Role of Serotonin Neurons in the Induction of Levodopa- and Graft-Induced Dyskinesias in Parkinson’s Disease

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Abstract: Recent studies in animal models of Parkinson’s disease (PD) have provided evidence that dopamine released from spared serotonin afferents can act as a trigger of dyskinetic movements induced by repetitive, low doses of levodopa. Serotonin neurons have the capacity to store and release dopamine synthesized from systemically administered levodopa. However, because of the lack of any autoregulatory feedback control, dopamine released from serotonin terminals results in excessive swings in extracellular dopamine levels after peripheral administration of levodopa. Such “dysregulated” release of levodopa-derived dopamine is likely to be responsible for the appearance of the abnormal movements in levodopa-primed animals. This mechanism may also play a role in the development of graft-induced dyskinesias in patients that receive fetal neuron transplants, possibly due to the inclusion of serotonin neurons in the grafted ventral midbrain tissue, which contribute to maintain dopamine receptors of the denervated striatum in a supersensitive state.© 2010 Movement Disorder Society

Key words: dyskinesia; l-dopa; serotonin; 5-HT1A receptor agonist; 5-HT1B receptor agonist; graft-induced dyskinesia

INTRODUCTION

The appearance of dyskinesias is a troublesome and complicating problem in the pharmacological management of motor symptoms in PD patients. In most patients, l-dopa therapy is effective during the first years of treatment. However, over time, patients start experiencing side effects, such as narrowing of the therapeutic window, swings in the efficacy of medication, and appearance of dyskinesias. Within 5 years of treatment about 50% of the patients have been reported to develop these motor complications, and this increases to about 90% after the first decade.1

The therapeutic effects of l-dopa, both positive and negative, are caused by its conversion to dopamine in the brain. During early stages of the disease l-dopa is likely to act by being taken up into the spared dopaminergic terminals, where it is converted to dopamine (DA), stored into synaptic vesicles and released in an activity-dependent manner. In this situation, feed-back control mediated by the D2 auto-receptor and DA transporter will help to ensure that the extracellular levels of DA are kept within the physiological range.2,3

As the disease progresses, fewer and fewer DA neurons survive and the serotonin neurons come to play an increasingly important role in DA production. The serotonergic neurons are particularly interesting because they contain the l-dopa-converting aminoacid aromatic decarboxylase (AADC) enzyme and express the vesicular monoamine transporter 2 (VMAT2), which provides the serotonergic neurons with the capacity to store and release DA.4–12 Studies in 6-hydroxydopamine (6-OHDA)-lesioned rats have shown that lesions of the forebrain serotonin afferents by 5,7-dihydroxytryptamine (5,7-DHT) reduced the l-dopa-derived extracellular levels of DA in the striatum by about 80%.13 In addition, it has been shown that release

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of DA, generated from a systemic injection of \(L\)-dopa in complete DA-lesioned rats, is greatly reduced (by more than 80%) when vesicular storage of DA is prevented (in serotonin neurons) by pretreatment with the VMAT-blocker reserpine.\(^{14}\) These results suggest that, in the DA denervated striatum, \(L\)-dopa-derived extracellular DA derives to a large degree from vesicular storage and it is released by an exocytosis mechanism, by the striatal serotonin terminals.

