Dopamine, but Not Norepinephrine or Serotonin, Reuptake Inhibition Reverses Motor Deficits in 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine-Treated Primates

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ABSTRACT
Monoamine reuptake inhibitors that do not discriminate between the transporters for dopamine (DA), norepinephrine (NE), or 5-hydroxytryptamine (5-HT, serotonin) can reverse locomotor deficits and motor disability in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated common marmosets. DA reuptake inhibition is presumed to be primarily responsible, but the role played by inhibition of NE and 5-HT reuptake is unknown. We now evaluate the efficacy of a range of monoamine reuptake inhibitors either alone or in combination in MPTP-treated common marmosets to determine the actions required for effective antiparkinsonian activity. Monoamine reuptake inhibitors not discriminating between the DA, NE, and 5-HT transporters [1-[1-(3,4-dichloroophenyl)cyclobutyl]-2-(3-dimethylaminopropylthio)ethanone monocitrate (BTS 74 398) and nomifensine] reversed locomotor deficits and motor disability in MPTP-treated marmosets but bupropion was without effect. The selective DA reuptake inhibitor 1-[2-(bis-(4-fluorophenyl)methoxy)ethyl]-4-(3-phenylpropyl) piperazine dihydrochloride (GBR 12909) also reversed these motor deficits. The relative efficacy of the compounds (BTS 74 398 > GBR 12909 > nomifensine > bupropion) paralleled their potency in inhibiting DA uptake in vitro and in vivo. In contrast, the selective NE reuptake inhibitor nisoxetine and the 5-HT reuptake inhibitor sertraline administered alone failed to improve motor function and tended to worsen the deficits. Coadministration of nisoxetine attenuated the improvement in motor deficits produced by GBR 12909. Coadministration of sertraline also abolished the reversal of motor deficits produced by GBR 12909. Coadministration of both sertraline and nisoxetine similarly abolished the improvement of motor deficits produced by GBR 12909. Molecules possessing potent DA reuptake inhibitory activity may be useful in the treatment of the motor symptoms of Parkinson’s disease. In contrast, there seems to be no role for NE or 5-HT reuptake inhibitors, and they may impair antiparkinsonian activity mediated through dopaminergic mechanisms.

Parkinson’s disease (PD) is characterized by akinesia or bradykinesia, rigidity, and resting tremor resulting from a primary loss of dopamine (DA)-containing neurons projecting from the substantia nigra, pars compacta to the caudate putamen (Ehringer and Hornykiewicz, 1960; Marsden, 1990). In addition, smaller reductions in brain norepinephrine (NE) and 5-hydroxytryptamine (5-HT, serotonin) levels occur as a result of degeneration of the locus coeruleus and raphe nuclei, respectively (Scatton et al., 1983). The clinical treatment of PD is centered on DA replacement therapy.

L-DOPA is the most commonly used drug but long-term treatment induces complications, particularly involuntary movements ( dyskinesia), psychosis, and a loss of drug efficacy (wearing off and “on-off”) (Hurtig, 1997, and references cited therein). DA agonists are increasingly being used as early monotherapy because they induce less dyskinesia than treatment with L-DOPA (Montastruc et al., 1994; Rascol et al., 2000). However, when used as an adjunct to L-DOPA therapy in patients already exhibiting established dyskinesia, DA agonists also evoke the same involuntary movements (Ol- anow et al., 1994; Lieberman et al., 1997).

As a consequence, alternative pharmacological strategies are being sought that are effective throughout the course of the illness and that do not prime basal ganglia for the induction of dyskinesia. Inhibition of DA reuptake may be one such approach, and it is surprising that they have not been examined previously in detail as potential antiparkinsonian

ABBREVIATIONS: PD, Parkinson’s disease; DA, dopamine; NE, norepinephrine; 5-HT, 5-hydroxytryptamine, serotonin; BTS 74 398, 1-[1-(3,4-dichloroophenyl)cyclobutyl]-2-(3-dimethylaminopropylthio)ethanone monocitrate; GBR 12909, 1-[2-(bis-(4-fluorophenyl)methoxy)ethyl]-4-(3-phenylpropyl) piperazine dihydrochloride; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; 6-OHDA, 6-hydroxydopamine.
agents. Early studies in PD patients using the monoamine reuptake inhibitors nomifensine, mazindol, and bupropion showed modest improvements in motor symptoms (Teychenne et al., 1976; Bedard et al., 1977; Park et al., 1977, 1981; Delwaide et al., 1983; Goetz et al., 1984). However, most studies focused on patients in the later stages of PD already receiving maximally tolerated doses of L-DOPA, exhibiting dyskinesia, and where the detection of further improvements would be difficult. Indeed, in patients with PD not previously treated with dopaminergic drugs, nomifensine did produce some improvement in motor function (Park et al., 1981). This suggests that monoamine reuptake inhibitors might be effective in the treatment of PD.

