneous apomorphine using subjective and objective measures and response to a levodopa

Table 1

Practical suggestions for pharmacological management of LID
(1) The optimal therapeutic approach for LID is to try avoiding their development
(2) Start PD treatment with an agonist if possible, particularly in young onset patients
(3) Save levodopa as long as you can hold the patient's requirements for daily life activities
(4) Adjust the drug schedule: reduce total daily doses and/or shorten the intake intervals
(5) Add amantadine 200–400 mg/day
(6) Low doses of quetiapine or clozapine may be helpful
(7) Propose continuous drug delivery devices: duodenal levodopa/carbidopa gel or subcutaneous apomorphine
(8) For refractory cases, when indication is set by an expert and the risks are assumable by the patient, surgery is the treatment of choice

challenge [125]. By the sixth month the mean levodopa dose had been reduced by 55% and the daily "off" time in patients' diaries was reduced by 38%. Levodopa challenge showed a reduction of 40–44% in the dyskinesia scores and patients' self-assessment scores reflected these significant changes positively. Overall, these results reinforce the concept that replacement of oral short-acting antiparkinsonian drugs with medication capable of providing more continuous dopamine receptor stimulation may at least partially avoid or reverse the sensitization process believed to mediate the development of LID. In theory, therefore, therapy with infusions capable of providing continuous dopaminergic stimulation might be the pharmacological treatment of choice for advanced PD patients. Nevertheless, the degree of control of LID achieved with infusions is not complete in many patients. Pharmacological tolerance appears in a large proportion after some time on treatment. It occurs more readily the more severe the underlying disease is, leading to "off" episodes or exacerbation of diphasic dyskinesias. The latter may cause a very troublesome dyskinetic status [122]. At this point, surgical treatment may still be the only and best therapeutic option for a proportion of patients with severe LID.

5. Surgical Treatments

The three main surgical targets for PD are the thalamus, GPi, and STN. In this section we review the antidyskinetic effect of stereotactic surgery directed towards these 3 different targets using either ablative surgery or DBS.

5.1. The Thalamus and LID

5.1.1. Vim-Thalamotomy. During the 1960s the ventral lateral nucleus (VL) of the thalamus was determined as the best target to remove tremor in PD. This target was later defined from physiology as the ventralis intermedius (Vim) and it became established as the target of choice for tremor of any origin [126–128]. Despite the thousands of thalamotomies performed over the years, no formal and prospective evaluation of the response of thalamic surgery against LID has been reported in the literature. Some reports described how the development of LID was prevented in patients with a previous thalamotomy [129–132], others described how the lesion improved tremor and also LID [133–135], or the concept that LID improvement should be correlated with daily levodopa reduction after surgery following tremor suppression [136]. However, there are also reports where no benefit was obtained with Vim-thalamotomy in patients with LID [137].

The best study, which is somewhat an exception to the above, is the observational paper published by Narabayashi et al. [138]. These authors report an interesting and detailed study of the effect of thalamotomy against LID, dividing the patients according to the thalamic target selected for surgery. The patients subjected to lesions in the ventralis oralis anterior nucleus (Voa) or posterior (Vop) prior to the introduction of levodopa did not develop LID, but patients subjected to Vim-thalamotomy for tremor did develop dyskinesias when levodopa was introduced as treatment [138]. The conclusion reached by Narabayashi et al. was that the GPi-Voa/Vop pathway mediated LID and lesions restricted to the Vim to treat tremor were not effective against LID. Interestingly, similar results were reported by Page et al. in parkinsonian monkeys with LID induced by dopamine agonists. Thalamotomy performed in the pallidal territory removed LID, but lesions in the nigral or cerebellar terminal territory of the thalamus had no antidyskinetic effect [139].

5.1.2. Vim-DBS. The introduction of high frequency stimulation coupled with stereotactic surgery supposed a marked advance for patients with movement disorders. Vim-DBS was initially performed as an additional contralateral treatment to patients who had had a previous thalamotomy [140]. In a group of parkinsonian patients, Benabid et al. described significant tremor improvement after Vim-DBS, which was accompanied by inconsistent responses or no alleviation of LID [141]. Similar results were obtained in other studies [142–144]. In contrast, successful alleviation or suppression of LID was described in association with a different positioning of the electrode which supposedly impinges upon the Vim and the Centromedian-parafascicular nucleus (CM-Pf) [145–147]. However, a more recent study in MPTP treated monkeys revealed that lesion of the CM-Pf had no effect against parkinsonian features or LID [148]. In conclusion, the available data indicate that Vim lies outside the pathways underlying LID and, accordingly, Vim's surgery conveys no effect against LID.

5.2. Surgery of the GPi and LID

5.2.1. Pallidotomy. Posteroventral pallidotomy was reintroduced as a treatment for PD, applying Leksell's concepts, by Laitinen et al. in 1992 [149]. The clinical response to pallidal lesion included a significant benefit of the cardinal features on the contralateral side and, unexpectedly according to the basal ganglia model, a large impact against LID. Thus, pallidotomy has been shown to portray a very significant and long lasting effect against peak dose dyskinesia, diphasic dyskinesia, and also "off" period dystonia on the side contralateral to the lesion. This antidyskinetic effect is enduring and long-lasting, for at least 10 years [150, 151], with a benefit that occurred without a significant reduction in daily levodopa dose.

5.2.2. GPi-DBS and LID. In the first multicentre DBS Cooperative Multicentre Study after GPi-DBS, patients showed a 76% reduction in LID severity ($P < 0.0001$) with no change in levodopa doses at 1 and 4 years follow up [152, 153]. Longer follow-up (5-6 years) continued to show that GPi-DBS maintained a significant improvement of LID with a significant increase in "on" time without LID [154]. Levodopa was not significantly reduced compared with baseline [155].

5.3. STN Surgery and LID

5.3.1. Subthalamotomy. The STN plays a capital role in the pathophysiology of parkinsonian and dyskinetic states. This anatomical target is typically considered a prodyskinetic structure and classically avoided in patients with severe LID. Subthalamotomy is performed on occasional patients, more frequently in countries where DBS is not affordable, with fairly good general results [156].

Assessing the evolution of LID after subthalamotomy is limited by the relatively reduced number of patients reported, and by the variables in controlling some important factors, such as levodopa dose pre- and postsurgery, surgical procedure, lesion placement and volume. A recent analysis described how in a group of 68 patients "peak dose dyskinesias" increased on the side contralateral to the lesion during the first postoperative year but decreased after two to three years, showing no significant change versus baseline at the last assessment. In the ipsilateral side to the lesion, LID increased significantly with the progressive increment of levodopa suggesting that the operated side has had an antidyskinetic effect. Diphasic dyskinesias and "off" period dystonia also improved significantly ($P < 0.01$) contralateral to the lesion at 12th and 24th months after surgery [156].

5.3.2. STN-DBS. Bilateral STN-DBS is currently the surgical procedure most often selected for PD patients given the large impact against "off" medication severity and the associated reduction in the daily levodopa dose [153, 157–162]. STN-DBS has generally been associated with significant reduction in LID, closely correlated with levodopa dosage reduction. Subthalamic stimulation appears to improve the whole spectrum of LID, such as peak dose dyskinesia (30%), biphasic dyskinesia (50%), and "off" dystonia (90%) with a 47% reduction in levodopa dosage as reported by Krack et al. [157]. DBS-STN also increases "on" time without LID and reduces "off" time periods [161–163]. After 5-6 years of follow-up, LID scores were significantly improved by 83.3% in total, with 75% reduction in dyskinesia duration and 100% drop of disability compared with baseline [153, 155, 161]. Levodopa reduction was also significantly reduced in the long term compared with baseline preoperative data (30%) [155]. In a survey of 38 studies involving 737 patients treated in 34 neurosurgical centers, STN-DBS improved LID assessed by UPDRS-IV scores 94% at 12 months in the on-stimulation/"on" medication state in comparison with "on" preoperative medication scores [163].

How STN-DBS may improve LID is not well understood [164]. For most authors, LID improvement by STN-DBS may be directly correlated with levodopa reduction [165–169]. However, it is difficult to interpret these studies, because there are very few patients who maintained similar levodopa equivalent doses after surgery. Thus, fluctuations and LID disappeared in patients with levodopa withdrawal postimplantation as Vingenhoerst et al. described, whereas they persisted in those patients on medication 2 years after surgery [167]. Similarly, another group reported that 1 year after implantation, patients receiving levodopa displayed a 47% LID reduction, whereas the reduction was 90% of LID in patients who did not receive levodopa ($P < 0.003$) [168]. On the other hand, the antidyskinetic response after STN-DBS could be related with the effect of continuous high frequency stimulation, providing antidyskinetic efficacy on its own [170–172]. This may be supported by some instances where improvement of LID occurred despite maintaining the same daily dose of levodopa [170]. Thus, STN surgery could induce a stable and continuous functional state with reduced fluctuations in basal ganglia network, somehow mimicking the effect of continous dopaminergic stimulation.

Finally, it has also been suggested that the antidyskinetic effect of STN-DBS (as well as subthalamotomy) may be due to an effect on the dorsal border of the nucleus, reaching the lenticularis fasciculus and zona incerta. In this context some studies have suggested that the real subthalamic target may be the region above the dorsal border of the nucleus [173–175].

In conclusion, STN-DBS probably interferes with abnormal discharge pattern in basal ganglia output nuclei associated with the parkinsonian condition, improving PD, and permitting a reduction of chronic levodopa therapy. The latter is likely responsible for the anti-LID effect. On the other hand, it is also possible that high frequency stimulation of the STN could modify the patterns of neuronal firing and the rhythms associated with LID having "per se" an antidyskinetic effect [176].

6. Conclusions

Most PD patients develop motor fluctuations and LID during chronic evolution and on levodopa treatment. Motor complications are directly related with disease progression and the effects of chronic levodopa therapy. Once

established, LID remains unabated throughout evolution. Pharmacological management is not simple but in recent years, the proportion of patients suffering severe LID has declined considerably, mainly in relation with the use smaller dose of levodopa. Surgical treatment has a potent anti-dyskinetic effect whose value has to be judged for every particular patient against the risk. LID is no longer the major cause of disability in PD patients nor a problem lacking several treatment options.

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Hindawi Publishing Corporation
Parkinson's Disease
Volume 2012, Article ID 489853, 8 pages
doi:10.1155/2012/489853

Review Article

A_{2A} Receptor Antagonism and Dyskinesia in Parkinson's Disease

Micaela Morelli,[1,2] Fabio Blandini,[3] Nicola Simola,[1] and Robert A. Hauser[4]

[1] *Department of Biomedical Sciences, University of Cagliari, Via Ospedale 72, 09124 Cagliari, Italy*
[2] *CNR Institute of Neuroscience, 09042 Cagliari, Italy*
[3] *Interdepartmental Research Center for Parkinson's Disease, National Neurological Institute C. Mondino, 27100 Pavia, Italy*
[4] *Department of Neurology, University of South Florida, Tampa, FL 33613, USA*

Correspondence should be addressed to Micaela Morelli, morelli@unica.it

Received 21 February 2012; Accepted 26 April 2012

Academic Editor: Anna Rosa Carta

Dyskinesia, a major complication of treatment of Parkinson's disease (PD), involves two phases: induction, which is responsible for dyskinesia onset, and expression, which underlies its clinical manifestation. The unique cellular and regional distribution of adenosine A_{2A} receptors in basal ganglia areas that are richly innervated by dopamine, and their antagonistic role towards dopamine receptor stimulation, have positioned A_{2A} receptor antagonists as an attractive nondopaminergic target to improve the motor deficits that characterize PD. In this paper, we describe the biochemical characteristics of A_{2A} receptors and the effects of adenosine A_{2A} antagonists in rodent and primate models of PD on L-DOPA-induced dyskinesia, together with relevant biomarker studies. We also review clinical trials of A_{2A} antagonists as adjuncts to L-DOPA in PD patients with motor fluctuations. These studies have generally demonstrated that the addition of an A_{2A} antagonist to a stable L-DOPA regimen reduces OFF time and mildly increases dyskinesia. However, limited clinical data suggest that the addition of an A_{2A} antagonist along with a reduction of L-DOPA might maintain anti-Parkinsonian benefit and reduce dyskinesia. Whether A_{2A} antagonists might reduce the development of dyskinesia has not yet been tested clinically.

1. Adenosine A_{2A} Receptor Localization and Biochemistry

Adenosine A_{2A} receptors are present in medium to high concentrations in several basal ganglia (BG) nuclei and may therefore be capable of influencing motor activity by acting at different BG levels. This feature renders A_{2A} receptors particularly attractive for modulation of dopamine receptor functions in a disease such as Parkinson's disease (PD), which is caused by degeneration of dopaminergic neurons in the nigrostriatal pathway, but associated with changes at several receptor levels. An interesting peculiarity of A_{2A} receptors is their selective localization in the indirect striatonigral GABAergic pathway, which contains enkephalin (ENK) and which is known to lead to inhibition of motor behavior [1, 2].

A_{2A} receptors are positively coupled to adenylate cyclase and, either at the level of second messengers or through the formation of receptor heterodimers, negatively influence dopamine D_2 receptor activity [3–6]. On the basis of this anatomical and functional organization, A_{2A} receptors acting in concert with D_2 and D_1 receptors are capable of affecting planning and execution of movements [7, 8]. Moreover, the low levels of A_{2A} receptors expressed in brain areas other than the BG are at the basis of the low incidence of nonmotor side effects observed in clinical trials so far performed [9]. A_{2A} receptors, however, are expressed in some peripheral organs and blood cells, underlying the importance of evaluating these elements in clinical trials testing the efficacy of A_{2A} receptor antagonists in PD [10, 11].

Interestingly, an abnormal increase in A_{2A} signaling, in the striatum of 6-hydroxydopamine- (6-OHDA-) lesioned rats, and in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine- (MPTP-) treated primates, as well as in PD patients chronically treated with L-DOPA [12–14], might produce a prevailing tone of A_{2A} receptors, the activation of which inhibits motor activity. Therefore, blockade of the A_{2A} receptor inhibitory tone could be one of the factors underlying the positive effects produced by A_{2A} antagonists in PD.

2. Adenosine A_{2A} Receptor Antagonists in Animal Models of Dyskinesia

2.1. Behavioral Studies. Preclinical behavioral investigations suggest that A_{2A} antagonists may be of interest in the management of dyskinesia in PD. The first preclinical evidence suggesting that A_{2A} antagonists may be utilized in patients rendered dyskinetic by L-DOPA was obtained in 6-OHDA unilaterally lesioned rats subchronically treated with L-DOPA [17]. In this paradigm, the repeated administration of L-DOPA causes a progressive, sensitized, increase in contraversive turning behavior, which is thought to reproduce some aspects of the abnormal motor responses induced by the prolonged treatment with L-DOPA [17–19]. Of great interest, sensitization in contraversive turning behavior did not take place when L-DOPA was administered at a low dose in association with an A_{2A} antagonist [17, 20]. Subsequent studies utilizing a full effective L-DOPA dose in rats with established dyskinesia [21] did not report any benefit, since L-DOPA treatment alone or in combination with an A_{2A} antagonist presented the same degree of dyskinesia. These results demonstrated that A_{2A} antagonists are not antidyskinetic drugs; however, in this model, they did not worsen existing dyskinesia while increasing the efficacy of L-DOPA on motor symptoms.

Studies in MPTP-treated primates, the best experimental model of PD and PD-associated dyskinesia, have confirmed the beneficial effects of blockade of A_{2A} receptors. A_{2A} antagonists were found not to be prodyskinetic drugs, since their administration to Parkinsonian primates with established dyskinesia induced by L-DOPA relieved motor impairment and did not worsen dyskinesia [22–24]. Moreover, an attenuation of dyskinesia induced by long-term apomorphine was observed when the drug was administered in combination with an A_{2A} antagonist [25], suggesting that A_{2A} antagonists might lower the dyskinetic potential of dopamine-replacement therapy in specific conditions. The previous coadministration of an A_{2A} antagonist was also found to delay the onset of severe dyskinesia when the same primates were maintained on apomorphine alone [25].

2.2. Biochemical Studies. Regarding the mechanisms underlying dyskinesia and the effects of A_{2A} antagonists in experimental models of dyskinesia, it seems likely that these drugs interfere with the neuroplastic changes induced by dopamine-replacement therapy in the dopamine-denervated BG (Figure 1). Studies in 6-OHDA-lesioned rats demonstrate that striatal dopamine denervation is associated with persistent modifications in the levels of the neuropeptides dynorphin (DYN) and ENK, as well as the enzyme glutamic acid decarboxylase 67 (GAD-67) [21, 26–28] (Figure 1). Moreover, it was observed that chronic treatment with L-DOPA, which induces a dyskinetic-like motor response, further contributes to these biochemical changes [21, 26, 27] (Figure 1). Importantly, the coadministration of an A_{2A} antagonist, besides resulting in a stable motor response, attenuated the effects of chronic L-DOPA treatment on ENK and GAD-67 [21, 26, 27]. It has to be acknowledged that, as of today, no evidence supports a direct role of DYN, ENK, and GAD-67 in dyskinesia. Nevertheless, changes in the expression of neuropeptides are a marker of the activity of striatal neurons [26]. Therefore, it can be suggested that A_{2A} antagonists modulate the effects of L-DOPA and mitigate the neuroplastic changes this drug induces in the striatum. These effects could arise from the opposite functional interactions involving adenosine A_{2A} and dopamine D_1 and D_2 receptors [29]. These interactions, by amplifying dopaminergic signaling, would regulate the activity of striatal output neurons in conditions of dopamine denervation and nonphysiological stimulation of dopamine receptors (Figure 1).

It has to be considered that A_{2A} receptor antagonists, in addition to their potential effects on biochemical and functional changes induced by dopamine-replacement therapy, potentiate the motor-activating effects of L-DOPA and dopaminergic agonists, allowing their use at lower, nondyskinetic doses [7]. Hence, the sparing of dopaminomimetic drugs in combination with an A_{2A} antagonist may contribute to the attenuation, or delay, of the maladaptive modifications in striatal function which underlie dyskinesia.

2.3. Role of Glutamate Transmission. Besides the facilitation of dopamine transmission, other mechanisms have been proposed to underlie, or at least participate in, the effects of A_{2A} receptor antagonists observed in experimental models of dyskinesia. Neuroanatomical studies demonstrate that striatal A_{2A} receptors are highly expressed at the postsynaptic level in asymmetric synapses, where they can interact with glutamate receptors [30]. Glutamate receptors are thought to participate in the pathophysiology of dyskinesia [31] and, interestingly, chronic administration of L-DOPA to 6-OHDA-lesioned rats was reported to induce a hyperphosphorylation state of the α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor [25, 32]. This effect was found to be significantly attenuated when L-DOPA was administered in combination with an A_{2A} antagonist [25, 32]. Evidence also exists that A_{2A} receptors may regulate the conductance of N-methyl-D-aspartate (NMDA) receptors [33]. This may have important implications for dyskinesia, since NMDA receptors play a major role in neuroplasticity phenomena [34, 35], including those which take place in motor circuits, and may underlie abnormal motor responses to dopamine-replacement therapy used in PD.

Interactions between A_{2A} receptors and type 5 metabotropic glutamate receptors (mGlu5) have also been reported [36–38]. In the light of the evidence showing that antagonism of mGlu5 receptors may reduce dyskinesia in MPTP-lesioned primates treated with L-DOPA [39], it is possible to envision that combined antagonism on the two receptors might contribute to the beneficial effects of A_{2A} antagonists on dyskinesia. Additional mechanisms involved in the modulation of therapy-induced abnormal motor responses by A_{2A} antagonists could include interaction with nondopaminergic and nonglutamatergic receptors, such as cannabinoid and serotonin receptors, and regulation of neurotransmitter release [40–42]. In this regard, it has to be recalled that A_{2A} receptors powerfully modulate extracellular concentrations

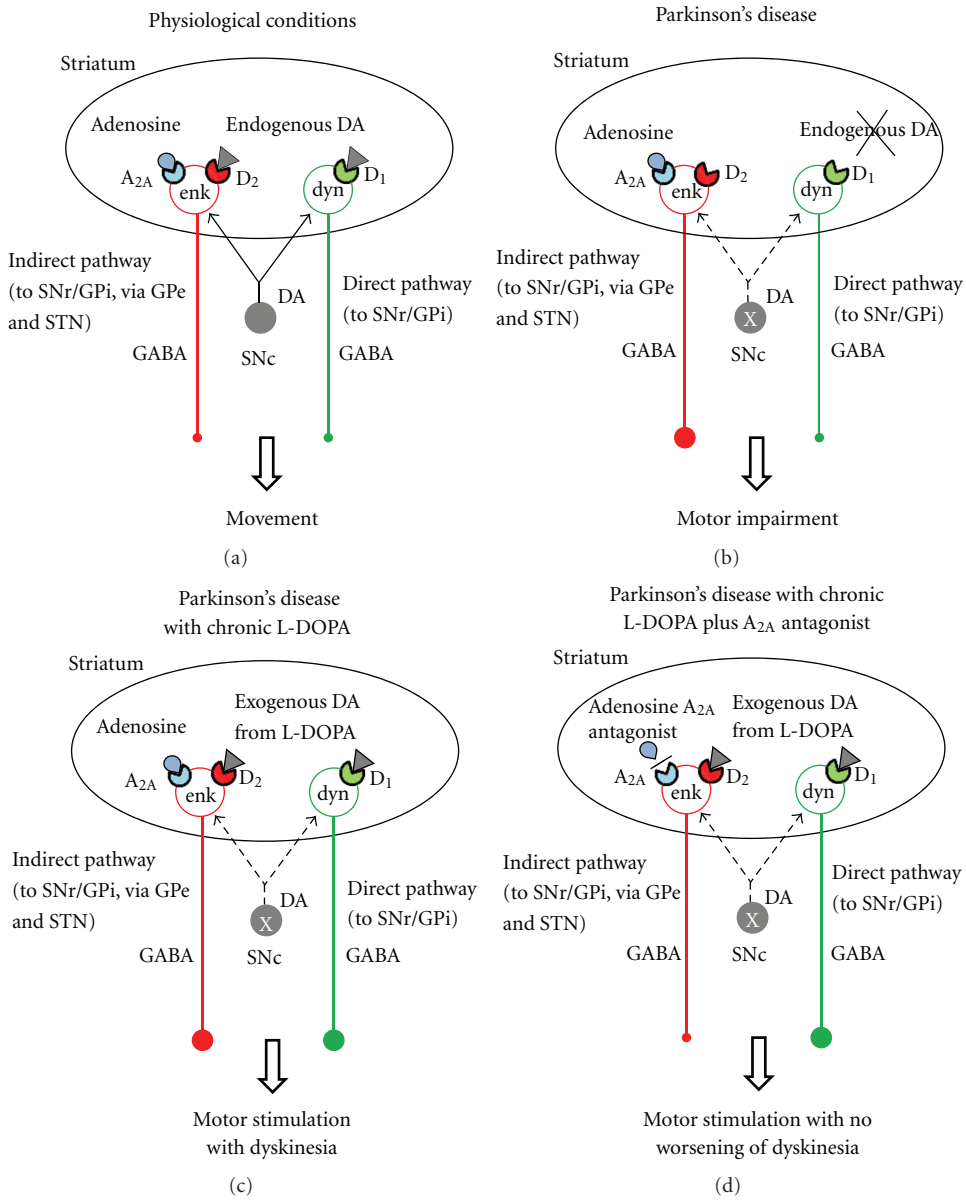

Figure 1: Role of A_{2A} receptors on modifications in the activity of the striatal efferent pathways. Under physiological conditions (a), striatal neurons receive dopaminergic inputs from the substantia nigra *pars compacta* (SNc). Endogenous dopamine (DA) activates the neurons belonging to the so-called direct pathway (in green), which send GABAergic projections to the substantia nigra *pars reticulata*/globus pallidus *pars interna* (SNr/GPi) and express D_1 stimulatory dopamine receptors, together with the neuropeptide dynorphin (dyn). At the same time, dopamine also depresses the neurons belonging to the so-called indirect pathway (in red) which send GABAergic projections to the SNr/GPi via globus pallidus *pars externa* (GPe) and subthalamic nucleus (STN) and express D_2 inhibitory dopamine receptors and the neuropeptide enkephalin (enk). Adenosine A_{2A} receptors stimulate the indirect pathway where they are selectively expressed, and their activation negatively modulates the function of D_2 receptors. A balanced level of activity of the direct and indirect pathways is at the basis of the correct processing of motor information and movement execution. In Parkinson's disease (b), the degeneration of the neurons located in the SNc leads to a drop in the dopaminergic input to the striatum. This results in a reduced activation of the direct pathway and in a disinhibition of the indirect pathway, which is associated with the elevation of A_{2A} receptor transmission. Such unbalanced activity of the striatal output pathways is at the basis of the motor impairment observed in Parkinson's disease (b). Administration of L-DOPA restores the compromised dopaminergic tone since it stimulates the direct pathway and inhibits the indirect one (not shown). However, chronic treatment with L-DOPA (c) leads to the overactivation of the direct pathway, which together with the increase of A_{2A} receptor activity [12, 15, 16] and enhanced indirect pathway transmission is at the basis of L-DOPA-induced dyskinesia and loss of efficacy. The addition of an A_{2A} antagonist to L-DOPA (d) although not counteracting the overactivity of the direct pathway (dyskinesia) stabilizes the activity of the indirect pathway, resulting in motor stimulation, potentially without a worsening of dyskinesia.

of glutamate [43, 44], the excessive increase of which plays a role in the abnormal functioning of BG existing in PD and in neuroplasticity phenomena.

3. Biomarkers and Neuroimaging Studies Involving the A_{2A} Receptor

A crucial need in the translation from preclinical studies to clinical trials is the availability of reliable biomarkers, which would give the opportunity of monitoring the effects of the compound on its biological target—the adenosine receptor—in addition to evaluating its clinical efficacy. In this field, substantial contributions have been made by neuroimaging studies, while biological findings in peripheral tissues have opened interesting perspectives.

3.1. Neuroimaging Studies in Humans. Neuroimaging techniques, based on positron emission tomography (PET), have been recently used to analyze A_{2A} receptor distribution in the human brain, either in normal subjects or in PD patients exposed to L-DOPA; in this latter case, the purpose was to draw potential *in vivo* correlations between changes in A_{2A} receptor availability and the presence of L-DOPA-induced dyskinesias.

In 2007, Mishina et al. examined the distribution of A_{2A} receptors in the brain of 5 normal subjects using PET tracer [7-methyl-^{11}C]-(E)-8-(3,4,5-trimethoxystyryl)-1,3,7-trimethylxanthine ([^{11}C]TMSX) [45]. Various brain regions were examined, including the cerebellum, brainstem, thalamus, head of caudate nucleus, anterior and posterior putamen, frontal lobe, temporal lobe, parietal lobe, occipital lobe, and posterior cingulate gyrus. Results showed the highest levels of A_{2A} receptor binding in the putamen, followed by the caudate nucleus and thalamus, while the lowest levels were detected in the cerebral cortex. Using a different A_{2A} receptor-specific radiotracer, [^{11}C]SCH442416, Brooks et al. assessed binding of vipadenant (3-(4-amino-3-methylbenzyl)-7-(2-furyl)-3H-[1, 2, 3]triazolo[4, 5-d]pyri-midine-5-amine), a selective nonxanthine A_{2A} receptor antagonist synthesized by Vernalis Plc (also known as BIIB014 or V2006) [15]. Displacement of the PET tracer by increasing doses of vipadenant (2.5–100 mg/day for 10 or 11 days) was investigated in various brain regions—including the putamen, caudate nucleus, nucleus accumbens, thalamus of both hemispheres, and cerebellum—of 15 healthy volunteers. The estimated receptor occupancy of vipadenant in the brain varied from 74% to 94% at the lowest daily dose (2.5 mg), with the highest value being observed in the putamen and the lowest value in the cerebellum. Saturation was reached in all regions at the highest dose administered (100 mg). It is noteworthy that double-blind, placebo-controlled, phase 2 clinical trials with vipadenant have been conducted in PD patients, showing modest anti-PD activity, until a review of preclinical toxicology studies, conducted by Vernalis Plc, led to discontinuation of this drug in July 2010 (http://www.vernalis.com/media-centre/latest-releases/2010-releases/584/).

Recently, Mishina et al., using PET with [^{11}C]TMSX, measured the binding ability of striatal A_{2A} receptors in 9 untreated PD patients, 7 PD patients with dyskinesia, and 6 age-matched control subjects [16]. They found that the distribution volume ratio of A_{2A} receptors in the putamen was larger in patients with L-DOPA-induced dyskinesias than in control subjects and that L-DOPA treatment tended to increase the presence of A_{2A} receptors in the putamen.

Further information on the relationship between A_{2A} receptors and L-DOPA-induced dyskinesias has been provided by Ramlackhansingh et al., who investigated adenosine A_{2A} receptor availability in the caudate and putamen of PD patients with ($n = 6$) and without L-DOPA-induced dyskinesias ($n = 6$) and in age-matched healthy controls ($n = 6$) [46]. In line with previous studies [12], they found that A_{2A} receptor binding was higher in the caudate and putamen of PD patients with L-DOPA-induced dyskinesias, with respect to both PD patients without L-DOPA-induced dyskinesias and controls, thereby lending further support to the view that A_{2A} antagonists may prove beneficial in the management of motor complications associated with L-DOPA treatment. It is worth mentioning that although their cohort was small and the power was probably too limited to detect a difference, Ramlackhansingh et al. did not find a correlation between striatal [11C]SCH442416 uptake and dyskinesia severity.

