Different Dyskinesias in Parkinson’s Disease and Their Relationship to Levodopa

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ABSTRACT

Levodopa is the principal agent in the treatment of Parkinson’s disease (PD). Unfortunately the therapeutic benefits are optimal only in the early stages of the disease, with long-term use associated with motor complications such as levodopa-induced dyskinesia (LID). Risk factors associated with the development of LID are generally accepted to involve the degree of dopamine (DA) denervation in the nigrostriatal pathway, levodopa dose, and duration of levodopa treatment. Little is known regarding the underlying mechanisms of LID, although it is known that levodopa plasma concentrations are closely associated with the onset of some types of LIDs (peak-dose and biphasic dyskinesias) and it appears that increased DA turnover plays a crucial role in LID development. Recent evidence suggests that other cell types such as serotonin neurons possess the ability to convert levodopa into DA, subsequently storing and releasing it thereby increasing the levels of extracellular DA, exacerbating LID. This review will highlight the evidence to date from in vitro and in vivo studies utilizing both animal models and patients, regarding the relationship between levodopa treatment and the development of LID. Understanding the pathogenesis of LID is a therapeutic priority in tackling motor complications related to levodopa treatment in PD.

Keywords: Parkinson’s disease, dyskinesia, levodopa, dopamine, serotonin

INTRODUCTION

Parkinson’s disease (PD) is a neurodegenerative disorder characterized by the motor features of bradykinesia, tremor, and rigidity due in part to a loss of dopamine (DA) neurons in the nigrostriatal pathway. However, there is established evidence that other neurotransmitter systems such as the serotonergic system also display reduced innervation that may be responsible for the appearance of nonmotor symptoms also commonly seen in the clinical course of the disease. Nonetheless, the principal agents for treating PD are dopaminergic drugs (eg, levodopa and DA agonists), which are effective in relieving the motor symptoms of the disease. Unfortunately, long-term use of dopaminergic drugs often leads to motor complications such as on-off fluctuations and dyskinesia. The term levodopa-induced dyskinesia (LID) specifically refers to the motor complication arising from long-term use of levodopa. It appears that DA agonists are less likely to induce dyskinesia in PD patients compared to levodopa.

Little is known regarding the pathogenesis of LID in PD; however, it has been established in animal models and patient studies that risk factors associated with the emergence of LID include the disease severity, the extent of striatal DA denervation, as well as the dose and duration of levodopa treatment. Motor function is expected to be dependent upon DA levels in the nigrostriatal system, and in PD the loss of DA terminals is associated with a decrease in endogenous synaptic DA. Therefore, the nigrostriatal system in PD patients is reliant upon exogenous sources of DA (levodopa) in order to maintain DA levels at the synapse. However, recent evidence also suggests that other neurotransmitter systems may play a role in the development of LID in PD, including the serotonergic system. Here, we aim to review the literature to date regarding the pharmacokinetics of levodopa in the development of dyskinesias in PD patients from both animal models and patient studies.
benefits while experiencing some form of dyskinesia, rather than reduce levodopa therapy with its associated decrease in mobility but attenuation of dyskinesia.

The most common form of dyskinesia is “peak-dose” dyskinesia, which consists of a combination of dystonic and choreiform movements and occur during the period in which levodopa reaches peak-plasma concentration (60-90 min after levodopa administration).4-15 Peak-dose dyskinesias are characterized by a sequence of Improvement-Dyskinesia-Improvement (IDI) and are usually alleviated by reducing the dose of levodopa (for review see Nutt et al14 and Fahn15). Biphasic dyskinesias occur when DA plasma concentration levels are rising or falling and typically consist of repetitive, stereotypic movements of the legs.17 This is the less common form of LID, although no systematic epidemiological data has been reported. Conversely to peak-dose dyskinesias, biphasic dyskinesias are characterized by a sequence of Dyskinesia-Improvement-Dyskinesia (DID). Another form of LID, the so-called yo-yo dyskinesia does not appear to follow an Improvement-Dyskinesia sequence and does not appear to be clearly related to levodopa dosing16 as the response to levodopa fluctuates from “on” to “off” and back again throughout the levodopa-dose cycle. An unusual form of dyskinesia termed “off-phase dyskinesia” occurs when patients are in the “off” state (ie, they are not taking any DA treatment). Off-phase dyskinesia has been observed both following deep brain stimulation surgery and neural transplantation with fetal tissue.9 The later is termed graft-induced dyskinesias (GID) and it is unclear whether GID and LID share the same pathogenic mechanisms.