More recently, a new generation of potent monoamine reuptake blockers, including brasofensine and BTS 74 398, were found to reverse motor deficits in MPTP-treated primates (Cheetham et al., 1998; Smith et al., 1998; Pearce et al., 2002). Importantly, in animals previously treated with L-DOPA to induce dyskinesia, these agents improved motor function without provoking involuntary movement (M. J. Hansard, L. A. Smith, M. J. Jackson, S. C. Chetham, and P. Jenner, unpublished observations; Pearce et al., 2002). DA reuptake inhibition is thought to be primarily responsible for the actions of brasofensine and BTS 74 398, but these compounds are also potent NE and 5-HT reuptake inhibitors. At this time, it is not known whether inhibition of NE and 5-HT reuptake contributes to their potential antiparkinsonian action.

There is evidence to support a role for both NE and 5-HT in the modulation of DA-mediated motor activity but the nature of this interaction is unclear. The α-2 adrenergic receptor antagonists, such as idazoxan, potentiate motor activity produced by directly and indirectly acting DA agonists in 6-hydroxydopamine (6-OHDA)-lesioned rats and in MPTP-treated primates, but provoke less established involuntary movements (Chopin et al., 1999; Grondin et al., 2000, and references therein). In contrast, the α-2 adrenergic receptor agonist clonidine inhibits apomorphine-induced rotational activity in 6-OHDA-lesioned rats (Chopin et al., 1999). Selective 5-HT reuptake inhibitors do not alter motor abnormalities in PD patients but can induce parkinsonism in normal individuals and reduce extracellular DA levels after L-DOPA administration (Korsgaard et al., 1985, 1986; Di Rocco et al., 1998; Ceravolo et al., 2000, and references herein; Yamato et al., 2001).

In this investigation, we have determined the roles of inhibition of DA, NE, and 5-HT reuptake in altering motor performance in MPTP-treated primates, the most predictive experimental model of drug effects in PD (Burns et al., 1983; Jenner et al., 1984; Langston et al., 1984; Bedard et al., 1986). The study has used a variety of monoamine reuptake inhibitors, namely, BTS 74 398 (nonselective), GBR 12909 (DA-selective), bupropion (weak DA-selective), nomifensine (NE > DA), nisoxetine (NE-selective), and sertraline (5-HT-selective). Corresponding K values and ability of these drugs to increase striatal DA levels are provided in Table 1. The effects of coadministration of GBR 12909 with nisoxetine and/or sertraline on improving motor performance were also evaluated.

**Materials and Methods**

**Drugs.** Drugs were obtained from the following sources: 1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-(3-diaminomethylpropyl)pipideridine (GBR 74 398) and sertraline hydrochloride (Knoll Ltd., Nottingham, UK); 1-2-(bis-(4-fluorophenyl)-methoxy) ethyl)-4-(3-phenylpropyl) piperazine (GBR 12909) and nisoxetine hydrochloride (Tocris Cookson, Bristol, UK); l-DOPA methyl ester (Sigma, Poole, Dorset, UK); 1-methyl-4-phenyl-1,2,3,6-tetrahydropropyridine (MPTP) hydrochloride, nomifensine maleate, and carbidopa (Sigma/RBI, Gillingham, UK); and bupropion hydrochloride (GlaxoSmithKline, Uxbridge, Middlesex, UK).

**Animals.** Adult male common marmosets (Callithrix jacchus; n = 8, 325–489 g) were used. Animals were housed either alone or in pairs, in a room maintained at constant temperature (27 ± 1°C), 50% relative humidity, and 12-h light/dark cycle. Fresh fruit was fed once daily and animals had ad libitum access to water and Mazuri food pellets (Special Diet Services, Essex, UK). All experiments were performed in accordance with Home Office regulations (Animals Scientific Procedures Act 1986) under project license number 70/03563.

**Administration of Drugs.** Locomotor deficits were induced by the administration of MPTP (2 mg/kg/day s.c.; dissolved in 0.9% sterile saline) for five consecutive days (Jenner et al., 1984; Smith et al., 1997). Animals were markedly parkinsonian immediately after MPTP treatment and were hand fed for the following 6 to 8 weeks until able to maintain themselves and normal body weight had been regained. At this time, animals had regained some motor function but all exhibited bradykinesia, rigidity, poor coordination and balance, and a loss of vocalization. BTS 74 398, GBR 12909, bupropion, nisoxetine, and L-DOPA were dissolved in 10% sucrose. Nomifensine and sertraline were dissolved in 0.5 to 1.0 ml of 5% gum arabic and made up to the required volume with 10% sucrose. Carbidopa was administered as a fine suspension.