An additional study tested the hypothesis that blockade of striatal A_{2A} receptors, caused by the selective antagonist SYN115, a benzothiazole derivative, may reduce the inhibitory output of the striatofugal indirect pathway [47]. For this purpose, the authors used a perfusion magnetic resonance imaging (MRI) technique, which gives a functional measure of the cerebral blood flow (CBF) reflecting neuronal activity. The study was conducted during a randomized, double-blind, placebo-controlled, crossover study with SYN115 in 21 PD patients on L-DOPA. The results showed that SYN115 produced a dose-dependent decrease in thalamic CBF, which the authors deemed consistent with reduced pallid-thalamic inhibition via the indirect pathway [47].

3.2. Peripheral Expression of Adenosine Receptors. To our knowledge, only one paper has reported the characterization of adenosine receptors in peripheral tissues (peripheral blood cells) of human Parkinsonian subjects [48]. In this study, Varani et al. investigated affinity and density of A_1, A_{2A}, A_{2B}, and A_{3A} receptors in lymphocyte and neutrophil membranes from PD patients and healthy control subjects; they also analyzed A_{2A} receptors density in autoptic samples of putamen from PD patients and control subjects. They found that A_{2A} receptors were significantly different between PD patients and controls, in terms of affinity and density, while no changes seemed to affect A_1, A_{2B}, or A_{3A} receptors. In particular, increased density of A_{2A} receptors, coupled with decreased affinity, was detected in lymphocyte and neutrophil membranes of PD patients, with respect to control subjects. This finding was associated with a reduction in the mRNA of A_{2A} receptors, while no changes were observed in the mRNAs of the other adenosine receptor subtypes

investigated. The postmortem study confirmed this result, showing increased A_{2A} receptor density in the putamen of PD patients [48].

4. Clinical Trials of A_{2A} Receptor Antagonists

4.1. Istradefylline. Clinical trials of A_{2A} antagonists in patients with motor complications have focused on reductions in OFF time rather than changes in dyskinesia. Istradefylline was the first A_{2A} receptor antagonist to enter clinical trials seeking an indication in PD. Bara-Jimenez et al. conducted an early proof-of-principle study using intravenous L-DOPA infusions in 15 moderate to advanced PD patients with motor fluctuations, 6 of whom had L-DOPA-induced peak-dose dyskinesia [49]. Twelve subjects were randomized to istradefylline, 3 to placebo, and 1 dropped out. Istradefylline 40 or 80 mg had no effect on Parkinsonian signs or dyskinesia when added to an optimal L-DOPA infusion. However, when added to a low-dose L-DOPA infusion, istradefylline 40 mg improved Unified Parkinson's Disease Rating Scale (UPDRS) motor scores by 24% ($P < 0.05$) and istradefylline 80 mg improved motor scores by 36% ($P < 0.05$). The anti-Parkinsonian response to a low-dose L-DOPA infusion plus istradefylline 80 mg was similar to an optimal-dose L-DOPA infusion. Notably, the severity of dyskinesia with a low-dose L-DOPA infusion plus istradefylline 80 mg was 45% less ($P < 0.05$) than with an optimal-dose L-DOPA infusion. This suggests that by lowering the L-DOPA dose and adding istradefylline, one might be able to maintain anti-Parkinsonian benefit and reduce dyskinesia, a paradigm that has not been studied in clinical trials using oral L-DOPA preparations.

Istradefylline was then studied in a 12-week, randomized, placebo-controlled exploratory trial in which patients with *both* motor fluctuations and dyskinesia were randomized to the addition of placebo ($n = 29$), istradefylline in ascending doses up to 20 mg/day ($n = 26$), or istradefylline in ascending doses up to 40 mg/day ($n = 28$) [50]. Anti-Parkinsonian medications were kept unchanged except that the total daily L-DOPA dose could be reduced, if necessary, to ameliorate L-DOPA-related adverse events. Over the course of the study, there were no significant changes in daily L-DOPA doses comparing istradefylline and placebo groups ($P = 0.96$). Diary results showed that the combined istradefylline groups experienced a reduction in OFF time of 1.2 hours, whereas the placebo group experienced an increase in OFF time of 0.5 hours ($P < 0.004$). Multiple assessments of change in dyskinesia did not demonstrate significant differences between the placebo and istradefylline groups, including Goetz dyskinesia scale scores (-0.2 versus -0.1, $P = 0.3$), Parkinson dyskinesia scale scores (-1.4 versus -1.3, $P = 0.9$), and UPDRS items 32–34 (-0.03 versus -0.4, $P = 0.8$). However, diary results indicated that ON time with dyskinesia was significantly more increased with istradefylline than placebo (0.6 hours versus -1.5 hours, $P = 0.001$). Troublesome dyskinesia was not included as a diary category in this study. As an adverse event, increased dyskinesia was reported by 13.8% of placebo patients and 16.7% of istradefylline patients.

This is an important study in that it is the largest study of an A_{2A} receptor antagonist in a population of patients, all of whom have L-DOPA-induced dyskinesia. In addition, dyskinesia was most thoroughly assessed by multiple scales. Clearly, the addition of istradefylline to a stable antiparkinson regimen did not reduce dyskinesia, nor was there a very substantial increase. Perhaps the most parsimonious interpretation is that overall severity of dyskinesia was essentially unchanged, but much or all of the reduction in OFF time was replaced by an increase in ON time with dyskinesia.

Subsequent trials in moderate to advanced PD patients all included subjects with motor fluctuations, some of whom had dyskinesia and some of whom did not. These included two phase 2 istradefylline trials. In one, istradefylline 40 mg/day reduced OFF time compared with placebo by 1.2 hours ($P = 0.005$) [51]. ON time with dyskinesia increased by 1.0 hour more in the istradefylline group than the placebo group ($P = 0.035$). Of this differential increase in ON time with dyskinesia, approximately 0.8 hours were ON time with nontroublesome dyskinesia ($P = 0.065$), and 0.2 hours were ON time with troublesome dyskinesia ($P = 0.347$). Dyskinesia was reported as an adverse event in 15.2% of placebo subjects and 30.2% of istradefylline subjects. In the other phase 2 study [52], istradefylline 20 mg/day reduced OFF time by 0.64 hours, and istradefylline 60 mg/day reduced OFF time by 0.77 hours (overall P value = 0.065). Compared with placebo, istradefylline 20 mg/day increased ON time with dyskinesia by 0.54 hours, and ON time with troublesome dyskinesia by 0.06 hours; istradefylline 60 mg/day increased ON time with dyskinesia by 0.23 hours and ON time with troublesome dyskinesia by 0.04 hours. Dyskinesia was reported as an adverse event in 14.3% of placebo subjects, 23.9% of istradefylline 20 mg/day subjects, and 22.6% of istradefylline 60 mg/day subjects.

In a phase 3 study, istradefylline 20 mg/day reduced OFF time compared with placebo 0.7 hours ($P = 0.03$) [53]. Increases in dyskinesia were similar in placebo and istradefylline groups (ON time with dyskinesia: 0.5 versus 0.7 hours, $P = 0.57$; ON time with nontroublesome dyskinesia: 0.4 versus 0.4 hours, $P = 0.82$; ON time with troublesome dyskinesia: 0.2 versus 0.3 hours, $P = 0.48$). However, dyskinesia was reported as an adverse event in 22.6% of istradefylline subjects compared with 12.2% of placebo subjects.

In a phase 3 study in Japan [54], istradefylline 20 mg/day reduced OFF time compared with placebo by 0.65 hours ($P = 0.013$) and 40 mg reduced OFF time compared with placebo by 0.92 hours ($P < 0.001$). Compared with placebo, istradefylline 40 mg/day significantly increased ON time with troublesome dyskinesia (0.35 hours, $P = 0.011$). As an adverse event, dyskinesia was reported in 2.5% of placebo subjects, 8.5% of istradefylline 20 mg/day subjects, and 6.4% of istradefylline 40 mg/day subjects.

Thus, in most of the clinical trials, the addition of istradefylline was associated with some increase in ON time with dyskinesia, and dyskinesia was reported as an adverse event more commonly in istradefylline- than placebo-treated subjects.

A recent population pharmacokinetic-pharmacodynamic study analyzed data from 1798 patients participating in

6 phase 2/3 istradefylline trials [55]. The analysis predicted a maximum probability of experiencing dyskinesia as an adverse event sometime during a study as 15.4% for placebo, 22.5% for istradefylline 20 mg/day, 24.1% for istradefylline 40 mg/day, and 24.3% for istradefylline 60 mg/day.

Thus, clinical data to date do not provide evidence for an antidyskinetic effect of istradefylline but rather suggest that istradefylline mildly increases dyskinesia in a dose-dependent fashion. Results vary slightly from trial to trial and may depend, in part, on the percentage of subjects with dyskinesia at baseline and the severity of their dyskinesia. Other potential factors may include concomitant medications such as amantadine and dietary intake of caffeine, a nonspecific adenosine antagonist, although these factors have not been systematically evaluated.

4.2. Preladenant. Preladenant was evaluated in a phase 2, 12-week, dose-finding study of PD patients experiencing motor fluctuations [56]. In this study, patients were randomized to preladenant 1, 2, 5, or 10 mg twice daily (BID) or matching placebo. OFF time was significantly reduced compared with placebo in subjects randomized to preladenant 5 mg BID (1.0 hours, $P = 0.0486$) and preladenant 10 mg BID (1.2 hours, $P = 0.019$). In the 5 mg BID group, compared with placebo, ON time with dyskinesia was increased 0.9 hours ($P = 0.185$), ON time with nontroublesome dyskinesia was increased by 1.0 hour ($P = 0.064$), and ON time with troublesome dyskinesia was decreased by 0.1 hours ($P = 0.812$). In the preladenant 10 mg BID group, compared with placebo, ON time with dyskinesia was increased by 1.3 hours ($P = 0.054$), ON time with nontroublesome dyskinesia was increased by 1.1 hours ($P = 0.047$), and ON time with troublesome dyskinesia was increased by 0.2 hours ($P = 0.540$). These results appear to be similar to some of the istradefylline findings in which much of the reduction in OFF time was replaced by ON time with nontroublesome dyskinesia. Dyskinesia was reported as an adverse event by 13% of placebo subjects, by 9% of preladenant 5 mg BID subjects, and by 13% of preladenant 10 mg BID subjects. This result may be different from what has been observed with istradefylline where dyskinesia was rather consistently reported more frequently as an adverse event in istradefylline-compared with placebo-treated groups. Thus, preliminary results suggest that like istradefylline, preladenant does not reduce dyskinesia, but it remains to be seen whether preladenant causes less dyskinesia than istradefylline, as suggested by these adverse event results.

To our knowledge, there have been no clinical trials evaluating whether an A_{2A} receptor antagonist can reduce the development of dyskinesia when administered in early disease concomitant with the introduction of dopaminergic therapy. Based on animal model data, this remains an important avenue for future investigation. Similarly, we are not aware of clinical trials of patients with L-DOPA-induced dyskinesia to determine whether lowering the L-DOPA dose and adding an A_{2A} receptor antagonist will allow maintenance of the anti-Parkinsonian response with reduction of dyskinesia.

5. Conclusions

The management of PD is most complex in the treatment of late, complicated PD, when the response to L-DOPA is associated with dyskinesia. From the studies described in the present paper, it is suggested that the management of the first (uncomplicated) phase has important consequences on the induction of dyskinesia that characterize the second (complicated) phase.

Preclinical studies suggest that A_{2A} antagonists might reduce the development of dyskinesia, but this has not yet been tested clinically. In PD patients, once dyskinesias are established, adding an A_{2A} antagonist to a stable dopaminergic therapeutic regimen does not appear to provide an antidyskinetic response, and most clinical trials have suggested a mild increase in dyskinesia in association with a reduction in OFF time. Limited clinical data suggest the possibility that in PD patients with established dyskinesia, one might be able to maintain the anti-Parkinsonian response and reduce dyskinesia by adding an A_{2A} antagonist and lowering the L-DOPA dose, but this remains to be proven. Thus, critical aspects of the potential benefits of A_{2A} antagonists with regard to dyskinesia are yet to be evaluated.

Abbreviations

AMPA:	α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid
BG:	Basal ganglia
BID:	Bis in die, twice a day
CBF:	Cerebral blood flow
PD:	Parkinson's disease
6-OHDA:	6-Hydroxydopamine
MPTP:	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
DYN:	Dynorphin
ENK:	Enkephalin
GAD-67:	Glutamic acid decarboxylase 67
mGLU5:	Type 5 metabotropic glutamate receptors 5
MRI:	Magnetic resonance imaging
NMDA:	N-Methyl-D-aspartate
PET:	Positron emission tomography
UPDRS:	Unified Parkinson's disease rating scale.

Acknowledgment

Dr. N. Simola is supported by Regione Autonoma della Sardegna (Project Master and Back, code PR-MAB-A2009-614).

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Hindawi Publishing Corporation
Parkinson's Disease
Volume 2012, Article ID 370190, 5 pages
doi:10.1155/2012/370190

Review Article

Role of Serotonin Neurons in L-DOPA- and Graft-Induced Dyskinesia in a Rat Model of Parkinson's Disease

Eunju Shin,[1] Elisabetta Tronci,[2] and Manolo Carta[2]

[1] *Division of Neurobiology, Wallenberg Neuroscience Center, Lund University, 221 84 Lund, Sweden*
[2] *Department of Biomedical Science, Cagliari University, Cittadella Universitaria, SS 554 km 4.500, 09042 Monserrato, Italy*

Correspondence should be addressed to Manolo Carta, manolocarta@unica.it

Received 16 February 2012; Revised 2 April 2012; Accepted 10 April 2012

Academic Editor: Gilberto Fisone

L-DOPA, the most effective drug to treat motor symptoms of Parkinson's disease, causes abnormal involuntary movements, limiting its use in advanced stages of the disease. An increasing body of evidence points to the serotonin system as a key player in the appearance of L-DOPA-induced dyskinesia (LID). In fact, exogenously administered L-DOPA can be taken up by serotonin neurons, converted to dopamine and released as a false transmitter, contributing to pulsatile stimulation of striatal dopamine receptors. Accordingly, destruction of serotonin fibers or silencing serotonin neurons by serotonin agonists could counteract LID in animal models. Recent clinical work has also shown that serotonin neurons are present in the caudate/putamen of patients grafted with embryonic ventral mesencephalic cells, producing intense serotonin hyperinnervation. These patients experience graft-induced dyskinesia (GID), a type of dyskinesia phenotypically similar to the one induced by L-DOPA but independent from its administration. Interestingly, the 5-HT_{1A} receptor agonist buspirone has been shown to suppress GID in these patients, suggesting that serotonin neurons might be involved in the etiology of GID as for LID. In this paper we will discuss the experimental and clinical evidence supporting the involvement of the serotonin system in both LID and GID.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease and is characterized by loss of dopamine (DA) neurons in the substantia nigra. The cell loss results in decreased activation of striatal DA receptors, thus causing motor impairments, such as tremor, rigidity, bradykinesia, and postural instability. The DA precursor L-3,4-dihydroxyphenylalanine (L-DOPA) represents the most effective drug to alleviate the motor symptoms. Although this medication is very efficient during the first few years of administration, its efficacy gradually diminishes overtime, and uncontrolled excessive movements, known as dyskinesia, appear as a side effect after a variable number of years in most of patients, limiting the use of L-DOPA in advanced stages of the disease.

A better understanding of the mechanisms underlying the appearance of dyskinesia has been achieved during recent years using animal models of L-DOPA-induced dyskinesia (LID). In fact, abnormal involuntary movements (AIMs) develop in response to sub-chronic L-DOPA treatment in 6-hydroxydopamine (6-OHDA)-lesioned rats and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys, resembling peak-dose dyskinesia seen in patients [1–4]. Using these models, a number of alterations have been identified at the level of striatal neurons of dyskinetic subjects, such as abnormal trafficking of DA D_1 and *N*-methyl-D-aspartate (NMDA) receptors [5, 6], leading to alterations in key striatal signaling pathways.

More recently, the serotonin system has emerged as a putative player in the induction of fluctuations in synaptic DA levels following administration of L-DOPA in animal models of PD, which cause pulsatile stimulation of DA receptors and promote the maladaptive changes that characterize the parkinsonian dyskinetic brain [7–11]. The emerging role of serotonin neurons in LID has also prompted researchers to investigate a possible involvement of these neurons in the appearance of *off-drug* dyskinesia that has emerged in a subset of PD patients following transplantation of fetal

ventral mesencephalic DA neuroblasts, namely, graft-induced dyskinesia (GID) [12, 13]. In this paper, we will discuss the recent experimental and clinical evidence supporting a role of serotonin neurons both in LID and GID.

2. The Role of Serotonin Neurons in the Induction of L-DOPA-Induced Dyskinesia

Progression of DA neuron degeneration represents the first risk factor for development of LID in patients. In fact, the efficacy of L-DOPA in providing its therapeutic effect during the first years of administration is conceivably due to the ability of spared DA neurons to take up exogenously administered L-DOPA, convert it to DA, and release it into the synaptic cleft, but also to regulate synaptic DA levels via the D_2 autoreceptor and DA transporter (DAT). When the disease is in its early stage, sufficient DA terminals remain in the striatum to efficiently mediate a feedback-controlled mechanism of release. The ability of the spared DA terminals to prevent development of AIMs upon L-DOPA treatment is well demonstrated in a recent report by Ulusoy et al. [14]. In this study, a significant DA deficiency was established in rats by viral vector delivery of short hairpin RNA for the tyrosine hydroxylase (TH) enzyme, without affecting cell survival. Animals were then made dyskinetic by subchronic treatment with the direct DA agonist apomorphine; however, when treated with L-DOPA, the same rats appeared to be fully resistant to the induction of LID, despite apomorphine treatment had already promoted postsynaptic alterations, such as increased striatal FosB expression.

The ability of the presynaptic DA compartment to prevent excessive DA receptor stimulation, and aberrant downstream signaling, even in presence of supersensitive striatal DA receptors is also confirmed in transplantation studies. In fact, ventral mesencephalic DA graft, which reconstitutes the presynaptic buffering capacity into the lesioned and maladapted striatum, normalizes the response of L-DOPA-primed dyskinetic rats to L-DOPA administration [7]. In light with these results, it is conceivable to think that the efficacy of L-DOPA during the first years of administration is also due to the presence of a sufficient number of DA neurons that can buffer the exogenously administered L-DOPA, and provide a source of regulated DA release. However, with the progression of DA degeneration, this buffering capacity, and thus the ability to provide physiological level of DA receptor stimulation, is progressively lost. In this situation, the serotonin neurons come to play a major role in L-DOPA-derived DA production and release, as they possess both the aromatic amino acid decarboxylase enzyme (AADC) and the vesicular monoamine transporter (VMAT). Unlike DA neurons, though, serotonin neurons cannot regulate the extracellular levels of DA due to the lack of the autoregulatory loop, hence, causing un-controlled DA release following L-DOPA administration. DA released from serotonin neurons will therefore act in concert with the intermittent nature of the orally administered L-DOPA to cause pulsatile stimulation of DA receptors, and thus, changes in downstream signaling pathways at striatal neurons. In support of this view, removal of serotonin innervation by toxin lesion was shown to produce about 80% reduction in L-DOPA-derived striatal extracellular DA levels [15], and to induce a near-to-complete suppression of LID in dyskinetic rats [8, 16]. Accordingly, pharmacological silencing of serotonin neuron activity by 5-HT_{1A} and 5-HT_{1B} receptor agonists has been shown to reduce L-DOPA-derived extracellular DA levels [17], and to suppress LID in rats [8] as well as in MPTP-treated monkeys [18]. In addition, chronic administration of the 5-HT_1 agonists was able to prevent the development of dyskinesia and upregulation of FosB expression in the striatum of 6-OHDA-lesioned rats [18], thus linking dysregulated DA release from serotonin terminals with the induction of a well-known striatal marker of dyskinesia. Interestingly, simultaneous activation of 5-HT_{1A} and 5-HT_{1B} receptors was found to trigger a potent synergistic effect in the suppression of LID in both rats and monkeys [8, 18]. In fact, LID was nearly fully abolished at doses of combined agonists that were ineffective when given individually. This finding has now led to the initiation of a first double-blind, proof-of-concept clinical trial employing a mixed 5-$HT_{1A/1B}$ receptor agonist in dyskinetic patients.

In confirming the interaction between exogenously administered L-DOPA and serotonin neurons, Navailles and coworkers have recently demonstrated that serotonin neuron-dependent DA release takes place, upon chronic L-DOPA treatment in 6-OHDA-lesioned rats, not only in the striatum but also in other brain areas receiving sufficient serotonin innervation, such as substantia nigra, hippocampus, and prefrontal cortex [19]. Moreover, L-DOPA administration appears to result in reduced striatal serotonin tissue content in 6-OHDA-lesioned rats [8]. The latter result supports the existence of a competition between serotonin and DA for serotonergic vesicles, which causes serotonin depletion. Thus, an increasing body of experimental evidence points to the serotonin system as a key player in the appearance of LID.

Progressive reduction of L-DOPA-derived extracellular DA levels upon chronic L-DOPA treatment has been recently found in 6-OHDA-lesioned rats [20, 21], leading some researcher to question the role of serotonin neurons in the appearance of LID [21]. Nevertheless, we believe that the potent inhibitory effect of 5,7-dihydroxytryptamine (5,7-DHT) lesion on both development and expression of dyskinesia in 6-OHDA-lesioned rats [8], together with the striking suppression of LID induced by low doses of 5-HT_{1A} + 5-HT_{1B} receptor agonists both in rats and macaques [18] provided unquestionable evidence supporting an important role of serotonin neurons, at least in animal models of PD. It should be taken into account that during chronic administration of L-DOPA, postsynaptic DA receptors become supersensitive; thus, the dyskinetic response to L-DOPA might be maintained by lower extracellular DA levels once postsynaptic alterations have been already induced. The relevance for the human disease of the progressive reduction of extracellular DA levels seen upon chronic L-DOPA in the rat 6-OHDA model remains to be established, as L-DOPA-derived synaptic DA levels were shown to increase with progression of the disease in a positron emission tomography (PET) imaging study in PD patients [22].

Interestingly, Rylander and coworkers have recently shown marked serotonin hyperinnervation in the lesioned striatum of parkinsonian dyskinetic subjects across different species, including patients, thus raising the possibility that serotonin neurons play a relevant role in the emergence of LID also in the patients [10, 11, 23]. This study suggested that L-DOPA treatment may be able to provoke sprouting of serotonin axon terminals and change their morphology, hence, possibly enhancing the fluctuations in extracellular DA concentration, consistent with findings of de la Fuente-Fernandez and coworkers in their PET imaging study [22, 24].

In further experimental support for a detrimental effect of serotonin neurons on LID, grafted serotonin neurons, which induced an intense hyperinnervation of the grafted striatum, exacerbated LID in both partial and complete DA lesioned rats [7, 25], raising the possibility that inclusion of these cells in the grafted tissue may have detrimental effects on LID in grafted PD patients.

3. The Role of Serotonin Neurons in the Modulation of Graft-Induced Dyskinesia

Transplantation of fetal ventral mesencephalic neurons is a therapeutic approach to PD that has already been tested in clinical trials [26–30]. While the variability in the outcome of these studies halted further investigations, the presence of highly responsive patients provided proof-of-concept that this therapeutic intervention can be significantly beneficial. Indeed, there is now general agreement that the reasons accounting for the observed variability rely on the lack of standardization of the cell preparations, surgical procedures, as well as on the selection of patients and presence or absence of postsurgical immunosuppressive treatment [31]. However, another element that has contributed to raise concern about fetal transplantation is the appearance in a subset of grafted patients of *off-drug* dyskinesia [29, 31–33], a form of involuntary movements that is phenotypically similar to the one induced by L-DOPA but independent from its administration. The recent findings on the role of serotonin neurons in the induction of LID has led to hypothesize that serotonin neurons included in the graft may also play a role in GID [8, 16, 18].

In fact, serotonin neuroblasts are located in close vicinity of the DA ones in the fetal ventral mesencephalic area that is dissected for transplantation. Accordingly, about 50% of grafted cells were found to be serotonin neurons in a postmortem analysis of the caudate-putamen of grafted patients [34].

In possible support of this hypothesis, in a recent PET study, Politis and colleagues have found intense serotonergic hyperinnervation in the striatum of grafted patients showing GID [12, 13]. Interestingly, administration of the partial 5-HT_{1A} agonist buspirone suppressed GID in all tested patients. An involvement of the serotonin neurons in GID is further supported by the high serotonin transporter (SERT)/DAT ratio found in one GID patient compared to both healthy age-matched control and non-grafted PD patients [12]. Thus, it is postulated that serotonin terminals may take up DA released by the graft through SERT, and release DA, as a false transmitter, away from the uptake site, in striatal regions lacking sufficient DA innervation, thus, leading to activation of supersensitive DA receptors. However, it should be acknowledged that these clinical observations have been made in a very few subjects, and further evidence should be provided. In particular, it would be important to investigate the state of the striatal serotonin innervation also in patients free of GID.

Although spontaneous GID, that is dyskinesia in the absence of any drug treatment, is inconsistent in grafted rodents [35, 36], it does appear after administration of a low dose of amphetamine [35, 37], which is known to evoke massive DA release from grafted DA neurons [38]. These abnormal movements can be scored with the same scale used for LID [35, 37], and are now widely used as a convenient and reproducible model of GID [7, 39–42]. While appearance of GID in this rat model is clearly dependent on the presence of an adequate number of DA neurons in the graft, we have recently found a bidirectional modulatory effect of endogenous serotonin neurons on GID. In fact, reduction of serotonin neuron activity, by a combination of 5-HT_{1A} and 5-HT_{1B} receptor agonists, produced a significant reduction of GID, while increased serotonin neuron release by fenfluramine exacerbated GID [43]. Strikingly, administration of a low dose of buspirone (1 mg/kg) completely suppressed GID, as seen in grafted patients. Interestingly, removal of the endogenous serotonin innervation by specific toxin lesions appeared to abolish the anti-GID effect of the selective 5-HT_1 agonists, both in serotonin-containing and serotonin-free grafts, suggesting that the modulatory effect on GID may be due to the endogenous rather than the graft-derived serotonin neurons, at least in our experimental conditions. By contrast, neither removal of the endogenous serotonin innervation nor pretreatment with the selective 5-HT_{1A} antagonist WAY100135 reduced the anti-GID efficacy of buspirone. In fact, buspirone is also known to possess antagonistic properties on D_2 receptors [44–47]. In support for a D_2-mediated effect of buspirone, similar anti-GID effect was induced by a low dose of the selective D_2 receptor antagonist eticlopride (0.03 mg/kg). Thus, our data support a modulatory role of the endogenous serotonin neurons on expression of GID, as well as a peculiar role of D_2 receptors. Indeed, both buspirone and eticlopride were ineffective against LID at doses fully suppressing GID [43].

Further work is required to understand whether inclusion of serotonin neurons in the graft can be detrimental for appearance of GID, although current experimental data do not support this hypothesis.

4. Conclusion

Overall, loss of DA in basal ganglia circuits and DA replacement by chronic L-DOPA administration result in complex alterations in the parkinsonian brain, that affect several systems and key signaling proteins, most of which remain poorly understood. DA released as a false transmitter from serotonin neurons appears to play a key role in initiating these events, at least in animal models. Serotonin neurons,

therefore, represent an intriguing pharmacological target to treat already established LID and/or to prevent the events leading to the appearance of LID from taking place. Recent evidence suggests that serotonin neurons may also participate to the induction of dyskinesia seen in the *off-state* in grafted PD patients. The upcoming new clinical trial, funded by the European Community, employing fetal ventral mesencephalic cells will answer the question whether optimization of the surgical procedures and preparation of the grafted material, including exclusion of serotonin neuroblasts, will improve clinical outcome and avoid appearance of GID.

Acknowledgments

E. Shin is supported by the Strategic Research Area Multipark at Lund University and E. Tronci is supported by Regione Autonoma delle Sardegna within the Master&Back Program at Cagliari University.

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Hindawi Publishing Corporation
Parkinson's Disease
Volume 2012, Article ID 745947, 12 pages
doi:10.1155/2012/745947

Review Article

Clinical Aspects and Management of Levodopa-Induced Dyskinesia

Nicola Tambasco,[1] Simone Simoni,[1] Erica Marsili,[1] Elisa Sacchini,[1] Donatella Murasecco,[1] Gabriela Cardaioli,[1] Aroldo Rossi,[1] and Paolo Calabresi[1,2]

[1] *Clinica Neurologica, Azienda Ospedaliera—Università di Perugia, S. Andrea delle Fratte, 06156 Perugia, Italy*
[2] *IRCCS Fondazione S. Lucia, Via Ardeatina 306, 00179 Roma, Italy*

Correspondence should be addressed to Nicola Tambasco, n.tambasco@libero.it

Received 5 February 2012; Accepted 2 April 2012

Academic Editor: Gilberto Fisone

In Parkinson's disease, one of the most troublesome dilemmas is the treatment of levodopa-induced dyskinesia. After a few years, chronic treatment with levodopa is associated with the development of dyskinesias. Strategies to delay or to reduce dyskinesias are based on the change of levodopa dosing or the early use of dopamine agonists. Dopamine agonists with different pharmacological profile are available. Our paper was aimed to analyse the clinical impact and the management of dyskinesias with dopamine agonists.

1. Introduction

Four decades after its introduction, levodopa remains the most effective agent to improve motor symptoms in PD, but chronic use is associated with the emergence of motor fluctuations, defined as a loss of clinical benefit before the next levodopa dose (wearing off), abnormal involuntary movements (dystonia, chorea, and athetosis—collectively referred to as dyskinesia) [1, 2], and nonmotor complications, as behavioural and cognitive changes [3]. Levodopa is initially well tolerated in most of the cases and allows a substantial improvement of motor performances despite its erratic pharmacokinetics [1, 4]. With the disease progression, therapeutic window of levodopa narrows, and the duration of each dose shortens. Motor fluctuations usually precede dyskinesias [5], and it has been observed that the development of one is a risk factor for the development of the other [5].

