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The serotonergic system in L-DOPA-induced dyskinesia: pre-clinical evidence and clinical perspective

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Abstract
During the last decade, the serotonergic system has emerged as a key player in the appearance of L-DOPA-induced dyskinesia in animal models of Parkinson's disease. Clinical investigations, based on imaging and postmortem analyses, suggest that the serotonin neurons are also involved in the etiology of this complication of long-term L-DOPA treatment in parkinsonian patients. These findings have stimulated efforts to develop new therapies using drugs targeting the malfunctioning serotonin neurons. In this review, we summarize the experimental and clinical data obtained so far and discuss the prospects for further development of this therapeutic strategy.

Keywords Parkinson's disease · Dyskinesia · Serotonin · Serotonin autoreceptors · L-DOPA

Introduction

The role of the serotonin system has emerged over the last decade as a leading new concept to understand the mechanism underlying the emergence and expression of dyskinesia in Parkinson's disease (PD). In fact, despite it was introduced almost 50 years ago for the treatment of this disease, L-DOPA still represents the most effective medication for alleviating the motor symptoms. However, the appearance of side effects, such as dyskinesias, limits its efficacy in advanced stages of disease.

Progression of dopamine neuron degeneration is most likely the predominant risk factor for the appearance of LIDs (Bastide et al. 2015; Hong et al. 2014). Indeed, in the standard neurotoxin models of PD, particularly rodents lesioned with 6-hydroxydopamine (6-OHDA) and non-human primates treated with 1-methyl-4-phenyl-tetrahydropyridine (MPTP), peak-dose dyskinesia can be reliably reproduced by repeated dosing of L-DOPA (Bastide et al. 2015; Cenci and Konradi 2010), but only in subjects with an extensive dopamine neuron degeneration, resulting in more than 80% reduction in striatal dopamine levels. Accordingly, Ulusoy et al. have shown that rats in which striatal dopamine levels had been reduced by 70%, without any damage to the striatal dopaminergic innervation (obtained by means of an AAV vector overexpressing a siRNA for the tyrosine hydroxylase) could develop dyskinesia induced by apomorphine, but were refractory to dyskinesia induced by L-DOPA (Ulusoy et al. 2010). These data suggest that LID cannot be induced as long as a sufficient number of spared dopamine terminals are present to mediate regulated release of L-DOPA-derived dopamine.

LID has been shown to be associated with a cascade of events that include: (1) alteration in signal transduction (affecting phosphorylation state of different intracellular mediators such as DARP-32, MAP kinases, mTOR, etc. (Santini et al. 2008, 2009; Subramaniam et al. 2011; Picconi et al. 2003; Westin et al. 2007; Cenci et al. 1998); (2) alterations in gene expression (Cenci et al. 1998; Pavon et al. 2006; Cenci 2002; Carta et al. 2010); (3) alterations in glutamatergic transmission (Gardoni et al. 2006; Hurley et al. 2005; Hallett et al. 2005); (4) reorganization of dendritic spines (Fieblinger and Cenci 2015; Fieblinger et al. 2014); (5) alteration of synaptic plasticity (particularly of LTD) (Bagetta et al. 2010; Picconi et al. 2005). At the beginning

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of our investigations, we set out to determine what was initiating this cascade of events.

Whereas the spared dopamine neurons are important in mediating the initial therapeutic efficacy of L-DOPA, this drug produces clear behavioral effects also in advanced stages of disease and in animals with complete unilateral dopamine depletion. Therefore, other system(s) must contribute to L-DOPA conversion in the absence of a significant dopaminergic innervation. The serotonergic neurons are obvious candidates since they share with the dopamine ones most of the enzymatic machinery responsible for L-DOPA conversion and vesicular storage. Early studies had shown that serotonin neurons could produce and release dopamine after exogenous L-DOPA administration (Arai et al. 1994, 1995; Tanaka et al. 1999). However, serotonergic neurons lack the feedback control mechanism for regulating dopamine release, which is triggered by the activation of presynaptic D2 receptors (Carta and Bezard 2011). Hence, it seemed possible that unregulated release of dopamine from serotonergic terminals could cause fluctuations in extracellular dopamine levels, not seen under normal physiological conditions, and that such swings may play a causative role in the appearance of LID.

