Minireviews

Dopamine Reuptake Inhibitors in Parkinson’s Disease: A Review of Nonhuman Primate Studies and Clinical Trials

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ABSTRACT

Striatal dopamine deficiency is the core feature of the pathology of Parkinson’s disease (PD), and dopamine replacement with L-3,4-dihydroxyphenylalanine (L-DOPA) is the mainstay of PD treatment. Unfortunately, chronic L-DOPA administration is marred by the emergence of dyskinesia and wearing-off. Alternatives to L-DOPA for alleviation of parkinsonism are of interest, although none can match the efficacy of L-DOPA to date. Catechol-O-methyltransferase and monoamine oxidase inhibitors are currently used to alleviate wearing-off, but they do not increase “on-time” without exacerbating dyskinesia.Alternate approaches to dopamine replacement in parkinsonism generally (and to wearing-off and dyskinesia, specifically) are therefore urgently needed. Inasmuch as they increase synaptic dopamine levels, dopamine transporter (DAT) inhibitors, whether they are selective or have actions on noradrenaline or serotonin transporters, theoretically represent an attractive way to alleviate parkinsonism per se and potentially enhance L-DOPA antiparkinsonian action (provided that sufficient dopamine terminals remain within the striatum). Several nonhuman primate studies and clinical trials have been performed to evaluate the potential of DAT inhibitors for PD. In this article, we review nonhuman primate studies and clinical trials, we summarize the current knowledge of DAT inhibitors in PD, and we propose a hypothesis as to how tailoring the selectivity of DAT inhibitors might maximize the benefits of DAT inhibition in PD.

Introduction

Parkinson’s disease (PD) is a neurodegenerative disorder in which striatal dopamine levels are diminished (Hornykiewicz and Kish, 1987). Treatment with the dopamine precursor L-3,4-dihydroxyphenylalanine (L-DOPA) has been the mainstay of PD therapy for the past 4 decades (Fahn, 2008). Unfortunately, chronic therapy with L-DOPA leads to the development of motor complications, including a shortening of duration of benefit, wearing-off, and abnormal involuntary movements (dyskinesia) (Hely et al., 2005).

There are several treatment options for early PD, including L-DOPA, dopamine agonists, amantadine, and monoamine oxidase type B (MAO-B) inhibitors. Treatment of early PD is a complex issue (Fox and Lang, 2014), and whether to initiate therapy with a DOPA-sparing approach or L-DOPA has been an area of intense research recently (Cilia et al., 2014; Gray et al., 2014). Therapies for the wearing-off phenomenon remain limited and essentially consist of inhibiting catechol-O-methyltransferase and MAO-B, the enzymes responsible for dopamine degradation (Parkinson Study Group, 2005; Rascol et al., 2005). However, it seems to be very difficult to extend the duration of L-DOPA antiparkinsonian benefit (i.e., alleviated wearing-off) without exacerbating dyskinesia; when catechol-O-methyltransferase and MAO-B inhibitors are used as adjunct therapy, the extra “on-time” gained is on-time with dyskinesia (Parkinson Study Group, 2005; Rascol et al., 2005).

Another potential approach to alleviate parkinsonian disability and wearing-off lies in increasing the time spent by dopamine in the synaptic cleft and maximizing its chances of interaction with postsynaptic dopaminergic receptors; this could be achieved by preventing the reuptake of dopamine into the presynaptic neuron by the dopamine transporter (DAT). By the same mechanism, blocking dopamine reuptake might...
also exert an antiparkinsonian action as monotherapy. These theoretical antiparkinsonian benefits form the rationale underly the potential use of DAT inhibitors in PD. Many DAT inhibitors have been identified and span a spectrum of selectivity for DAT over other monoamine transporters; the pharmacology of these was recently reviewed in detail elsewhere (Huot et al., 2015).

In this article, we review the literature on selective and nonselective DAT inhibitors, their antiparkinsonian effect as monotherapy, and their effects on on-time and dyskinesia as adjunct therapy. We also propose a hypothesis as to how the pharmacoselectivity of DAT inhibitors might be best tailored to maximize benefit in PD. Throughout, we divide the monoamine reuptake inhibitors based on their affinity for DATs, noradrenaline transporters (NATs), and serotonin transporters (SERTs). As in a previous article (Huot et al., 2015), we considered that a compound was selective for a transporter when its affinity for that transporter was greater than 10-fold its affinity for that of the other transporters.