Although more commonly associated with levodopa, dyskinesias can also occur with dopamine agonist monotherapy [6–8]. The development of dyskinesia in some patients treated with dopamine agonists that have relatively long half-lives (ropinirole, 6 h; pramipexole, 8 h) or very long half-lives (cabergoline, 68 h) suggests that, to some extent, even dopamine stimulation provided in a continuous fashion can cause dyskinesias.

2. Epidemiology and Clinical Aspects of Motor Complications

The three most important risk factors positively associated with increased occurrence of dyskinesias are younger age at disease onset [9, 10], longer disease duration [11, 12], and longer duration of pulsatile dopaminergic treatment (typically, levodopa) [13, 14]. The first two factors are interrelated and almost all patients with early-onset PD [15] develop dyskinesias, whereas they are less frequent in patients with late-onset PD [16]. PD patients with early disease onset have a high probability to carry mutations for monogenic PD forms, and therefore, early onset and genetic predisposition are two overlapping and possibly interrelated risk factors. Other risk factors associated with increased risk of dyskinesias are female gender [17, 18] and the occurrence of specific polymorphisms for dopamine receptors or dopamine transporters [19–21].

Dyskinesias more commonly appear as choreiform, but in some cases, they may resemble dystonia, myoclonus, or

other movement disorders. Peak-dose dyskinesias are the most common type of dyskinesia. They occur during peaks of levodopa-derived dopamine in the brain, when the patient is otherwise experiencing a beneficial response (the "on" state). Peak-dose dyskinesias worsen with increases in dopaminergic dose and lessen with its reductions. In certain cases, dyskinesias seem to appear with a more particular pattern, as dyskinesia-improvement-dyskinesia. This is termed diphasic dyskinesia, and it tends to occur when levodopa-derived dopamine concentrations are increasing or decreasing, whereas the clinical condition of the patient turns "on" and "off" [22]. Diphasic dyskinesias are typically displayed with large-amplitude stereotypic, rhythmic, and repetitive movements, more often of the legs, that may be associated with Parkinsonian features in other body regions. In extreme cases, patients treated with levodopa can cycle between "on" periods, which are complicated by disabling dyskinesias, and "off" periods in which Parkinsonism is uncontrolled and the patient is akinetic and frozen.

Motor complications occur in about 50% of patients with PD who have been in therapy with levodopa for more than 5 years, and in almost 100% of patients with young-onset disease [23, 24]. Achieving an acceptable clinical control once these motor fluctuations have appeared is usually a relatively simple matter, nearing together the levodopa doses or adding medications that reduce "off" time. However, when a patient develops peak-dose dyskinesias too, it becomes difficult to smooth the clinical response. Although for many patients, dyskinesias are not disabling, they create a barrier to adequate treatment of fluctuations and Parkinsonian symptoms.

3. Pathophysiology of Dyskinesias

A primary condition in LID pathophysiology is the presence of dopaminergic cell loss in substantia nigra [25–27]. The nonappearance of dyskinesia in normal humans chronically treated with levodopa (i.e., mistaken diagnosis [28]) and its rapid emergence in PD patients either with late diagnosis or a young onset, where denervation is high at diagnosis [15, 29, 30], heavily support this theory. Moreover, the progression of nigral denervation seems to be closely related with the lowering of the dyskinesia onset threshold in MPTP-exposed primates [31]. Nonetheless, denervation cannot be the unique factor responsible for dyskinesia, whereas not all patients with advanced illness and extensive nigral denervation develop dyskinesia when treated with levodopa [32, 33]. Thus, a chronic dopaminergic stimulation on a denervated substantia nigra induces a process of sensitisation such that each following administration modifies the response to subsequent dopaminergic treatments. This process, called priming, increases over time of treatment the chance of eliciting dyskinesias and, once dyskinesias have been established, their severity. The priming process, which is responsible for the insidious evolution of dyskinesias over time of treatment, is associated with changes in receptors for dopamine or other neurotransmitters [34, 35]. A crucial role has been postulated for both dopamine receptors and NMDA glutamate receptors in the induction of priming; this mechanism could be regarded as an increased responsiveness of postsynaptic striatal dopamine receptors (mainly D_1-like), which are activated in conjunction with glutamatergic inputs [1]. Dyskinesias are probably generated by a persistent enhancement of the responsiveness of striatal medium-sized spiny neurones to dopaminergic treatment. This is an aftermath of dopamine depletion and is associated with overexpression of specific components of the signal transduction machinery. If protracted, this condition may ultimately lead to long-term changes in gene expression, which will permanently affect the function of striatal medium spiny neurones [36]. Following priming, the development of dyskinesias largely depends on two additional factors, the pulsatile administration of levodopa (or another short-acting dopaminergic agent) and the severity of dopaminergic denervation in the striatum. The latter plays an important role in setting the threshold required in developing dyskinesias [37]. A direct relationship between the severity of striatal denervation and the time required to develop dyskinesias has been demonstrated in PD patients [38] and has been indirectly confirmed by the finding that patients with dopa-responsive dystonia, who have Parkinsonism without nigrostriatal denervation, uncommonly develop dyskinesias [39].

In early PD patients, levodopa-derived dopamine is packaged into synaptic vesicles by vesicular monoamine transporter 2 (VMAT-2), stored, and released in both tonic and phasic bursts in response to impulse flow [40, 41], in order to preserve dopamine receptors from levodopa plasma concentration fluctuations and, therefore, to maintain physiological dopaminergic transmission [42, 43]. With the progression of the disease, and the striatal dopaminergic cell loss, the formation of dopamine from levodopa and its storage capacity are increasingly compromised, and the response to levodopa becomes dominated by its pharmacokinetic characteristics and general bioavailability [4]. Thus, in advanced PD, peak concentrations of drug in plasma become coincidental with the expression of dyskinesia. As observed in animal models, the continuous release of dopamine leads to improvements in motor function and, together, to a marked reduction in the expression of involuntary movements [44]. These studies support the clinical findings that the continuous intravenous or intraduodenal administration of levodopa or the continuous subcutaneous or intravenous infusion of apomorphine results in improved motor response but also with a marked reduction of dyskinesia [45, 46].

Other mechanisms are involved to explain the underlying cause and expression of dyskinesia. Although dopamine agonists when used as monotherapy in early PD are associated to a lower incidence of dyskinesia, involuntary movements are still observed, reflecting some kind of activity at the postsynaptic dopamine receptor level, as dopamine agonists are not dependent on the presence of presynaptic terminals.

Subtle changes in D_1 and D_2 receptor density as well as the complex interaction between receptor activation and synaptic plasticity [1] have been proposed as playing significant roles in dyskinesia induction and expression. Although the exact molecular mechanisms of LID still remain to be fully elucidated, exaggerated signalling of the striatal D_1 [47–49], the reduction of the modulating function of D_2/D_3

Table 1: Pharmacological characteristics of dopamine agonists.

	Pramipexole	Ropinirole	Rotigotine	Pergolide	Bromocriptine	Cabergoline	Apomorphine	Lisuride
D_1	0	0	+	+	−	0/+	+++	−
D_2	+++	+++	+++	++++	++	+++	++	++++
D_3	++++	++++	++++	+++	++	++	++++	+++
Type	Nonergot	Nonergot	Nonergot	Ergoline	Ergoline	Ergoline	Morphine deriv.	Ergoline
Routes	os	os	td	os	os	os	sc	sc
Metabolism	—	Hepatic	Hepatic	Hepatic	?	Hepatic	Hepatic	Hepatic
Elimin.	Urine	Urine	Urine/fecal	Urine/fecal	Fecal	Fecal/urine	Urine/fecal	Urine/fecal
Half-life (h)	8–12	5–6	5–7	27	12–14	63–69	40 min.	2

td: transdermal; sc: subcutaneous.

receptors [42, 43, 50–52], and the interaction between D_2 and A2A adenosine receptors [53] have been implicated in both rodents and primates, suggesting that a normalisation of signalling may be beneficial in the treatment of dyskinesia.

In clinical practice, postsynaptic mechanisms can be partially explained by the dopamine agonists capability to prime for involuntary movements. Switching from a chronic dopamine agonist administration that usually results in a low expression and intensity of dyskinesia to an equivalent dose of levodopa in fact immediately results in the appearance of dramatic involuntary movements [54, 55]. These findings suggest that dopamine agonists principally prime for, but less commonly express dyskinesia. Vice versa, when considering the expression of dyskinesia in patients with PD with a history of levodopa exposure, switching to a dopamine agonist after the introduction of levodopa, established dyskinesia still occurred [56]. Moreover, patients receiving a combination of levodopa and the dopamine D_2/D_3 agonist pramipexole showed a level of dyskinesia that was greater than the additive effect of the individual drug [57]. Once established, dopamine agonists produce the same pattern of dyskinesia although its intensity is reduced, suggesting that agonists do not express dyskinesia to the same extent as levodopa [54, 55, 58]. Both the lower priming for dyskinesia and the lower expression of involuntary movements by dopamine agonists may be a reflection of their more specific pharmacology compared to levodopa.

4. Reducing or Delaying Parkinsonian Dyskinesias

Any type of exogenous dopaminergic stimulation in a denervated striatum can cause dyskinesias [59], but pulsatile stimulation produced by short-acting drugs (as typically occurs with levodopa) particularly favours their occurrence [60]. The expression LID is still currently used, although levodopa is not the only drug causing dyskinesias in PD patients [61]. Based on published series, it has been estimated that PD patients treated for less than 5 years have a 11% risk of developing dyskinesias, those treated for 6–9 years have a risk of 32%, whereas patients treated for more than 10 years have a risk of 89% [13].

Levodopa, however, seems to be the most important factor in inducing dyskinesia expression in chronically treated PD patients; therefore, it appears that the benefit of initial treatment with a dopamine agonist in lowering the incidence of dyskinesias is related to the ability of the agonist to delay the need for levodopa [12, 62]. Moreover, experimental data suggest that the administration of long-acting dopamine agonists results in significantly less dyskinesia than does levodopa [63, 64] and other short-acting agents administrated in a pulsatile fashion [65]. However, once a long-acting agonist is administered to animals already primed to exhibit dyskinesias with levodopa, the resultant dyskinesias are comparable to those seen in the levodopa group [63]. Clinical studies randomly assigning patients to initial treatment with a dopamine agonist or levodopa have shown a lower risk for dyskinesias in the groups treated with pramipexole [7], ropinirole [8, 12], bromocriptine [66, 67], pergolide [68], and cabergoline [6]; nevertheless, once levodopa was added, the rate of development of dyskinesias was similar in both groups.

One therapeutic strategy that has been tried in this sense is to use higher doses of a dopamine agonist to reduce both the total daily levodopa dose and its frequency [69] or to gradually substitute a dopamine agonist for levodopa [70]. Unfortunately, these strategies are unsatisfactory and typically reduce dyskinesias at the expense of less control of Parkinsonian symptoms. Indeed, the evidence that early levodopa exposure adversely affects the course of disease and leads to disabling dyskinesias and motor fluctuations constituted the rationale for the initial treatment with dopamine agonist.

5. Different Profile and Efficacy of Dopamine Agonists in Reducing Dyskinesia

In order to create a valid alternative to levodopa, and with the aim of eliminating its related complications, many different drugs acting on dopaminergic receptors have been developed and studied during the last years. They have different metabolism, plasma half-life, affinity to receptors subtypes, excretion, and routes of administration (Table 1). Moreover, these drugs have different efficacies on reducing the incidence of dyskinesia, improving motor symptoms, and reducing the daily levodopa dose (Table 2, Figure 1).

Initially dopamine agonists have been used as adjuvant therapy to improve levodopa-induced complications, but

Table 2: Adjuvant therapy versus placebo.

	Pramipexole	Ropinirole	Pergolide*	Bromocriptine	Cabergoline
Off-time reduction (h/day)	−1.81	−0.93	−1.60	−1.78	−1.29
LEDD red (mg/day)	−114.82	−119.81	−183.90	−52.17	−149.60
UPDRS ADL reduction (pts)					−1.78
UPDRS III reduction (pts)		−4.80			−1.74
Incidence of dyskinesia (OR)	2.63	3.21	4.64	2.52	1.44

* Based on data from just one trial [71].

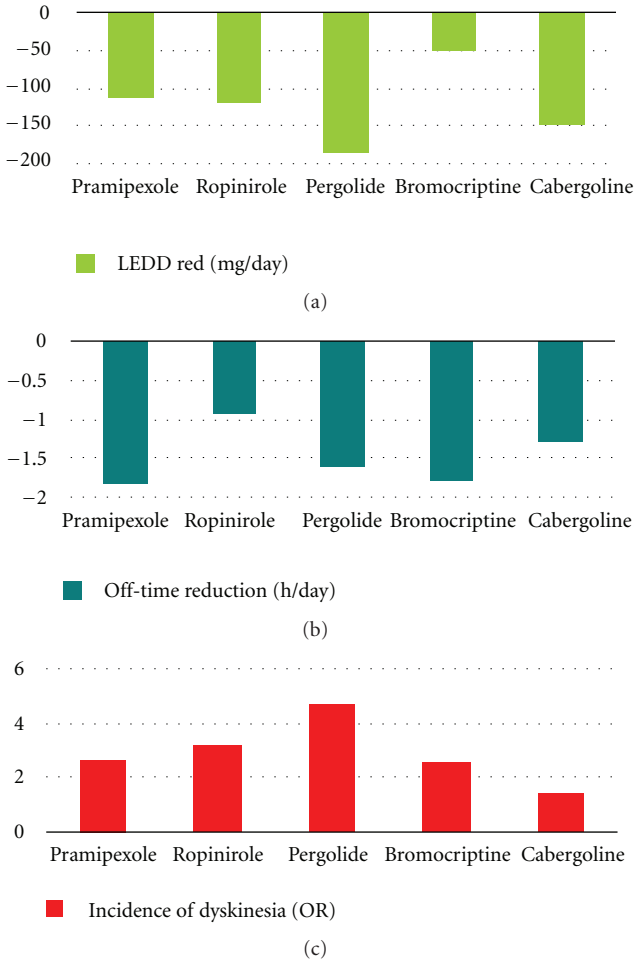

Figure 1: Effects of dopamine agonists on (a) reducing off time, (b) reducing levodopa daily dose, and (c) inducing dyskinesia.

once their effects on delaying the need for levodopa have been demonstrated, they have often been prescribed before the introduction of levodopa. Patients receiving dopamine agonists rather than levodopa as initial monotherapy showed a reduced risk for developing dyskinesias [7, 8, 12, 62, 72–76] (Table 3).

5.1. Dopamine Agonists Monotherapy and the Risk of Dyskinesia. The CALM-PD trial (Comparison of the Agonist Pramipexole versus Levodopa on Motor Complications of Parkinson's Disease) was a randomised controlled trial evaluating the risk of developing dyskinesias in patients with early PD initially treated with either pramipexole or levodopa. After 24 months, pramipexole-treated patients were receiving pramipexole plus levodopa, compared with levodopa alone. A minority of pramipexole-treated patients reached the endpoint of time to first occurrence of wearing off, dyskinesias, or on-off motor fluctuations (27.8% versus 50.7%, $P < 0.001$). Moreover, a significantly lower incidence of dyskinesias (9.9% versus 30.7%, $P < 0.001$) also has been demonstrated in patients in the pramipexole group. However, after a mean 6-year followup, >90% of patients were receiving levodopa therapy regardless of their initial treatment assignment. Compared to those taking pramipexole, patients initially treated with levodopa had significantly more dyskinesias (20.4% versus 36.8%), but there was no difference between groups in the incidence of disabling or painful dyskinesias [62, 74]. Interestingly, 5 subjects taking pramipexole developed dyskinesias before the supplemental levodopa, and 4 of them had no prior levodopa exposure [73]. No significant difference in the Lang-Fahn activities of daily living dyskinesia score was observed (1.3 versus 1.1 with pramipexole, $P < 0.06$) [7, 62, 72–74].

In a randomised, double-blind 5-year study of patients with early PD, the risk of developing dyskinesias after initial monotherapy with ropinirole was less than with levodopabenserazide (hazard ratio (HR), 2.82 (1.78, 4.44); $P < 0.001$) [8]. However, many of these patients eventually required supplemental levodopa to control the symptoms of the disease [8, 12]. When patients receiving ropinirole monotherapy required the addition of levodopa, the risk for developing dyskinesias increased and then did not differ significantly from that associated with levodopa alone [12]. The use of ropinirole as monotherapy, with only later addition of levodopa, delayed the onset of dyskinesias by up to 3 years, although it was associated with a higher incidence of neuropsychiatric complications than levodopa monotherapy.

Apomorphine, a subcutaneous nonergolinic dopaminergic agent, has been studied in 2 retrospective chronic monotherapy trials in which no oral anti-parkinsonian therapies were permitted from the time the pump was turned on in the morning until it was turned off in the evening [77, 78]. The mean maximum reduction of dyskinesia per patient was 64% ($P < 0.005$), and the mean time to achieve maximal dyskinesia improvement was 12.1 months.

Lisuride, another subcutaneously administered dopamine agonist, given as a continuous daytime infusion via pump, has been utilised as a strategy for minimising dyskinesias in 40 patients with advanced, levodopa-responsive PD

Table 3: Series on adjuvant therapy with dopamine agonists*. In italic, dyskinesia evaluation.

Author	Duration	Characteristics of participants	Interventions	Primary outcomes	Secondary outcomes
Poewe et al. [79]	*(6 months)*	*N: 302; MFs. Mean duration of PD: 8.5 y*	*Pramipexole (n = 201) versus placebo (n = 101)*	*Disability; motor complications; on/off time*	*SE*
Pahwa et al. [80, 81]; *Sethi et al.* [82, 83]; *Stacy et al.* [84]; *Stocchi et al.* [85, 86]	*(24 weeks)*	*N: 393; MFs. Mean duration of PD: 8.6 y*	*Ropinirole (24-h) (n = 202) versus placebo (n = 191)*	*Disability; patient-rated QoL; on/off time; levodopa dose*	*SE Depression sleep scales*
Oertel et al. [87]; *Pogarell et al.* [88]	*(32 weeks)*	*N: 363 (354 analysed); MFs. Mean duration of PD: 7.8 y*	*Pramipexole (n = 180) versus placebo (n = 183)*	*Disability; off time; levodopa dose*	*SE*
Wong et al. [89]	(15 weeks)	*N*: 150; Mean duration of PD: 4.4 y	Pramipexole (*n* = 73) versus placebo (*n* = 77)	Disability; off time	SE
Musch and Bonura [90]	*(24 weeks)*	*N: 218; on levodopa. Mean duration of PD: NA*	*Cabergoline (n = 145) versus placebo (n = 73)*	*Disability; off time; levodopa dose*	*SE*
Pinter et al. [91]	*(11 weeks)*	*N: 78; MFs. Mean duration of PD: 8.2 y*	*Pramipexole (n = 34) versus placebo (n = 44)*	*Disability; off time; levodopa dose*	*SE*
Wermuth [92]	*(12 weeks)*	*N: 69; MFs. Mean duration of PD: 10 y (range: 3–27 y)*	*Pramipexole (n = 36) versus placebo (n = 33)*	*Disability; motor complications; off time; levodopa dose*	*SE*
Lieberman et al. [93]; *Weiner et al.* [94]	*(32 weeks)*	*N: 360; MFs. Mean duration of PD: 9.2 y*	*Pramipexole (n = 181) versus placebo (n = 179)*	*Disability; on/off time; levodopa dose*	*SE*
Guttman [95]	*(9 months)*	*N: 247; MFs. Mean duration of PD: 7 y (range: 0.67–36 y)*	*Pramipexole (n = 79) versus bromocriptine (n = 84) versus placebo (n = 83)*	*Disability; off time*	*SE*
Kreider et al. [96]; *Lieberman et al.* [97]	*(6 months)*	*N: 149; predictable MFs. Mean duration of PD: 9 y*	*Ropinirole (n = 95) versus placebo (n = 54)*	*Disability; motor complications; off time; levodopa dose*	*SE*
Rascol et al. [98, 99]	*(12 weeks)*	*N: 46; not optimally controlled with levodopa. Mean duration of PD: 8 y*	*Ropinirole (n = 23) versus placebo (n = 23)*	*Disability; motor complications; off time*	*SE*

Table 3: Continued.

Author	Duration	Characteristics of participants	Interventions	Primary outcomes	Secondary outcomes
Steiger et al. [100]	(6 months)	*N*: 37; MFs. Mean duration of PD: 12.8 y (range: 3–33 y)	Cabergoline ($n = 19$) versus placebo ($n = 18$)	Disability; motor complications; off time; levodopa dose	SE
Hutton et al. [101]; *Lieberman and Hutton* [102]; *Schoenfelder et al.* [103]	*(24 weeks)*	*N: 188; MFs. Mean duration of PD: 10.6 y (range: 2–30 y)*	*Cabergoline ($n = 123$) versus placebo ($n = 65$)*	*Disability; on/off time; levodopa dose*	*SE*
Olanow et al. [104]	*(6 months)*	*N: 376; MFs. Mean duration of PD: 10.9 y*	*Pergolide ($n = 189$) versus placebo ($n = 187$)*	*Disability; motor complications; off time; levodopa dose*	*SE*
Temlett et al. [105]	(5 weeks)	*N*: 44 (40 analysed); Mean duration of PD: 13.4 y	Bromocriptine ($n = 22$) versus placebo ($n = 18$)	Levodopa dose	SE
Toyokura et al. [106]	*(8 weeks)*	*N: 222; not optimally controlled with levodopa. Mean duration of PD: 6.6 y*	*Bromocriptine ($n = 114$) versus placebo ($n = 108$)*	*Motor complications; on/off time*	*SE*
Schneider and Fischer [107]	(4 weeks)	*N*: 40; not optimally controlled with levodopa. Mean duration of PD: 9.1 y	Bromocriptine ($n = 20$) versus placebo ($n = 20$)	On/off time; levodopa dose	
Jansen [108]	(5 months)	*N*: 23; not optimally controlled with levodopa. Mean duration of PD: 8.7 y	Bromocriptine ($n = 12$) versus placebo ($n = 11$)	Disability	

* Performed on PD patients, parallel groups, double blind.
MFs: motor fluctuations; SE: side effects.

characterised by motor fluctuations and dyskinesias [109]. After 4 years, the lisuride-treated patients had improved their baseline dyskinesia scores (measured by AIMS) by 49% ($P < 0.0001$), whereas the levodopa-treated patients had worsened their scores by 59% ($P < 0.0001$).

5.2. Long-Acting Dopamine Agonists and the Risk of Dyskinesia. In animal-model studies, the long-acting dopamine agonists have been demonstrated to prevent or reduce the onset time for LIDs. In a study of monkeys with MPTP-induced parkinsonism, small doses of subcutaneously administered cabergoline, a D_2-selective dopamine agonist with a relatively long half-life, were added as adjuvant therapy to orally administered levodopa/benserazide (100/25 mg) for 1 month, showing significantly lower dyskinesia scores (sum for all body segments) than when levodopa/benserazide was given alone for 1 month ($P < 0.01$).

A report on the effect of cabergoline compared to levodopa showed a reduced incidence of dyskinesias [110]. Nevertheless, more recently, an increased incidence of dyskinesia and confusion in patients treated with bromocriptine was reported [111].

5.3. Differences among Drugs in Adjuvant Therapy. A recent systematic meta-analysis, which performs indirect comparisons among three classes of drugs, including nondopaminergic agents as catechol-O-methyl transferase inhibitors (COMTIs) or monoamine oxidase type B inhibitors (MAO-BIs), used as add-on (adjuvant) treatment to levodopa therapy in PD patients with motor complications, suggests that dopamine agonists may provide more effective symptomatic control [112].

5.3.1. Off-Time Reduction. There is no (or little) evidence of a difference across the different dopamine agonists for the overall reduction in off-time [pramipexole (−1.81 hours/day, CI −2.19 to −1.43; $P < 0.00001$); bromocriptine (−1.78 hours/day, CI −2.91 to −0.65; $P = 0.002$); pergolide (−1.60 hours/day, CI −2.57 to −0.63; $P = 0.001$); cabergoline (−1.29 hours/day, CI −1.89 to −0.69; $P < 0.0001$); ropinirole (−0.93 hours/day, CI −1.53 to −0.33; $P = 0.002$)] [112].

5.3.2. Levodopa Daily Dose Reduction. The largest reduction was with pergolide (−183.90 mg/day, CI −259.09 to −72.71; $P = 0.001$), though this was based on data from just one trial [71]. Cabergoline reduced the required levodopa dose by 149.60 mg/day (CI −208.79 to −90.41; $P < 0.00001$), ropinirole by 119.81 mg/day (CI −150.63 to −89.00; $P < 0.00001$), pramipexole by 114.82 mg/day (CI −143.01 to −86.64; $P < 0.00001$), and bromocriptine by 52.17 mg/day (CI −95.16 to −9.18; $P = 0.02$) [112].

5.3.3. UPDRS Scores Improvement. The agonist pramipexole appeared to produce larger improvements for UPDRS motor score (−6.31 points, CI −7.69 to −4.93; $P < 0.00001$) compared to ropinirole (UPDRS motor: −4.80 points, CI −7.32 to −2.28; $P = 0.0002$) and cabergoline (UPDRS motor: −1.74 points, CI −3.78 to 0.30; $P = 0.09$) [112].

5.3.4. Incidence of Dyskinesia. The analysis included 6476 participants, which represented 85% of the 7590 randomised participants included in the meta-analysis. Compared to placebo, the incidence of dyskinesia was increased with adjuvant therapy. The incidence of dyskinesia was greatest with pergolide (OR 4.64, CI 3.09 to 6.97; $P < 0.00001$), although the data were obtained from just one trial [71], followed by ropinirole (OR 3.21, CI 1.98 to 5.21; $P < 0.00001$), pramipexole (OR 2.63, CI 2.01 to 3.42; $P < 0.00001$), bromocriptine (OR 2.52, CI 1.42 to 4.48; $P = 0.002$), and cabergoline (OR 1.44, CI 0.96 to 2.16; $P = 0.08$) [112].

Though this meta-analysis indirectly compares several series on dopaminergic agents as adjuvant treatment, the need of large randomised studies that directly compare different agents administered as monotherapy with patient-rated overall quality of life and health economic measures as primary outcomes is recommended.

6. Alternative Treatments to Reduce Dyskinesia

As seen earlier, the primary therapeutic strategy for managing LIDs in PD patients is to delay their occurrence through delaying the introduction of levodopa therapy administering dopaminergic agents.

Once dyskinesias have occurred, other strategies should be attempted: (1) substitution of immediate release for controlled-release levodopa. The immediate-release preparation is easier to adjust, as onset of its effects is sooner, and duration of action (and dyskinesias) is shorter than with controlled-release preparations. For the same reason, agents that prolong the half-life of levodopa, such as entacapone, should be stopped; (2) discontinuation of other therapy that may embitter dyskinesias, as dopamine agonists or other factors delaying dopamine degradation as selegiline and rasagiline; (3) incrementation of the number of administrations of levodopa, in lower doses; (4) addition of an antidyskinetic agent as amantadine, an NMDA receptor antagonist. Diphasic dyskinesias that may manifest at the beginning and the end of a dosing cycle should be managed by utilising more frequent doses of levodopa, and the therapy should be sewed on the patient [113].

6.1. Amantadine. The NMDA receptor-binding and neurotoxic effects of excessive glutamate have led to the hypothesis that an NMDA antagonist may have antidyskinetic effects and reduce the severity of LIDs. Amantadine has been studied as adjuvant treatment in levodopa-treated patients experiencing motor complications, including dyskinesias, with the aim of reducing these effects without worsening Parkinsonian symptoms [114–117]. Three randomized placebo-controlled crossover clinical studies in a group of 53 PD patients showed a reduction (up to 60%) in the severity of LIDs after challenge with acute levodopa administration, without impacting the beneficial effects of levodopa on motor function.

6.2. Clozapine. It is an atypical antipsychotic that has been assessed for the treatment of drug-induced psychosis in PD.

It may also be effective in decreasing dyskinesias [70], and a few studies have focused on its antidyskinetic effect [118, 119].

6.3. Intraduodenal Levodopa. It provides direct delivery of levodopa to the duodenum and jejunum. The method involves insertion of a permanent access tube in the abdominal wall by percutaneous endoscopic gastrostomy. Several clinical studies have been conducted using this approach, demonstrating significant reductions in "off" time and dyskinesia after 6 months. It may be an option for patients with marked fluctuations and dyskinesia in whom deep-brain stimulation (DBS) is contraindicated or not possible due to advanced age, or it may provide an alternative to DBS.

6.4. Surgical Treatment. Patients with PD who may benefit from surgery include those who have substantial dyskinesias unresponsive to medication adjustments, are levodopa responsive, do not have dementia, and do not have neuropsychiatric impairment [80]. DBS is the most frequently performed surgery for PD in North America [80]. In patients with advanced PD, DBS of the globus pallidus interna (GPi) or the subthalamic nucleus (STN) has been shown to reduce dyskinesia severity by up to 89% [120, 121] and to reduce the duration of dyskinesias by 86% [122]. It provides significant improvement in Parkinsonian motor features and allows a reduction of dyskinesias, in part through the subsequent reduction of levodopa [123, 124].

