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REVIEW ARTICLE

FACING DYSKINESIA IN PARKINSON'S DISEASE: NONDOPAMINERGIC APPROACHES

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SUMMARY

L-DOPA has been the gold standard for the treatment of Parkinson's disease for the last 5 decades. Nevertheless, problems with long-term use, such as motor fluctuations and dyskinesias, have led investigators to search for alternative therapies and for various approaches designed to minimize or ameliorate dyskinesias. Dopaminergic strategies are being studied, including continuous drug infusion. Moreover, nondopaminergic approaches such as serotonergic agents, adenosine A_{2A} receptor antagonists and amantadine are also being investigated. Serotonin 5-HT_{2A} receptor antagonists and 5-HT_{1A} receptor agonists have been studied for their antidyskinetic effects. Adenosine A_{2A} receptor antagonists exert antiparkinsonian effects in animal models and several candidates have progressed to phase II or III clinical testing. Generally, these agents have been shown to decrease L-DOPA "off" time and increase "on" time, without worsening L-DOPA-induced dyskinesias. Of all the drugs tested so far, amantadine appears to produce the most consistent antidyskinetic actions. In conclusion, numerous approaches appear to offer promise for the management of dyskinesias, one of the most troubling aspects of the current treatment of Parkinson's disease.

INTRODUCTION

Parkinsonism is a family of motor disorders with symptoms that include bradykinesia, rigidity and tremor. Idiopathic Parkinson's disease is the second most common neurodegenerative disease. Parkinson's disease results from degeneration of nigrostriatal dopamine (DA) neurons (1), and is also associated with various other neuropathological features, including the development of intraneuronal protein inclusions (Lewy bodies) and increased production of α-synuclein (2). For the last 40 years, the most effective treatment for Parkinson's disease has been administration of the DA precursor L-DOPA, usually in combination with a peripheral decarboxylase inhibitor (1, 3). Despite the positive features of L-DOPA therapy for Parkinson's disease, extensive research has identified numerous problems associated with the long-term use of L-DOPA. Many patients develop psychotic reactions to L-DOPA, which resemble the positive symptoms (i.e., delusions and hallucinations) of schizophrenia (4). "On-off" motor fluctuations that emerge after several years of treatment pose a severe limitation on the long-term utility of L-DOPA treatment (5, 6). In addition to these problems, L-DOPA pharmacotherapy is also associated with the development of dyskinesias (3, 7-11), abnormal involuntary movements that primarily affect the extremities, trunk or jaw. These movements can be choreiform in nature (i.e., resembling dancing), but may include dystonias, myoclonus or other motor disorders (6). Initial treatment with L-DOPA only rarely induces dyskinesia, but with chronic treatment the likelihood of displaying L-DOPA-induced dyskinesia becomes substantially increased (8, 12); approximately one-third of parkinsonian patients develop dyskinesias after 2 years on L-DOPA, while more than half manifest this side effect after 5 or more years of treatment (13).

Because L-DOPA-induced dyskinesias represent a major problem for the management of Parkinson's disease symptoms, there is considerable interest in finding treatments that provide some degree of protection. Thus, investigators are attempting to identify antiparkinsonian treatments that minimize the induction of dyskinesias, or treatments that can be given as adjuncts to L-DOPA that either reduce dyskinesias or at least would not exacerbate them. In order to accomplish this goal, there has been considerable research over the last few years both in human patients and animal models (14, 15). This research has attempted to identify the mechanisms involved in the generation of dyskinesias and to characterize the effects of various dopaminergic and nondopaminergic strategies for the minimization of dyskinesias.

The precise cause of dyskinesias in parkinsonian patients remains unknown (16). Some researchers suggest that the ongoing degener-

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ative processes that underlie the progression of the disease also act to make dyskinesias more likely with advancing degeneration. It has also been hypothesized that L-DOPA-induced dyskinesias result from the repeated pulsatile stimulation of DA receptors that results from fluctuating levels of the drugs that are given to treat Parkinson's disease (17, 18). Based on this hypothesis, it is suggested that repeated administration of L-DOPA progressively lowers the threshold for induction of dyskinesias through a process of sensitization. This hypothesis has led to the suggestion that continuous application of dopaminergic agents, whether the precursor L-DOPA or various DA agonists, could minimize the development of dyskinesias by providing nonpulsatile stimulation of DA receptors (17-23). This approach is consistent with observations made in studies with animal models. In MPTP-treated primates, long-acting DA agonists appear to be less likely to produce signs of dyskinesias than short-acting agonists (11). In addition, comparisons between continuous versus intermittent administration of DA agonists have indicated that intermittent administration is more likely to produce dyskinetic-like responses in MPTP monkeys (20, 21).