**PATHOGENESIS OF LEVODOPA-INDUCED DYSKINESIA (LID) IN PARKINSON’S DISEASE (PD)**

**Evidence in animals**

The most common animal models of LID pathogenesis primarily consist of the 1-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine (MPTP)-lesioned primate model and 6-hydroxydopamine (6-OHDA)-lesioned rat model. The MPTP is a lipophilic substance that can efficiently cross the blood-brain-barrier, whereby it is then taken up by the DA transporters, inducing Parkinssonian behavioral, neurological, and pathological effects.21 Permanent DA depletion, specific to the nigrostriatal pathway can be achieved using the 6-OHDA-lesioned rat model. The 6-OHDA is a nonspecific catecholaminergic toxin and is administered via stereotaxical surgery to induce usually unilateral lesions at various points along the nigrostriatal pathway in order to achieve DA degeneration and subsequent Parkinssonian deficits. In both models, levodopa treatment will be administered in order to reproduce human LID (dyskinetic group) and at least one control group, which may or may not be lesioned, but will not have dyskinesia induced (nondyskinetic group).

The majority of animal studies corroborate what is observed clinically (ie, that degree of DA denervation is associated with the development of dyskinesia). One interesting finding is that MPTP-lesioned primates who did not develop Parkinson motor symptoms did go on to develop dyskinesia, which indicates that the threshold of DA denervation is lower for the production of LID compared to PD symptoms. Furthermore, there are findings that dyskinesia can be induced in normal, unlesioned primates.22,23 However, it must be noted that levodopa doses administered in such animal studies are invariably much higher than those for PD patients within the clinical setting and, therefore, may account for the rapid development of involuntary movements.24

The pathogenesis of LID can be studies in animal models by reproducing risk factors associated with LID development in PD patients. The 6-OHDA-lesioned rats that have been subjected to daily administration of levodopa, during which normal movements not ascribed to the execution of purposeful behavior (ie, dyskinesia) are exhibited in the animals. These movements emerge 20–30 min after administration of levodopa reproducing peak-dose dyskinesia observed in PD patients.25 It has been demonstrated that the levodopa dose has an effect on dyskinesia exhibited in 6-OHDA-lesioned rats.26 When a therapeutic dose of levodopa was applied (6–10 mg/kg levodopa/day), nearly all developed dyskinesia within 2–3 weeks. Following an increase in a levodopa dose (50 mg/kg levodopa/day), latency was shortened and severity and incidence of dyskinesia increased.

It has also been reported that exposure to levodopa may lead to a priming effect as evidence in MPTP-treated primate who were administered levodopa but did not develop Parkinson symptoms. These primates also experienced a reoccurrence of dyskinesia more readily than the primates who have not received levodopa and those that were only partially lesioned. Indeed, primates severely lesioned developed dyskinesia following the first dose of levodopa compared to those that were only partially lesioned and requiring several doses before the involuntary movements are exhibited. The authors concluded that the degree of DA denervation correlated with the severity of dyskinesia experienced once primed for levodopa.24 The extent of nigrostriatal lesions in 6-OHDA-lesioned rats (ie, injecting different amounts of 6-OHDA to create either partial or complete lesions) has revealed that a threshold value of 80% loss of nigrostriatal neurons was required for the animals to develop dyskinetic movements.7 In addition, the same study demonstrated that some animals that had complete DA denervation did not go on to develop dyskinesia. This finding indicates that the complete DA denervation is not solely responsible for the induction of LID in rats, and likely not the only contributory factor for LID in PD patients. Although, it must be noted that complete DA denervation is never reached in PD patients and end-stage patients will not only have a great loss of presynaptic DA but also a reduction in autoregulatory feedback from DA transporters. It is not known whether these end-stage patients will experience less dyskinesia as a result and is an area warranting further research.
One proposed presynaptic mechanism contributing to LID is related to a dramatic increase in synaptic DA levels, which would lead to alterations in the degree of receptor stimulation, induced by levodopa administration. This suggestion is supported clinically by the demonstration that peak-dose LID are dose dependent with a reduction of the levodopa dose leading to an increased severity of dyskinetic movements.\(^{27,28}\) It has been suggested that a decrease in the presynaptic “buffering” is not dependent upon the degree of presynaptic denervation.\(^{23}\)