In a first series of experiments, published in Brain in 2007, we found that destruction of the striatal serotonergic innervation by a selective serotonin neurotoxin, 5,7-dihydroxytryptamine (5,7-DHT), was able to cause a near-complete suppression of LID in dyskinetic hemiparkinsonian rats (Carta et al. 2007). The critical role of serotonin neurons in the induction of LIDs was observed not only in rats with already established dyskinesia, but also in non-dyskinetic, drug-naïve 6-OHDA-lesioned rats where the development of dyskinesia in response to repetitive, low doses of L-DOPA (6 mg/kg) was almost completely blocked when the serotonin afferents had been removed. A similar LID-blocking effect was obtained using a pharmacological approach to silence serotonin neuron activity by activation of serotonergic autoreceptors, particularly when agonists for the two main types of autoreceptors, 5-HT1A and 5-HT1B, were administered in combination, showing that the two agonists, 8-OH-DPAT and CP-94283, acted synergistically to block LIDs at doses that were only marginally effective when the drugs were given separately. Importantly, at the doses used, the same drug combination was not able to affect dyskinesia induced by apomorphine pointing to a pre-synaptic effect in the reduction of LID (Carta et al. 2007). Further support for a pre-synaptic mechanism of action was provided by Lindgren et al., who showed that the striatal dopamine levels induced by L-DOPA are dose-dependently reduced by this drug combination (Lindgren et al. 2010).

Consistent with the results in 6-OHDA-lesioned rats, we next found, in a collaborative work with Erwan Bezard, that combined treatment with the two 5-HT1A and 5-HT1B agonists was able to produce a near-complete suppression of LID in the primate model, at doses that individually produced no effect (Muñoz et al. 2008), thus confirming the existence of a synergistic effect in the activation of the two types of serotonin autoreceptors. Years later, Beaudoin-Gobert et al., found that a serotonin lesion, induced by 3,4-metylendioximetamfetamin (MDMA), in MPTP-treated macaques, produced an almost complete suppression of LID, in agreement with our rodent and primate data (Beaudoin-Gobert et al. 2015).

The key role of the serotonin system has been recently confirmed by the fact that, opposite to the lesion experiments, increasing the striatal serotonin innervation, by BDNF overexpression, which has trophic effect on serotonin axons, lead to striking exacerbation of LID in parkinsonian rats, confirming the striatum as the most important brain area in dyskinesia (Tronci et al. 2017).

Based on these results, we have proposed a model for the pre-synaptic events involved in the induction of LIDs (Carta et al. 2007). At an early stage of disease (Fig. 1a), the full therapeutic effect of L-DOPA would be maintained as long as there are enough spared dopaminergic terminals to mediate L-DOPA conversion to dopamine and its vesicular storage, providing the necessary fine-tuning of dopamine release and the maintenance of synaptic dopamine at physiological levels due to the presence of the D2 autoreceptor and the dopamine transporter (DAT). At this stage, serotonin neurons are also likely to provide some contribution to striatal dopamine production and release (Navailles et al. 2010); however, this contribution would at this stage not be detrimental due to the ability of the spared dopamine terminals to buffer the swings in serotonin neuron-derived dopamine.

At an advanced stage of disease (Fig. 1b), when most of the dopaminergic terminals are lost, the serotonergic neurons would come to play a major role in the conversion of L-DOPA to dopamine. However, serotonin neurons are not able to regulate dopamine release due the lack of the presynaptic feedback control mediated by D2 receptors. The dysregulated release of dopamine from serotonergic terminals would cooperate with the intermittent oral administration of L-DOPA to produce abnormal swings in extracellular dopamine (Carta and Bezard 2011; Mosharov et al. 2015). In this situation, activation of serotonin autoreceptors by selective agonists will reduce the amount of dopamine released from these neurons and dampen excessive synaptic dopamine peaks.