Here, we review preclinical studies performed in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)–lesioned nonhuman primate and clinical trials performed with patients suffering from idiopathic PD (published prior to April 2015). Studies performed in the 6-hydroxydopamine–lesioned rat were not included in our review because the vast majority of these studies employed rotational behavior as an endpoint, which can be difficult to interpret with respect to parkinsonism and dyskinesia benefits/ liability (Marin et al., 2006). The effects of the drugs discussed in the article are summarized in Tables 1 and 2.

### Selective DAT Inhibitors

GBR-12,909 (vanoxerine; 1-[2-[[4-fluorophenyl]methoxy]ethyl]-4-(3-phenylpropyl)piperazine dihydrochloride) and SEP-228,791 are selective DAT inhibitors (Huot et al., 2015) that have been evaluated in the MPTP-lesioned monkey. To date, neither GBR-12,909 nor SEP-228,791 has been studied in nonhuman primate and, based on one single study, they appear effective at enhancing the antiparkinsonian action of low-dose L-DOPA. However, the nonhuman primate studies have not addressed the important question of combining dual DAT/NAT inhibitors to high-dose L-DOPA in Parkinson monkeys with established dyskinesia.

Unlike selective DAT inhibitors, dual DAT/NAT inhibitors have undergone clinical testing. In a small escalating-dose study, brasofensine did not enhance L-DOPA antiparkinsonian action and did not alter L-DOPA–induced dyskinesia severity (Archibald, 2000; Cutler et al., 2000; Frackiewicz et al., 2002). In a phase II trial, the administration of brasofensine as monotherapy to patients with recently diagnosed PD initially improved parkinsonism, but the improvement was not maintained after 2 weeks (Yu, 2000). In contrast with brasofensine, bupropion effectively alleviated parkinsonism in a small add-on trial but exacerbated dyskinesia severity in one patient (Goetz et al., 1984). In two small trials, monotherapy with nomifensine significantly alleviated parkinsonism (Park et al., 1977, 1981). The effect of nomifensine as adjunct therapy is unclear; nomifensine failed to enhance L-DOPA antiparkinsonian action in one study (Bedard et al., 1977) but effectively enhanced L-DOPA antiparkinsonian efficacy in a second one, although at the expense of worsening dyskinesia in 30% of enrolled patients (Teychenne et al., 1976). Methylphenidate has not been studied in the parkinsonian nonhuman primate, but a small number of clinical trials have assessed its antiparkinsonian efficacy. When administered to patients in the “off” state, methylphenidate had no effect on motor symptoms. When administered in combination with L-DOPA, methylphenidate increased tapping and walking speed (Nutt et al., 2004) but did not increase the duration of on-time (Nutt et al., 2007). Methylphenidate had no effect on dyskinesia severity in either study.

In summary, the antiparkinsonian efficacy of dual DAT/NAT inhibitors is worthy of further investigation. It seems likely that they have potential to supply antiparkinsonian benefits as monotherapy and in some situations, at least, can enhance L-DOPA benefits, although this might be at the expense of exacerbating dyskinesia. Interestingly, methylphenidate improved speed of movement without extending on-time duration, suggesting that dual DAT/NAT inhibitors

### Dual DAT and NAT Inhibitors

Brasofensine, bupropion, methylphenidate, and nomifensine are dual DAT and NAT inhibitors (with a DAT/NAT ratio between 0.5 and 4; Huot et al., 2015) and have been studied as potential therapies for PD.