### ROLE OF THE SEROTONIN NEURONS IN THE INDUCTION OF L-DOPA-INDUCED DYSKINESIAS

Earlier it has been assumed that the role of serotonin neurons in delivery of \(L\)-dopa-derived DA is beneficial, and that DA released from serotonin terminals may contribute to the therapeutic effect of \(L\)-dopa therapy. However, because the serotonin neurons lack the autoregulatory feed-back control normally present on DA terminals, the physiological feed-back controlled release of DA from the spared striatal dopaminergic terminals is replaced, in the DA-denervated striatum, by a nonphysiological, uncontrolled release from the serotonin terminals. An increasing body of experimental evidence points to these excessive swings in extracellular DA, released as “false transmitter” from the striatal serotonin terminals, as the main presynaptic trigger of \(L\)-dopa-induced dyskinesia in animal models of PD.\(^{13–18}\) In line with this, we have shown that dyskinesia induced by a daily low-dose of \(L\)-dopa (6–12 mg/kg/day) was almost completely eliminated when the serotonin afferents were removed in animals with either partial or complete lesions of the nigrostriatal DA system.\(^{16}\) Removal of the serotonin system was effective in blocking the induction of dyskinesia, not only in rats with already established dyskinesias but also in non-\(L\)-dopa primed animals, thus supporting the view that DA released from serotonin terminals is responsible for both the induction and maintenance of \(L\)-dopa-induced dyskinesia in \(6\)OHD\(-\)lesioned rats.\(^{16}\)

Some moderate level of dyskinesia reappeared when the \(L\)-dopa dose was increased to 24 or 48 mg/kg, suggesting that other, nonneuronal sites of DA synthesis (e.g., glial cells) may come into play at higher doses of the drug.\(^{19–21}\)

Consistent with this model, de la Fuente-Fernandez et al\(^{22}\) have shown that peak-dose dyskinesias in patients with advanced PD is associated with excessive swings in synaptic DA after oral \(L\)-dopa administration. These synaptic swings, in turn, are proposed to result in a “pulsatile” stimulation of DA receptors on the striatal target neurons. Indeed, continuous delivery of \(L\)-dopa or DA agonists by duodenal or subcutaneous infusion are less prone to induce these side effects.\(^{23–25}\) Pulsatile, intermittent delivery of \(L\)-dopa and dysregulated release of \(L\)-dopa-derived DA from spared serotonin terminals would thus cooperate in the induction of changes located postsynaptically on the striatal neurons.

### BLOCKADE OF DYSKINESIA BY SEROTONIN AGONIST DRUGS

Drugs acting as agonists on the 5-HT\(_{1A}\) and 5-HT\(_{1B}\) autoreceptors provide interesting tools to block or dampen serotonin release—and hence also the release of \(L\)-dopa-derived DA—from serotonin terminals. The serotonergic neurons are known to express three subtypes of autoreceptors, among which the 5-HT\(_{1A}\) and 5-HT\(_{1B}\) are most abundant. 5-HT\(_{1A}\) receptors are located at the cell body level in the dorsal and median raphe nuclei, where they regulate the firing of the serotonergic neurons.\(^{26,27}\) The 5-HT\(_{1B}\) receptors, by contrast, are more abundant on the serotonin terminals in areas innervated by the serotonin system, including the striatum, where they serve to control the terminal release of the transmitter.\(^{28–30}\) Acting together, these two autoreceptor subtypes are able to fine-tune serotonin release and keep the extracellular level of this neurotransmitter within the physiological range.\(^{31}\) In addition to this autoreceptor-mediated control, cortical postsynaptic 5-HT\(_{1A}\) receptors have been shown to contribute to the control of firing rate of serotonin neurons via a polysynaptic feed-back loop.\(^{32,33}\)

In a recent study, we have demonstrated that 5-HT\(_{1A}\) and 5-HT\(_{1B}\) receptor agonists (8-OHDPAT and CP-94253, respectively) act synergistically in blocking \(L\)-dopa-induced dyskinesia.\(^{16}\) Sub-threshold doses of the two compounds, which individually produced only marginal effects, completely suppressed dyskinesia when administered in combination. These results have been obtained not only in the rat but also in the MPTP-treated monkey model of PD.\(^{18}\) Importantly, reduction of dyskinesia in MPTP-treated macaques did not occur at the expenses of the antiparkinsonian effect of \(L\)-dopa. Previous primate studies have given conflicting results on the possibility of reducing the release from the serotonin neurons by 5-HT\(_{1A}\) or 5-HT\(_{1B}\) receptor agonists without interfering with the therapeutic efficacy of \(L\)-dopa medication. In one study,\(^{34}\) a partial reduction of the \(L\)-dopa efficacy was reported in MPTP-lesioned marmosets treated with (+)-8-OHDPAT.\(^{34}\) Others, however, have shown that the partial 5-HT\(_{1A}\) agonist Sarizotan can reduce \(L\)-dopa-induced...
dyskinesia in MPTP-treated macaques without affecting the anti-parkinsonian efficacy of the medication.\textsuperscript{35,36} The different species used and/or differences in the magnitude of MPTP-induced DA depletion might account for the discrepancies in these studies. Preservation of a residual DA innervation, in fact, could have profound consequences on the therapeutic efficacy of L-dopa when DA release from serotonin neurons is silenced, as spared DA terminals are likely to serve as a buffer for L-dopa-derived DA release at synaptic sites after L-dopa administration.