Several other studies have provided further support to the above scenario and contributed to clarify the mechanisms of the serotonin system involvement in dyskinesia. In a series of studies, Christopher Bishop and collaborators have helped not only to clarify the role of serotonin neurons in LID (Eskow et al. 2007, 2009), but also to dissect out the relative contribution of the pre- and post-synaptic 5HT1 receptors to

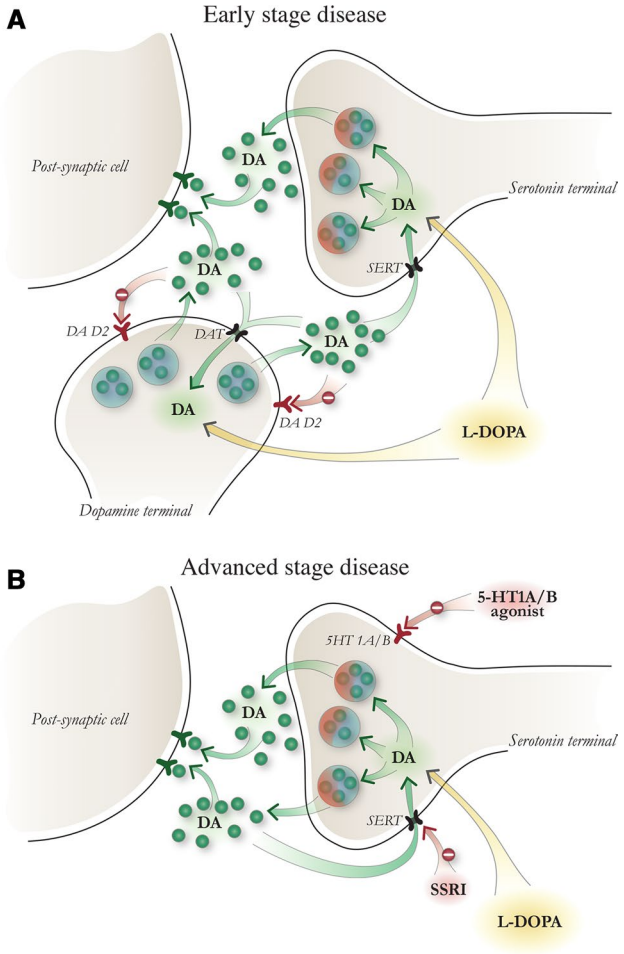

Fig. 1 **a** represents the situation at an early stage of disease. In this case, spared dopaminergic terminals can mediate L-DOPA conversion to dopamine and its vesicular storage, providing the necessary fine-tuning of dopamine release, and the maintenance of synaptic dopamine at physiological levels due to the presence of the D2 autoreceptor and the dopamine transporter. At this stage, serotonin neurons are also likely to provide some contribution to striatal dopamine production and release, but the buffering capacity of the dopaminergic terminal would avoid excessive synaptic dopamine. **b** represents the situation at an advanced stage of disease. In this scenario, most of the dopaminergic terminals are lost, and serotonergic neurons come to play a major role in the conversion of L-DOPA to dopamine. However, serotonin neurons are not able to regulate dopamine release due to the lack of the pre-synaptic feedback control mediated by D2 receptors. The dysregulated release of dopamine from serotonergic terminals would cooperate with the intermittent oral administration of L-DOPA to produce abnormal swings in extracellular dopamine. In this situation, activation of serotonin autoreceptors by selective agonists will reduce the amount of dopamine released from these neurons and dampen excessive synaptic dopamine peaks. Similarly, the administration of SERT blockers would prevent extracellular dopamine to be recycled into serotonergic neurons and may also lead to activation of serotonin autoreceptors

the antidyskinetic effect of 5-HT1 receptor agonists (Meadows et al. 2017; Lindenbach et al. 2013; Dupre et al. 2013; Jaunarajs et al. 2009; Bishop et al. 2009; Dupre et al. 2008).

In fact, 5-HT1A and 5-HT1B receptors exist not only as autoreceptors on serotonin cell bodies and axons, respectively, but also as heteroreceptors on cortical and striatal neurons, where they serve to control striatal glutamate and GABA release (Zhang et al. 2008; Mignon and Wolf 2005). Glutamate is highly involved in the induction and expression of dyskinesia in Parkinson's disease; indeed, the NMDA antagonist amantadine is the only compound with proved clinical efficacy against dyskinesia in PD (Ory-Magne et al. 2014; Rascol et al. 2011). Thus, activation of striatal and cortical 5-HT1A receptors has been demonstrated to provide significant antidyskinetic effect in the rat 6-OHDA model of PD, and 5-HT1A receptor agonists have been shown to suppress not only LID, but also abnormal movements induced by direct dopamine receptor agonists (Meadows et al. 2017; Lindenbach et al. 2013; Dupre et al. 2013; Jaunarajs et al. 2009; Bishop et al. 2009; Dupre et al. 2008). This effect is independent from the serotonin neurons, and takes place at doses of agonists that are higher than those effective on LID (Muñoz et al. 2009; Carta et al. 2007); however, a new class of highly selective 5-HT1A receptor agonists are being developed with the goal to preferentially activate either pre- or post-synaptic 5-HT1A receptors, and appear to be effective at very low doses (Meadows et al. 2017).