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Hindawi Publishing Corporation
Parkinson's Disease
Volume 2012, Article ID 910454, 4 pages
doi:10.1155/2012/910454

Clinical Study

Intensive Rehabilitation Treatment in Parkinsonian Patients with Dyskinesias: A Preliminary Study with 6-Month Followup

Giuseppe Frazzitta,[1] Micaela Morelli,[2] Gabriella Bertotti,[1] Guido Felicetti,[1] Gianni Pezzoli,[3] and Roberto Maestri[4]

[1] *Department of Neurorehabilitation, Scientific Institute of Montescano, S. Maugeri Foundation IRCCS, 27040 Montescano, Italy*
[2] *Department of Toxicology and Centre of Excellence for Neurobiology of Dependence, University of Cagliari, and CNR Institute for Neuroscience, 09126 Cagliari, Italy*
[3] *Parkinson Institute, Istituti Clinici di Perfezionamento, Milano, Italy*
[4] *Department of Biomedical Engineering, Scientific Institute of Montescano, S. Maugeri Foundation IRCCS, 27040 Montescano, Italy*

Correspondence should be addressed to Giuseppe Frazzitta, giuseppe.frazzitta@fsm.it

Received 16 February 2012; Accepted 16 April 2012

Academic Editor: Anna Rosa Carta

A major adverse effect of levodopa therapy is the development of dyskinesia, which affects 30–40% of chronically treated Parkinsonian patients. We hypothesized that our rehabilitation protocol might allow a reduction in levodopa dosage without worsening motor performances, thus reducing frequency and severity of dyskinesias. Ten Parkinsonian patients underwent a 4-week intensive rehabilitation treatment (IRT). Patients were evaluated at baseline, at the end of the rehabilitation treatment and at 6-month followup. Outcome measures were the Unified Parkinson's Disease Rating Scale Sections II, III, and IV (UPDRS II, III, IV) and the Abnormal Involuntary Movement Scale (AIMS). At the end of the IRT, levodopa dosage was significantly reduced ($P = 0.0035$), passing from 1016 ± 327 to 777 ± 333 mg/day. All outcome variables improved significantly ($P < 0.0005$ all) by the end of IRT. At followup, all variables still maintained better values with respect to admission ($P < 0.02$ all). In particular AIMS score improved passing from 11.90 ± 6.5 at admission to 3.10 ± 2.3 at discharge and to 4.20 ± 2.7 at followup. Our results suggest that it is possible to act on dyskinesias in Parkinsonian patients with properly designed rehabilitation protocols. Intensive rehabilitation treatment, whose acute beneficial effects are maintained over time, might be considered a valid noninvasive therapeutic support for Parkinsonian patients suffering from diskinesia, allowing a reduction in drugs dosage and related adverse effects.

1. Introduction

A variety of drugs have been developed in the last fifty years and are currently used to control the disability related to Parkinson's disease (PD): levodopa, dopamine-agonists, monoaminoxidase B inhibitors, catechol-*O*-methyltransferase inhibitors.

A major limiting factor in levodopa therapy is the development of motor complications, in particular dyskinesia, which affects 30–40% of chronically treated PD patients [1].

Dyskinesias can improve by reducing the dopaminergic therapy, but it is usually cumbersome to decrease the levodopa dosage since this reduction elicits a worsening of motor symptoms: an increased bradykinesia, an increased "off time," a reduction of motor performance, and autonomy in daily activities.

In the last decade, a considerable number of studies have shown that exercise is effective in improving gait, balance, freezing, and motor performance in PD. In particular, recent studies on animals allow hypothesizing a direct action of physical activity on the mechanisms responsible for dyskinesias [2, 3].

In this study we present preliminary data on the effectiveness of intensive rehabilitation treatment (IRT) in PD patients with dyskinesias and on the persistence over time of its beneficial effects.

2. Methods

2.1. Study Population. Patients were screened from among those consecutively admitted to the movement disorder ambulatories of the Rehabilitation Institute of Montescano.

Eligibility criteria for patients were (a) diagnosis of "clinically probable" idiopathic Parkinson's disease according to Gelb et al. [4], (b) development of dyskinesias in the last 3 years and a history of several failed attempts to improve dyskinesia by reducing or modifying drug dosage, (c) ability to walk without any physical assistance, (d) no cognitive impairment (mini-mental state examination score ≥26), (e) no comorbidity unrelated to Parkinson's disease, (f) no vestibular/visual dysfunction limiting locomotion or balance, and (h) antiparkinsonian medications stable for >4 weeks.

Ten eligible patients were invited to be admitted to the Rehabilitation Institute of Montescano for a 4-week intensive rehabilitation treatment.

Patients were examined by the same neurologist expert in movement disorders, in the morning, one hour after they had taken the first dose of levodopa, at baseline, at the end of the rehabilitation treatment, and at 6-month followup. The neurologist was blinded with respect to the study design for the entire period.

The outcome measures used were the Unified Parkinson's Disease Rating Scale Sections II, III, and IV (UPDRS II, III, IV) [5] and the Abnormal Involuntary Movement Scale (AIMS) [6].

Patients were treated with different drugs (levodopa, I-COMT, I-MAOB, or dopamine agonist), and we evaluated the drug dosage as levodopa equivalent (mg/day).

The study was approved by the local ethics committee, and all subjects gave their informed written consent before participation.

2.2. Intervention. IRT consisted of a 4-week cycle of physiotherapy that entailed three daily sessions (two, not consecutive, in the morning and one in the afternoon), 5 days a week. The global duration of each session, including recovery periods, was about one hour. The first session comprised cardiovascular warm-up activities, relaxation exercises, muscle-stretching exercises (scapular muscle group, hip flexor, hamstring and gastrocnemius muscles), exercises to improve the range of motion of spinal, pelvic, and scapular joints, exercises to improve the functionality of the abdominal muscles, and postural changes in the supine position.

The second session comprised exercises to improve balance and gait using a stabilometric platform with a visual cue (patients were asked to follow a circular pathway on the screen by using a cursor sensitive to their feet movements on the platform) and treadmill plus (treadmill training with both a visual and an auditory cue) [7]. The last session was a session of occupational therapy aimed at improving autonomy in daily living activities: transferring from sitting position to standing position, rolling from supine position to sitting position and from sitting to supine, dressing, use of tools, and exercises to improve hand functionality and skills (e.g., using screws and bolts). Moreover, patients spent 20 minutes every day in front of a mirror in order to control involuntary and exaggerated movements.

Table 1: Outcome variables at admission, at discharge after a 4-week intensive rehabilitation treatment, and at 6-month followup.

Variable	Admission	Discharge	6-month followup
UPDRS_II	14.30 ± 4.7	9.40 ± 5.1	9.40 ± 3.0
UPDRS_III	20.00 ± 4.9	14.10 ± 4.3	11.60 ± 4.1
UPDRS_IV	7.50 ± 3.7	1.70 ± 1.6	2.60 ± 2.1
AIMS	11.90 ± 6.5	3.10 ± 2.3	4.20 ± 2.7
Levodopa equivalent (mg/day)	1016 ± 327	777 ± 333	777 ± 333

UPDRS: Unified Parkinson's Disease Rating Scale (Sections II, III, and IV). AIMS: Abnormal Involuntary Movement Scale.

During the follow-up period, patients were invited to continue some simple exercises learnt during hospitalization period.

2.3. Statistical Analysis. Descriptive statistics are given as mean ± SD. The Shapiro-Wilk statistic was used to test the normality of the distribution of all variables.

The effect of treatment on each outcome variable and the persistence over the 6-month follow-up period were assessed by repeated measurements analysis of variance with three repeated measurements: admission, discharge, and 6-month followup. Pairwise comparisons (discharge versus admission and 6-month followup versus admission) were carried out by contrast analysis in repeated measurements analysis of variance. A P value <0.05 was considered statistically significant. All analyses were carried out using the SAS/STAT statistical package, release 9.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

All 10 patients (aged 70 ± 8 years, duration of the disease 11.4 ± 2.4 years) completed the intensive rehabilitation treatment and the 6-month follow-up control. The characteristics of patients at admission, discharge and at the follow-up time are reported in Table 1.

At the end of IRT, levodopa-equivalent dosage was significantly reduced ($P = 0.0035$), passing from 1016 ± 327 to 777 ± 333 mg/day. At follow-up the levodopa-equivalent dosage was unchanged.

All outcome variables improved significantly by the end of the rehabilitation treatment ($P = 0.0003$, $P < 0.0001$, $P < 0.0001$ and $P = 0.0005$ for UPDRS_II, UPDRS_III, UPDRS_IV and AIMS, resp.). At followup, all variables still maintained better values with respect to admission ($P = 0.0176$, $P < 0.0001$, $P < 0.0001$ and $P = 0.0026$, resp.).

4. Conclusion

In this study we investigated the efficacy of IRT in PD patients with dyskinesias and the persistence over time of the beneficial effects of this treatment. We found a statistically and clinically significant improvement in all

outcome variables after the 4-week rehabilitation period, which was largely preserved even after a 6-month period.

The improvement in UPDRS II and III observed in this study is in accordance with our preview studies, in which we demonstrated that IRT acts slowing the disease progression in Parkinsonian patients in a very long followup [8]. The patients continued to perform the recommended exercises during the follow-up period and this may explain the persistence of the beneficial effects obtained during hospitalization. Moreover, the simple reduction of intensity and duration of dyskinesias during the day leads the patients to improve their motor performance and autonomy during activity of daily life.

Our results suggest that it is possible to act on dyskinesias in Parkinsonian patients with an IRT. Several preclinical investigations carried out in animal models of PD have demonstrated that an overload of redundant motor information is stored in the basal ganglia motor circuits of dopamine-denervated animals.

In particular, the striatum receives the most important glutamatergic innervation, is the site of interaction glutamate/dopamine, is the source of the inhibitory outputs, and is involved in the generation of motor fluctuation linked to L-dopa treatment [2]. In animal models, after denervation, the striatal plasticity is lost, but the chronic L-dopa treatment is able to restore the long term potentiation (LTP) of synaptic transmission [9, 10].

The reversal of synaptic strength from the potentiated state to pre-LTP levels is named depotentiation, and this process represents the synaptic process of erasing unnecessary motor information. In Parkinsonian animal models treated with L-dopa which show dyskinesias movement, the synaptic depotentiation is lost [2]. The inability of corticostriatal synapses to depotentiate might represent the cellular basis of dyskinesias.

The execution of movements plays a fundamental role in determining the outcome of subsequent motor responses elicited by dopamine receptor stimulation [11]. Exaggerated movements in response to a stimulation of dopaminergic receptors, such as those occurring during dyskinesia, might consequently convey erroneous information to the motor striate circuits. Therefore, when concomitant, competing correct movements are performed (as during rehabilitation treatment), the manifestation of abnormal dyskinetic movements may be attenuated.

This study, therefore, suggests the possibility that the competition between a correct motor behaviour and an abnormal motor response may depend on the balance between the trace memory of the two.

Another possible explanation may be related to a neurorestorative strategy. The effects of intensive exercise in promoting cell proliferation and neuronal differentiation in animal models are reported in a large cohort of studies.

In animals with cerebral lesions produced by 6-hydroxydopamine (6-OHDA) or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), the intensive use of a treadmill or running wheels led to improvement in motor performance as compared to animals that did not use these devices. Both in unilateral and bilateral models of PD, intensive treadmill exercise produced improvement in motor symptoms, which was related to a reduction in the neurochemical deficit: preservation of both tyrosine hydroxylase-positive fibres in the striatum and substantia nigra, as well as of vesicular monoamine transporter and dopamine transporter levels [12–17]. Increased dopamine availability, especially within the dorsolateral striatum, has been found in an MPTP mice model after intensive exercise with a motorized treadmill [18]. Overall, these findings show that intensive exercise exerts beneficial effects on dopamine transmission in parkinsonian mice models.

These neuroplastic effects of intensive exercise are probably related to increased expression of a variety of neurotrophic factors. In particular, brain-derived neurotrophic factor (BDNF) and glia-derived neurotrophic factor (GDNF) are the most likely growth factors involved in this process. BDNF is a key component of a number of aspects of neuroplasticity: neurogenesis, synaptogenesis, and cell survival [19, 20], while GDNF has been shown to promote the survival and differentiation of dopamine neurons and to maintain the survival of adult catecholaminergic neurons in mice [21, 22]. Tajiri et al. [17] have recently shown that rat models of PD performing intensive treadmill exercise experience upregulation of BDNF and GDNF in the striatum in comparison to rats that do not exercise. These findings are consistent with the findings of another study by Lau et al. [23], who showed that intensive treadmill exercise raises the level of endogenous BDNF and GDNF in the substantia nigra and striatum.

In conclusion, our findings suggest that properly designed intensive multidisciplinary rehabilitation treatment using treadmill should be considered as a valid noninvasive therapeutic support for patients who show dyskinesias.

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Hindawi Publishing Corporation
Parkinson's Disease
Volume 2012, Article ID 640815, 9 pages
doi:10.1155/2012/640815

Review Article

Understanding and Prevention of "Therapy-" Induced Dyskinesias

Iciar Aviles-Olmos, Zinovia Kefalopoulou, and Thomas Foltynie

Unit of Functional Neurosurgery Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, London WC1N3BG, UK

Correspondence should be addressed to Iciar Aviles-Olmos, i.aviles-olmos@ucl.ac.uk

Received 12 September 2011; Revised 9 March 2012; Accepted 26 March 2012

Academic Editor: Anna Rosa Carta

L-dopa is the most effective, currently available treatment for Parkinson's disease (PD), but it leads to the development of involuntary movements known as L-dopa-induced dyskinesia (LID) in the majority of patients after long-term use. Both gene and cell therapy approaches are the subject of multiple ongoing studies as potential ways of relieving symptoms of PD without the complication of dyskinesia. However, the spectre of dyskinesia in the absence of L-dopa, the so-called "off-phase" or graft-induced dyskinesia (GID), remains a major obstacle particularly in the further development of cell therapy in PD, but it is also a concern for proponents of gene therapy approaches. LID results from nonphysiological dopamine release, supersensitivity of dopamine receptors, and consequent abnormal signalling through mechanisms of synaptic plasticity. Restoration of physiological circuitry within the basal ganglia loops is ultimately the aim of all cell and gene therapy approaches but each using distinctive strategies and accompanied by risks of exacerbation of LID or development of "off-phase"/GID. In this paper we discuss the details of what is understood regarding the development of dyskinesias with relevance to cell and gene therapy and potential strategies to minimize their occurrence.

1. Introduction

L-dopa is the most effective treatment for Parkinson's disease currently available and for many patients can provide effective relief of symptoms for many years after diagnosis. In most patients, L-dopa treatment leads to a "honeymoon" period during which the motor symptoms are well controlled. However, after 5 years of treatment, approximately 40% of patients will develop fluctuations in symptom control in response to the drug, as well as involuntary movements known as "L-dopa-induced dyskinesias" (LID) [1]. These complications affect as many as 89% of PD patients after 10 years of L-dopa treatment [2]. LID can be seen during "peak dose" periods, during "off" medication periods or in a "biphasic" pattern as L-dopa levels rise and fall following oral intake. For this reason, other strategies have been developed to try and restore normal function of the basal ganglia circuitry. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) or globus pallidus pars interna (GPi) have both been shown to be highly successful ways of controlling symptoms of PD. Dyskinesia is generally reduced following STN DBS as a result of reduction in L-dopa dose. GPi DBS is a highly effective way of reducing LID, but many patients remain reliant on frequent high doses of L-dopa to maintain control of PD symptoms [3, 4].

To improve upon the limitations of currently available therapies, studies are being performed to assess the role of either gene therapy or cell therapy to provide PD symptom relief without the complication of dyskinesia. Cell therapy trials have been seriously hindered by reports of dyskinesia occurring in the absence of L-dopa—the so-called "off-phase" or graft-induced dyskinesia (GID) [5, 6]. There are also theoretical concerns that such "off-phase" dyskinesias might limit the ability of gene therapy to lead to an effective PD therapy. As a prelude to discussing the origin of "therapy-" induced dyskinesia, and strategies to minimize or control them, a discussion of our current understanding of LID is required.

2. Origin of LID

Risk factors for the development of LID include younger age [7, 8], dose of L-dopa [9], pattern of L-dopa administration [9–12], and stage of disease [13–15]. The neural mechanisms that underlie LID in PD are not completely understood; however, the study of basal ganglia anatomy and physiology in the normal and dopamine-depleted states has been of great help. In PD, the degeneration of the dopaminergic neurons of the substantia nigra compacta (SNc) compromises the equilibrium between the direct (D1 receptor) and indirect (D2 receptor) pathways resulting in abnormal GPi hyperactivity. Initially, the clinical features of PD were thought to follow simple increases in the "rate" of activity of the GPi, which through inhibition of the motor thalamus acted as a brake to activity in the supplementary motor area. It was further considered that excessive levodopa stimulation might induce dyskinesia by reduction of the inhibition of thalamocortical neurons resulting in an overactivity of motor cortical areas [16].

This model, is however, inconsistent with several clinical and experimental findings. During LID in the nonhuman primate model of PD, there is decreased rather than increased metabolic activity in the ventral anterior (VA) and ventrolateral (VL) thalamic nuclei, regions of the thalamus that receive input from the GPi [17]. Furthermore, among patients with PD and LID, creation of a lesion within the GPi (pallidotomy) is associated with a reduction in LID rather than a deterioration in LID that would have been predicted by the previously described "rate model" [18].

The pathophysiological changes that underlie the development of LID must therefore be far more complex. Recordings taken from PD patients undergoing DBS surgery have revealed that during periods of LID there is an increase in 4–10 Hz activity in the contralateral STN, suggesting that there is an abnormal pattern of oscillatory activity throughout the basal ganglia [19]. The cause of this oscillatory activity is likely to be multifactorial involving both pre and post synaptic components.

2.1. Dysfunctional Dopamine Release. The surviving dopaminergic neurons in the progressively denervated striatum, sprout branches that successfully compensate for the neurodegenerative process until ~60% of neurons, are lost. Until this point, administration of L-dopa does not alter the concentration of striatal dopamine, but beyond the 60% deficit, the concentration of dopamine in the striatum increases 3-fold after L-dopa administration [20]. While L-dopa administration continues to enhance dopamine synthesis and release by the surviving dopaminergic neurons, L-dopa is also decarboxylated and released as dopamine by serotonergic terminals, noradrenergic neurons, striatal capillaries, and nonaminergic striatal interneurons [20–23]. These terminals do not store and release dopamine in a regulated way, thus leading to nonphysiological dopamine receptor stimulation [24].

The role of serotonergic neurons in the development of LID has been the subject of particular study. In rats with 6-hydroxy dopamine lesions, approximately 80% of the peak dopamine (DA) efflux measured in the striatum following the administration of L-dopa originates from serotonergic neurons [25–28].This nonphysiological DA release is highly dyskinesigenic; indeed recent evidence shows that dyskinetic rodents have increased numbers of serotonergic terminals and sprouting of serotonin axon varicosities stimulated by L-dopa exposure, leading to larger swings of extracellular DA release [29].

2.2. Dopamine Receptor Supersensitivity. Under conditions of chronic denervation, dopamine receptors develop supersensitivity, involving an increased expression of receptors on the postsynaptic membrane of medium spiny neurons [30, 31]. D1 receptor supersensitivity has been shown to have a direct relationship with LID severity [32]. Persistent stimulation of dopamine receptors normally leads to their desensitisation and induces receptor internalisation, and it is hypothesised that, in LID, this desensitisation and internalisation process is impaired [33–35]. In a rodent model of LID, it seems that D1 receptors become "anchored" on the plasma membrane of medium spiny neurons due to crosstalk with D3 receptors following chronic administration of L-dopa [34]. Consistent with this it has been shown that the use of a D3 antagonist restores normal levels of D1 receptors on the plasma membrane and has been associated with reduction in LID in both the rodent and primate models [36, 37]. However, it is clear that LID does not occur solely as a result of abnormal D1 receptor expression or sensitivity alone since D2 selective agonists can also provoke dyskinesia [38].

2.3. Synaptic Plasticity. Physiological dopaminergic input from nigrostriatal neurons onto the striatal medium spiny neurons plays an important role in the potentiation and depotentiation of synapses of the corticostriatal pathway. Repetitive stimulation can cause either a long-lasting increase in synaptic strength known as long-term potentiation (LTP), or an enduring decrease known as long-term depression (LTD), a phenomenon known as synaptic plasticity [39, 40]. It is this process that allows deletion of unwanted or unnecessary connections and strengthening of desirable motor programs.

Disruption of normal synaptic plasticity is strongly linked to the appearance of dyskinesia [41–45]. It is hypothesized that the disrupted motor control underlying dyskinesia is attributable to specific changes occurring along the dopamine D1 receptor/protein kinase A/dopamine and cyclic AMP-regulated phosphoprotein-32 (D1/PKA/DARPP-32) intracellular signalling pathway leading to the loss of synaptic depotentiation at corticostriatal synapses and to the development of nonphysiological motor circuits within the basal ganglia [39].

L-dopa can restore normal synaptic plasticity among individuals free of dyskinesia, but not when dyskinesias are already developed [46]. It has been proposed that patients with LID have lost the ability to depotentiate synapses normally, that is, they have lost the mechanism that underlies "synaptic forgetting," resulting in pathological storage of information that would normally be erased, leading to the development of abnormal motor patterns, that is,

LID [42, 47]. Possible consequences of this process include increased phosphorylation of N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor subunits [48] and increased striatal dynorphin mRNA levels [49]. Amelioration of abnormal glutamatergic NMDA transmission likely explains the beneficial effects of Amantadine [50–52] on reversal of LID.

3. Graft-Induced Dyskinesia

Graft-induced dyskinesia (GID) was first brought to widespread attention following the publication of the randomised sham-surgery-controlled trials of fetal dopaminergic cell transplantation [5, 6]. GIDs are characterized by the presence of both hyperkinesias and dystonic postures occurring in the "off phase," generally considered to be greater than 12 hours following the last dose of L-dopa. In the Freed trial, "off phase" GID was seen in 5/33 (15%) of transplanted patients, more than 1 year after transplant [5]. The second sham-surgery-randomised-controlled trial (Olanow trial) reported the presence of "off-phase" GID in 13/23 (56.5%) of the grafted patients, 6–12 months after transplantation [6]. In 3 of the patients from the Olanow trial the GIDs were disabling enough to require further neurosurgical intervention [6]. In contrast to the worrying appearance of "off-phase" GID, neither trial reported any increase in L-dopa-induced or "on-phase" dyskinesia.

Patients receiving open label transplants that predated the Freed and Olanow trials had also experienced GID [53–55] but these had caused only mild to moderate disability to the patients even with follow-up extending to 11 years [55]. Speculation regarding the origin of "off-phase" dyskinesias has included the possibility of excessive dopamine production by the grafts, dopamine receptor supersensitivity away from "islands" of grafted cells, individual factors related to the patient and their PD phenotype, a relationship with immune rejection, or contamination of the grafts with cells of a nondopaminergic phenotype.

3.1. Excess Dopamine Release? Initial hypotheses were that GID occurred due to excessive dopamine release by the grafts. This has not, however, been supported by functional imaging of the patients in the Olanow trial or the Hagell patient series [55–57]. Dyskinesia severity was not related to the magnitude of graft-derived dopaminergic reinnervation, as judged by 18F-dopa positron emission tomography (PET), indicating that "off-phase" dyskinesias probably do not result from excessive growth of grafted dopaminergic neurons. Furthermore, the severity of GID was not correlated with improvement in the "off" UPDRS motor scores [55, 58]. The fact that GIDs have not been seen in patients without any benefit from their transplants suggests that a functional graft is necessary for GID development although their appearance does not simply relate to excess dopamine release.

3.2. Imbalanced Dopamine Release? It was further proposed that islands of excessive dopaminergic activity might relate to GID [59]. Indeed the patients with the best functional outcome after transplantation exhibited no dopaminergic denervation in areas outside the grafted areas, either preoperatively or at 1 or 2 years postoperatively. Comparing PET signal among patients with and without GID, there was a greater increase of putaminal 18F-Dopa uptake seen in the posterodorsal zone of GID patients. However, the GID group also showed a relative increase ventrally not seen at all in the GID-negative patients suggesting that unbalanced increases in dopaminergic function might complicate the outcome of neuronal transplantation for parkinsonism. The implantation of dopamine cells into the ventrocaudal putamen, may also contribute to the unusual distribution of GID, in which the face, neck, and arms tend to be the most clinically involved. These data are corroborated by animal models showing that dyskinesias occur following transplantation of cells to a particular prodyskinetic subregion of the putamen [49].

3.3. Patient Phenotype? In the same clinical studies, the severity of GID was not found to correlate with the severity of pretransplant L-dopa-induced dyskinesias (LID). However, a negative correlation was seen between the severity of postoperative "off-phase" GID and preoperative putaminal 18F-Dopa uptake [55, 57]. This finding indicates that the manifestation of "off-phase" dyskinesias after grafting, similar to that of L-dopa-induced "on-phase" dyskinesias [60, 61] might be related to the baseline severity of striatal dopaminergic denervation.

3.4. Tissue Storage? In the Freed trial, cells were stored for up to 4 weeks before transplantation, In the Hagell series, the appearance of GID was reported in patients with grafts stored for 1–8 days. However, any hypothetical relationship between tissue storage and GID hypothesis was not supported by the Olanow trial, in which no grafts were stored for >48 hours.

3.5. Immunosuppression? In the Olanow trial, the initial significant improvement in the grafted patients compared with sham-operated cases [6] was lost following withdrawal of immune suppression after 6 months. Also in two patients who came to autopsy, the grafts were surrounded by activated microglia suggesting an immune response [6]. Such inflammatory reactions could lead to reduced graft survival and functional deterioration [62, 63]. GIDs develop slowly over time and appear to be most pronounced in patients that have received no immune-suppression [5] or only mild immunosuppressive treatment [56]. There has been speculation, therefore, that such an ongoing inflammatory/immune process could affect the way the grafted DA neurons release and/or handle DA at the synaptic level, which in turn may constitute a triggering factor for the induction of dyskinesias [64].

3.6. Serotonergic Contamination? It has now been shown that in 2 patients experiencing GID, there was excessive serotonergic innervation in their brains following transplant, (252–285% higher than comparable advanced PD patients). This was measured using functional imaging with ((11)C)-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl) benzonitrile positron emission tomography (C^{11}-DASB PET). Importantly this excessive serotonergic

innervation was seen restricted to the areas of their grafts. There is mounting evidence that serotonergic neurons contaminating the original graft release dopamine in an uncontrolled manner and then lack the ability to reuptake DA and buffer extracellular DA levels leading to GID [65].

4. The Relationship between LID and GID

The clinical similarity between LID and GID suggests that similar pathophysiological mechanisms may underlie the development of both. Animal models strongly support the suggestion that the severity of LID in animals that have received putaminal grafts are related to the number of serotonergic neurons contained within the graft, as well as the severity of the dopaminergic lesion. Among animals receiving serotonin grafts [66], there was no impact on either motor asymmetry in the amphetamine-induced rotation test or spontaneous forelimb use in the cylinder test, but in contrast there was a progressive worsening of LID. Other studies have also confirmed that removal of serotonin innervation, or dampening of serotonin neuron activity by agonist drugs, results in a near complete blockade of LID in 6-OHDA lesioned rats [27].

It would appear that the relative abundance of dopaminergic compared to serotonergic neurons (whether host or grafted) is a critical factor in LID development after graft [67, 68]. It appears that, in the presence of a severe dopaminergic deficit, dopamine released from serotonergic neurons may trigger severe dyskinetic responses, but provided ~10–20% of the dopamine innervation remained intact, the grafted serotonin neurons have limited detrimental effect on dyskinesia severity. This has been corroborated independently showing that serotonergic neurons are not detrimental, provided sufficient dopamine neurons remain in the graft [69].

The appearance of LID after graft may occur via (i) dysregulated DA release from serotonergic neurons themselves, (ii) lack of reuptake of released DA due to insufficient DA neurons, (iii) inhibition of the dopamine transporter (DAT) on DA neurons by 5HT release thus preventing DA reuptake by DA neurons, and (iv) abnormal dopamine receptor supersensitivity (i.e., a postsynaptic component) as evidenced by increases in apomorphine-induced rotations [28, 68].

Despite these consistent findings of LID appearance following serotonergic contamination of cell grafts, "off-phase" dyskinesias (GID) do not appear to occur in animal models of PD undergoing cell grafts with the exception of very mild abnormal movements occurring in 2 studies [70, 71]. This is of major importance since there is little or no relationship between the change in LID following transplantation in patients (which tends to improve) and the development of GID. Given that the patients exhibiting GID are those that had the most severe dopaminergic deficits, in the absence of exogenous L-dopa administration, it seems likely that GID appearance must relate to dopamine production from the graft itself. Dopamine released into the extracellular space can be taken up by serotonergic neurons via the serotonin transporter and subsequently be rereleased as a false transmitter [72]. Furthermore, serotonin release can block the dopamine transporter and add to abnormal accumulation of dopamine in the synaptic cleft and onset of dyskinesia [65, 73]. Whether serotonergic neurons have a role in the development of "off-phase" GID simply by maintaining postsynaptic dopamine receptors in a supersensitive state has not yet been confirmed. Any relevance of abnormal synaptic plasticity as a secondary or parallel process in the development of GID has also yet to be comprehensively studied.

5. Gene Therapy for PD and Its Effects on Dyskinesia

Gene therapy represents an exciting new prospect for the treatment of patients with PD. This technology exploits the properties of viral vectors to invade host cells and incorporate DNA into the host genome. Appropriate modification of viral vectors allows control over which genes are incorporated and within PD research the main focus has been predominantly on genes encoding growth factors or enzymes involved in dopamine synthesis [74, 75]. Gene transfer offers a practical means of solving the problems associated with implanted hardware while still providing a continuous and selective delivery system of the desired gene/protein at the targeted site.

There are 4 gene therapy programs that have already reached the stage of clinical trial evaluation.