Further evidence for an autoreceptor-mediated antidyskinetic effect of 5-HT\textsubscript{1A} agonists have been recently provided by Eskow et al., by infusing 8-OH-DPAT directly into the dorsal raphe nucleus in L-dopa-treated, dyskinetic rats.\textsuperscript{37} However, inhibition of excessive DA release from serotonin terminals is not the only mechanism that may explain the anti-dyskinetic effect of 5-HT\textsubscript{1A} and 5-HT\textsubscript{1B} agonists. Previous studies have shown that activation of postsynaptic 5-HT\textsubscript{1A} receptors located on the cortico-striatal projection neurons, and their terminals in the striatum, has an inhibitory effect on striatal glutamate release and may therefore contribute to the antidysskinetic effect of 5-HT\textsubscript{1A} agonists.\textsuperscript{38–41} 5-HT\textsubscript{1B} receptors are also expressed postsynaptically in striatum and substantia nigra, and their activation has been suggested to provide an anti-dyskinetic effect by inhibiting GABA release.\textsuperscript{42} In line with this view, we and others have found that 5-HT\textsubscript{1A} and 5-HT\textsubscript{1B} agonists can also suppress dyskinesia induced by direct DA agonists.\textsuperscript{16,39,40} However, higher doses of 5-HT\textsubscript{1A} and 5-HT\textsubscript{1B} agonists are required to induce this anti-dyskinetic effect, compared to the doses needed to suppress L-dopa-induced dyskinesia.\textsuperscript{43} Importantly, however, activation of postsynaptic 5-HT\textsubscript{1A} receptors by higher doses of the agonists is associated with appearance of side effects such as serotonin syndrome components.\textsuperscript{44–46} The decreased anti-parkinsonian effect of L-dopa reported by Iravani and coworkers after (+)-8-OH-DPAT treatment in MPTP-treated marmosets could, at least in part, also be due to the high dose of 5-HT\textsubscript{1A} agonist needed to obtain a significant anti-dyskinetic effect, when given alone. In fact, in the same study, the authors observed a similar reduction in the anti-parkinsonian effect of the D\textsubscript{2}/D\textsubscript{3} direct agonist pramipexole after coadministration with (+)-8-OH-DPAT, suggesting a postsynaptic related side effect due to the high dose of the drug. The advantage of the combined action on the 5-HT\textsubscript{1A} and 5-HT\textsubscript{1B} receptors is due to the fact that the potent anti-dyskinetic effect is obtained at low doses of the agonists. At such doses no side effects have been observed in our studies.\textsuperscript{16,18}

\section*{ROLE OF SEROTONIN NEURONS IN GRAFT-INDUCED DYSKINESIA}

Graft-induced \textit{off-state} dyskinesias (GIDs), seen in the absence of any L-dopa treatment, have emerged as a potentially serious side effects in PD patients that receive transplants of DA-rich ventral mesencephalic tissue.\textsuperscript{47,48} For further progress in the development of cell replacement therapy, it will be important to clarify the mechanisms underlying this problematic adverse effect. One possible explanation, which has gained some interesting imaging and animal experimental support,\textsuperscript{49–51} is that this type of dyskinesia is induced by small, focal transplants, which provide a local “hot-spot” of DA release in an otherwise supersensitive striatum. Recent studies in rodent models of PD, however, suggest that the serotonin neurons included in the grafted tissue may also play a role.