In the MPTP-lesioned marmoset, monotherapy with brasofensine reversed parkinsonian disability without eliciting dyskinesia (Pearce et al., 1995), and adjunct therapy with brasofensine enhanced the antiparkinsonian action of low-dose L-DOPA. Similarly, in the parkinsonian marmoset, monotherapy with nomifensine significantly improved parkinsonian disability (Hansard et al., 2002b). In contrast, monotherapy with bupropion had no effect on parkinsonian disability (Hansard et al., 2002b). Therefore, on balance, it seems that dual DAT/NAT inhibitors can be effective as antiparkinsonian molecules when administered as monotherapy to the parkinsonian monkey and, based on one single study, they appear effective at enhancing the antiparkinsonian action of low-dose L-DOPA. Nevertheless, many DAT inhibitors have undergone clinical testing. In a small escalating-dose study, brasofensine did not enhance L-DOPA antiparkinsonian action and did not alter L-DOPA–induced dyskinesia severity (Archibald, 2000; Cutler et al., 2000; Frackiewicz et al., 2002). In a phase II trial, the administration of brasofensine as monotherapy to patients with recently diagnosed PD initially improved parkinsonism, but the improvement was not maintained after 2 weeks (Yu, 2000). In contrast with brasofensine, bupropion effectively alleviated parkinsonism in a small add-on trial but exacerbated dyskinesia severity in one patient (Goetz et al., 1984). In two small trials, monotherapy with nomifensine significantly alleviated parkinsonism (Park et al., 1977, 1981). The effect of nomifensine as adjunct therapy is unclear; nomifensine failed to enhance L-DOPA antiparkinsonian action in one study (Bedard et al., 1977) but effectively enhanced L-DOPA antiparkinsonian efficacy in a second one, although at the expense of worsening dyskinesia in 30% of enrolled patients (Teychenne et al., 1976). Methylphenidate has not been studied in the parkinsonian nonhuman primate, but a small number of clinical trials have assessed its antiparkinsonian efficacy. When administered to patients in the “off” state, methylphenidate had no effect on motor symptoms. When administered in combination with L-DOPA, methylphenidate increased tapping and walking speed (Nutt et al., 2004) but did not increase the duration of on-time (Nutt et al., 2007). Methylphenidate had no effect on dyskinesia severity in either study.

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<tr>
<th>Inhibitor</th>
<th>Monoamine Reuptake Inhibition Profile</th>
<th>Affinity for Other Receptors</th>
<th>Standard Clinical Use</th>
<th>Nonhuman Primate Use</th>
<th>Idiopathic PD Use</th>
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<tr>
<td>Brasofensine</td>
<td>DAT = NAT (Singh, 2000)</td>
<td>Undisclosed</td>
<td>Antiparkinsonian action as monotherapy (Pearce et al., 1995)</td>
<td>No effect on l-DOPA antiparkinsonian action (Archibald, 2000; Cutler et al., 2000; Frackiewicz et al., 2002)</td>
<td>Does not elicit dyskinesia as monotherapy (Pearce et al., 1995)</td>
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<td>Enhances the antiparkinsonian action of low-dose l-DOPA (Moldt et al., 1998; Pearce et al., 2002)</td>
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<td>Transient antiparkinsonian benefit as monotherapy (Yu, 2000)</td>
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<td>Not tested in combination with high-dose L-DOPA</td>
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<tr>
<td>BTS-74,398</td>
<td>DAT = NAT = SERT (Cheetham et al., 1998)</td>
<td>Undisclosed</td>
<td>Antiparkinsonian action as monotherapy (Hansard et al., 2002b, 2004)</td>
<td>n/a</td>
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<td>Not tested in combination with high-dose L-DOPA</td>
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<tr>
<td>Bupropion</td>
<td>DAT = NAT (Bolden-Watson and Richelson, 1993; Tatsumi et al., 1997)</td>
<td>Nicotinic acetylcholine receptors</td>
<td>Antidepressant effect as monotherapy (Hansard et al., 2002b)</td>
<td>Enhances l-DOPA antiparkinsonian action (Goetz et al., 1984)</td>
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<td>Smoking cessation (Wu et al., 2006; Moreira, 2011)</td>
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<td>Not tested in combination with high-dose L-DOPA</td>
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<tr>
<td>GBR-12,909</td>
<td>DAT (Heikkila and Manzino, 1984; Andersen, 1989)</td>
<td>σ receptors</td>
<td>Under investigation as an antiarrhythmic agent (Dittrich et al., 2015)</td>
<td>Antiparkinsonian action as monotherapy (Hansard et al., 2002a,b)</td>
<td>n/a</td>
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<td>(vanoxerine)</td>
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<td>Not tested in combination with L-DOPA</td>
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<tr>
<td>Methylphenidate</td>
<td>DAT = NAT (Richelson and Pfenning, 1984; Tatsumi et al., 1997)</td>
<td>5-HT1A and 5-HT2B receptors</td>
<td>Attention deficit hyperactivity disorder</td>
<td>n/a</td>
<td>No effect on parkinsonism as monotherapy (Nutt et al., 2004)</td>
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<tbody>
<tr>
<td>Nomifensine</td>
<td>DAT = NAT (Gianutsos et al., 1982; Richelson and Pfenning, 1984)</td>
<td>5-HT&lt;sub&gt;1A&lt;/sub&gt;, 5-HT&lt;sub&gt;2A&lt;/sub&gt;, and 5-HT&lt;sub&gt;2C&lt;/sub&gt; receptors</td>
<td>None; initially used as an antidepressant (Brogden et al., 1979); nomifensine has been withdrawn from the market due to the occurrence of hemolytic anemia (<a href="http://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_03_WL35.pdf">http://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_03_WL35.pdf</a>)</td>
<td>Antiparkinsonian action as monotherapy (Hansard et al., 2002b)</td>
<td>Increases tapping and walking speed when administered with L-DOPA (Nutt et al., 2004) No effect on on-time duration (Nutt et al., 2007) No effect on L-DOPA-induced dyskinesia severity (Nutt et al., 2004, 2007) Antiparkinsonian action as monotherapy (Park et al., 1977, 1981)</td>
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<td>S-MDMA</td>
<td>SERT &gt; DAT (Huot et al., 2011)</td>
<td>To the best of our knowledge, the pharmacologic profile of S-MDMA has not been well characterized outside of its affinity for the monoamine transporters</td>
<td>None (recreational drug)</td>
<td>Enhances L-DOPA antiparkinsonian action (Huot et al., 2011)</td>
<td>n/a</td>
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<tr>
<td>SEP-228,791</td>
<td>DAT &gt; NAT (Johnston et al., 2010)</td>
<td>Undisclosed</td>
<td>None</td>
<td>Antiparkinsonian action as monotherapy (Johnston et al., 2009, 2010) Does not elicit dyskinesia as monotherapy (Johnston et al., 2009, 2010) No effect on L-DOPA antiparkinsonian action (Johnston et al., 2009, 2010) No effect on L-DOPA-induced dyskinesia severity (Johnston et al., 2009, 2010)</td>
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(continued)
might be more effective against bradykinesia than other components of the parkinsonian syndrome.