5.1. AAV2-Neurturin. AAV2-Neurturin, an analogue of glial-cell-derived neurotrophic factor (GDNF), has been developed in an attempt to provide trophic support to neurons/glia and thus manipulate the progression of PD. Both (GDNF) and Neurturin enhance dopaminergic neuron survival and nigrostriatal function in animal models of PD. Both factors provide protection from 6-OHDA-induced degeneration in rats [76] and provide neuroprotection in parkinsonian monkeys [77]. In a clinical trial of 58 patients at 12 months, delivery of neurturin to the striatum failed to show any change in the primary outcome measure (off-medication part III-UPDRS) [78]. There was not any change in dyskinesia scores in neither the Neurturin nor the sham surgery groups. Retrograde transport to the substantia nigra pars compacta (SNc) was lower (or possibly slower) than expected and therefore a follow-up evaluation is underway targeting both the striatum and SNc. It seems unlikely that this approach would lead to worsening of dyskinesia severity, indeed beneficial effects on dopaminergic number, survival or function should lead in theory to improvement in LID. Nevertheless, any disproportionate neurotrophic action on serotonergic neurons might in theory lead to provocation of dyskinesia, and these should be specifically sought during clinical evaluation of patients receiving this treatment.

5.2. AAV2-GAD. Gene therapy consisting of insertion of the glutamic acid decarboxylase gene (*GAD*) into the neurons of the STN offers an alternative therapeutic strategy. Inspired by the effectiveness of STN DBS, the hypothesis emerged that expression of GAD (the rate-limiting enzyme for GABA production) would inhibit overactivity in the STN and would

improve off-medication UPDRS motor score. This strategy has been effective in the rat model of PD [79]. It is known that STN DBS can itself provoke "off-medication dyskinesia" but this is usually a transient phenomenon when it occurs and may be relieved by adjustment of the stimulation amplitude. Since the mechanism of action of STN DBS remains controversial, it remains theoretically possible that GAD gene therapy might also provoke "off-phase" dyskinesia. However in the results published to date in a double blind evaluation, no increase in dyskinesias was reported, while a modest improvement in PD severity was observed [80]. Open label follow up of these patients will allow further quantitative estimates of the extent to which LID may improve or deteriorate following this approach.

5.3. AAV-hAADC. Bilateral intraputaminal infusion of AAV-hAADC (adeno-associated virus-human aromatic L-amino acid decarboxylase), the enzyme that converts L-dopa into dopamine, aims to improve the conversion of exogenously administered L-dopa. Since this therapy remains dependent on exogenous administration of L-dopa, "off-phase" dyskinesia is unlikely to occur. However, striatal transfection with AAV-hAADC has been shown to increase LID in primate parkinsonian models if delivered in a nonhomogeneous way [81], reminiscent of the experience of "off-phase" graft-induced dyskinesia in cell therapy experiments. Despite these theoretical concerns, data published to date have shown an increase in on-time and reduction in off-time without any increase in LID [75]. Two patients had a transient increase in mild LID, but none experienced "troublesome LID," which were reduced for the group as a whole [75].

5.4. LV-TH-GCH1-AADC-ProSavin. The ProSavin approach incorporates all 3 enzymes required for dopamine biosynthesis (tyrosine hydroxylase (TH), AADC, and GTP cyclohydrolase L1(GCH1)), with the aim of transfection of nondopaminergic cells so that they may produce and release dopamine endogenously. Again the theoretical concern is that transfected neurons may synthesize dopamine but may not be able to store and release this dopamine in a physiological manner, and an increase in dyskinesia may follow. The pilot phases of this program are using a dose escalation strategy, with careful evaluation of efficacy and dyskinesia severity at each stage, before proceeding with dose increases in subsequent patient cohorts. So far, there have been no concerns regarding "off-phase" dyskinesias. Further addition of the vesicular monoamine transporter 2 (VMAT2) gene to allow dopamine transport by transfected cells has not shown any advantage over the ProSavin approach in laboratory experiments [82].

An additional gene therapy program that has not yet reached clinical trial stage aims to deliver continuous dopamine therapy using AAV-TH-GCH1. By omitting the AADC enzyme, transfected cells would be able to synthesize L-dopa but rely on endogenous AADC activity to produce dopamine. This reduces the risk of uncontrolled dopamine production that cannot be stored or transported physiologically and aims to deliver "continuous dopaminergic stimulation (CDS)," to mimic the advantages observed using other methods of CDS [12]. In rodent models, this therapy has been shown to allow resistance to LID development [83].

All of the current gene therapy approaches, if successful, could permit a reduction of L-dopa dose and, therefore, achieve greater control of LID. No major concerns regarding "off-phase" dyskinesias have been reported among patients exposed to PD gene therapy. However, dose escalation to try and achieve greater efficacy from these approaches will necessitate continued vigilance with regard to dyskinesia emergence.

6. Preventing "Therapy-" Induced Dyskinesias

Our knowledge regarding the underlying causes of LID is growing, and it is clear that the pathophysiological processes are complex, depending on the number of intact dopaminergic terminals, the chronicity, and pattern of administration of L-dopa replacement as well as the possibility of genetic variability in pathways controlling receptor supersensitivity/internalization and synaptic plasticity. There is converging evidence to implicate nondopaminergic neurons, in particular serotonergic neurons releasing dopamine in a nonphysiological manner, as a major contributory factor in LID and also GID.

This knowledge is vital in trying to minimize the likelihood of "off-phase" GID developing in PD patients participating in future trials of fetal cell therapy. Careful attention must be paid to selecting the optimal patients phenotype with respect to the severity of their PD and by implication the number of surviving dopaminergic terminals at the time of transplantation. Patients with advanced dopaminergic degeneration will be at greater risk of developing dyskinesia from grafts that contain an excessive number of serotonergic neurons. Patients with less advanced dopaminergic cells loss should be more tolerant of a greater number of serotonin contaminating cells. The relative extent of dopamine/serotonin striatal innervations can be revealed using preoperative functional imaging, to quantify the extent and severity of both dopaminergic and serotonergic innervations in the striatum.

The perioperative and intraoperative details are also extremely important. It is possible to manipulate the number of contaminating serotonergic neurons within grafts, through optimisation of the dissection margins in the ventral mesencephalon of the fetal tissue, during graft harvesting. Furthermore, clinical and animal data both suggest that surgical targeting should avoid the ventral putamen. While the type and duration of immunosuppressive regimes may or may not have major relevance for GID development, it is likely that overall cell survival is improved by maintaining immunosuppression for longer than the 6 months adopted in previous cell therapy trials.

6.1. Additional Use of Nondopaminergic Medications. The use of serotonin (5HT-1A) agonists as antidyskinetic agents is not new. Buspirone, a (5-hydroxytryptamine (5HT 1A) receptor agonist, has previously showed beneficial effects lessening the severity of LID [84], by dampening transmitter release from serotonergic neurons through activation of

inhibitory 5HT-1A autoreceptors without any worsening of extrapyramidal symptoms. Beneficial effects seen among patients with GID have also been reported [65]. Sarizotan (also a 5-HT1A receptor agonist but with additional high affinity for D3 and D4 receptors) showed encouraging results in an open-label evaluation [85]; however, in a blinded trial the effects of Sarizotan on LID were disappointing [86]. While the mechanism(s) remain unclear, one likely explanation for the possible beneficial effect of serotonin receptor agonists on LID is that stimulating 5HT1A receptors diminish dysregulated release of dopamine from raphe-striatal serotonergic neurons. However, it has also been shown that 5HT1A agonist drugs alleviate dyskinesias provoked by direct D1 receptor agonists, suggesting a further interaction between D1 and 5-HT1A receptors [87].

The beneficial effects of Amantadine on LID through its action on NMDA receptors have prompted further study of agents acting on the corticostriatal glutamatergic input evaluating the effects of metabotropic glutamate receptor (mGLUR) antagonists and Adenosine A2A receptor antagonists. AFQ056 is a potent, selective mGLUR5 antagonist that shows antidyskinetic effects in a rodent PD model and has been shown to have significant antidyskinetic effects in 2 small blinded trials [88]. Istradefylline (an A2A antagonist) has been shown to improve motor function and reduce the development of LID in nonhuman primates [89]; indeed rodent A2a knockout animals do not develop LID [90]. In patients with PD, however, multiple randomised trials have failed to show beneficial effects of Istradefylline on LID severity [80, 91]. α2Adrenergic agonists modulate the activity of the direct striatopallidal pathway and have been shown to reduce LID in PD patients but their use in PD patients has been limited by development of side effects [92, 93]. Given the demonstration of beneficial effects in animal models [36, 37], a further emerging possibility might be the use of D3 antagonists to allow D1 receptor internalisation, with the aim of reducing the postsynaptic "supersensitive" state [94]; however, this approach has yet to be evaluated in patients.

7. Conclusions

The current and future gene therapy and cell therapy programs represent a great source of optimism for patients with PD. However, PD is a heterogeneous disease and only a subset of patients are likely to benefit—perhaps the subgroup of patients with young onset PD that remain with a predominantly motor deficit for many years [95]. In these individuals, LID is a major problem and the success of cell or gene therapy will depend on providing relief of PD "off" symptoms without "off-phase"/therapy-induced dyskinesia.

Dyskinesia development has multiple determinants, and therefore multiple potential opportunities exist to intervene and prevent their occurrence. Some of these processes may be relevant solely as a secondary consequence of nonphysiological dopamine release (presynaptic component) from serotonergic or other neurons, or as a downstream effect of chronic dopamine receptor supersensitivity (postsynaptic component). Consequent downstream changes in synaptic plasticity may account for abnormal oscillatory firing patterns, throughout the basal ganglia circuitry. L-dopa itself (presumably when released physiologically) has been identified as having a role in the restoration of normal synaptic plasticity, as evidenced from recordings of patients undergoing high-frequency stimulation of the substantia nigra pars reticulata, in both on- and off-medication states [96, 97]. Whether other pharmacological options such as Buspirone, AFQ056, or D3 receptor antagonists can be exploited to relieve off-medication GID needs further study.

In parallel with approaches to relieve LID and GID, our understanding of the importance of the ratio of serotonin and dopaminergic neurons allows optimisation of future interventions and accompanying trial design. Our greater understanding of the causes of dyskinesia, either L-dopa related or graft and gene therapy induced, represents a considerable step towards ensuring the success of future gene and cell therapy programs.

Conflict of Interests

There is no actual or potential conflict of interests in relation to this paper.

Acknowledgments

This work was undertaken at UCL/UCLH and was funded in part by the Department of Health NIHR Biomedical Research Centres funding scheme. The Unit of Functional Neurosurgery, UCL Institute of Neurology, Queen Square, London is supported by the Parkinson's Appeal. Dr. T. Foltynie is supported by the Parkinson's Appeal and holds grants from Parkinson's UK, the Cure Parkinson's Trust, and the Brain Research Trust and is on the organising committee for the Transeuro project supported by an EU FP7 grant. Dr. I. Aviles-Olmos is a Ph.D. student supported by Cure Parkinson's Trust.

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Hindawi Publishing Corporation
Parkinson's Disease
Volume 2012, Article ID 358176, 10 pages
doi:10.1155/2012/358176

Review Article

Corticostriatal Plastic Changes in Experimental L-DOPA-Induced Dyskinesia

Veronica Ghiglieri,[1] Vincenza Bagetta,[1] Valentina Pendolino,[1] Barbara Picconi,[1] and Paolo Calabresi[1,2]

[1] *Laboratorio di Neurofisiologia, Fondazione Santa Lucia, IRCCS, Via del Fosso di Fiorano 64, 00143 Rome, Italy*
[2] *Clinica Neurologica, Dipartimento Specialità Medico Chirurgiche e Sanità Pubblica, Università di Perugia, S. Maria della Misericordia, 06156 Perugia, Italy*

Correspondence should be addressed to Veronica Ghiglieri, v.ghiglieri@hsantalucia.it

Received 17 January 2012; Accepted 6 March 2012

Academic Editor: Anna Rosa Carta

In Parkinson's disease (PD), alteration of dopamine- (DA-) dependent striatal functions and pulsatile stimulation of DA receptors caused by the discontinuous administration of levodopa (L-DOPA) lead to a complex cascade of events affecting the postsynaptic striatal neurons that might account for the appearance of L-DOPA-induced dyskinesia (LID). Experimental models of LID have been widely used and extensively characterized in rodents and electrophysiological studies provided remarkable insights into the inner mechanisms underlying L-DOPA-induced corticostriatal plastic changes. Here we provide an overview of recent findings that represent a further step into the comprehension of mechanisms underlying maladaptive changes of basal ganglia functions in response to L-DOPA and associated to development of LID.

1. Introduction

In Parkinson's disease (PD), degeneration of dopaminergic neurons of the *substantia nigra* causes critical reduction in dopamine (DA) levels in the target areas. The subsequent abnormal DA receptor stimulation exerts its main effects in the striatum, the principal input structure of basal ganglia-thalamo-cortical network, producing changes in input integration that lead to imbalance between direct and indirect striatofugal pathways and dysfunctional changes in basal ganglia output.

Impairment in the induction of the two forms of striatal synaptic plasticity, the long-term depression (LTD) and the long-term potentiation (LTP), has been found to correlate with DA depletion and onset of symptoms in experimental models of PD. DA depletion initially affects LTP and then, when symptoms are fully manifested, also LTD is impaired [1].

The resulting motor symptoms are effectively treated with a replacement therapy that uses the DA precursor L-3,4-dihydroxyphenylalanine (L-DOPA) to rescue striatal DA-dependent neuronal activity. However, L-DOPA treatment does not arrest disease progression and, with time, neuronal degeneration advances and leads to the emergence of a complex pattern of alterations that involves other basal ganglia nuclei, causing symptoms that are refractory to conventional therapy. In addition, the initial excellent antiparkinsonian effects of L-DOPA are lost in the long run, and the route of drug administration utilized in the clinical practice leads to a pulsatile stimulation of DA receptors that causes a broader neuronal destabilization. Therefore, new motor complications unavoidably develop, resulting in L-DOPA-induced dyskinesia (LID), a very disabling long-term side effect of L-DOPA therapy associated with the loss of corticostriatal bidirectional plasticity [2].

The expression of an aberrant plasticity following chronic L-DOPA treatment has been also demonstrated in PD patients [3–5], further supporting the notion that a treatment with a drug able to ameliorate disease symptoms can be associated with the recovery of a selective form of synaptic plasticity.

This review provides an overview of papers that contributed to characterize the plastic changes occurring at striatal synapses in experimental models of LID. After a

description of the main forms of DA-dependent synaptic plasticity at glutamatergic corticostriatal synapses, we will introduce seminal studies focusing on the plastic changes observed in dyskinetic models. We will then review the most recent papers that further explored mechanisms underlying L-DOPA-induced changes in experimental PD models and discuss recent findings that, in our opinion, represent new promising avenues to future electrophysiological studies on dyskinetic animals.

2. DA-Dependent Synaptic Plasticity at Corticostriatal Synapses

At corticostriatal synapses, repetitive cortical activation can induce either LTD or LTP in the striatal medium spiny neurons (MSNs), depending on the level of membrane depolarization, the subtype of glutamate receptor activated [6–8], and the interneuronal subtypes involved in the induction process [9]. Unique characteristic of striatal neurons is that DA critically regulates both the induction and the maintenance of neuroplasticity via DA D_1-like (D_1) and D_2-like (D_2) receptors activation. Specifically, DA acting on D_1 receptors cooperates to the induction of LTP, whereas activation of both D_1 and D_2 receptors is required for LTD [2, 10, 11].

Electrophysiological studies in corticostriatal slices from 6-hydroxydopamine- (6-OHDA-) lesioned parkinsonian rats have shed light on the pivotal role that DA exerts in modulating glutamatergic transmission and synaptic plasticity within the striatum [12].

A complete DA denervation abolishes both forms of corticostriatal plasticity [11, 13] that can be restored by treatment with either DA receptor agonists or the DA precursor L-DOPA [2, 11, 14].

We have recently shown that distinct degrees of DA denervation influence the two forms of plasticity in different ways, as full DA denervation blocks the induction of both LTP and LTD, while partial DA depletion allows LTP induction but selectively alters its maintenance, leaving LTD induction unaffected [1].

A third form of striatal plasticity, distinct from LTD, called synaptic depotentiation, results from the reversal of an established LTP by the application of a low-frequency stimulation (LFS) of corticostriatal fibers [2, 15]. This form of plasticity critically relies on glutamatergic N-methyl-D-aspartate (NMDA) receptor activation [16] and striatal endogenous tone of acetylcholine [17]. During LTP, protein kinase A (PKA), a downstream effector of DA D_1 receptors, phosphorylates and activates DA- and cAMP-regulated phosphoprotein of 32 KDa (DARPP-32), a potent inhibitor of protein phosphatase 1 (PP-1). PP-1 dephosphorylates several downstream targets of PKA, thereby amplifying behavioral responses produced by activation of cAMP signalling [18–20], and it is necessary for depotentiation, as this form of plasticity is blocked by application of PP-1 inhibitors.

DA and glutamate receptors functional interaction in the striatum has been shown to regulate locomotion, positive reinforcement, attention, and working memory. In particular, activation of D_1 receptors is needed for the correct integration of cortical glutamatergic signals to the striatum [21]. In striatal MSNs, D_1 receptors are located within dendritic spines, where they colocalize with NMDA receptors [22, 23] regulate the rapid trafficking of NMDA receptor subunits [24] and the potentiation of NMDA responses [25], leading to activity-dependent adaptive changes [10] and also to the activation of excitotoxic pathways. Among the signalling cascades regulating D_1 receptor-dependent enhancement of NMDA responses in the striatum, the most important involves PKA- and DARPP-32-regulated phosphorylation of NMDA receptor NR1 subunits [26].

D_1 DA receptor stimulation also enhances phosphorylation of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor subunit GluR1 at the PKA site, increases surface expression of AMPA receptors, and facilitates their synaptic insertion in several brain areas [27, 28].

Besides the concurrent activation of glutamatergic and dopaminergic receptors, activity-dependent plasticity of glutamatergic synapses at MSNs is also modulated by other signalling pathways like endocannabinoids, adenosine (presynaptically), and metabotropic glutamate (pre- and postsynaptic) receptors [29] and by striatal interneurons [30, 31], which represent a minority of total striatal population but play a crucial role in the modulation of basal ganglia function, contributing to the processing of corticostriatal information [9, 13, 32]. In particular, two interneuronal subtypes have been suggested to play a critical role in the pathogenesis of LID: the large-aspiny cholinergic interneurons and the nitric-oxide-synthase- (NOS-) positive interneurons.

The cholinergic interneurons, which represent the main source of acetylcholine within the striatum [33], play a permissive role in corticostriatal synaptic plasticity by modulating the striatal cholinergic tone [9, 34]. These interneurons respond to cortical stimulations with long lasting changes of synaptic efficacy [17, 35] and are important sites of interaction among DA, adenosine, and endocannabinoid receptor signalling systems [36], further supporting the idea that cholinergic interneuronal activity contributes to striatal-dependent learning and motor habit formation.

The NOS-immunoreactive neurons represent, along with the cholinergic interneurons, the other interneuronal subtype that plays an important role in the induction of LTD [13, 31, 34]. These interneurons express mRNA encoding for ionotropic glutamate receptors that appear to be coupled to nitric oxide production [37–40]. Nitric oxide activates soluble guanylyl cyclase (sGC), which in turn induces increases of intracellular cyclic guanosine monophosphate (cGMP) levels to activate the protein kinase G (PKG) [41–43], whose levels are regulated by the action of phosphodiesterases (PDEs), a family of enzymes responsible for the conversion of cGMP to GMP. Accordingly, pharmacological LTD can occur in MSNs following the application of phosphodiesterases inhibitors [13], as a consequence of increased cGMP levels. In fact, the amount of this nucleotide is crucial for the activity of PKG and DARPP-32, which in turn control the phosphorylation

of AMPA receptor, a main player in the induction of LTD [10].

In summary, the integrative action exerted by striatal projection neurons on the converging information arising from the cortex, the nigral DA neurons and the striatal interneurons, shapes the activity of neurons throughout the entire basal ganglia circuitry.

3. L-DOPA-Induced Plastic Changes at Glutamatergic Synapses

The effects of L-DOPA administration in the DA-depleted striatum have been extensively studied in experimental models of LID, leading to the concept that a combination of presynaptic and postsynaptic maladaptive changes is needed for the parkinsonian animals to develop dyskinesia [3, 44, 45].

During progressive degeneration of nigrostriatal terminals, sprouting of DA terminals and reduced DA uptake contribute to preserve DA striatal levels [46], and increase in glutamate transmission is observed in corticostriatal pathway [47–51] as well as in basal ganglia output nuclei [52, 53].

However, such presynaptic adaptive changes together with changed presynaptic and postsynaptic DA receptor sensitivity and density lead to an altered substrate in which L-DOPA exerts its actions. Thus, initially, L-DOPA is converted into DA, stored in synaptic vesicles, and released by surviving DA-releasing terminals. However, when degeneration advances, DA catabolism and uptake are reduced and decarboxylation of L-DOPA to DA and release occur in nondopaminergic cells [54, 55], causing a failure in the buffering of DA levels.

The consequent large fluctuations in extracellular DA concentrations, mainly relying on the drug-dosing cycle, contribute to the establishment of further morphological and functional changes at both pre- and postsynaptic levels.

During chronic treatment with L-DOPA, several postsynaptic pathways downstream DA and glutamate receptors activation are progressively dysregulated, causing a loss of control of phosphorylation cascades with increase of phosphorylated striatal substrates such as NMDA receptor subunits [56, 57], AMPA receptor subunits [58], and extracellular signal-regulated kinase (ERK)1/2 [44, 58–60]. One crucial pathway that has been extensively investigated is the signalling activated by D_1 receptor stimulation [61]. In the DA-depleted striatum, in fact, chronic L-DOPA treatment, through stimulation of sensitized D_1 receptors causes hyperactivation of PKA and increased striatal phosphorylation of DARPP-32 at the threonine-34 residue [58, 62]. As above mentioned, this protein plays a pivotal role in the synaptic alterations caused by unphysiological stimulation of DA D_1 receptors. In fact, DARPP-32 is a potent inhibitor of PP-1 activity, which in turn is necessary to depotentiate the synapse.

A critical link between abnormal involuntary movements (AIMs), resembling human dyskinesia, and loss of bidirectional synaptic plasticity at corticostriatal synapses of dyskinetic rats has been firstly provided by our group [2, 63]. In the unilateral 6-OHDA model of PD, chronic treatment with either high or low doses of L-DOPA is able to restore LTP expression. However, in a consistent number of treated animals, the corticostriatal glutamatergic signalling undergoes further adaptive changes and AIMs develop [2, 64, 65]. Hyperphosphorylation of DARPP-32 at the threonine-34 residue occurs selectively in animals developing dyskinetic behavior and is associated to the loss of capability to depotentiate the corticostriatal synapse [2]. Moreover, in dyskinetic animals, prolonged L-DOPA treatment remarkably reduces synaptic D_1/NMDA receptor complexes without changing their interaction [23]. However, further complex molecular alterations take place at glutamatergic synapse that are strictly correlated to abnormal synaptic plasticity and motor behavior in L-DOPA-treated dyskinetic rats [2, 16]. Specifically, levels of NR2A subunit are higher in dyskinetic animals compared to nondyskinetic ones, and this effect is paralleled by decreased levels of NR_{2B} subunit, which are found increased in extrasynaptic sites [16]. Such redistribution of NMDA receptor subunits is associated with alterations in the binding of NMDA receptor subunits with their cargo proteins, in particular, SAP-97 and SAP-102 [16]. Impairment of the physiological trafficking of NMDA receptor subunits from the reticulum toward the postsynaptic density may, therefore, determine the enhancement of NMDA receptor signalling in dyskinesia.

Accordingly, pharmacological manipulation aimed at reducing synaptic localization of NR_{2B}, and consequently increasing NR_{2A}/NR_{2B} ratio at synaptic sites, causes in nondyskinetic subjects a worsening of motor symptoms with appearance of dyskinetic behaviours [16]. Intracerebral administration of a cell-permeable peptide (TAT2B), able to alter the NR_{2B} synaptic localization by perturbing its binding with scaffolding proteins, causes loss of depotentiation that correlated with AIMs in nondyskinetic animals [16].

Taken together, these findings support the notion that abnormal activation of PKA and concomitant hyperphosphorylation of DARPP-32 observed in experimental models of LID are two of the main causes of changes in the state of phosphorylation state of target effector proteins, with consequent profound repercussion on the excitability and plasticity of striatal MSNs.

4. Novel Insights into L-DOPA-Induced Changes in Corticostriatal Synaptic Plasticity

Three new studies have investigated further on the mechanisms underlying the loss of synaptic scaling down at corticostriatal synapses.

Gardoni and coworkers have recently shown that pharmacological manipulations interfering with the interactions between NMDA receptor subunits and their scaffolding proteins, responsible for their trafficking and correct assembly at synaptic membranes, prevents the unbalance of NR_{2A}/NR_{2B} subunit ratio by reducing the synaptic localization of NR_{2A} subunit. Systemic coadministration of the cell-permeable

peptide TAT2A and L-DOPA reduces the percentage of animals developing dyskinesia [66]. However, once the AIMs are established, the administration of TAT2A fails to reduce incidence of dyskinesia, indicating that altered NMDA receptor composition has a critical role in initiating the dyskinetic phenotype. Moreover, these data support the concept that molecular disturbances of the glutamatergic synapse, initially caused by DA denervation, create a pathological substrate that induce and maintain the overworking synapse at an altered steady state that triggers the development of LID [2, 16].

A further advance in the characterization of bidirectional synaptic plasticity following L-DOPA therapy has been made in a recent study conducted by our group. Based on the evidence that striatal cGMP signalling is decreased in dyskinetic animals [67], we explored the possibility that LTD, which strictly relies on the nitric oxide-dependent activation of PKG, was altered following L-DOPA treatment. We found that MSNs recorded from L-DOPA-treated dyskinetic parkinsonian rats do not express activity-dependent LTD. Increase of cGMP levels by PDEs inhibitors leads to the activation of PKG, mimicking the action of nitric oxide released from NOS-positive neurons that represents a critical factor for LTD induction following HFS [13]. Accordingly, application of a low dose of PDEs inhibitor, unable to induce *per se* a pharmacological LTD in dyskinetic parkinsonian rats, is sufficient to rescue activity-dependent LTD in these animals.

Interestingly, application of PDEs inhibitors induces pharmacological LTD in both dyskinetic and nondyskinetic rats but not in untreated parkinsonian animals, indicating that the presence of endogenous striatal DA represents a critical condition also for the induction of this form of pharmacological plasticity. Local injection of these drugs into the striatum of dyskinetic rats rescues LTD and reduces the dyskinetic response to L-DOPA [62].

This phenomenon, together with the loss of depotentiation [2], is in line with the view that LID is caused by impaired control of striatal excitatory synapses with excessive increase of glutamatergic transmission.

Accordingly, the third study by Usiello and coworkers investigated the contribution of a basal hyperglutamatergic tone in the development of dyskinesia associated to altered DA-dependent bidirectional synaptic plasticity.

Using mutant mice lacking the D-Aspartate Oxidase (Ddo) enzyme ($Ddo^{-/-}$ mice), showing nonphysiological high levels of the excitatory free D-amino acids D-aspartate and NMDA [68], they found that a condition of persistent hyperstimulation of glutamatergic transmission results in an aberrant striatal synaptic plasticity. In the MSNs recorded from $Ddo^{-/-}$ mice, similar to what observed in dyskinetic animals, LFS protocol fails to reverse the synaptic transmission levels to those preceding LTP.

When subjected to 6-OHDA lesion, $Ddo^{-/-}$ mice display increased sensitivity to L-DOPA and early onset of dyskinetic behavior [69] further supporting the concept that increased glutamatergic release is a critical risk factor to develop LID.

5. New Promising Avenues to Further Investigate L-DOPA-Induced Corticostriatal Plastic Changes

In the recent past, new molecular targets for LID have been explored that may play a critical role in the synaptic alterations underlying plastic changes in the DA-depleted striatum exposed to long-term L-DOPA. An important contribution to the understanding of mechanisms involved in the development of dyskinesia has been provided by the evidence that not only ERK but also its downstream targets, including molecules involved in the regulation of protein translation and gene transcription [60, 70], are entailed in the dysregulation of phosphorylation cascades induced by L-DOPA. The group of Fisone and coworkers has recently demonstrated that abnormal activation of ERK is associated to increased signalling of mammalian target of rapamycin complex 1 (mTORC1) via inhibitory control of tuberous sclerosis complex (TSC) 1 and 2 that, in turn, suppresses activation of Ras homolog enriched in brain (Rheb), a highly conserved member of the Ras superfamily of G-proteins, ultimately responsible for mTORC1 activity. Coadministration of L-DOPA and rapamycin, a selective allosteric inhibitor of mTOR complex, diminishes the development of LID without interfering with the therapeutic effects of L-DOPA [56]. Recently, it has been shown that besides Rheb, another small G protein, the Ras homologue enriched in striatum (Rhes), is critically involved in the pathological upregulation of mTORC1 during LID [71]. These data further strengthen the hypothesis of an involvement of mTORC1 signalling in LID, as Rhes knockout mice show reduced dyskinesia in response to L-DOPA, but the therapeutic improvement of limb motion remains unchanged. Interestingly, a role of mTORC1 in synaptic plasticity has been recently put forward [72]. Relevant to corticostriatal pathway, it has been shown that inhibition of mTORC complexes is able to block a pathological form of persistent LTP associated to increased glutamatergic signalling and neurodegeneration [73].

Taken together, these data suggest that enhanced mRNA translation, leading to abnormal local protein synthesis in the cytoplasm, may participate in the development of aberrant enhancement of synaptic strength, as observed in LID.

Another intriguing aspect that has been recently investigated is the capability of L-DOPA to exert its action through nondopaminergic systems. Indeed, as PD progresses, degeneration of nigrostriatal terminals also advances, and L-DOPA is converted in DA, stored, and released also from other cellular elements within the striatum, including the serotonin (5-HT) terminals [54, 74, 75]. This action might have both beneficial and detrimental consequences in that it allows L-DOPA to maintain DA levels in the virtual absence of dopaminergic neurons but it also enhances the non-physiological DA receptor stimulation as the feedback control of DA release is absent in the 5-HT system. This might have important implications for corticostriatal synaptic plasticity as unregulated DA transmission may induce further adaptive rearrangement of DA/glutamatergic

ionotropic receptors interactions at postsynaptic sites that would critically affect the bidirectional synaptic plasticity.