Postsynaptic changes have been suggested as leading to the development of LIDs. It is suggested that dysplastic changes occur following the destruction of dopaminergic input to the striatum and subsequent levodopa treatment.\(^{29}\) It is thought that alterations at the receptor level (denervation supersensitivity)\(^{30}\) create a downstream cascade of modifications, which include the second messenger and signaling pathways\(^{31}\) ultimately leading to the emergence of LIDs.

Investigating the mechanisms underlying LID in animal models typically involves the destruction of presynaptic DA terminals following the administration of a specific neurotoxin. It is generally thought that both presynaptic (production, storage, release, and reuptake of DA by dopaminergic neurons in the nigrostriatal pathway) and postsynaptic (receptor and second messenger signaling pathway status in striatal neurons) components are crucial in the development of LID.\(^{31}\) However, dissociating changes induced by each compartment independently is complicated by the fact that following destruction of the presynaptic DA neurons, plastic changes of the postsynaptic neurons occur simultaneously.\(^{32,33}\)

The pharmacokinetics of levodopa require intestinal or mucosal absorption and transportation from plasma to the brain across the blood-brain-barrier to reach the striatum where levodopa decarboxylation occurs for conversion to DA.\(^{35}\) The duration of dyskinesia is closely related to plasma levodopa concentrations although severity of the LID experience does not appear to be influenced by levodopa dose or concentration.\(^{34}\) It has been demonstrated that peripheral pharmacokinetics of levodopa (ie, before levodopa reaches the brain) do not differ between dyskinetic rats and nondyskinetic rats. This finding suggests that any differences in striatal levodopa levels between such groups are not caused by a differential absorption of the amino acid in the blood.\(^{35}\) Considering the rate of levodopa decarboxylation is not influenced by extracellular levodopa concentrations\(^{36}\) and that DA levels are greater in dyskinetic rats compared to nondyskinetic rats, the authors suggest that dyskinetic cases are able to transport levodopa from the blood to the brain more rapidly and that striatal levodopa levels are the most prominent risk factor for the development of LID.\(^{35}\) However, several studies in patients have concluded that motor complications, including LID, after chronic levodopa therapy in PD patients correlate with fluctuating plasma concentrations of levodopa.\(^{37-39}\)

Evidence in patients: imaging studies

Considering the role of DA denervation in the pathogenesis of PD, the use of PET techniques allows the assessment of presynaptic and postsynaptic dopaminergic systems in relation to LID in PD patients.

Fluorine-18-6-fluorodopa (\(^{18}\)F-Dopa) PET can be used to assess several monaminergic systems, including the presynaptic dopaminergic system by targeting l-aromatic-amino-acid-decarboxylase (AADC). An \(^{18}\)F-Dopa PET study has reported a 28% decrease in presynaptic terminal function in the putamen in PD subjects who had a fluctuating motor response to levodopa (namely “wearing-off” effect) compared to patients who had a stable response to levodopa.\(^{40}\)

The authors suggested that the differences observed support the “storage hypothesis” ie, that loss of DA terminals in the nigrostriatal pathway is responsible for the motor fluctuations observed in PD patients. They also suggested that their results might reflect an altered “buffering” capacity of the DA terminals in response to differences in the degree of nigrostriatal damage between groups. However, there was considerable overlap between the two groups studied indicating that other factors may play a role. Another study of presynaptic mechanisms in relation to motor complications that utilized \(^{11}\)C-methylphenidate (DA transporter [DAT] marker) demonstrated that greater DAT levels were directly related to lower DA turnover and lower changes in the synaptic DA concentration.\(^{41}\) This is implicit of a crucial role of DAT in maintaining consistent levels of DA in the synapse and terminals. Therefore, a decrease in DAT may lead to an increase in DA turnover and higher oscillations in synaptic DA concentration, thereby possibly predisposing a patient to the occurrence of motor complications as disease processes. A more recent study assessing PD patients with motor fluctuations (27/36 patients presenting dyskinesia) using the presynaptic DA markers, \(^{11}\)C-d-threo-methylphenidate (MP) and \(^{[11]}\)C-Dihydrotetrabenazine (DTBZ) PET demonstrated that putaminal MP/DTBZ was decreased in the motor fluctuation group compared to stable responders,\(^{42}\) ie, that DA transporter levels per surviving nigrostriatal DA nerve terminal were lower in the dyskinetic group. These findings are further support for presynaptic alterations playing a role in the appearance of dyskinesia due to continued DAT downregulation leading to increased levels of extracellular DA.