Although there continues to be a substantial focus upon dopaminergic strategies, such as sustained-release formulations, for the treatment of dyskinesias (e.g., 23), several important issues remain. Researchers disagree about the long-term advantages of using sustained-release formulations of dopaminergic agents for the management of dyskinesias (22). Some investigators have advocated a focus upon DA-related signal transduction cascades rather than DA receptor stimulation per se for the treatment of dyskinesias (16). In addition, the idea that the dyskinetic response shows a different pattern of sensitization from the therapeutic response to L-DOPA has been challenged (12). Thus, there is still considerable uncertainty about the mechanisms that underlie the development of dyskinesias and the most useful approach for dealing with them. Motor functions related to parkinsonian symptoms are not simply dependent upon dopaminergic mechanisms, but instead are characterized by complex neurotransmitter interactions involving multiple transmitters, signaling cascades and basal ganglia structures. For those reasons, multiple strategies for the management of dyskinesias, including nondopaminergic treatments, need to be considered (24, 25). Several neurotransmitter systems have been identified as potential targets for developing antidyskinetic drugs, including α-adrenergic, opiate, serotonergic, purinergic and excitatory amino acid systems (24-27). The present paper is focused on recent exploration of nondopaminergic approaches for the management of L-DOPA-induced dyskinesias, with a particular emphasis on drugs that act on 5-HT receptors, adenosine A_{2A} receptor antagonists and the NMDA antagonist amantadine.

SEROTONERGIC APPROACHES

Several lines of evidence link serotonin systems to striatal motor function and dysfunction, including the regulation of dyskinetic movements. The possible link between tardive dyskinesia induced by chronic administration of antipsychotic drugs and L-DOPA-induced dyskinesias has been one of the factors stimulating interest in the possibility that drugs acting on 5-HT receptors could be useful for the treatment of L-DOPA-induced dyskinesias. Although "typical" antipsychotic drugs such as haloperidol or pimozide frequently produce dyskinesia after long-term administration, the "atypical" antipsychotic drug clozapine has a relatively low propensity for inducing tardive dyskinesia (28-30). In addition to binding to DA receptors, clozapine also has high affinity for 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_6 and 5-HT_7 receptors (31), and it is thought to act as an antagonist or inverse agonist at these receptors (32, 33). It has been suggested that the serotonergic actions of clozapine are related to the apparent protection against various types of dyskinesias that this drug affords (28).

5-HT_2 family receptors have been implicated in motor functions related to parkinsonism and dyskinesia. 5-HT_{2A} receptors are expressed in the striatum, suggesting a major role for these receptors in motor function (34). Blockade of 5-HT_2 receptors, including 5-HT_{2A} receptors, has been shown to affect motor functions related to parkinsonism. The 5-$HT_{2A/C}$ receptor antagonist mianserin was shown to be effective in reducing oral tremor in a rodent model of parkinsonism (35), motor dysfunction in haloperidol-treated monkeys (36) and parkinsonian symptoms in human patients (37). Ritanserin, another 5-HT_{2A} receptor antagonist, improved motor function in patients with tremor-dominant Parkinson's disease (38). Clozapine, which is known to bind to 5-HT_{2A} receptors and act as an antagonist/inverse agonist, suppresses tremor in a rodent model of parkinsonism (39), and attenuates tremor and other motor dysfunctions in patients with idiopathic Parkinson's disease (40). In addition, clozapine and quetiapine, which both act as 5-HT_{2A} receptor antagonists or inverse agonists, have been shown to reduce L-DOPA-induced dyskinesias in MPTP-treated primates (41-43). Recently, it was reported that the novel 5-HT_{2A} receptor inverse agonist ACP-103 reduced oral tremor in a rodent model of parkinsonism, and also reduced L-DOPA-induced dyskinesias in primates (44). Consistent with these observations, studies have shown that ritanserin and clozapine can attenuate L-DOPA-induced dyskinesias in patients with Parkinson's disease (41, 45).