The hypothesis of the involvement of 5-HT terminals in LID has gained support from recent evidence showing that lesion of the 5-HT system by 5,7-dihydroxytryptamine [75] or pharmacological manipulation of serotoninergic transmission [54, 74] significantly reduces L-DOPA-induced increase of extracellular DA levels in the striatum and abolishes dyskinetic movements in parkinsonian rats chronically treated with L-DOPA [54]. However, decrease of corticostriatal glutamate release could be another mechanism underlying additional antidyskinetic effect [76–78].

A potent synergistic interaction between 5-HT_{1A} and 5-HT_{1B} receptors in counteracting the induction of dyskinetic movements has also been demonstrated in the 1-methyl-4-phenyl 1,2,3,6-tetrahydropyridine- (MPTP-) treated macaques, in which administration of 5-HT_{1A} and 5-HT_{1B} agonists reduces the upregulated levels of FosB, the main postsynaptic striatal marker for LID [79, 80].

Most recently, it has been demonstrated that profound structural changes are associated to the capability of serotoninergic terminals to release DA as "false transmitter." Cenci and coworkers provided evidence that L-DOPA treatment induces the sprouting of 5-HT axon terminals (increased number of synaptic contacts between 5-HT terminals and striatal neurons) [55]. This specific morphological feature positively correlates with the severity of dyskinesia as shown by increased binding levels of the plasma membrane 5-HT transporter in both experimental models (rodents and nonhuman primates) and in PD patients subjected to L-DOPA therapy. Such increase was correlated with the dyskinetic score and paralleled by the upregulation of brain-derived neurotrophic factor (BDNF) expression [55, 81], which exerts complex functional and structural actions within the striatum.

These results are consistent with the evidence that increased concentrations of striatal BDNF are associated with LID [82] although the role of this neurotrophin in LID development is still under debate [83].

A link between BDNF and LID is also suggested by the fact that striatal BDNF is regulated by the activity of another nondopaminergic pathway involved in the development of LID, the striatal purinergic system. Indeed striatal adenosine, through A_{2A} receptors, has been suggested to play a pivotal role in the regulation of BDNF function and levels in the brain [84, 85] and it has been also implicated in the development of LID [86].

Presynaptically, A_{2A} receptors act to finely tune glutamate release from corticostriatal terminals and they are also present postsynaptically on striatopallidal MSNs of the indirect pathway that express DA D_2 receptors.

In control condition, concomitant activation of DA D_2 receptors and blockade of A_{2A} adenosine receptors is able to decrease striatal glutamatergic transmission [87]. This interaction is made possible by a retrograde action of endocannabinoids released by postsynaptic MSNs and acting on CB1 cannabinoid receptors located on glutamatergic terminals [36] suggesting that the convergence of DA D_2 and A_{2A} signalling systems on the endocannabinoids pathway represents a potent feedback mechanism to control glutamatergic transmission in the striatum. While in control condition, concurrent activation of D_2 and blockade of A_{2A} are necessary to reduce glutamate release via an endocannabinoid-dependent mechanism, in DA-depleted animals, D_2 receptor agonism alone is able to reduce glutamatergic transmission due to D_2 receptor sensitization. This effect could be further enhanced by A_{2A} receptor antagonists providing a solid experimental support for the combined use of D_2 receptor agonists and A_{2A} receptor antagonists in clinical settings. In fact, alterations in A_{2A} receptor expression and signalling have been extensively observed in PD patients undergoing L-DOPA therapy and in experimental models of LID and A_{2A} antagonists have proven to be effective in clinical and preclinical studies [86].

Notably, striatal cholinergic interneurons, coexpressing D_2 and A_{2A} receptors, are also interested in this pharmacological modulation, since concomitant activation of D_2 DA receptors and blockade of A_{2A} receptors reduces the firing rate of this neuronal subtype and muscarinic M_1 receptor antagonism blocks the D_2/A_{2A} receptor-mediated modulation of excitatory transmission in both D_2- and D_1-expressing MSNs [36]. These results are in agreement with previous studies showing altered acetylcholine signalling in DA-denervated striatum [88] resulting in a loss of feedback control of acetylcholine release [89]. Striatal acetylcholine levels critically determine the direction of synaptic plasticity at corticostriatal synapses with low levels of acetylcholine facilitating LTD and high levels facilitating LTP [90].

Taken together, these data suggest a strong involvement of the striatal cholinergic interneurons in LID pathogenesis. A recent paper [91] shows that in animals lacking the transcription factor Pitx3, modeling PD, chronic L-DOPA enhances baseline and DA-induced firing rate in striatal cholinergic interneurons. This effect is seen also in 6-OHDA-lesioned mice and is associated with increased phospho-ERK immunoreactivity in this neuronal population as inhibition of ERK is able to restore firing rate at control values [91]. In both the unilateral lesion and the genetic models, chronic L-DOPA caused development of LID that was attenuated by administration of dicyclomine, a muscarinic antagonist, without affecting L-DOPA's beneficial antiparkinsonian action.

These findings provide new lines of evidence that L-DOPA exerts its widespread action at multiple levels in the functional organization of the striatum (Figure 1). However, a clear-cut definition of a scenario comprising the various maladaptive changes is made difficult by the fact that striatal response to DA-denervation and subsequent DA replacement may vary between the two distinct populations of striatal projecting neurons, the striatopallidal and the striatonigral MSNs, with the latter population being more consistently involved in LID induction, as suggested by some recent reports [61, 70, 92]. A recent *in vivo* electrophysiological study has given substantial foundation to the distinction between direct and indirect pathways suggesting that a range of different dysfunctional changes in these two populations of projecting neurons may concur to the induction of LID. One interesting aspect that comes out from this paper is

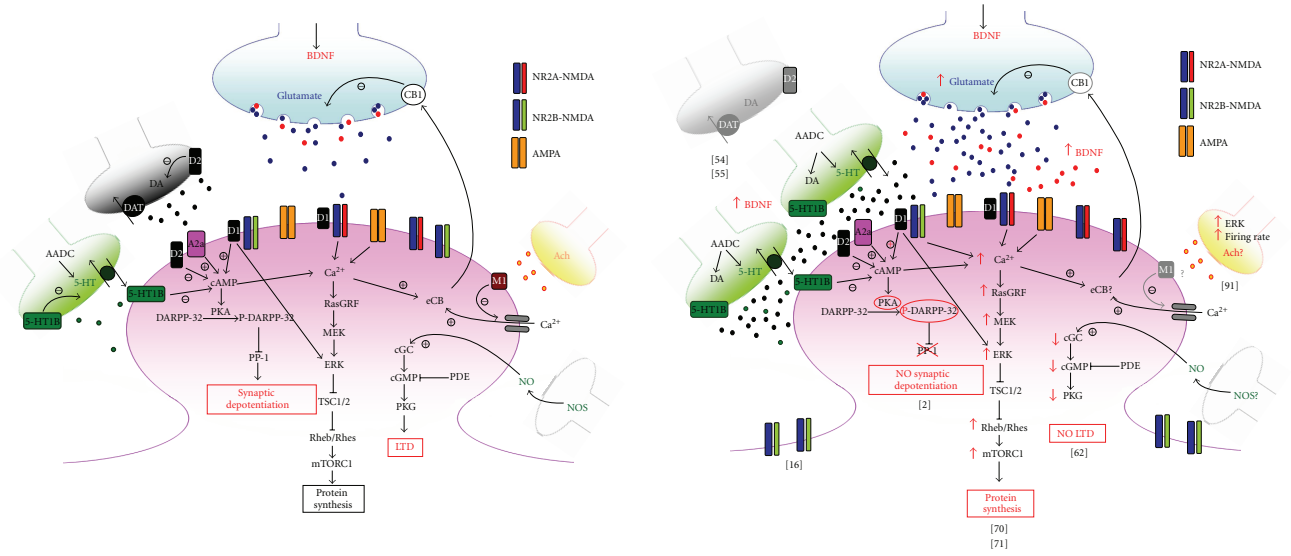

FIGURE 1: (a) In control condition, dopamine (DA) transmission is regulated by feedback control of release from nigrostriatal terminals (black) through D2 autoreceptors and uptake processes. DA binds striatal postsynaptic D1 receptors inducing the formation of cAMP, which in turn favours the activation of PKA, able to phosphorylate and activate DA- and cAMP-regulated phosphoprotein of 32 KDa (DARPP-32) and extracellular signal-regulated kinase (ERK). Once phosphorylated, DARPP-32 is able to inhibit protein phosphatase 1 (PP-1). Glutamate (blue) and BDNF (red) are released from corticostriatal terminals into the striatum. Glutamate release is regulated by endocannabinoids (eCB) activated by increases in intracellular calcium (Ca^{2+}) concentrations through adenosine A2a and muscarinic M1 receptors activation, among other mechanisms, and retrogradely released by postsynaptic striatal neurons. Once released, glutamate activates metabotropic as well as NMDA and AMPA ionotropic receptors, whose activity and surface expression at postsynaptic membrane is also regulated by D1 receptors. In serotoninergic afferents, 5-hydroxytryptophan is converted to serotonin (5-HT) (green) by Aromatic-L-Amino Acid Decarboxylase (AADC) and released into the striatum. Cholinergic and nitric oxide synthase (NOS)-positive interneurons cooperate to induction of corticostriatal LTP and LTD. (b) In dyskinetic state L-DOPA is converted to DA by AADC and released from serotoninergic terminals in unregulated manner. Higher levels of striatal BDNF may support morphological changes in serotoninergic neurons. Excess of DA abnormally stimulates D1 pathway with hyperphosphorylation of ERK and uncontrolled activation of PKA that results in hyperphosphorylation of DARPP32, which persistently blocks PP-1 causing loss of synaptic depotentiation. Abnormal D1 receptor stimulation is associated to increased intracellular Ca^{2+} levels and dysregulation of NMDAR subunit composition with reduction of NR2B-containing NMDAR at synaptic sites, leading to increase in NR2A/NR2B ratio that has been suggested to have a role in the loss of depotentiation. Hyperactivation of ERK through convergent altered signalling pathways brings to increased inhibition of tuberous sclerosis complex (TSC)1/2, and consequent disinhibition of Rheb/Rhes, leading to excessive increase of signalling of mTORC1 that, in turn, exerts its long term effects through changes in protein synthesis. After chronic L-DOPA, cholinergic interneurons show increased phospho-ERK immunoreactivity and higher firing rates with increased release of acetylcholine (Ach). Striatal cGMP signalling is decreased and corticostriatal LTD, which strictly relies on the nitric-oxide- (NO-) dependent activation of protein kinase G (PKG) is abolished in dyskinetic state.

that also striatopallidal neurons present specific alterations of synaptic plasticity in response to L-DOPA, although the study leaves open unresolved questions regarding the relevance of these findings for *in vivo* behavior [93].

Besides the distinct contribution of direct and indirect pathways to LID, several lines of evidence support the idea that also striatal regional compartmentalization matters in the response to L-DOPA. Within the striatum, it is possible to distinguish two compartmentalizations, whose activation can be modulated by striatal interneurons: the matrix, including the direct and indirect pathway MSNs that form parts of sensorimotor and associative circuits, and the striosomes, which contain MSNs that receive input from parts of limbic cortex and project directly or indirectly to the dopamine-releasing neurons of the *substantia nigra pars compacta*.

An interesting recent review has strengthened this idea, discussing the role of imbalances between striatal striosome and matrix functions in relation to neurodegenerative disorders, including LID [94]. Findings in support of this idea may have important implications in the perspective of considering PD and LID as network disorders that cause a range of motor and nonmotor symptoms.

6. Concluding Remarks

We have discussed seminal and recent papers that explored the mechanisms underlying the establishment of aberrant forms of synaptic plasticity at glutamatergic corticostriatal synapses in LID experimental models. We have also provided an overview of recent studies dealing with novel aspects of the multifaceted L-DOPA effect. Taken together, all the reviewed studies strongly support the notion of a failure of the principal scaling down mechanisms at corticostriatal synapses as a major mechanism in the development of LID.

The scenario emerging from these findings is predictive of a more complex pattern of altered plasticity that involves structural and functional changes within the striatal circuitry and opens new perspectives for future electrophysiological investigations.

Acknowledgment

This work was supported by a grant from European Community contract number 222918 (REPLACES) FP7-Thematic priority HEALTH (PC).

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Hindawi Publishing Corporation
Parkinson's Disease
Volume 2012, Article ID 473769, 8 pages
doi:10.1155/2012/473769

Review Article

Dyskinesias and Treatment with Pramipexole in Patients with Parkinson's Disease

John C. P. Piedad[1,2] and Andrea E. Cavanna[1,3]

[1] *Michael Trimble Neuropsychiatry Research Group, University of Birmingham and BSMHFT, Birmingham, UK*
[2] *Department of Neuropsychiatry and Barberry National Centre for Mental Health, University of Birmingham and BSMHFT, 25 Vincent Drive, Birmingham B15 2FG, UK*
[3] *Sobell Department of Motor Neuroscience and Movement Disorders, UCL, Institute of Neurology, London WC1N 3BG, UK*

Correspondence should be addressed to Andrea E. Cavanna, a.cavanna@ion.ucl.ac.uk

Received 1 July 2011; Revised 30 October 2011; Accepted 14 November 2011

Academic Editor: Gilberto Fisone

Dopamine agonists such as pramipexole (PPX) have first been proposed as adjunctive treatment to levodopa (L-DOPA) for patients with Parkinson's disease (PD) and then as a monotherapy alternative to alleviate dyskinesia. Treatment with PPX has overall been associated with improvement in parkinsonian symptoms. Although the majority of placebo-controlled studies demonstrated that dyskinesia was more prevalent in the PPX compared to the placebo groups, some studies did not detect any dyskinesia as a side effect of this medication. PPX was consistently associated with lower risk for developing dyskinesia compared to L-DOPA. Moreover, the presence of these symptoms in the placebo groups suggests involvement of non-PPX-related factors for developing dyskinesia. It is suggested that future research should aim at ascertaining whether cotherapy with L-DOPA, PPX dosage, and other patient characteristics are contributory factors for the development of PPX-related dyskinesia in patients with PD.

1. Dyskinesia in Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disease characterised by motor (particularly tremor, rigidity, and bradykinesia) as well as cognitive and behavioural symptoms. The pathophysiology of PD has been related to the degeneration of nigrostriatal dopaminergic pathways [1], and this has allowed the treatment for PD to be targeted towards modulating dopamine (DA) neurotransmission (Figure 1).

Levodopa (L-DOPA) has long been the mainstay of PD treatment although over time patients on L-DOPA develop motor complications including dyskinesias, which are associated with the timing of drug administration. Dyskinesias are involuntary muscular contractions and include choreic, dystonic, myoclonic, and tic movements [2]. After 5 and 10 years of L-DOPA therapy, 91% and all of the participants in a longitudinal cohort ($N = 99$), respectively, experienced dyskinesias [3]. Another study also identified that cumulative L-DOPA dosage was significantly associated with the development of dyskinesia [4].

Given that dyskinesias has been consistently shown to negatively affect patients' quality of life [5, 6], there is considerable debate on how to forestall its onset, including initial treatment with another class of drugs: the dopamine receptor agonists (DAAs) [7, 8]. Pramipexole (PPX) belongs to this drug class and is selective for the D_2-like receptor subfamily, particularly the D_3 compared to the D_2 and D_4 subtypes [9]. Following the observation by Hauser et al. [4] that treatment with PPX was significantly associated with later onset of dyskinesia, we carried out a systematic literature review to examine the effects of PPX therapy on dyskinetic events in patients with PD.

2. Literature Search Methodology

This paper systematically reviews the existing evidence on the development of dyskinesia during PPX therapy for PD. We performed a literature search across the databases Medline, EMBASE and PsycInfo via the NHS Evidence tool (http://www.library.nhs.uk). We used the search terms

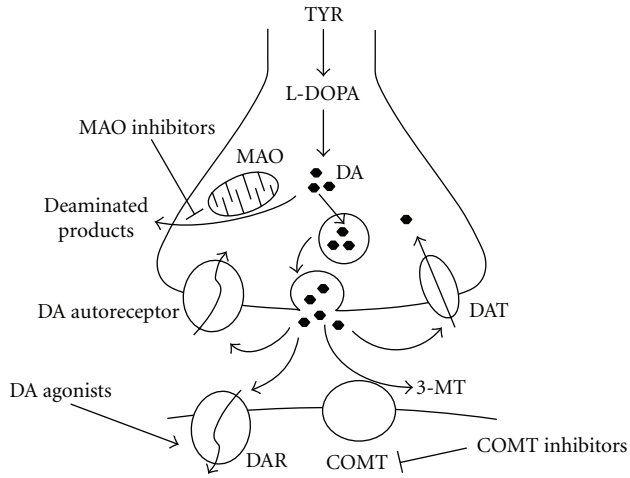

Figure 1: Treatment of Parkinson's disease: anti-Parkinson's medications modulate key stages of dopaminergic neurotransmission. Abbreviations: TYR: tyrosine, L-DOPA: L-3, 4-dihydroxyphenylalanine, DA: dopamine, MAO: monoamine oxidase, DAT: DA reuptake transporter, COMT: catechol-O-methyltransferase, 3-MT: 3-methoxytyramine, DAR: DA receptor. Anti-Parkinson's drugs are highlighted in bold. Pointed arrows indicate stimulatory, and closed arrows indicate inhibitory activity.

"Parkinson*," "dyskinesi*," and "pramipexole". The Cochrane Library was also searched for randomised and double-blind human trials of PPX in patients with PD. We limited our search to papers published in English language.

3. Pramipexole-Placebo Comparisons

The majority of the studies on PPX included in this review were comparisons with placebo only (Table 1). Six out of ten of these studies found that dyskinesia in PPX-treated patients was prevalent, at a higher rate than in the placebo group. The incidence of dyskinesia was 7.0–61.3% and 3.0–40.8% in the PPX and placebo groups, respectively [10–15]. The differences in rates of dyskinesia were between 4.9 and 20.5%. Two of these studies had follow-up data. An extension to the Lieberman et al. [10] protocol by up to 50 months was carried out, in which both PPX and placebo groups were retitrated onto open-label PPX [16]. Out of the sample ($N = 306$), 61.1% reported dyskinesias, but there were no related discontinuations. Furthermore, UPDRS IV scores remained below the baseline values, indicating some improvements in these symptoms. Möller et al. [13] reported an open-label extension to their study of up to 57 months follow-up. Out of their cohort, 34.4% ($N = 262$) developed dyskinesias. This led to study discontinuation in 2.3% of participants. Two studies reported the incidence of dyskinesia to be higher with the placebo than the PPX groups: 0.6% versus 0.0% [17] and 6.1% versus 5.6% [18]. However, it should be noted that the strength of such evidence is weak. One study [17] was specifically designed to assess the antiparkinsonian properties in early PD, rather than the potential dyskinetic effects of pramipexole. The other one [18] found 2 dyskinetic patients in a group of 33 patients treated with placebo and 2 dyskinetic patients in a group of 36 patients treated with PPX. Of note, a further study failed to identify participants who experienced dyskinesia with PPX treatment or placebo [19, 20].

In terms of neurological scales as a measure of dyskinesia, Lieberman et al. [10] reported that % change in UPDRS IV scores was significantly ($P < .0001$) higher in the PPX group compared to the placebo group. Changes in the PDS were not statistically significant. These exact patterns in UPDRS IV and PDS scores were reproduced by Pinter et al. [11] and Möller et al. [13]. In these studies, however, the incidence of dyskinesia was higher with PPX treatment than placebo. Wermuth et al. [18] did not find significant changes in UPDRS IV or PDS scores. In a cross-over design with PPX and placebo, as well as L-DOPA infusion before and after the switch-over, Brodsky et al. [32] found that PPX treatment increased PDS scores to statistically significant levels ($P = .05$). Furthermore, L-DOPA infusion also increased peak dyskinesia scores.

4. Studies with Active Comparators

4.1. Pramipexole Only. There have been two studies comparing different dosages and other two looking at different preparations of PPX. One of the earliest investigations on PPX was carried out by the Parkinson Study Group [21], which compared four different dosages of the drug (1.5, 3.0, 4.5, and 6.0 mg) against placebo. Another study by the same group compared different low-dose schedules of PPX [21]. Both did not detect any incidence of dyskinesia. Likewise, comparisons of immediate release (IR) and extended release (ER) PPX preparations failed to detect any incidence of dyskinesia symptoms in either treatment or placebo group [26, 27].

4.2. Pramipexole versus Other Dopamine Agonists. Other DAAs have been compared with PPX. Two studies reported a comparison with bromocriptine (BRC), showing that dyskinesias were found more often with DAAs compared with placebo. In terms of UPDRS IV and PDS scores, there were no significant changes in one trial [29], whereas, in

Table 1: Dyskinesia with pramipexole treatment: summary of double-blind randomised-controlled trials of pramipexole in Parkinson's disease.

Disease stage*	Study	Drug regimen (N): mean daily dose, mg (SD/range)	Incidence of dyskinesia (%), change in UPDRS IV or PDS (%)	Concomitant L-DOPA (% usage and/or mean dose, mg (SD/range))	Other concomitant APDs	Study duration	PPX group characteristics: H-Y stage, age, disease duration (mean (SD))
Early	Hubble et al. [20]	PPX (28), PL (27): 4.5	None	None	MAOBI	9 wks	1–3, 63.5 (12.3), 2.1 (2.5)
	PSG [21]	PPX (213), PL (151): fixed dose at 1.5, 3.0, 4.5, 6.0	None	PPX: 24.4%, PL: 27.5%	MAOBI	10 wks	1–4 (1.9, 0.6), 62.0 (10.9), 2.0 (1.6)
	Shannon et al. [17]	PPX (164): 3.8, PL (171): 0.375–4.5	PPX: 0%, PL: 0.6% (leading to discontinuation)	None	MAOBI	31 wks	1–3, 62.7, 1.8
	PSG [22]†	PPX (151): 1.5–4.5, L-DOPA (150): 300–600	PPX: 9.9%, L-DOPA: 30.7% (HR 0.33 (95% CI, 0.18–0.60); $P < .001$)-↑66.7% (PPX), ↑82.6% after O/L L-DOPA	Part of study intervention	MAOBI, amantadine, AC	23.5 mos	1–3 (82.8% ≤ 2), 61.5 (10.1), 1.5 (1.4)
	Pogarell et al. [19]	PPX (44), PL (39): 0.375–4.5	None	PPX: 11%, PL: 13%	MAOBI and amantadine	11 wks	1–3 (72.7% ≤ 2), 62.0 (10.1), 6.5 (4.0)
	Navan et al. [23]	PPX, PGL, PL (10): 4.5	PPX: 10.0%, PGL: 10.0%, PL: 0.0%	PPX: 60%, 400 (200–600), PGL: 60%, 383 (300–700), PL: 40%, 550 (300–800)	MAOBI, amantadine, and AC	3 mos	1-2 (1), 66 (55–80), 4 (0.5–10)
	Wong et al. [12]	PPX (73), PL (77): 0.375–4.5	PPX: 12.3%, PL: 5.2%	PPX: 68.5%, PL: 70.1%	None	15 wks	2.2 (0.07), 58.8 (1.28), 4.5 (0.4)
	PSG [24]†	PPX (83): 2.78 (1.1), L-DOPA (100): 427 (112)	PPX: 24.5.5, L-DOPA: 54.0 (HR 0.37 (95% CI 0.25–0.56); $P < .001$)	PPX: 434 (498), L-DOPA: 274 (442)	MAOBI, amantadine, AC	4 yrs	1–3 (79.5% ≤ 2), 61.1 (9.6), 1.4 (1.3)
	Navan et al. [25]	PPX (9): 3.09, PGL (8): 3.0, cross-over	PPX: 33.3%, PGL: 37.5%	52.9%; 544 (300–1000)	AC	12 wks–9 wks cross-over	1-2 (1.4), 68.4 (55–84), 3.9 (0.2–12.0)
	Barone et al. [15]	PPX (139): 2.18 (0.83), PL (148): 2.51 (1.66)	PPX: 7%, PL: 3%	PPX: 76%, PL: 74%	Amantadine, MAOBI, ACI, and ODD	12 wks	1–3 (79% ≥ 2), 67.4 (9.0), 4.0 (4.5)
	Hauser et al. [26]	PPX IR (103), PPX ER (106), PL (50): 0.375–4.5	None	PPX IR: 1.0%, PPX ER: 2.9%, PL: 14.0%	None	18 wks	1–3 (72.3% 2-3), 61.8 (8.9), 1.0 (1.3)
	Rascol et al. [27]	PPX IR (52), PPX ER (104): 1.5–4.5	None	PPX IR: 51.9%, PPX ER: 56.7%	MAOBI, COMTI, AC, and amantadine	4 wks IR + 9 wks IR/ER	1–3 (80.8% 1-2), 63.7 (9.1), 3.3 (2.0)
	PSG [28]	PPX 0.5 bd (81), 0.75 bd (73), 0.5 td (80), PL (77)	None	None	MAOBI, AC, and amantadine	12 wks	1–2.5 (89.7% 1-2), 63.3 (10.0), 2.6 (2.6)

Table 1: Continued.

Disease stage*	Study	Drug regimen (N): mean daily dose, mg (SD/range)	Incidence of dyskinesia (%), change in UPDRS IV or PDS (%)	Concomitant L-DOPA (% usage and/or mean dose, mg (SD/range))	Other concomitant APDs	Study duration	PPX group characteristics: H-Y stage, age, disease duration (mean (SD))
Advanced	Guttman et al. [29]	PPX (79): 3.4, BRC (84): 22.6, PL (83)	PPX: 40%, BRC: 45%, PL: 27%; NS changes in UPDRS IV and PDS	100%	AC, amantadine, and MAOBI	9 mos	2–4, 62.9 (10.0), 0.67–36
	Lieberman et al. [10]	PPX (181), PL (179): 0.375–4.5	PPX: 61.3%, PL: 40.8%; UPDRS IV PPX > PL ($P < .0001$), PDS PPX > PL (P = NS)	100%; PPX: 843.4 (578.9), PL: 819.2 (466.1)	MAOBI and amantadine	31 wks	2–4 (3.0), 63.4, 9.4
	Wermuth et al. [18]	PPX (36): 4.59 (0.95), PL (33): 4.77	PPX: 5.6%, PL: 6.1%; NS change in PDS; NS change in UPDRS IV	PPX: 100% (61.1% > 600), PL: 100% (66.7% > 600)	MAOBI, ACI, and amantadine	11 wks	2–4 (91.7% 2-3),63.2 (7.9), 10.1 (5.0)
	Pinter et al. [11]	PPX (34), PL (44): 0.2–5.0	PPX: 14.7%, PL: 4.5%; UPDRS IV PPX > PL ($P = .0092$); PDS PPX < PL (P = NS)	PPX: 26.5% (11.8% > 600), PL: 34.1% (18.2% > 600)	MAOBI and amantadine	11 wks	2–4 (79.4% ≥ 3), 59.3 (8.3), 7.8 (4.3)
	Mizuno et al. [30]	PPX (102): 3.24 (1.33), BRC (105): 17.8 (5.8), PL (108)	PPX: 15.7%, BRC: 8.6%, PL: 5.6%; UPDRS IV PPX < PL ($P = .006$), PPX ≈ BRC (P = NS)	PPX: 404.9 (275.2), BRC: 377.9 (237.8), PL: 422.4 (330.3)	ACI, amantadine, ODD, and MAOBI	12 wks	2.7 (0.7), 65.5 (9.5), 4.8 (4.2)
	Möller et al. [13]	PPX (168): 3.7, PL: 0.375–4.5	PPX: 30.0%, PL: 8.7%; UPDRS IV PPX > PL ($P = .0114$), PDS ($P = NS$)	PPX: 637.7, PL: 648.8	MAOBI and AC	31 wks	1–4 (85.0% 2-3), 63.4, 7.6
	Poewe et al. [31]	PPX (200): 3.1 (1.2), RTG (201): 13.0 (3.5), PL (100)	PPX: 15%, RTG: 12%, PL: 3%; hrs "on" without troublesome dyskinesia PPX > PL ($P. = 0429$), PPX < RTG (P = NS)	PPX: 813 (459), RTG: 795 (380), PL: 814 (398)	AC, COMTI, amantadine, and MAOBI	23 wks	2–4, 63.2 (9.7), 8.4 (4.7)
	PSG [14]	PPX (109), PL (35): 0.375–4.5	PPX: 21.1%, PL: 11.4%	100%; PPX: 278.9 (211.6), PL: 272.9 (204.1)	NR	10 wks	2–4 (2.5, 0.5), 64.8 (10.6), 6.1 (5.1)
	Brodsky et al. [32]	PPX/PL cross-over (13): 3.0	PPX ↑ PDS scores compared to baseline ($P. = 05$), ↑ peak scores with L-DOPA infusion	100%, 871.2 (448.6); + infusion at 5 + 10 wks	Unclear on which APDs	10 wks–5 wks cross-over	NR, 61.9 (8.0), 10.3 (4.3)

* Studies were categorised according to the disease stage (early versus advanced, plus Hoehn and Yahr stage, where available).