Consistent with the observations in rats with lesions of the nigro-striatal pathway, as described earlier, we have shown that transplants of serotonin neurons, which generate a greater-than-normal serotonin innervation in the striatum, will exacerbate L-dopa-induced dyskinesias in the rat PD model, while transplants of DA neurons will have the opposite effect. As in animals with 6-OHDA lesions alone, administration of 5-HT\textsubscript{1A/1B} agonists will provide an almost complete suppression of abnormal movements in these animals.\textsuperscript{15} In a follow-up study, we have found that transplants of serotonin neurons can trigger L-dopa-induced dyskinesias in non-dyskinetic rats and exacerbate the abnormal movements in mildly dyskinetic animals.\textsuperscript{52}

On the basis of these observations, we propose that the serotonin neurons included in the ventral mesencephalic (VM) grafts may play a role in the induction of dyskinesias in grafted patients. The graft-induced serotonin innervation will provide an additional source of excessive, dysregulated release of DA, generated from systemically administered L-dopa, and thus serve as a trigger for the induction and progressive worsening of L-dopa-induced dyskinesias. Our results indicate that this effect is more pronounced in the absence of a functional striatal DA innervation, and hence in transplants with a low number of surviving DA neurons and a restricted dopaminergic innervation of the host striatum.\textsuperscript{52} In such cases, we propose that the DA release by the serotonin terminals will induce a “dyskinetic” supersensitive state in the striatal target neurons that will increase the risk for the development of graft-induced dyskinesias. The enhanced “uncontrolled” release of L-dopa-derived DA due to the serotonin neurons in the graft may act to further increase the sensitivity of the striatal target neurons to induce dyskinesia.
in response to DA released from the grafted DA neurons.

It is well known that the fetal VM tissue used for transplantation, in addition to DA neurons, also contains serotonin neurons. The number of serotonin neurons will vary from patient to patient, however, depending on the dissection used. This may explain why off-state dyskinesias have been observed only in some, but not all, grafted patients. Our data indicate that as long as a spared portion (in the range of 10–20%) of the DA innervation still remains, the increased serotonin innervation derived from the grafted serotonin neurons will have limited effect on the development or severity of L-dopa-induced dyskinesia. At more advanced stages of the disease, however, when the residual DA input is lost, the serotonin neurons are likely to have a deleterious effect. This close interaction between the DA and serotonin terminals suggests that it is the relative densities of DA and serotonin innervation and not the absolute number of serotonin neurons in the graft, which is the critical factor in determining the impact of grafted serotonin neurons on the development of dyskinesia in grafted patients. In future clinical trials, therefore, more attention should be paid to avoid inclusion of serotonin neurons in the graft cell preparation to provide the maximal functional efficacy in absence of detrimental effects.

**STUDIES IN HUMANS**

Buspirone, a 5-HT$_{1A}$ partial agonist in clinical use for the treatment of anxiety in patients, has been tested as anti-dyskinetic agent with conflicting results in small clinical trials.$^{55,54}$ Bonifati et al.$^{55}$ reported a significant reduction of L-dopa-induced dyskinesia in advanced dyskinetic patients after administration of 10 mg of buspirone. More recently, the partial 5-HT$_{1A}$ agonist Sarizotan was tested in for its anti-dyskinetic effect in patients with PD. An initial open-label study$^{55}$ showed promising results with a significant increase in percent on time without dyskinesia during the waking day (from a mean of 3.7 to 6.0 hours) and a decrease in on time with troublesome dyskinesia (from a mean of 4.5 to 2.5 hours at the final treatment visit). The percent of patients with moderate or severe dyskinesia was decreased from 81.2 to 38.5%. The most common adverse effect was related to worsening of parkinsonism and was partly resolved by reducing the dose. In a subsequent double-blind, placebo-controlled, proof-of-concept study, Bara-Jimenez et al.$^{56}$ investigated the effect of Sarizotan, given orally at 2 and 5 mg twice daily, in 18 relatively advanced PD patients. This study reported a dose-dependent decrease in the dyskinesia score, which was statistically significant at 5 mg, and a prolonged duration of the anti-parkinsonian action of L-dopa, without diminishing the therapeutic efficacy. The magnitude of the anti-dyskinetic effect, however, was less than what was reported in a previous study in MPTP-treated parkinsonian monkeys.$^{35}$ Up to this point, the overall results of these initial clinical studies seem consistent with a role of dysregulated serotonin-neuron dependent DA release in the induction of dyskinesia also in patients with PD, thus supporting the preclinical data discussed earlier.