5-HT_1 family receptors have also been implicated in the regulation of dyskinesias. The 5-HT_{1A} receptor agonist sarizotan suppressed signs of L-DOPA-induced dyskinesia in both DA-depleted rats and MPTP-treated primates (27). The 5-HT_{1A} receptor partial agonist and atypical anxiolytic drug buspirone reduced signs of dyksinesia in a rodent model (46) and attenuated L-DOPA-induced dyskinesias in Parkinson's disease patients (47, 48). However, human studies with sarizotan have yielded mixed results. Barra-Jimenez et al. (49) found that 5 mg of sarizotan increased the percentage of "on" time without dyskinesias in L-DOPA-treated patients and decreased the dyskinesia score, but a more recent double-blind, multicenter clinical study yielded only modest results (50). On the one hand, 2 mg of sarizotan significantly decreased dyskinesia scores, as measured by the Unified Parkinson's Disease Rating Scale (UPDRS, items 32 and 33), but sarizotan treatment did not significantly affect "on" time without dyskinesias. Another avenue being pursued is the 5-HT_{1A} receptor agonist piclozotan. In a recent phase IIa clinical trial, piclozotan given as adjunctive treatment with L-DOPA improved "on" time without dyskinesias, as well as reducing "off" time (51).

Despite these mixed results, it is possible that future research will identify serotonergic treatments that consistently act to suppress L-DOPA-induced dyskinesias. In a recent review, Carta et al. (52) argued that considerable evidence implicates serotonin systems in the dyskinesias induced by L-DOPA, and also those resulting from

striatal grafts. They point out that the pharmacology of drugs that act on 5-HT_{1A} receptors can be quite complex, because there are both presynaptic and postsynaptic 5-HT_{1A} receptors. The presynaptic receptors modulate release as autoreceptors, so stimulation of these receptors actually lowers 5-HT transmission. Moreover, there is evidence that 5-HT_{1A} and 5-HT_{1B} receptors interact synergistically, and therefore combined treatments may be able to exploit this synergy in the future.

ADENOSINE A_{2A} RECEPTOR ANTAGONISTS

Considerable evidence indicates that the purine nucleoside adenosine plays an important role in regulating striatal motor functions (53-55). The adenosine A_{2A} receptor subtype is expressed to a high degree in striatal areas that are rich in DA (55-58). Striatal adenosine A_{2A} receptors are typically expressed on enkephalin-positive striatopallidal neurons and are most frequently co-localized with dopamine D_2 receptors (55, 59-61). Adenosine A_{2A} and dopamine D_2 receptors converge on the same cAMP-related signal transduction pathways, and also show the capacity to form heteromers (62-64). Over the last few years, there has been increasing interest in the use of adenosine A_{2A} receptor antagonists as potential nondopaminergic treatments for parkinsonism. Moreover, in view of the likelihood of using adenosine A_{2A} receptor antagonists in combination with L-DOPA, the impact that these drugs may have on the management of L-DOPA-induced dyskinesias has been the focus of considerable attention.

Adenosine A_{2A} receptor antagonists produce effects in both rodent and primate models of motor function related to parkinsonism. In rats, haloperidol-induced rigidity was reversed by the adenosine A_{2A} receptor antagonist SCH-58261 (65). DA antagonist-induced catalepsy has also been consistently reversed by coadministration of adenosine A_{2A} receptor antagonists (66, 67). The adenosine A_{2A} receptor antagonist KW-6002 (istradefylline) reversed the suppression of locomotion induced by the DA-depleting agent reserpine (68), and also rescued the impairment of locomotion shown by D_2 receptor-deficient mice (69). Systemic injections of the adenosine A_{2A} receptor antagonists KF-17837, istradefylline and MSX-3 were shown to reverse the suppression of locomotion induced by acute or repeated injections of DA antagonists such as haloperidol, pimozide and eticlopride (67, 70-72).