PET has also been used to assess the possible postsynaptic mechanisms of LID. The \(^{11}\)C-SCH23390 (D1 receptor) and \(^{11}\)C-raclopride (RAC) (D2 receptor) have been used in studies of PD patients with and without dyskinesia.\(^{43-44}\) Findings from these demonstrate that the mean D1 receptor availability is within normal range in the caudate nucleus and putamen and mean D2 receptor availability in the putamen during the baseline condition in both dyskinetic and nondyskinetic PD patients. However, mean D2 receptor availability is reduced by around 15% in the caudate nucleus in both groups. From this, it may indicate that changes in postsynaptic receptor availability are possibly not involved in the pathophysiology
of LID in PD as the reductions in caudate may be a result of disease progression and not due to the development of LID.

The RAC PET can be used in conjunction with levodopa challenge in order to assess in vivo increases in synaptic DA through the decrease of D2 receptor availability. An early study found that RAC binding decreases in the putamen by 23% following a single intravenous injection of levodopa compared to 10% decrease in stable responders. This is suggestive of exogenous levodopa provoking greater DA release in the putamen of fluctuating responders than stable responders. Moreover, Unified Parkinson’s Disease Rating Scale (UPDRS) scores in the “off” medication state inversely correlated with the reduction of putaminal binding. Therefore, it seems that as the disease progresses, evidenced by the decline in motor function, the regulation of DA release following exogenous administration of levodopa is impaired. The authors speculate that the regulation of DA back in to the synapse is impaired following levodopa administration due to the remaining terminals increasing DA synthesis and DAT is unable to compensate by reuptaking the excess DA. Another RAC PET study performed a baseline scan on two groups of PD patients, with and without motor fluctuations following a levodopa challenge. The authors reported that synaptic levels of DA in PD patients with motor fluctuations were three times higher than that in those with a stable response to levodopa 1 hour after administration, which provides an explanation for their rapid response to the medication. Moreover, stable responders maintained increased DA levels for 4 hours after levodopa administration, whereas the synaptic levels in patients with a fluctuating response dropped to baseline (“off”) state. A more recent study positively correlated the presence of dyskinesia with increased levels of DA in the synapse as measured by RAC PET. More specifically, dyskinetics cases showed significantly decreased levels of putaminal RAC binding reflecting greater levels of synaptic DA, following levodopa administration compared to nondonkinesics. Furthermore, in the same study the author’s correlated levodopa induced increases in synaptic DA with corresponding motor scores. It was found that rigidity and bradykinesia but not tremor correlated with DA release in the putamen.

Opioid neuropeptides are abundant in the basal ganglia and are known that the opioid system is involved in the pathophysiology of PD. However, the involvement of the opioid system in the genesis of LID is unknown. Altered opioid transmission has been investigated using [18F]-Diprenorphine PET in relation to the development of LID. In this study, it was demonstrated that PD patients with LID had reduced binding in both striatal (caudate nucleus and putamen) and extra-striatal (thalamus and anterior cingulate) regions compared to stable responders, suggestive of a possible opioid system involvement in the underlying mechanisms of LID. Animal studies have also supported these findings, with 6-OHDA-lesioned rats displaying reduced kappa opioid receptor density in striatal and nigral sites. Furthermore, the selective kappa opioid receptor agonist, U50,488 (trans)-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl] benzeneacetamide methanesulfonate), has been shown to abate LID in 6-OHDA-lesioned rats. The [18F]-L829165 is a selective marker of Neurokinin 1 (NK1) receptor availability. The NK1 receptors belong to the family of neuropeptides called Tachykinins and can be found in both the central and peripheral nervous system. In a preliminary study, it has been demonstrated that thalamic NK1 availability is reduced in dyskinetic patients while remaining within the normal range in stable responders. The latter two in vivo findings are suggestive of the presence of elevated levels of endogenous neuropeptides in the basal ganglia of dyskinetic PD and may be, in part, responsible for the appearance of LID in PD patients.