A more recent larger double-blind multicenter study gave more unclear results.$^{57}$ In this study, 381 patients were included and 338 completed the full program of 12 weeks. Mean disease duration was 13.2 and dyskinesias were present for a mean of 5.1 years. The doses evaluated were 2, 4, and 10 mg/day given in two daily doses. Although mean improvements in on time without dyskinesias were observed in the Sarizotan treated group, these differences were not significantly different from the placebo controls. Significant improvements with Sarizotan at 2 mg/day, however, were found when considering items 32 and 33 in the UPDRS, which evaluate dyskinesia duration and disability. On the basis of these results, a large phase III clinical trial was designed to investigate the efficacy of Sarizotan at 2 mg/day on dyskinesia in patients with advance PD. However, despite the promising results of the earlier studies, this trial was terminated due to lack of efficacy (see Merck web site at http://media.merck.de).

Although a detailed report of this phase III trial has not been published, there are several reasons why this trial failed. First, one may argue that the dose used (2 mg/day) was too low, as suggested by the Bibbiano et al.$^{35}$ experiments in primates. Second, Sarizotan has also some antagonistic properties on DA receptors, which could explain, at least in part, the side effects seen at higher doses in the Goetz et al.$^{57}$ trial, particularly in the worsening of parkinsonism. Third, assuming that the serotonin neurons play a similar role in mediating L-dopa-derived DA release in human as in rodents, the rodent data discussed earlier suggest that targeting the 5-HT$_{1A}$ receptors alone may not be sufficient to provide a significant control of DA release and associated dyskinesias, at least not at doses free of side effects.

In advanced disease, where most of the dopaminergic terminals have degenerated, the serotonin system is likely to provide the main source of DA production and release also in patients with PD. In this situation,
drugs that act to reduce release of DA from the serotonin terminals may reduce not only dyskinesias but also interfere possibly with the beneficial, therapeutic effect of L-dopa medication. It is possible, therefore, that patients with some residual DA innervation, may benefit more from treatments silencing the serotonin neurons than patients with more advanced disease. Maximal benefit from serotonin receptor agonist treatment may thus depend on the selection of those patients which are likely to benefit most.

Despite the failure in the recent Sarizotan trial, serotonin autoreceptor agonists remain a promising tool to control the dyskinetic side effect of L-dopa medication in patients with PD. One should keep in mind, however, that 5-HT₁A agonists, when given in higher doses, are known to activate not only the presynaptic autoreceptors but also the receptors located postsynaptically on other neuronal types, such as the cortical glutamatergic neurons and their striatal terminals. Activation of these receptors is, however, associated with appearance of side effects and may limit the usefulness of 5-HT₁A receptor agonists as anti-dyskinetic agents. The potent synergistic effect of 5-HT₁A and 5-HT₁B agonists, however, might provide a solution. According to the rodent and primate data, the anti-dyskinetic effect induced by co-activation of these two autoreceptors is seen at doses that are below the ones needed to provide significant postsynaptic effects. Whether this is the case also in humans needs to be established, and may represent a critical point for the feasibility of this approach to treat L-dopa-induced dyskinesia in PD patients.

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