Several recent studies have focused on the antitremor effects of adenosine A_{2A} receptor antagonists by employing the tremulous jaw movement model (73, 74). Adenosine A_{2A} receptor antagonists, including KF-17837, istradefylline, MSX-3 and SCH-58261, have been shown to attenuate the tremulous jaw movements induced by reserpine (67), dopamine D_2 receptor antagonists (67, 70, 75) and cholinomimetic drugs (76-79). Grondin et al. (80) assessed the effects of istradefylline (60-90 mg/kg) in MPTP-treated cynomolgus monkeys, and reported that it produced an antiparkinsonian motor effect in terms of increasing locomotion and reducing disability scores. When given in combination with L-DOPA, istradefylline potentiated the antiparkinsonian effects of L-DOPA. Moreover, istradefylline did not appear to worsen dyskinesias, either on its own or in combination with L-DOPA. Kanda et al. (81) and Bibbiani et al. (82) also observed that istradefylline produced antiparkinsonian effects in MPTP monkeys without inducing or exacerbating dyskinesias. These findings in primate studies are consistent with the work of Cenci and colleagues, who reported that istradefylline failed to induce dyskinesias in a rodent model of dyskinesia in DA-depleted animals (83). Another adenosine A_{2A} antagonist that has received considerable attention is preladenant (SCH-420814), which is a highly selective adenosine A_{2A} receptor antagonist (84, 85). Preladenant reverses haloperidol-induced catalepsy in rodents and improves motor function in MPTP-treated primates (84-86). Like istradefylline, preladenant did not induce any signs of dyskinesia in primate models (86).

In view of these positive preclinical results, it has been widely suggested that adenosine A_{2A} receptor antagonists could be used as nondopaminergic agents for the treatment of idiopathic Parkinson's disease (54, 87-91). Currently, the first generation of adenosine A_{2A} receptor antagonists is undergoing initial clinical assessment. As described above, istradefylline (KW-600; Kyowa Hakko Kogyo) has undergone thorough evaluation in preclinical studies and has also progressed through phase III clinical trials. Istradefylline administration produced antiparkinsonian effects in initial clinical studies (92), and a more recent phase III clinical trial showed that istradefylline reduced "off" time when given in combination with L-DOPA (93). Other drugs also are being assessed in phase I and II clinical trials (94), including ST-1535 (Sigma-Tau), BIIB-014 (vepadenant; Vernalis, Biogen Idec) and preladenant (Merck & Co.). Phase II clinical studies have reported positive effects for preladenant in Parkinson's disease patients. In a 12-week, randomized, placebo-controlled, double-blind study, doses of 1.0, 2.0, 5.0 and 10.0 mg b.i.d. of preladenant were assessed for their efficacy in combination with L-DOPA and other treatments. The doses of 5.0 and 10.0 mg produced a significant reduction in awake time spent in the "off" state relative to placebo, and also significantly increased awake time spent in the "on" state (95).

Importantly, none of the adenosine A_{2A} receptor antagonists assessed in clinical trials to date has produced an enhancement of L-DOPA-induced troublesome dyskinesias. Istradefylline did not induce dyskinesias when administered on its own, and it also did not worsen dyskinesias when given in combination with L-DOPA (92, 93). Although preladenant increased "on" time in L-DOPA-treated patients, it did not increase the proportion of "on" time with dyskinesias across the 12 weeks of treatment (95, 96). Taken together, these results indicate that adenosine A_{2A} receptor antagonists can enhance the therapeutic effects of L-DOPA without worsening troublesome dyskinesias. Moreover, these drugs could contribute to the management of dyskinesias if they allow the patient to obtain a therapeutic effect at a lower dose of L-DOPA.

AMANTADINE AND OTHER GLUTAMATERGIC APPROACHES

Amantadine is an antiparkinsonian drug that has been available for many years (97). Although the mechanism of action was unknown for a considerable time, it is now recognized that amantadine acts as an NMDA receptor antagonist (98), and that this effect contributes to its antiparkinsonian actions (99). Studies with animal models have also reported positive effects for amantadine on measures of motor function related to parkinsonism, including locomotion, rotation and tremor (99, 100). After several decades of use as an antiparkinsonian drug, it was reported that amantadine can attenu-

ate L-DOPA-induced dyskinesias in humans (101, 102). Snow et al. (103) found that amantadine produced a significant reduction in the total dyskinesia score in L-DOPA-treated patients. The antidyskinetic effects of amantadine were also characterized in a 5-week, double-blind, crossover trial; amantadine produced a reduction in self-reported dyskinesias of approximately 50%, and also lowered ratings of dyskinesia as measured by the UPDRS (104). Since these initial reports, additional research in double-blind, placebo-controlled studies has confirmed that amantadine can produce a clinically significant reduction in L-DOPA-induced dyskinesias (13, 105, 106). These clinical studies are consistent with research using rodent and primate models showing that amantadine can exhibit antidyskinetic effects (107-109).