Philippe De Deurwaerdère and collaborators have provided further insights into the role of serotonin neurons in the rat model of PD (Porras et al. 2014; Navailles and De Deurwaerdere 2012; Navailles et al. 2010). In particular, these authors have demonstrated that the contribution of serotonin neurons to dopamine production (after exogenous L-DOPA administration) is not restricted to the lesioned striatum, but applies to all brain regions receiving relevant serotonergic innervation both in 6-OHDA-lesioned and intact rats (Navailles and De Deurwaerdere 2012; Navailles et al. 2013). Moreover, these authors have provided evidence that long-term L-DOPA treatment reduces basal 5-HT release and metabolism, with concomitant reduction in serotonin tissue content, in several brain areas (Navailles et al. 2011). Thus, the impairment in 5-HT neuronal function induced by chronic L-DOPA may be involved not only in the induction of LIDs, but also in the emergence of non-motor side effects of L-DOPA pharmacotherapy, such as depression or anxiety, where the serotonergic system plays a relevant role (Navailles et al. 2011).

Studies in PD patients

Whereas the pre-clinical evidence is compelling, the relevance for the human condition has been more debated. However, PET imaging has provided convincing support for the involvement of serotonin neurons in the development and expression of LIDs in PD patients. In their 2004 PET study, de la Fuente-Fernandez et al. showed that

extracellular dopamine levels are higher in dyskinetic versus non-dyskinetic patients 1 h after L-DOPA administration (de la Fuente-Fernandez et al. 2004). Using the same ^{11}C-raclopride displacement method to measure dopamine release, Politis and colleagues not only confirmed that dyskinetic patients present higher extracellular dopamine levels after L-DOPA administration, compared to non-dyskinetic subjects, but showed also that these levels are decreased by the administration of buspirone, a partial 5-HT1A receptor agonist known to reduce the activity of serotonin neurons (Politis et al. 2014). Furthermore, buspirone produced a significant reduction of moderate dyskinesia, without worsening of the motor deficits, in line with previous animal studies (Eskow et al. 2007).

The role of the serotonin system is further supported by studies using SERT binding as a measure of the status of the serotonin innervation in the basal ganglia. In line with the ^{11}C-raclopride displacement studies, Angela Cenci's group was the first to show that SERT binding is increased in dyskinetic subjects, both in animal models and in PD patients (Rylander et al. 2010). In subsequent studies using PET imaging, Politis and collaborators (Smith et al. 2015; Rousakis et al. 2016) and Lee et al. (Lee et al. 2015) have shown that the SERT-to-DAT binding ratio is increased in putamen and globus pallidus of dyskinetic patients compared to non-dyskinetic ones, further pointing to the state of the serotonin innervation as a key determinant in the appearance of dyskinesia. In further support of the predictive value of the animal models, Conti et al. have shown that the SERT-to-DAT ratio is strongly correlated with LID also in L-DOPA treated hemi-parkinsonian rats (Conti et al. 2016), suggesting that this measure could provide a potential biomarker for the development of dyskinesia.

Thus, striatal serotonin hyperinnervation appears to take place not only in lesioned rats but also in patients that develop LID, and it is likely to contribute to the dysregulated release of L-DOPA-derived dopamine (Politis et al. 2014; Rylander et al. 2010).

Interestingly, the above findings suggest that SERT binding can be used not only as a marker for the state of the serotonin innervation, but it may also have direct functional implications for the induction of LID. It has been shown that SERT is able to bind and transport extracellular dopamine, as it does for extracellular serotonin (Kannari et al. 2006). Hence, uptake of extracellular dopamine by SERT may contribute to, and amplify, the dysregulated release of dopamine from serotonergic neurons.