A therapeutic alternative to the standard oral levodopa therapy is continuous dopaminergic stimulation (CDS). The rational of such therapy is to overcome the pusitile stimulation of DA receptors, which may contribute to the fluctuating motor responses to levodopa due to disease progression and the loss of functioning DA terminals. The CDS treatment option to date includes the subcutaneous apomorphine infusion and intestinal infusion of levodopa. To date, the findings are somewhat encouraging with the reduction of “off” time and a better control of motor fluctuations as well as the improvement of dyskinesia. The authors suggest that even following the use of levodopa equivalent doses dyskinesia experience is improved, suggesting that the levodopa dose is not solely responsible for the development of dyskinesia but the pusitile stimulation of DA receptors. Further studies should utilize in vivo imaging techniques to assess the CDS effect on attenuating LID.

**LEVODOPA-INDUCED DYSKINESIA (LID) AND THE SEROTONERGIC SYSTEM**

It is generally accepted that levodopa acts in the early stages of the disease by being taken up into the spared DA terminals, where it is converted to DA, stored in synaptic vesicles, and released in an activity-dependent manner. However, as the disease progresses, fewer DA terminals are available for this conversion and other cell types have been suggested to play a role in the decarboxylation of levodopa in the advanced disease. Serotoninergic neurons express AADC, the enzyme that converts l-DOPA to DA, and vesicular monamine transporter 2 (VMAT-2), which enables the vesicular storage of synthesized DA. Moreover, serotonin neurons in the dorsal and median raphe nuclei innervate the striatum. Therefore, the presence of AADC and VMAT-2 in serotonin neurons provides the possibility for levodopa-derived DA to be formed, stored, and released thus acting as a “false neurotransmitter” in serotonergic terminals. However, serotonergic neurons are unable to regulate DA release in a normal way. Dopaminergic synapses maintain extracellular DA levels within a narrow physiological range via a combination of autoreceptor-mediated feedback control and reuptake via DAT. The process of DA reuptake allows effective elimination of excess DA from the synaptic cleft, with the D2 autoreceptor maintaining the release from DA terminals in response to changes in the extracellular DA levels within the desired
range. Serotonin neurons do not possess this autoregulatory mechanism; therefore, DA released from serotonergic terminals is likely to generate excessive swings in extracellular levels of DA in response to levodopa administration. To date, the possible role of serotonin in LID has been studied only in animal models in PD. The response to levodopa in PD patients is complex due to various factors including age, disease duration, disease severity (degree of DA denervation and motor dysfunction), levodopa dose, and duration of levodopa treatment. The occurrence of LID in PD patients is a troublesome side effect; therefore, delineating the underlying mechanisms is a therapeutic priority in the management of PD. However, evidence to date from both animal models and patient studies are revealing a much more complex pathophysiology than initially thought. It does not appear that the degree of DA denervation, which is the principal characteristic of PD, is the sole mediator in the emergence of LID. Indeed, other neurotransmitter systems such as the serotonergic system may play a crucial role in the development of LID.

CONCLUSIONS

The response to levodopa in PD patients is complex due to various factors including age, disease duration, disease severity (degree of DA denervation and motor dysfunction), levodopa dose, and duration of levodopa treatment. The occurrence of LID in PD patients is a troublesome side effect; therefore, delineating the underlying mechanisms is a therapeutic priority in the management of PD. However, evidence to date from both animal models and patient studies are revealing a much more complex pathophysiology than initially thought. It does not appear that the degree of DA denervation, which is the principal characteristic of PD, is the sole mediator in the emergence of LID. Indeed, other neurotransmitter systems such as the serotonergic system may play a crucial role in the development of LID.

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