One of the concerns related to the use of amantadine for the management of dyskinesias is the duration of the antidyskinetic effect. Although a 1-year follow-up study by Metman et al. (102) reported that most patients showed continued effectiveness of amantadine after 1 year, another open-label study found that the effect of amantadine on L-DOPA-induced dyskinesias tended to wear off after an average of 5 months (105). This point was recently addressed in a randomized, placebo-controlled, parallel-group study in patients who had been on amantadine for at least a year. One group of patients was maintained on amantadine plus L-DOPA, while the other group was switched to placebo plus L-DOPA; both groups were observed for an additional 3 weeks and the primary outcome measure was the UPDRS IV items related to dyskinesias (i.e., items 32 and 33). The group that was switched from amantadine to placebo demonstrated a significant increase in dyskinesia-related scores, while there was no change in the group maintained on amantadine. These results demonstrate that amantadine appears to have a significant and relatively long-lasting suppressive effect on L-DOPA-induced dyskinesias. Moreover, they suggest that discontinuation of amantadine therapy may increase the risk for developing dyskinesias. In summarizing the current work on the effects of amantadine, Wolf et al. (13) stated that "amantadine remains the only drug for which there is solid evidence of antidyskinetic efficacy in PD patients with LID's".

Consistent with the hypothesized role of glutamatergic transmission in the modulation of dyskinesias, Adex Pharmaceuticals is currently assessing the potential antidyskinetic effects of ADX-48621, which is a negative allosteric modulator of metabotropic glutamate $mGlu_5$ receptors. Very little has been published on this compound, although two phase I studies have recently been completed and phase II studies are under way to demonstrate proof of concept in parkinsonian patients with dyskinesias (see www.addexpharma.com). The use of negative allosteric modulators for the management of dyskinesias is consistent with studies indicating that $mGlu_5$ receptor antagonists have shown positive results in animal models of dyskinesia (110, 111).

CONCLUSIONS

In summary, L-DOPA treatment for parkinsonism is essentially a double-edged sword. On the one hand, it is still the most effective drug treatment known, giving most patients several years of improved motor function. On the other hand, its use as a treatment for parkinsonism is complicated by the motor fluctuations and dyskinesias that result from long-term treatment. The major dopaminergic strategy for the management of dyskinesias has been the use of sustained-release formulations of L-DOPA or DA receptor agonists, which has provided positive results in clinical studies. In addition to these dopaminergic approaches, several nondopaminergic strategies have been investigated, including serotonergic agents, adenosine A_{2A} receptor antagonists, amantadine and drugs that interfere with $mGlu_5$ transmission. Some of these treatments may be able to augment the therapeutic effects of L-DOPA without worsening dyskinesias (e.g., adenosine A_{2A} receptor antagonists), while other drugs may be able to exert antidyskinetic effects (e.g., amantadine). Additional approaches are focusing on other transmitters as well. For example, the α_2-adrenoceptor antagonist fipamezole has yielded positive results in animal studies (112) and will soon undergo assessment in phase III clinical trials (113). Recent evidence from animal models has implicated basal ganglia opiate transmission in the expression of dyskinesias (114), and opiate receptor antagonists such as naltrexone and cyprodime have been shown to suppress L-DOPA-induced dyskinesias in MPTP-treated primates (115). There is also evidence that deep brain stimulation may reduce the risk of dyskinesias in Parkinson's disease patients (116). The focus on nondopaminergic targets for the treatment of dyskinesias reflects a growing understanding of the circuitry of the basal ganglia and the complex nature of the neurotransmitter interactions that take place in those structures. Ongoing research suggests that L-DOPA-induced dyskinesia, which is one of the most vexing problems in the field, may become more manageable in the future through the use of a variety of approaches.

DISCLOSURES

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