**Dual DAT and SERT Inhibitors**

S-3,4-methylenedioxymethamphetamine (MDMA), UWA-101 [2-(1,3-benzodioxol-5-yl)-1-cyclopropyl-N-methylethanamine], and UWA-121 are the three dual DAT/SERT inhibitors, with different relative affinities for DAT/SERT, that have been evaluated in the parkinsonian monkey. To our knowledge, none of the dual DAT/SERT inhibitors has undergone clinical testing and the preclinical efficacy of these molecules requires confirmation in the context of clinical studies.

S-MDMA is the S-enantiomer of the recreational drug MDMA (“ecstasy”). S-MDMA is a monoamine reuptake inhibitor that also enhances monoamine release (Fleckenstein et al., 2007). In the MPTP-lesioned marmoset, S-MDMA (1:10 DAT/SERT ratio) significantly extended the duration of on-time after l-DOPA administration. However, this extension of l-DOPA antiparkinsonian benefit was marred by an exacerbation of dyskinesia (Huo et al., 2011). UWA-101 was the first equipotent DAT = SERT inhibitor to be developed for the treatment of PD. In the MPTP-lesioned marmoset UWA-101, in combination with l-DOPA, significantly increased the duration of on-time, without adversely affecting the severity of dyskinesia (Huo et al., 2012; Johnston et al., 2012). UWA-121 is the R-enantiomer of UWA-101 and retains the affinity of its racemate for both DAT and SERT. Unlike UWA-101, UWA-121 is primarily a DAT > SERT inhibitor (10:1 ratio); however, like UWA-101, UWA-121 extends the duration of on-time without exacerbating the severity of dyskinesia (Huo et al., 2014). The results of these studies suggest that the DAT/SERT ratio is crucial in determining the quality of the extra on-time gained by dual DAT/SERT inhibitors and that the most effective compounds might be those in which DAT affinity is equal to if not greater than SERT. To our knowledge, S-MDMA, UWA-101, and UWA-121 have not been tested as monotherapy, and the effects of dual DAT/SERT inhibitors on parkinsonism remain uncertain. However, the combination of GBR-12,909 and the selective serotonin reuptake inhibitor sertraline as monotherapy was studied in the parkinsonian marmoset. In this study, sertraline reduced the Antiparkinsonian actions of GBR-12,909 alone (Hansard et al., 2002b), suggesting that it is unlikely that a dual DAT/SERT inhibitor would be as efficacious as monotherapy as a DAT-selective compound.