Abbreviations: *N*: number of patients, SD: standard deviation, PSG: Parkinson Study Group, NR: not reported, HR: hazard ratio (risk ratio of developing dyskinesia per unit of time for patients assigned to PPX compared to risk ratio for L-DOPA), CI: confidence interval, †the report by PSG [22] is an extension of the PSG [31] protocol, H-Y stage: Hoehn-Yahr stage (a staging system to describe PD progression from 0 to 5 with stages 1.5 and 2.5 in the modified version, incorporated into the UPDRS), PPX: pramipexole, PL: placebo, BRC: bromocriptine, L-DOPA: levodopa (with or without carbidopa), PGL: pergolide, RTG: rotigotine, APDs: anti-Parkinson's drugs, MAOBI: monoamine oxidase-B inhibitors (e.g., selegiline), AC: anticholinergics (e.g., orphenadrine, benzhexol), ODD: other dopaminergic drugs (e.g., droxidopa), UPDRS IV: Unified Parkinson's Disease Rating Scale part IV (complications of therapy, higher scores indicate more severe dyskinesia), which also includes subitems on dyskinesia symptoms [33], PDS: Parkinson's Dyskinesia Scale (higher scores indicate more severe dyskinesia), which rates the severity of dyskinesia according to body regions [34].

the other, % UPDRS IV score changes were significantly lower in the PPX compared to the placebo group [30]. When comparing PPX and BRC, Guttman et al. [29] found that the incidence of dyskinesia between these treatment groups was approximately similar (5% difference). On the other hand, dyskinesia was found to be nearly twice as prevalent with PPX treatment compared to BRC [30].

Two studies compared pergolide (PGL) with PPX. One of these studies found that dyskinesia was equally prevalent with PPX and PGL ($N = 1$) but was not reported in the placebo group [23]. Another trial by the same group with a cross-over design found an overall lower incidence of dyskinesia with PPX treatment than PGL: 33.3% versus 37.5% [25]. Transdermally administered rotigotine (RTG) was also compared with PPX [31]. The placebo group had less dyskinesia than the active treatment groups, with PPX having slightly higher incidence than RTG (3% versus 15% versus 12%). Furthermore, this group reported that participants in the PPX group had significantly more time in the day "on" without troublesome dyskinesias compared to placebo ($P = .0429$), whereas the difference between PPX and RTG was not significant.

4.3. Pramipexole versus L-DOPA. Only one cohort was involved with a trial comparing PPX and L-DOPA. The first report was the two-year completion of initial treatment with PPX and L-DOPA, with open-label L-DOPA for emerging disability [22]. There was a significantly lower incidence of dyskinesia in the PPX compared to the L-DOPA group: 9.9% versus 30.7%, hazard ratio (HR) 0.33 (confidence interval (CI) 0.18–0.60), $P < .001$. Some of the participants who completed the two-year trial were also enrolled for a further two-year follow-up study, with the randomised and blinded protocol maintained [24]. This showed a similar pattern of the incidence of dyskinesia, which was significantly lower in the PPX ($N = 83$) compared to the L-DOPA ($N = 100$) group: 24.5% versus 54.0%, HR 0.37 (95% CI 0.25–0.56), $P < .001$. None of the PPX cohort withdrew from follow-up due to dyskinesia, whereas dyskinesia-related discontinuation was found in 2.0% of the L-DOPA group. Some of the patients in the 2-and 4-year trials were also recruited to the open-label extension study with mean follow-up of 6.0 (SD 0.2) years, the majority of whom were in H-Y stages 2 [35]. Both the initial PPX ($N = 108$) and L-DOPA ($N = 114$) groups showed overall reductions in the incidence of dyskinesia: 20.4% and 36.8%, respectively. Despite changes in the incidence of dyskinesia in the treatment groups compared to the previous reports of this cohort, L-DOPA treatment was associated with higher events. Furthermore, disability associated with dyskinesia in the PPX group was comparably lower than that in the L-DOPA group, which was at trend-level significance ($P = .06$).

5. Are There Indicators for the Development of Dyskinesia with PPX Treatment?

The majority of placebo-controlled studies demonstrated that dyskinesias can develop during PPX treatment. The incidence of these events in the placebo groups ranged between 0 and 40.8%, and the differences compared to the PPX group ranged between 4.0 and 21.3%. Two studies demonstrated slightly more dyskinesia in the placebo compared to the PPX group [17, 18]. These results clearly indicate that there are non-PPX-related factors contributing to the development of dyskinesias in PD.

Table 2: Pharmacokinetic profiles of selected anti-Parkinson's drugs.

APD	Half-life (hrs)
PPX	8–12
L-DOPA/carbidopa	1–1.5
RTG	5–7
PGL	7–16
BRC	12–15

Abbreviations: APD: anti-Parkinson's drug, PPX: pramipexole, L-DOPA: levodopa, RTG: rotigotine, PGL: pergolide, BRC: bromocriptine.

Treatment of L-DOPA has been proposed as an important factor for the development of dyskinesia in PD [4]. From the two trials and the long-term follow-up of their cohort [22, 24, 35], the PSG consistently demonstrated a higher incidence of dyskinesia associated with L-DOPA therapy. Furthermore, Brodsky et al. [32] showed that PPX treatment increased L-DOPA-related dyskinesias and increased the severity and duration of dyskinesia. They hypothesised that the observed effects in their study are beyond potential additive effects, given that DAAs rarely cause dyskinesia. The 2-hour infusion of therapeutic dose L-DOPA (1.0 mg/kg/hr) also produced more dyskinesia compared to subtherapeutic doses (0.5 mg/kg/hr), regardless of PPX treatment. These findings suggest that L-DOPA on its own can have some effect on dyskinesia events during PPX therapy. Although a study distinguished between L-DOPA and non-L-DOPA-treated participants, the report about adverse event-related withdrawals (including dyskinesia) in the L-DOPA group was not supplemented by information about what proportions were affected [12]. The effects of L-DOPA in other studies are also less clear because L-DOPA usage is reported for the whole sample and there is no differentiation of which patients were dyskinetic.

The literature also allows limited exploration from clinical studies whether continuous dopaminergic stimulation (CDS) is a protective factor for dyskinesia [36]. CDS is a proposed strategy to prevent fluctuations in DA transmission and therefore the development of dyskinesia [37]. Studies with PPX and other DAAs as active comparators show similar incidence of dyskinesia. In all studies with placebo comparisons, DAAs have consistently been associated with more dyskinesia events, suggesting the involvement of dopaminergic activation. In terms of the pharmacokinetic profile of PPX (Table 2), its longer half-life compared to L-DOPA makes it difficult to explain the higher incidence of dyskinesias with this treatment. In fact, the shorter half-life of L-DOPA compared to other antiparkinsonian medications (such as dopamine D2 receptor agonists) is regarded as a factor contributing to its pulsatile action and

ultimately to dyskinesia [38]. Moreover, studies on the ER preparation of PPX, which produces a continuous release of active ingredient over a twenty-four-hour period [39], did not find high rates of dyskinesia. Finally, there were no differences whether the DAA was ergoline (BRC, PGL) or non-ergoline-based (PPX, RTG). It has therefore been suggested that previous exposure to L-DOPA (i.e., priming) can lead to increased susceptibility to develop dyskinesias after exposure to drugs which would not otherwise have had this effect. Specifically, pulsatile activation of type D2 dopamine receptors is reported to be the principal factor in the triggering of dyskinesias and may well be involved in the priming phenomenon [40].

Dose-ranging studies of PPX allow some degree of examination of the hypothesis that PPX-related dyskinesia may be dosage dependent. One study examining PPX at doses of 1.5, 3.0, 4.5, and 6.0 mg did not report any incidence of dyskinesia in either treatment or placebo groups [21]. Another study of different schedules of low-dose PPX (0.5 bd, 0.75 bd, and 0.5 mg td) also did not report dyskinetic events in the participants [28]. These findings suggest that dyskinesia may not be PPX dose dependent. Exploration of this hypothesis with other studies is difficult because PPX dosages are reported as a mean or range of values for the whole sample. Therefore, it is not possible to determine what doses were administered to patients with dyskinesia.

Due to insufficient details in published reports, it has also been difficult to explore whether concomitant APD usage or patient characteristics (such as illness stage, age, and duration of disease) are associated with dyskinesia. APDs were either kept constant at baseline dosages or used as add-on therapy for emerging disability and the majority of studies allowed concomitant usage. Furthermore, patient characteristics were reported as mean or range values without differentiating which patients exhibited dyskinesia. However, it is interesting to note that patients with dyskinesias were generally older (early sixties and above). The patients in PPX-only studies in which there was no incidence of dyskinesia were newly diagnosed with PD.

In terms of methodological issues, the duration of the treatment phase (i.e., titration and maintenance) has overall been adequate to allow sufficient time in detecting or establishing a timeframe for the onset of dyskinesia. The sample size has also generally been statistically viable to allow detection of clinically relevant findings, including dyskinetic adverse events, although there have been some studies with small sample sizes. Most studies also maintained some equivalency with patient characteristics in their treatment groups by carrying out block randomisations and statistical tests before and after treatment to investigate related differences in outcome measures.

More problematic issues, however, may confound conclusions about the effects of PPX on dyskinesia. In particular, some studies only reported adverse events including dyskinesia that occurred above threshold incidence, for example, ≥2%, ≥5%, or 10%. Thus, PPX-related dyskinesias may be underreported and contribute to the lower incidence in certain studies. Indeed, the studies which did not detect dyskinesia in their participants had thresholds of reporting these events at ≥5% [26–28] and 10% [19]. There have also been studies in which patients already experiencing motor fluctuations including dyskinesia were enrolled for PPX treatment. These studies examined whether PPX is a suitable adjuvant medication for L-DOPA-related dyskinesia. However, from these studies it is difficult to establish whether PPX can contribute to the development of dyskinesias since it was not described whether the incidence of dyskinesia is treatment-emergent and relevant neurological scales were not used to measure effects on these symptoms. The reporting of dyskinesia in follow-up studies also does not allow the differentiation between patients with treatment-emergent events and those who continued to experience such symptoms. Additionally, the combination of ratings of dyskinesia and neurological scales to measure effects of PPX further confound conclusions without differentiating which patients had dyskinetic events. For example, the incidence of dyskinesia may be high in the PPX group even if the scales show significant improvement associated with PPX treatment [10, 11, 13].

6. Conclusions

We systematically reviewed the existing evidence on the use of PPX in PD with focus on the development of dyskinesia. Treatment with PPX has overall been associated with significantly better improvement in motor and daily function compared to placebo. The majority of placebo-controlled studies demonstrated that dyskinesias can develop during PPX treatment, as these symptoms were generally (except for two studies) more prevalent compared to the placebo groups. Therefore, the evidence in support of lower incidence of dyskinesia in combination with PPX is far from convincing. However, in six studies, no dyskinesia events were reported. Four of these six studies were PPX comparisons (i.e., dose-ranging or immediate versus extended release preparation). Active comparator studies showed that the incidence of dyskinesia events was quite similar relative to other DAAs. An L-DOPA comparison study in one cohort with long-term follow-up consistently showed that PPX treatment was associated with lower risk for developing dyskinesia. These symptoms have also been reported in the placebo groups (albeit at generally lower rates), suggesting the potential involvement of non-PPX-related factors in the development of dyskinesia. It is still to be established whether L-DOPA treatment, PPX dosage, and other patient characteristics such as age or disease stage can play a role as contributory factors. Elucidation of such factors is likely to optimise the efficacy of anti-Parkinson's treatment and its compliance.

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Hindawi Publishing Corporation
Parkinson's Disease
Volume 2012, Article ID 323686, 16 pages
doi:10.1155/2012/323686

Review Article

Imbalanced Dopaminergic Transmission Mediated by Serotonergic Neurons in L-DOPA-Induced Dyskinesia

Sylvia Navailles and Philippe De Deurwaerdère

Institut des Maladies Neurodégénératives, Université Victor Segalen Bordeaux 2, 33076 Bordeaux, France

Correspondence should be addressed to Sylvia Navailles, sylvia.navailles@u-bordeaux2.fr

Received 1 July 2011; Accepted 2 August 2011

Academic Editor: Anna Rosa Carta

L-DOPA-induced dyskinesias (LIDs) are one of the main motor side effects of L-DOPA therapy in Parkinson's disease. The review will consider the biochemical evidence indicating that the serotonergic neurons are involved in the dopaminergic effects of L-DOPA in the brain. The consequences are an ectopic and aberrant release of dopamine that follows the serotonergic innervation of the brain. After mid- to long-term treatment with L-DOPA, the pattern of L-DOPA-induced dopamine release is modified. In several brain regions, its effect is dramatically reduced while, in the striatum, its effect is quite preserved. LIDs could appear when the dopaminergic effects of L-DOPA fall in brain areas such as the cortex, enhancing the subcortical impact of dopamine and promoting aberrant motor responses. The consideration of the serotonergic system in the core mechanism of action of L-DOPA opens an important reserve of possible strategies to limit LIDs.

1. Introduction

Parkinson's disease is the second most devastating neurodegenerative disease affecting more than 6 million people worldwide and whose prevalence is expected to double within the next twenty years [1]. This neurological disorder is characterized by the progressive loss of mesencephalic dopaminergic (DA) neurons from the substantia nigra pars compacta and associated with numerous motor symptoms (bradykinesia, rigidity, and tremor) [2, 3]. L-DOPA, the precursor of DA, has been introduced in the mid 60's as a miracle pill to prevent the motor symptoms [4, 5]. However, upon chronic use of this medication, its efficacy slowly decreases leading to increase the doses of L-DOPA, which generate numerous side effects. After 5 to 10 years of L-DOPA treatment, Parkinsonian patients develop dyskinesias [6], which consist of stereotypical choreic or ballistic movements involving mostly the head, trunk, and limbs [7]. These abnormal involuntary movements are often more debilitating than the motor symptoms themselves.

Preclinical research has permitted validating animal models to study the mechanisms of L-DOPA-induced dyskinesias (LIDs). The most commonly used rat model that shows best face and predictive validity, has been developed by Cenci and collaborators [8, 9] by producing severe lesion of the nigrostriatal DA pathway in adult rats with the unilateral injection of 6-hydroxydopamine (6-OHDA) in the medial forebrain bundle [10, 11]. A chronic treatment with L-DOPA for 3 weeks at low therapeutic doses (6–10 mg/kg) induced axial, limb, and orolingual abnormal involuntary movements (ALO AIMs) of variable occurrence and severity in rats [9, 12]. Despite extensive research done to understand how these motor complications develop in the Parkinsonian brain, all hypotheses could not be fully validated and new insights in this field need to be pushed forward to further gain in understanding of LIDs. In the present review, we will focus on the literature showing a prominent role of serotonergic neurons (5-HT) in the mechanisms of action of L-DOPA and how these neurons may contribute to the development of LIDs. Specifically, we will try to develop a new hypothesis that LIDs appear when the effect of L-DOPA falls in brain areas such as the cortex, then enhancing the subcortical impact of DA at the risk to elicit LIDs.

2. Mechanism of Action of L-DOPA in 5-HT Neurons and Collateral Consequences

It has long been thought that the therapeutic benefit of L-DOPA may depend on its ability to restore DA extracellular levels in the striatum through spared DA neurons [13–15]. However, contradictory data have shown that the fewer DA neurons that are spared, the more pronounced is the release of DA induced by L-DOPA [16–21]. Furthermore, L-DOPA-induced DA release is not sensitive to DA autoregulatory processes (DA-D2 autoreceptor stimulation and DAT blockade) [19]. Other monoaminergic cells [22, 23], namely serotonergic (5-HT) neurons, that are able to convert L-DOPA into DA, store and induce an exocytotic release of DA, rather participate in the mechanism of action of L-DOPA [24].

2.1. L-DOPA and 5-HT Neurons. 5-HT neurons express the amino acid decarboxylase (AADC) that converts L-DOPA into DA and the vesicular membrane transporter VMAT2 that packages DA into exocytosis vesicles [25–28]. In line with these molecular features, 5-HT neurons have been shown for several years to release the newly synthesized DA from their cell bodies and terminals [25, 29, 30]. Indeed, 5-HT neurons are responsible for the TTX-sensitive, reserpine-sensitive, and DA drugs-insensitive release of DA induced by L-DOPA. The lesion of 5-HT neurons by the selective neurotoxin 5,7-DHT drastically reduces the increase in DA extracellular levels induced by a wide range of L-DOPA doses (3–100 mg/kg) [31, 32]. This effect is dependent on the extent of 5-HT denervation [31], which excludes the involvement of any other cellular system in the release of DA induced by L-DOPA. Furthermore, L-DOPA-induced DA release is sensitive to 5-HT autoregulatory mechanisms. Both the stimulation of 5-HT_{1A} autoreceptors by the 5-HT_{1A} agonist 8-OHDPAT [33] and the blockade of 5-HT transporters (SERT) by the selective serotonergic reuptake inhibitors (SSRI) fluoxetine [34] or citalopram [31] reduce the increase in L-DOPA-derived DA extracellular levels. These effects are thought to occur *via* the inhibition of 5-HT neuron activity [35–42]. Accordingly, it has been recently shown that high-frequency stimulation of the subthalamic nucleus, a surgical approach in Parkinson's disease able to inhibit 5-HT neuronal firing [43], also reduces L-DOPA-induced DA release [44].

5-HT neurons send a widespread innervation from the raphe nuclei to the entire forebrain including the striatum [46, 47]. Beyond the increase in striatal DA extracellular levels, L-DOPA also induces a massive rise in DA levels in the prefrontal cortex (PFC), the substantia nigra pars reticulata (SNr), and the hippocampus (HIPP) [31]. In all brain regions, L-DOPA-induced DA release is sensitive to 5-HT pharmacological manipulation and the lesion of 5-HT neurons [31, 44, 48]. This ectopic release of DA induced by L-DOPA *via* 5-HT neurons creates a new balance in DA chemistry throughout the Parkinsonian brain (Figure 1) [24, 31]. In physiological conditions, basal DA concentrations are more than 30 times higher in the striatum compared to other brain regions, in line with the restricted innervation of mesencephalic DA neurons to striatal territories [5, 49]. While DA extracellular levels are from 4.6 to 7.8 fmol/uL, they are barely detectable depending on experimental conditions (below 0.2 fmol/uL) in the PFC, SNr, and HIPP although DA receptors are expressed [50]. In Parkinsonian conditions, the dose of L-DOPA required to "restore" similar DA concentrations in the DA-denervated striatum is about 12 mg/kg while it increases about 10 to 25 times DA concentrations in other brain regions (see Figure 1). Interestingly, L-DOPA at 3 mg/kg enhances DA levels to similar amounts (0.7 to 1.3 fmol) in the PFC, SNr, HIPP, and striatum. Therefore, huge amounts of DA can be released beyond the striatum [51] and may impact on DA receptors throughout the Parkinsonian brain. In keeping with the increased sensitivity of DA receptors that develops after DA denervation [52–54], such an imbalanced DA transmission between the striatum and other brain regions may participate in the emergence in both short-term benefits and long-term side effects of L-DOPA treatment (see Section 4).

2.2. Chronic Impact of L-DOPA on DA Release Pattern in the Entire Forebrain. The therapeutic efficacy of L-DOPA treatment decreases over time with the development of numerous side effects including L-DOPA-induced dyskinesias (LIDs). LIDs are thought to emerge as a consequence of the dysregulated release of DA as a "false neurotransmitter" from 5-HT neurons [12, 31, 33, 44, 48, 57–63]. Indeed, the inhibition of L-DOPA-induced DA release by 5-HT_1 autoreceptors stimulation [33, 48] and/or 5,7-DHT lesion [31, 32] is associated with a marked reduction in LIDs [48, 61]. However, these mechanisms have been described mostly in the striatum while other brain regions could be involved in the development of LIDs [60, 64–69]. Furthermore, the dose of L-DOPA used, even within the therapeutic range (3–12 mg/kg), represents a critical parameter to consider in the understanding of LIDs [70].

The occurrence and severity of LIDs in animals treated chronically with L-DOPA depend on numerous parameters, that is, the dose of L-DOPA, the site of 6-OHDA injection, the extent of DA lesion, and rat strain. About half of animals treated chronically with 3 mg/kg of L-DOPA develop LIDs. At 6 mg/kg, about 2/3 of the animals treated with L-DOPA display severe LIDs. At 12 mg/kg and above, almost all animals develop LIDs [9]. One consistent result observed after chronic L-DOPA treatment is that, whatever the dose, basal DA extracellular levels remain barely detectable in all brain regions. In our experimental conditions (12 mg/kg for 10 days), basal DA levels were below the detection limit in the striatum, SNr, PFC, and HIPP (Figure 1) [45]. In another study using a 14-day treatment with 6 mg/kg L-DOPA, baseline DA concentrations were reduced by 99% to 0.04 fmol/μL in the striatum compared to intact animals (4 fmol/μL) without changes in the SNr (0.1-0.2 fmol/μL) [48]. One study showed a slight increase in basal DA levels in the striatum (reaching about 0.6 fmol/μL) by using a higher dose (25 mg/kg) of L-DOPA administered twice a day [81].

Dynamics in the increase in DA release after each L-DOPA administration may, however, differ regarding the dose of L-DOPA used. Some authors have proposed that

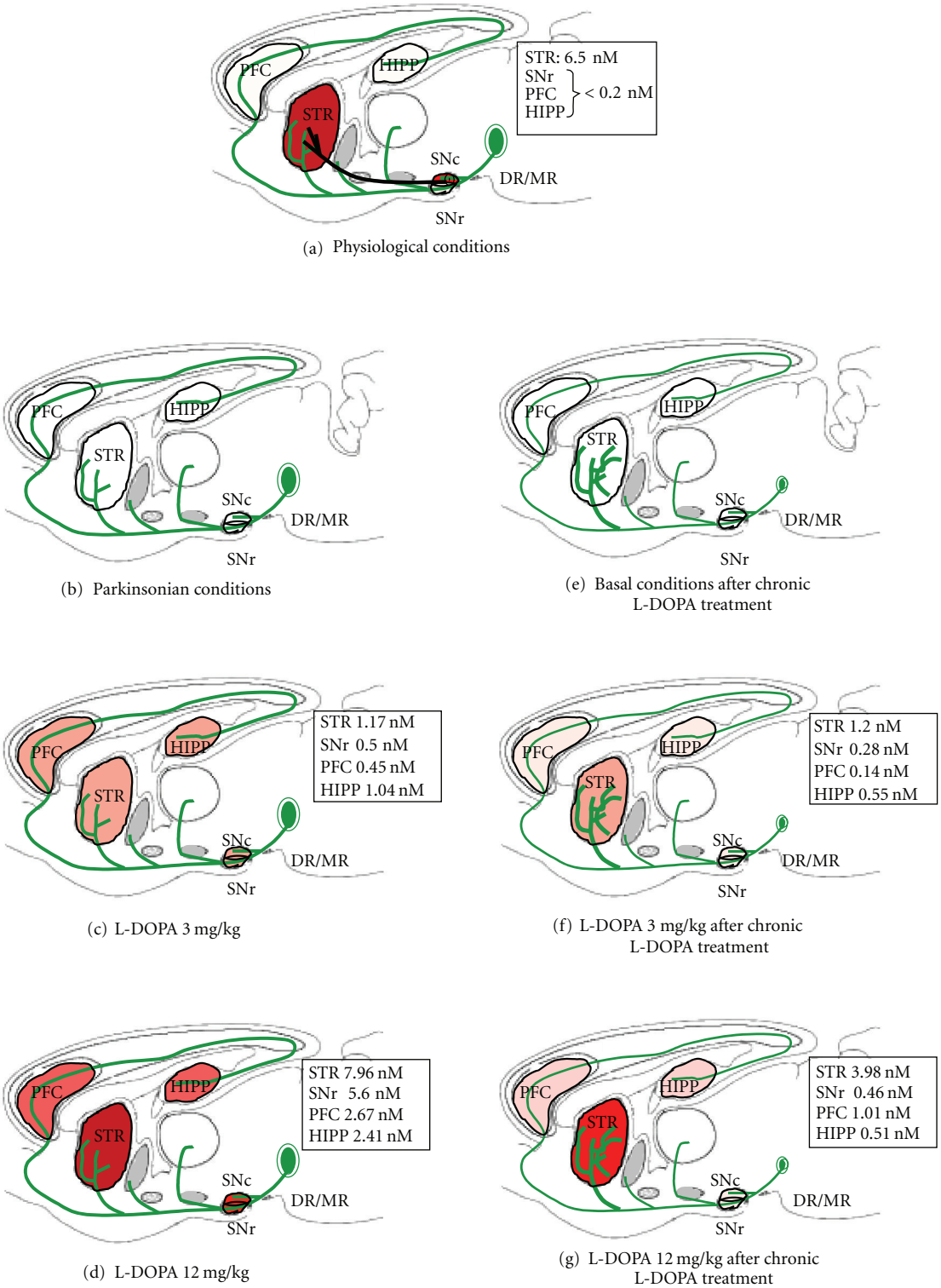

Figure 1: Serotonergic neurons are responsible for an imbalance of dopamine chemistry within brain regions in the Parkinsonian brain after acute and chronic L-DOPA treatment. Data taken from [31, 45].

LIDs may emerge as a consequence of abnormal fluctuations in synaptic DA levels induced by L-DOPA treatment in dyskinetic animals [48, 58, 59, 61, 73]. Larger increases in synaptic DA levels induced by L-DOPA have been proposed to be responsible for the emergence of peak-dose dyskinesia in PD patients [59]. Data obtained with a chronic L-DOPA treatment at 6 mg/kg have shown that the kinetics of DA release are different in animals developing LIDs or not [73]. Although a higher magnitude of DA release was observed in the striatum and SNr of dyskinetic animals compared to nondyskinetic animals [48], this has not been consistently observed [73]. In a recent report, our data have provided new evidence for reconsidering the mechanisms of L-DOPA within the Parkinsonian brain and the putative consequences in many side effects including LIDs [45]. We showed that after a chronic L-DOPA treatment at 12 mg/kg for 10 days, the reactivity of 5-HT neurons to an acute challenge at 3 or 12 mg/kg of L-DOPA was modified and resulted in a potent loss of efficacy of L-DOPA to increase DA release (Figure 1). Most importantly, our data could depict a new imbalance created by chronic L-DOPA treatment within the striatum and other brain regions. The capacity of 5-HT neurons to increase DA release in the SNr, HIPP, and PFC was drastically reduced (about 70 to 90%) while it was less affected in the striatum. Indeed, the increase in striatal DA release induced by 3 mg/kg of L-DOPA after a 12 mg/kg treatment for 10 days was similar to that induced by an acute administration of 3 mg/kg. At 12 mg/kg, the effect of L-DOPA was reduced by only 50% after chronic compared to acute treatment. It appears that different mechanisms may be processed in the striatum compared to other brain structures that may account for the relatively preserved striatal DA effect of L-DOPA. Some of these mechanisms may be directly related to the specific features and heterogeneity of 5-HT terminals within brain regions. The resulted imbalance between cortical versus subcortical brain regions in DA transmission may potentially participate in development of LIDs.

The following paragraph corresponds to the description of the Figure 1, (a) in physiological conditions, dopaminergic neurons originating from the substantia nigra pars compacta (SNc) densely innervate the striatum (STR) where basal dopamine (DA) concentrations range between 4.6 and 7.8 nM. In the prefrontal cortex (PFC), the hippocampus (HIPP), and the substantia nigra pars reticulata (SNr), basal DA concentrations are much lower (<0.2 nM). All these brain regions express DA receptors and are innervated by serotonergic neurons that originate from the dorsal and medial raphe nuclei (DR/MR). (b) In Parkinsonian conditions (i.e., unilateral 6-hydroxydopamine lesion in rats, 6-OHDA rats), the neurodegeneration of DA neurons leads to undetectable levels of DA in any brain region examined. (c) In the absence of DA neurons, L-DOPA is decarboxylated into DA, stored into exocytosis vesicles, and released in the extracellular space by serotonergic neurons. In such physiopathological condition, an acute administration of L-DOPA at the low therapeutic dose of 3 mg/kg induces a homogeneous increase in DA concentrations in all brain regions (see values in the square box). These concentrations are 2, 2.5, and 5 times higher than in physiological conditions in the SNr, PFC, and HIPP, respectively, while they are 5 times lower in the STR. (d) An acute administration of L-DOPA at the moderate therapeutic dose of 12 mg/kg increases DA concentrations in the STR within the range of physiological values. Similar concentrations of DA are observed in the SNr and corresponded to >25 times the physiological concentrations. In the PFC and HIPP, DA concentrations are >10 times higher than in physiological conditions. (e) After a chronic L-DOPA treatment at a dose known to induce dyskinesias in all 6-OHDA rats (12 mg/kg/day for 10 days), basal DA concentrations remain below the detection limit in all brain regions. All biochemical 5-HT indexes (extracellular and tissue levels of 5-HT and its metabolite 5-HIAA) are decreased after chronic L-DOPA treatment, suggesting that 5-HT neurons suffer from chronic exposure to L-DOPA. Numerous data provide evidence for a 5-HT sprouting occurring specifically in the striatum [55, 56]. (f) After a chronic L-DOPA treatment (12 mg/kg/day for 10 days), a subsequent administration of 3 mg/kg L-DOPA is less efficient to increase DA release in the SNr, PFC, and HIPP compared to an acute administration of the same dose in L-DOPA-naïve 6-OHDA rats (see (c)). The ability of L-DOPA to increase DA levels is reduced by 43%, 68%, and 45% in the SNr, PFC, and HIPP, respectively. However, the efficacy of L-DOPA is not altered in the STR as DA levels reached similar concentrations in both L-DOPA-treated and L-DOPA-naïve 6-OHDA rats. (g) The ability of L-DOPA at 12 mg/kg to increase DA release is diminished in all brain regions after chronic L-DOPA treatment (12 mg/kg/day for 10 days). The highest loss of efficacy is observed in the SNr (−92%), then in the HIPP (−79%) and the PFC (62%). By comparison, the efficacy of L-DOPA remained mostly preserved in the STR (−50%), an effect that may be related to the striatal 5-HT hyperinnervation [55].