In support of this scenario, we have shown, along with Bishop and collaborators, that inhibition of SERT by selective serotonin reuptake inhibitors (SSRIs) produces striking suppression of LID in dyskinetic rats and MPTP-treated macaques (Fidalgo et al. 2015; Conti et al. 2014; Bishop et al. 2012), although in the latter model the effect is accompanied by worsening of the parkinsonian score. This effect may be due, at least in part, to blockade of dopamine reuptake by SERT, but it seems possible that SERT blockade may suppress LID expression also via activation of the inhibitory 5-HT1A and 5-HT1B receptors caused by increased extracellular levels of serotonin. In support, Conti et al. (2014) have shown that pretreatment of dyskinetic rats with 5-HT1 receptor antagonists is effective in suppressing the antidyskinetic effect of SSRIs.

A major objection to this view is that such an antidyskinetic effect has not been reported in PD patients treated with SSRIs for depression, although, in a retrospective study, patients under SSRIs have been reported to present a delayed onset and reduced severity of dyskinesia compared to control subjects (Mazzucchi et al. 2015). It should be recalled, however, that chronic SSRI treatment is likely to produce desensitization of serotonin autoreceptors in patients, which may explain the delayed effect of these compounds on symptoms of depression. If so, the most common clinical conditions where SSRIs are used may not be ideal to detect a possible antidyskinetic effect, as SSRIs when administered chronically would not be accompanied by a reduction in serotonin neuron activity sufficient to dampen the swings in L-DOPA-induced DA release.

Serotonin neurons as a therapeutic target

Whereas the experimental evidence for the involvement of the serotonin system in the development and expression of LID is compelling, not only in PD models but also in patients, the therapeutic feasibility of approaches aimed to dampen serotonin neuron activity remains to be established. The clinical trials performed so far have used drugs that act as agonists of the 5-HT1A receptor, i.e. buspirone (Politis et al. 2014), sarizotan (Bara-Jimenez et al. 2005; Goetz et al. 2007; Olanow et al. 2004) and tandospirone (Kannari et al. 2002). The promising antidyskinetic effect observed in the early open label trials, however, was not confirmed in the larger placebo-controlled sarizotan study performed by Goetz and collaborators (Goetz et al. 2007). At the higher doses tested, 4 and 10 mg/day, the treatment was associated with a worsening of the clinical condition seen as an increase in the patients´ OFF-time. This is consistent with observations in MPTP-treated non-human primates showing that at higher doses of the drug the effect on LID is accompanied by a deterioration of the antiparkinsonian response (Gregoire et al. 2009).

The use of 5-HT1A agonists as antidyskinetic agents is complicated by the fact that these receptors are widely expressed in the brain. Thus, they are present not only as autoreceptors on serotonin neurons but also postsynaptically on neurons in areas involved in motor control, including motor cortex and striatum. Studies in rodents from

Christopher Bishop´s lab have shown that local activation of 5-HT1A receptors in motor cortex or striatum can attenuate both the onset and expression of LID (Meadows et al. 2017; Ostock et al. 2011), probably due to an inhibitory effect on striatal glutamate release (Antonelli et al. 2005; Dupre et al. 2011), indicating that dampening of the striatal glutamatergic input contributes to the anti-LID effect of 5-HT1A agonists. At higher doses, however, there is a risk that more profound inhibition of the corticostriatal glutamatergic pathway will worsen the parkinsonian symptoms.

These clinical and experimental data show that selective 5-HT1A agonists, such as sarizotan, are highly effective antidyskinetic agents, but that their clinical usefulness may be limited by their propensity to interfere with the beneficial effects of L-DOPA. Indeed, in case of sarizotan and buspirone, this therapeutic window may be further narrowed by their antagonistic action on dopamine receptors. It seems possible, therefore, that activation of only one type of serotonin autoreceptor may not be sufficient to obtain a clinically significant antidyskinetic effect at doses that are devoid of side effects. Based on the finding that agonists selective for 5-HT1A and 5-HT1B receptors act synergistically to block LID, summarized above, it seems possible that agonists with dual 1A/1B affinity (and without antagonist action on DA receptors) could have a more favorable pharmacological profile and provide a wider therapeutic window where effective suppression of LID can be obtained without a concomitant reduction of the therapeutic effect. In our search, we identified two such mixed 5-HT1A/1B receptor agonists, eltoprazine and anpirtoline, that had already been tested in humans for different conditions. We found that both drugs were able to provide near-complete suppression of dyskinesia in both rodents and primates; at higher doses, however, this effect was accompanied by a partial reduction of the therapeutic effect of L-DOPA (Bezard et al. 2013a, b). From our previous experiments using mixtures of individual, selective 5-HT1A and 1B compounds (Carta et al. 2007; Muñoz et al. 2008), it seems that the two autoreceptors have to be activated in a precise ratio to avoid detrimental effects, which may be difficult to obtain with a mixed action compound. Nevertheless, eltoprazine was recently investigated in a first double-blind, dose-finding, acute study in 22 dyskinetic subjects with advanced disease (Svenningsson et al. 2015). The results showed that eltoprazine administered as a single dose was able to induce a statistically significant reduction of LID at the middle dose tested without any negative effect on the antiparkinsonian action of L-DOPA. Although the reduction in LID was relatively modest, it seems possible that chronic administration of eltoprazine at higher doses may improve its antidyskinetic effect and that this could be obtained in the absence of any complicating side effects (Bezard and Carta 2015).