**Triple DAT, NAT, and SAT Inhibitors**

BTS-74,398 [1-[(1-(3,4-dichlorophenyl)cyclobutyl]-2-(3-dimethylaminopropyl)ethanone] and tesofensine are nonselective DAT/NAT/SERT inhibitors that have been considered as potential treatments for PD.
In the MPTP-lesioned marmoset, monotherapy with BTS-74,398 significantly reversed parkinsonism, without eliciting dyskinesia, and combining BTS-74,398 with a low dose of L-DOPA did not enhance L-DOPA antiparkinsonian action or exacerbate the severity of dyskinesia (Hansard et al., 2002b, 2004). BTS-74,398 has not yet been subjected to a clinical trial.

Tesofensine has not been tested in the parkinsonian monkey, but three clinical trials with tesofensine were performed (Barr-Jimenez et al., 2004; Hauser et al., 2007; Rascol et al., 2008). In a proof-of-concept phase II trial, monotherapy formed (Bara-Jimenez et al., 2004; Hauser et al., 2007; Rascol et al., 2008). BTS-74,398 has not yet been subjected to a clinical trial.

As for dual DAT/NAT inhibitors, it seems likely that triple DAT/NAT/SERT inhibitors might have potential for the treatment of parkinsonism as monotherapy. However, the antiparkinsonian efficacy afforded by DAT inhibition might be only transient in the clinical setting, since both brasofensine and tesofensine effects waned over weeks of repeat treatment. As with dual DAT/NAT inhibitors, triple DAT/NAT/SERT inhibitors might adversely affect the severity of L-DOPA–induced dyskinesia, although more studies are needed to verify that possibility.

**DAT Inhibitors in PD: Where Next?**

As presented in Table 2, significant nonhuman primate and clinical work has advanced our knowledge of the effects of DAT inhibitors on parkinsonism, on-time, and dyskinesia. Although relatively few molecules have been tested to date and some important studies remain to be performed (e.g., the effect of selective DAT and dual DAT/SERT inhibitors in clinical trials), the combination of studies conducted in the MPTP-lesioned monkey and well performed clinical evaluations allows several hypotheses to be generated.

At the preclinical level, DAT inhibitors (whether DAT-selective, DAT/NAT, or triple inhibitors) appear to exert some antiparkinsonian action when administered as monotherapy. Where direct comparison between nonhuman primate and phase II studies is possible, it appears that the monkey is predictive of acute monotherapy efficacy (e.g., brasofensine). It is difficult to compare relative efficacy of these DAT-selective inhibitors compared with dual or triple inhibitor approaches, given differences in experimental paradigms. It is also not clear how maximal efficacy might compare with dopamine receptor agonists or L-DOPA, and the magnitude of benefits may limit their use to early-stage, mild disease. DAT/SERT inhibitors, which have not been tested in this monotherapy paradigm, may have less potential in this respect, given that a selective SERT inhibitor reduced antiparkinsonian actions of a selective DAT inhibitor (Hansard et al., 2002b).

Although DAT inhibitors seem to be effective as antiparkinsonian agents as monotherapy, it is not necessarily the case that they would enhance L-DOPA benefits. Indeed, there is no evidence for robust enhancement of L-DOPA effects by DAT-selective compounds. DAT/NAT and triple inhibitors may enhance L-DOPA actions but only at the expense of exacerbating dyskinesia. The most promising approach to DAT inhibition/L-DOPA adjunctive therapy seems to be the combination of L-DOPA with a DAT/SERT inhibitor, in which the relative DAT/SERT affinity is equal to or favors DAT.

However, the limited clinical experience with brasofensine and tesofensine suggests that the antiparkinsonian benefit afforded by DAT inhibitors as monotherapy may fade over time. This raises important questions as to the potential use of these agents as monotherapy in PD. The long-term adjunctive effect of DAT inhibitors on L-DOPA has not been assessed, and whether the extra on-time provided by DAT inhibition would be maintained over the long term remains unknown.

It should also be pointed out that most of the molecules discussed here harbor affinity for receptors outside of the three monoamine transporters. The role of these off-target receptors in the overall therapeutic action of the DAT inhibitors discussed here is yet to be determined.
Concluding Remarks

Dopamine reuptake inhibitors represent potential molecules in the treatment of PD. Based on the studies cited above and considering the limitations outlined, we propose the following hypotheses: 1) monotherapy with selective DAT, mixed DAT/NAT, and triple DAT/NAT/SERT inhibitors has potential to exert an antiparkinsonian benefit; and 2) mixed DAT/SERT inhibitors have potential to extend the on-time duration in combination with L-DOPA without exacerbating dyskinesia.

Authorship Contributions

Participated in research design: Huot, Fox, Brothie.

Wrote or contributed to the writing of the manuscript: Huot, Fox, Brothie.

References


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