3. Changes in 5-HT Transmission Associated with L-DOPA Treatment

L-DOPA, by entering 5-HT neurons, mediates numerous changes in 5-HT neuron homeostasis [45]. The production of massive amounts of DA has tremendous impact on 5-HT function at the level of the metabolism, the activity, and the morphology of 5-HT neurons (Table 1). Changes in 5-HT indexes have been associated with the emergence of LIDs (Table 2). Such changes may represent critical indicators of the physiopathological state of the Parkinsonian brain that should be taken into consideration to better control 5-HT transmission and L-DOPA's side effects [24, 82, 83].

3.1. Impact of L-DOPA on 5-HT Transmission. Since the beginning of the 70's, numerous evidences started accumulating for an alteration of 5-HT neuron activity in response to L-DOPA (Table 1) [86–88]. The first report in 1970 by Ng et al. [25] showed that L-DOPA-enhanced [^{3}H]-5-HT release from [^{3}H]-5-HT preloaded midbrain slices. This increase in 5-HT release has been later confirmed *in vivo* by local administration of L-DOPA in the substantia nigra [71, 89].

Table 1: Changes in biochemical, morphological, and molecular 5-HT indexes in response to L-DOPA treatment.

Animal model	L-DOPA treatment	Biochemical 5-HT indexes	% of change	Reference
[^{3}H]-5-HT preloaded rat midbrain slices	10 μM	[^{3}H]-5-HT release	+60%	[25, 29, 30]
naive rats	intra-SNr 5 μM	*ext* 5-HT: STR and SNr	+55% in STR +102% in SNr	[71]
6-OHDA rats	3, 6, 12, 100 mg/kg/d ip	*ext* 5-HT: STR, SNr, HIPP, PFC	**3:** ∅ **6:** STR/PFC ∅, SNr −22%, HIPP −27% **12:** STR/HIPP ∅, SNr −17%, PFC −27% **100:** STR/SNr/HIPP ∅, PFC −28%	[31] + unpublished observations
		tiss 5-HT: STR	**3–12:** ∅ **100:**−73%	[31] [45]
6-OHDA rats	12 mg/kg/d ip 14 d	*ext* 5-HT and 5-HIAA: STR, SNr, HIPP, PFC	**5-HT:** STR −39%, SNr −45%, HIPP −29%, PFC –47% **5-HIAA:** STR −32%, SNr −58%, HIPP −44%, PFC −51%	
		tiss 5-HT and 5-HIAA: STR and CX	**5-HT:** STR −48%, CX −63%, **5-HIAA:** STR −67%, CX −73%	
6-OHDA rats	6 mg/kg/d ip 14 d	*ext* 5-HT and 5-HIAA: STR and SNr	**5-HT:** STR-LID +125%, STR-LND +75%; SNr-LID +104%, SNr-LND +108% **5-HIAA:** STR-LID −30%, STR-LND −73%; SNr-LID −28%, SNr-LND −37%	[48]
		tiss 5-HT and 5-HIAA: STR and SNr	**5-HT:** STR-LID −32%, STR-LND −78% 5-**HIAA:** STR-LND −76%	
6-OHDA rats	6 mg/kg/d ip 14 d	*tiss* 5-HT: STR	−48%	[61]
6-OHDA rats	6 mg/kg/d ip 21 d	*tiss* 5-HT: STR	+150%	[72]

Table 1: Continued.

Animal model	L-DOPA treatment	Morphological 5-HT indexes	% of change	Reference
6-OHDA rats	5 mg/kg/d ip 14 d	SERT immunoreactivity: STR	+266%	[73]
6-OHDA rats	6 mg/kg/d ip 21 d	5-HT immunoreactivity: STR	+70% in STR-LID ∅ in STR-LND	[74]
6-OHDA rats	6 and 50 mg/kg/d ip 14–21 d	SERT-binding density: STR and CX	**6:** STR +37.5%, CX +75% **50:** STR +87.5%, CX +125%	
		5-HT immunoreactivity: number of varicosities, STR	**6:** +125% **50:** +200%	[55]
		5-HT immunoreactivity: synapse incidence in STR	**6:** +155%	
MPTP monkeys	Modopar (4 : 1) 15–20 mg/kg po 6–8 m	SERT-binding density: PUT and GP	PUT-LID +72%, GP-LID +400%, LND ∅	[55]
MPTP monkeys	12.5 mg/kg/d po 1 m	TPH immunoreactivity: STR and GP	**STR:** increased number and size of varicosities and enlargement **GP:** enlargement in GPi/e + increased number of varicosities and length of fibres in GPe	[56]
Animal model	L-DOPA treatment	Molecular 5-HT indexes	% of change	Reference
6-OHDA mice and rats	(1) mice: 50 mg/kg/d ip 28 d (2) rat: 100 mg/kg 2×d ip 5 d (3) rat: 10 mg/kg/d ip 28 d	5-HT_{1B}R binding: STR, GP and SNr	(1) STR +20%, GP ∅, SNr +30% (2) STR +17%, GP +38%, SNr + 61% (3) STR +25%, GP ∅, SNr +55%	[75]
6-OHDA rats	100 mg/kg 2×d ip 5 d	5-HT_{1B}R protein: STR	+33%	[75]
6-OHDA rats	100 mg/kg 2×d ip 5 d	5-HT_{2A}R mRNA: STR	−57%	
		5-HT_{2C}R mRNA: STR and STN	∅	[76]
MPTP monkeys	Modopar acute: 14.6 mg/kg po chronic: 14.6 mg/kg 2×d po 120 d	5-HT_{1A}R-binding: STR, premotor-motor CX, HIPP	acute: ∅ chronic: +140% in Caud matrix	[77]
MPTP monkeys	Prolopa 100/25 mg/kg po 1 m	5-HT_{2A}R binding: STR and PFC	+58% in DM Caud	[78]
PD patients (LIDs)		5-HT_{2C}R binding: SNr	+108%	[79, 80]

6-OHDA: 6-hydroxydopamine; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; ip: intraperitoneal; sc: subcutaneous; po: oral; d: day; m: month; 2×d: twice a day; *tiss*: tissue; *ext*: extracellular; 5-HT: serotonin; 5-HIAA: 5-hydroxyindolacetic acid; AADC: amino acid decarboxylase; SERT: serotonergic transporter; 5-HT_{1A}R: serotonin 1A receptor; 5-HT_{1B}R: serotonin 1B receptor; 5-HT_{2A}R: serotonin 2A receptor; 5-HT_{2C}R: serotonin 2C receptor; STR: striatum; CX: cortex; PFC: prefrontal cortex; HIPP: hippocampus; SNr: substantia nigra pars reticulata; PUT: putamen; PFC: prefrontal cortex; STN: subthalamic nucleus; GPi/e: globus pallidus, internal/external part; DM Caud: dorsomedial caudate nucleus; LID: L-DOPA-treated dyskinetic animals; LND: L-DOPA-treated nondyskinetic animals; LIDs: L-DOPA-induced dyskinesias.

Table 2: Changes in biochemical, morphological, and molecular 5-HT indexes in dyskinetic (LID) *versus* nondyskinetic (LND) animals: correlation with dyskinesias (R).

Animal model	L-DOPA treatment	Biochemical 5-HT indexes	LID versus LND (R)	Reference
6-OHDA rats	6 mg/kg/d ip 14 d	*tiss* 5-HT: STR and CX	LID > LND R = 0.73 in CX	[84]
6-OHDA rats	12 mg/kg/d sc 5 d	*tiss* 5-HT (5,7-DHT): STR	R = 0.713	[85]
6-OHDA rats	6 mg/kg/d sc 14 d	*ext* and *tiss* 5-HT and 5-HIAA: STR and SNr	LID > LND in STR	[48]
6-OHDA rats	6 mg/kg/d ip 21 d	*tiss* 5-HT: STR	LID > LND R = −0.655	[72]
Animal model	L-DOPA treatment	Morphological 5-HT indexes	LID versus LND (R)	Reference
6-OHDA rats	5 mg/kg/d ip 14 d	SERT immunoreactivity: STR	LID > LND	[73]
6-OHDA rats	6 mg/kg/d ip 21 d	5-HT immunoreactivity and AADC levels: STR	LID > LND	[74]
6-OHDA rats	6 and 50 mg/kg/d ip 14–21 d	SERT-binding density: STR and CX	LID > LND, R = 0.796 in STR	[55]
MPTP monkeys	Modopar (4 : 1) 15–20 mg/kg po 6–8 m	SERT-binding density: PUT and GP	LID > LND in PUT	[55]
Animal model	L-DOPA treatment	Molecular 5-HT indexes	LID versus LND (R)	Reference
MPTP monkeys	Prolopa 100/25 mg/kg po 1 m	5-HT_{2A}R-binding: STR and PFC	LID > LND in DM Caud and anterior cingulate gyrus	[78]

6-OHDA: 6-hydroxydopamine; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; ip: intraperitoneal; sc: subcutaneous; po: oral; d: day; m: month; *tiss*: tissue; *ext*: extracellular; 5-HT: serotonin; 5-HIAA: 5-hydroxyindolacetic acid; 5,7-DHT: 5,7-dihydroxytryptamine; AADC: amino acid decarboxylase; SERT: serotonergic transporter; 5-HT_{2A}R: serotonin 2A receptor; STR: striatum; CX: cortex; SNr: substantia nigra pars reticulata; PUT: putamen; PFC: prefrontal cortex; GP: globus pallidus; DM Caud: dorsomedial caudate nucleus; LID: L-DOPA-treated dyskinetic animals; LND: L-DOPA-treated nondyskinetic animals; R: correlation.

The potent increase in 5-HT levels observed in these studies has been suggested to account for a nonexocytotic efflux of 5-HT *via* 5-HT transporters due to the strong displacement of 5-HT from exocytosis vesicles by the newly synthesized DA [24]. However, recent data using systemic administration of L-DOPA at moderate doses (3–12 mg/kg) have reported distinct effects on 5-HT release depending on the dose and the brain region dialysated. While an acute injection of 12 mg/kg L-DOPA decreases 5-HT extracellular levels in the PFC and SNr, a biphasic effect was observed in the HIPP and no effect in the striatum [44, 45]. A transient increase in 5-HT levels has been observed only after the very high dose of 100 mg/kg in all brain regions (Navailles et al., unpublished observation; see Table 1). Different mechanisms could be triggered regarding the dose of L-DOPA used (exocytotic versus nonexocytotic) while the region-dependent effects of L-DOPA on 5-HT release may reflect the anatomo-functional heterogeneity of 5-HT terminals [24].

After a chronic L-DOPA treatment (12 mg/kg/day for 10 days), the reactivity of 5-HT terminals to a subsequent challenge of L-DOPA (3–12 mg/gk) was further modified in a region-dependent manner [45]. The inhibitory effect of L-DOPA at 3 and 12 mg/kg on 5-HT release was potentiated in the SNr and HIPP of L-DOPA-treated rats but not in the PFC. In the striatum of L-DOPA-treated rats, 5-HT release remained unaltered by L-DOPA whatever the dose used. Interestingly, this region-dependent reactivity of 5-HT terminals appears to correlate with the ability of L-DOPA to increase DA release after a chronic treatment (see Section 2). Of particular interest, the lack of sensitivity of striatal 5-HT terminals to L-DOPA on 5-HT release is associated with a preserved increase in L-DOPA-induced DA release while the highest sensitivity of 5-HT terminals observed in the SNr leads to the most profound loss of efficacy of L-DOPA to increase DA release [45]. This imbalance between the striatum and the SNr could not be unmasked after a chronic treatment with L-DOPA at 6 mg/kg, which did not change the effect of L-DOPA on 5-HT release [48]. Nevertheless, it appears that, for a moderate though therapeutic dose of L-DOPA (12 mg/kg), its effects on DA transmission occur in detriment of 5-HT transmission [45]. The distinct molecular (variable expression and sensitivity to 5-$HT_{1A/1B}$ receptors, SERT, VGLUT3, cation channels) [90–97], anatomical (originating from the medial or dorsal raphe nuclei) [46, 98], ontogenesis (pet1-dependent versus pet1-resistant 5-HT neurons) [99, 100] characteristics of 5-HT neurons projecting to these different brain regions may participate in this region-dependent changes in 5-HT and DA releases [24]. In addition, chronic L-DOPA treatment by itself also alters the morphology of these 5-HT neurons and the synaptic plasticity in various brain regions (Table 1) [55, 56, 101–104], an effect that may participate in the

imbalanced 5-HT and DA transmissions within structures in the Parkinsonian brain and favor the onset of LIDs (see below).

Beyond the changes of 5-HT release (Table 1), chronic L-DOPA also alters 5-HT transmission by modifying the expression and function of numerous 5-HT receptors. Studies that aimed at improving L-DOPA's effects have focused on 5-$HT_{1A/1B}$ receptors. Although a decrease in 5-HT_{1A} receptor expression in the dorsal raphe (and hippocampus) [105, 106] may be directly linked to the loss of 5-HT neurons in Parkinsonian patients [107–111], an increase has been described in the neocortex of Parkinson's disease patients [112], the putamen [105], caudate nucleus, and middle layers of premotor-motor cortices of MPTP-treated monkeys [77]. Although it remains difficult to attribute these effects to the progression of the disease or to L-DOPA therapy in Parkinsonian patients [107, 113], a massive increase in 5-HT_{1A} receptor binding could be observed in the caudate nucleus of L-DOPA-treated MPTP-lesioned monkeys [77]. No alteration in 5-HT_{1B} binding has been observed in the striatum and substantia nigra of Parkinsonian patients [114] and 6-OHDA rats [115] while an increase in 5-HT_{1B} receptor expression in these brain regions has been reported after chronic L-DOPA treatment in 6-OHDA-lesioned rats [75]. Other 5-HT receptors such as 5-HT_{2A} and 5-HT_{2C} receptors have been proposed to improve L-DOPA therapy in Parkinson's disease [69, 79, 116–119]. These receptors are known to be sensitive to chronic alteration of DA transmission [119–122]. However, the few data available have reported conflicting results. 5-HT_{2A} receptor expression has been shown to increase in the striatum of 6-OHDA rats [76] and the neocortex of Parkinsonian patients [112] while it did not change in the putamen and PFC of MPTP-treated monkeys [78]. Although L-DOPA reversed the increase in the striatum of 6-OHDA rats [76], it increased 5-HT_{2A} receptor binding in the dorsomedial caudate nucleus of MPTP-treated monkeys [78]. 5-HT_{2C} receptor expression was decreased in the striatum but not in the subthalamic nucleus of 6-OHDA rats without any change after L-DOPA treatment [76]. However, the increased expression of 5-HT_{2C} receptors in the substantia nigra pars reticulata in Parkinsonian patients [80] appears to participate in the overactivity of this brain region by dampening the antiparkinsonian action of DA drugs in 6-OHDA rats primed with L-DOPA [120, 121]. Altogether, these data indicate that chronic L-DOPA treatment alters 5-HT function and the resulted changes in 5-HT markers have been mostly associated with the genesis and expression of LIDs.

3.2. Biochemical, Morphological, and Molecular Changes in 5-HT Indexes Associated with LIDs. Changes in 5-HT indexes have recently gained growing importance as they may reflect fluctuations in L-DOPA-induced DA release from 5-HT neurons that have been associated with the emergence of LIDs (Table 2) [61, 62]. In this attempt, most studies have focused on modifications of tissue and extracellular levels of 5-HT together with changes in 5-HT terminals density and morphology in 6-OHDA rats developing or not dyskinesias after a chronic treatment with 6 mg/kg of L-DOPA. Conflicting results, however, have emerged regarding 5-HT tissue and extracellular levels. Independently of the emergence of LIDs, chronic L-DOPA treatment either reduced [45, 48, 61], did not affect [72, 78], or tended to increase [84] 5-HT tissue and extracellular levels in the striatum. In most studies, however, tissue and extracellular 5-HT levels in the striatum and the cortex, but not the SNr, of rats developing LIDs were significantly higher than in nondyskinetic rats [48, 72, 84] suggesting a positive correlation to LIDs. Accordingly, Eskow et al. [85], by using selective 5,7-DHT lesions that are known to abolish both LIDs [61] and L-DOPA-induced DA release [31], could establish a positive correlation between striatal 5-HT levels and LIDs. These results are in contrast with the study by Gil et al. [72] in which 5-HT tissue levels were negatively correlated to axial, limb, and orolingual abnormal involuntary movements (AIMs). Interestingly, Carta et al. [84] could not establish a link between striatal 5-HT levels but did observe a positive correlation between 5-HT levels in the PFC and AIMs providing further evidence for a role of 5-HT function beyond the striatum in the emergence of LIDs.

In support of an increased 5-HT function in the genesis of LIDs, chronic L-DOPA treatment has been shown to increase AADC protein expression without increasing tyrosine hydroxylase expression in the lesioned-side striatum of dyskinetic rats [74]. This effect was associated with a higher 5-HT immunoreactivity compared to nondyskinetic animals, highlighting an increased 5-HT fiber density mediated by L-DOPA [74]. In line with this, Rylander et al. [55] have shown that chronic L-DOPA induced a dose-dependent increase in SERT-binding densities on the lesioned striatum (and motor-premotor cortices) that was associated with an increased number of striatal 5-HT varicosities but not with an increase in the number of 5-HT cell bodies or expression of SERT mRNA in raphe cells. Both striatal SERT binding and number of 5-HT varicosities correlated positively with the AIMs scores, showing that L-DOPA induced a sprouting of striatal 5-HT terminals in dyskinetic animals [55]. Furthermore, SERT-immunoreactive varicosities displayed larger synaptic incidence with striatal neurons and resulted in larger amount of stimulated (KCl evoked) [^{3}H]-DA release in striatal slices from L-DOPA-treated dyskinetic rats [55]. However, Lundblad et al. [73] failed to correlate the higher 5-HT nerve density in the lesioned striatum of dyskinetic rats with the magnitude of KCl-evoked DA release measured *in vivo* by chronoamperometry after chronic L-DOPA treatment. Although SERT binding was decreased in the putamen and globus pallidus (GP) of MPTP-treated monkeys [55], a marked hyperinnervation of TPH-positive fibers (increase in number and diameter of TPH-positive axon varicosities) was observed in the dorsal caudate and putamen, but not the GP of MPTP-intoxicated monkeys [56]. Nevertheless, using both 5-HT markers, these studies have consistently shown an elevated SERT binding and a further increase in the number and enlargement of TPH positive axonal varicosities in caudate nucleus and putamen of MPTP-treated monkeys that develop LIDs [55, 56]. In Parkinsonian patients, SERT-binding levels were also significantly increased in both the putamen and GP of dyskinetic

patients [55]. Regarding the lifetime L-DOPA medication, results indicate that patients with highest levels of SERT binding were those developing LIDs earliest during their PD treatment [55]. However, by using another marker of serotonin transporter (^{11}C-DASP) in PET, Politis et al. [123] could not establish a correlation between ^{11}C-DASP binding and exposure to dopaminergic therapy. Altogether, these data suggest that L-DOPA pharmacotherapy induced a maladaptive plasticity of 5-HT axon terminals that may predispose to LIDs. Indeed, the 5-HT hyperinnervation together with marked hypertrophy of 5-HT axon varicosities may worsen the fluctuations of L-DOPA-induced DA release [48, 55, 56, 59].

The combination of 5-HT$_{1A}$ and 5-HT$_{1B}$ agonists provides useful pharmacological manipulation to reduce the large increases in DA efflux and the occurrence of LIDs [48, 61, 124]. Their efficacy is reached when combining subthreshold doses of 5-HT$_{1A}$ and 5-HT$_{1B}$ agonists that are thought to activate presynaptic 5-HT$_1$ receptors and dampen the release of L-DOPA-derived DA from 5-HT neurons [64]. The stimulation of postsynaptic 5-HT$_1$ receptors on non-5-HT neurons may also contribute to their antidyskinetic effect by modulating GABA and glutamate release [64]. However, adverse effects involving the stimulation of postsynaptic 5-HT$_{1A}$ receptors could worsen their therapeutic efficacy [125, 126]. Some studies have identified specific changes induced by chronic L-DOPA treatment on 5-HT$_{1B}$ postsynaptic receptors that may be directly involved in the development of LIDs. Chronic L-DOPA treatment increased the expression of 5-HT$_{1B}$ receptors and its adaptor protein p11 at striatonigral neurons [75]. The ability of 5-HT$_{1B}$ agonist to reduce LIDs was p11 dependent [75]. Moreover, in L-DOPA-treated 6-OHDA rats that recovered from AIMs after a chronic treatment with citalopram (a selective serotonergic reuptake inhibitor, SSRI), the expression of 5-HT$_{1B}$ receptors in the striatum was almost fully abolished [127]. The authors could reveal a positive correlation between the decreased anxiety induced by citalopram and its ability to reduce AIMs that involves a marked reduction in 5-HT$_{1B}$ receptor expression (Table 2). However, in keeping with data obtained in the study by Zhang et al. [75], the reduction of LIDs by citalopram may not solely account for its effect on 5-HT$_{1B}$ receptor expression but may also involve the ability of citalopram to abolish L-DOPA-induced DA release [31]. Nevertheless, these data allow identifying a new association between 5-HT$_{1B}$ receptors and LIDs. A recent work could also highlight a relationship between 5-HT$_{2A}$ receptors and LIDs in MPTP-treated monkeys [78]. [^{3}H]Ketanserin-specific binding to 5-HT$_{2A}$ receptors was increased in the dorsomedial caudate nucleus and anterior cingulated gyrus of dyskinetic L-DOPA-treated MPTP-intoxicated monkeys, an effect reversed by drugs inhibiting the expression of LIDs. The authors could reveal a positive correlation between the maximal dyskinesia scores at the end of L-DOPA treatment and 5-HT$_{2A}$ receptor-specific binding in the anterior and posterior caudate nucleus as well as the nucleus accumbens [78].

Despite the high degree of variability observed in the changes of 5-HT markers across studies performed in different animal models and Parkinsonian patients, the available data to date allow establishing a clear role of the 5-HT system in the induction and maintenance of LIDs. The numerous 5-HT indexes used could provide interesting insights into the mechanisms of action of L-DOPA in mediating LIDs. However, the failure to fully correlate one change in 5-HT markers with a complex behavior such as LIDs may encourage future studies to reconsider the heterogeneity and the widespread influence of the 5-HT system as a whole fundamental index in the genesis of LIDs. Indeed, the numerous changes in 5-HT function induced by L-DOPA in multiple brain regions may concur in synergy to an imbalanced DA transmission that may participate in the emergence of LIDs.

4. Functional Outcomes of 5-HT Neuron-Mediated DA Transmission in LIDs

Because the 5-HT terminals are responsible for the gross increase in DA, leading to a homogeneous and ectopic release of DA in the brain, one may wonder the extent to which the striatum is involved in the therapeutic benefit of L-DOPA. It is far from our purpose to rule out many years of research centred on striatal DA transmission, but it is important to conceive that other brain regions play an important role in motor responses induced by L-DOPA. The main argument to look beyond the striatum is the success of the deep brain stimulation of the subthalamic nucleus in Parkinson patients, a surgical approach of the disease that does not rely on striatal DA release.

4.1. Role of Imbalanced Cortical-Subcortical DA Transmission in Motor Output. It is a common sense to reaffirm that DA transmission is altered in PD and that the relationships between DA transmission, symptoms severity, and medication coevolve with the deleterious progression of the disease. Nonetheless, adding the evidence that 5-HT neurons participate in the raise of extracellular DA offers a larger picture of the putative scenarios. In early stages of the disease, the presence of spared DA terminals and DAT in the striatum limits the excessive increase in DA extracellular levels induced by L-DOPA from 5-HT neurons. However, the increase in DA from 5-HT terminals in the striatum likely introduces a noise in the "coherent" DA transmission. Indeed, this aberrant release is not regulated while the "coherent" release from spared DA neurons is impaired due to the inhibitory effect of electrical activity of L-DOPA on DA neurons activity [19]. The more the disease progresses, the higher should be the contribution of 5-HT neurons in L-DOPA-induced DA release. Thus, even in the early stages of the disease, it is noticeable that L-DOPA is efficient to treat the core symptoms of the disease (tremor, bradykinesia, rigidity, posture) but has limited effects on precise coordinated movements or some impaired cognitive functions [128]. In the advanced stages of the disease, spared DA neurons are no longer able to buffer excessive swings of

DA released from 5-HT neurons, a condition favoring motor fluctuations and LIDs [61].

Whatever the stage of the disease, the small release of DA from 5-HT neurons has potentially a larger impact beyond the striatum where DAT are poorly expressed. The impact may also be magnified due to altered pattern of activities found in extrastriatal territories such as the cortex or the HIPP. Indeed, numerous studies in humans using functional imaging have reported changes in activities in several cortical territories and the HIPP [129]. These brain areas expressing substantial amount of DA receptors [50], the excessive increase in DA release induced by L-DOPA in these territories could have a higher impact on the functions exerted by these brain regions. Of note, it has been described for many years that an increase in cortical DA may counteract aberrant DA signaling in subcortical areas. For instance, the catalepsy induced by the DA antagonist haloperidol, a rat model of Parkinsonism, is reversed by the direct infusion of DA into the PFC. Moreover, the increase in DA release induced by L-DOPA is very high in the SN, one of the brain regions receiving the strongest 5-HT innervation [46], and it has been shown for several years that the SN directly participates in the motor effects of L-DOPA in the 6-OHDA rat model of Parkinson's disease [68, 130].

The minimal release of striatal DA after therapeutic doses of L-DOPA could be compensated by an increase in D_2 receptor efficiency. An increase in striatal D_2 receptors has been reported in early stages of the disease, but some data have reported that DA "replacement" therapy reduced the excessive expression of striatal D_2 receptors to levels comparable to matched controls [131, 132]. Based on the neurochemical data in the 6-OHDA rat model of Parkinson's disease, the benefit of L-DOPA could be an uneven release of DA or a hypodopaminergy in the striatum combined with an extrastriatal hyperdopaminergy.

4.2. Role of Imbalanced Cortical-Subcortical DA Transmission in LIDs. The increase in DA release induced by L-DOPA has been directly incriminated in LIDs [133]. Our data showing that chronic treatment with L-DOPA is associated with a dramatic loss of DA release in various rat brain areas compared to the striatum [45] points to an inverse schema. First, the inhibitory tone provided by cortical DA upon subcortical DA function would be lowered after chronic treatment, and subcortical DA release by 5-HT fibers would be preserved due to some sprouting of striatal 5-HT fibers [55, 56]. The situation is not known for several brain regions though it has been reported that LIDs in rodents is associated with an increase in c-Fos expression in the STN [134]. Besides, chronic L-DOPA treatment has been shown to increase c-Fos expression also in the cortex and globus pallidus [135, 136]. In addition, excessive DA tone in some brain regions other than the striatum may promote abnormal involuntary movement of the face, one clinical manifestation reported in LIDs in primates and rodents [7–9]. Second, the aberrant release of DA *via* 5-HT neurons would favor abnormal learning, at least in the striatum. Indeed, DA is critically involved in procedural learning, and LIDs is thought to result in part from aberrant molecular events at the level of medium spiny neurons of the striatum that involve DA receptors [104, 137, 138]. The postulated pathological form of synaptic plasticity may occur in the different territories of the striatum. It has been reported in MPTP-treated monkeys that LID involved not only the sensorimotor part of the striatum, but also its associative and limbic territories [139]. Third, as noted above, 5-HT processes could be involved as well [122, 140], particularly in considering that the "coherent" 5-HT transmission is altered by L-DOPA [24]. As for DA transmission, alteration in 5-HT transmission occurring elsewhere than the sensorimotor part of the striatum may promote abnormal movements in rodents [122, 141].

In a therapeutic point of view, one possibility is to limit the excessive DA transmission by administering a neuroleptic at risk of generating Parkinsonism. Nevertheless, the atypical neuroleptic clozapine has been shown to limit dyskinesia without aggravating the motor score [117]. It is difficult to interpret the origin of its efficacy as clozapine or other atypical antipsychotic drugs may slightly block subcortical DA transmission and enhance cortical DA transmission [142, 143]. Similar effects could account for the proposed efficacy of the antipsychotic and partial DA agonist drug aripiprazole [144]. According to the hypothesis above, treatment that is enhancing DA transmission in the cortex, that would limit the impact of cortico-subcortical glutamate transmission [145], could be a focus of future strategy against LIDs. It is noticeable that blockers of the N-methyl-d-aspartate receptor such as amantadine can also limit LIDs in patients [146].

The direct control of striatal DA transmission *via* 5-HT drugs is difficult to manage because the biochemical and behavioral relationships between 5-HT receptors and DA transmission are not well understood [147]. The use of 5-HT drugs able to control 5-HT nerve activity, to control the output of DA from 5-HT neurons, is a great opportunity, and clinical trials are currently underwent to alleviate LIDs using this strategy. The limit of this approach is that 5-HT drugs used may also act directly on cells other than 5-HT neurons due to the widespread distribution of 5-HT receptors in the brain. Also, a general decrease in DA release from 5-HT neurons may counteract dyskinesia and aggravate Parkinsonism [148–153]. Again, 5-HT drugs could be used to reinforce the initial imbalance created by L-DOPA, namely, the quite homogeneous pattern of DA release induced by L-DOPA, through cortical mechanisms.

5. Conclusion

The consideration of the 5-HT system in the core mechanism of action of L-DOPA opens many opportunities to better apprehend LIDs and to propose diverse therapeutic strategies in the treatment of LIDs. The excess of striatal DA released by L-DOPA remains an important preoccupation, but the possibility to facilitate DA transmission in the cortex could be also an interesting strategy. Additional studies are warranted to further study the imbalance of DA transmission promoted by the intervention of 5-HT neurons in the mechanism of action of L-DOPA to propose additional brain targets.

Acknowledgments

This work was supported by grants from "Centre National de la Recherche Scientifique" and the University of Bordeaux. The authors wish to thank the "Fondation de France" for the financial support and the "Société Française de Physiologie" for the award attributed to Sylvia Navailles in 2010.

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