In addition to sarizotan and eltoprazine, buspirone has been tested in dyskinetic patient within a PET imaging study (Politis et al. 2014). Results showed that a single dose of buspirone, administered 15 min before L-DOPA, could produce significant and marked reduction of LID and that this was accompanied by parallel reduction in extracellular dopamine as assessed by ^{11}C-raclopride PET. This effect was most prominent in patients with moderate dyskinesia, with a mean reduction in the peak AIMS score of about 50%. There was a trend to a reduction also in patients with more severe dyskinesia, but this effect (around 25% reduction) did not reach significance. At the dose used (0.35 mg/kg) buspirone did not affect the L-DOPA induced motor response. In addition to its activity on 5-HT1A receptors, buspirone acts as a weak antagonist on D2 receptors. However, since striatal ^{11}C-raclopride binding was unaffected by the buspirone treatment it seems that DA receptors are not involved when the drug is given at the dose used in this study.

What next?

The encouraging results obtained with eltoprazine and buspirone in these two single-dose trials call for further studies in placebo-controlled trials where the drugs are given chronically at escalating doses. In such dose-finding studies, it will be important to find a balance between the dampening of the excessive synaptic dopamine peaks, induced by the activation of 5-HT autoreceptors, and the maintenance of sufficient dopamine receptor occupancy to sustain the therapeutic effect. In patients with advanced disease, when most of the striatal dopaminergic innervation has degenerated, the serotonin neurons are likely to represent the major source of dopamine production from exogenous L-DOPA. Thus, in advanced PD, at least, serotonin neuron-derived dopamine may not only be responsible for the induction of LID, but also for the residual therapeutic effect (Carta and Tronci 2014).

This dual role of serotonin-derived dopamine may explain the worsening of the PD score seen at higher doses of eltoprazine and anpirtoline in MPTP-treated non-human primates (Bezard et al. 2013a, b). In future trials, therefore, it may be necessary to include not only patients with severe dyskinesia, but also subjects presenting a more moderate form, since they may be more likely to benefit from the antidyskinetic effect of these drugs, while avoiding worsening of parkinsonism. Since swings in L-DOPA-induced DA release induced by intermittent L-DOPA treatment are likely to drive the development of LID, it seems possible that an early intervention with 5-HT1 agonists at a dose sufficient to dampen these swings could prevent the development of more severe and disabling dyskinesia.

An interesting alternative possibility is to combine 5-HT1 receptor agonist treatment with drugs that act to modulate

striatal glutamatergic function. In our eltoprazine study (Bezard et al. 2013b) we found that eltoprazine and the NMDA receptor antagonist amantadine act synergistically to reduce LID in MPTP-treated monkeys, showing that eltoprazine can be used to potentiate the antidyskinetic effect of amantadine, combined with a marked increase in good ON-time without any detrimental effect on the PD disability score. This points to the possibility to use 5-HT1 agonists (at a dose sufficient to dampen the abnormal swings in L-DOPA-derived dopamine release) in combination with drugs aimed to normalize glutamate release from the overactive corticostriatal neurons. Amantadine, which is already in use in the clinic, is an obvious candidate, but other glutamate receptor agonists that now are in development could be explored for this purpose. This combined approach may offer the best opportunity to obtain an effective antidyskinetic therapy in the absence of any worsening of parkinsonism or other negative side effects, effective also in advanced stages of the disease.

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