**TABLE 1**

Effects of selected monoamine reuptake inhibitors on monoamine uptake and striatal dopamine levels

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<td></td>
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<tr>
<td>BTS 74 398</td>
<td>4.2</td>
<td>6.9</td>
<td>19°</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
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<tr>
<td>GBR 12909</td>
<td>42</td>
<td>624</td>
<td>488°</td>
<td>51</td>
<td>2,600</td>
<td>691</td>
<td>100°</td>
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<tr>
<td>Bupropion</td>
<td>409</td>
<td>2,590</td>
<td>18,312°</td>
<td>630</td>
<td>2,300</td>
<td>742</td>
<td>1,000°</td>
</tr>
<tr>
<td>Nomifensine</td>
<td>88</td>
<td>8.0</td>
<td>2,660°</td>
<td>51</td>
<td>5.0</td>
<td>2,117</td>
<td>1,000°</td>
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<tr>
<td>Nisoxetine</td>
<td>279</td>
<td>2.1</td>
<td>296°</td>
<td>510</td>
<td>1.3</td>
<td>31°</td>
<td></td>
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<tr>
<td>Sertraline</td>
<td>101</td>
<td>2,763</td>
<td>2.8°</td>
<td>1.1</td>
<td>1.2</td>
<td>0.05°</td>
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n/a, data not available.
in 10% sucrose. All solutions were made fresh on the day of use. On each experimental day, the animals were weighed and placed into individual locomotor activity cages and allowed to acclimatize for up to 1 h. After 45 to 60 min, drug or its vehicle was administered orally by gavage. The following doses of each compound were examined: L-DOPA (12.5 mg/kg p.o.) 45–60 min after 12.5 mg/kg p.o. carbidopa), BTS 74 398 (2.5, 5.0, 10.0, and 20.0 mg/kg p.o.), GBR 12909 (2.5, 5.0, and 10.0 mg/kg p.o.), bupropion (6.0, 12.5, 18.0, and 25.0 mg/kg p.o.), nomifensine (1.0, 5.0, 10.0, 20.0, and 25.0 mg/kg p.o.), nisoxetine (0.3, 1.0, 3.0, and 5.0 mg/kg p.o.), and sertraline (1.0, 5.0, and 10.0 mg/kg p.o.). Subsequently, the effects of coadministration of 10.0 mg/kg GBR 12909 with 1.0 mg/kg nisoxetine and/or 1.0 mg/kg sertraline were examined. All doses refer to the free base equivalent and were often selected based upon preliminary studies and the known pharmacology of the compounds.

Experiments were performed using an open Latin square design with a 1-week washout period between administrations of each drug dosage. During the combination studies the drugs were administered in the order of GBR 12909 or vehicle, followed by nisoxetine or vehicle and then sertraline or vehicle.

**Assessment of Locomotor Activity.** Locomotor activity was assessed according to Smith et al. (1997). Locomotor activity cages were identical to home cages with the exception of a clear perspex door replacing a metal cage door to improve visibility for behavioral assessment. Each cage was fitted with eight infrared photocell emitters and their corresponding beam detectors. Every beam breakage was automatically recorded as a single locomotor count. The photocells were arranged so as to detect climbing, and floor and perch activity. Locomotor activity monitoring started immediately after drug or vehicle administration and was monitored over 10-min periods for 6 h (bupropion) or 10 h.

**Rating of Motor Disability.** Motor disability was assessed by a blinded observer through a one-way mirror. The following items were assessed and scored: alertness (normal, 0; reduced, 1; or sleepy, 2), checking movements (normal, 0; reduced, 1; or absent, 2), posture (normal, 0; abnormal trunk, 1; abnormal limbs, +1; or flexed, +1 up to a maximum of 4), balance/coordinating (normal, 0; reduced, 1; unstable, 2; or falling, 3), reaction (normal, 0; reduced, 1; slow, 2; or absent, 3), vocalization (normal, 0; reduced, 2; or absent, 3), and motility (normal, 0; bradykinesia or hyperkinesia, 1; or akinesia or severe hyperkinesia, 2). A score of zero would indicate a normal marmoset, whereas a maximum score of 18 indicates an animal with marked motor impairment. Before drug administration basal disability was determined. Thereafter, motor disability was scored every 10 min for the first 3 h after drug treatment, the last 10 min of every 30 min for 3 to 6 h and then the last 10 min of each hour for 6 to 9 h. Disability was scored for 6 h (bupropion) or 9 h.

**Statistical Analysis.** The locomotor data were amassed over 30-min periods and cumulative counts were summed over either 6 or 10 h. The disability data were averaged over 6 (bupropion) or 9 h. A two-way analysis of variance of the locomotor and disability data was performed. In the dose-response studies, further analysis of the locomotor and disability data was undertaken using either Williams’ test (drug versus vehicle) or multiple t tests (L-DOPA versus vehicle). In the combination studies, all further analysis of the locomotor and disability data was performed using multiple t tests. Unless otherwise stated, all data were from four animals with statistical significance set at $P < 0.05$. The locomotor data are represented as the back-transformed mean ± the back-transformed S.E.M., whereas the disability data are adjusted for differences between the treatment groups at baseline.

**Results**

**Effect of L-DOPA Plus Carbidopa on Locomotor Deficits and Motor Disability.** Vehicle-treated, MPTP-treated common marmosets showed little locomotor activity and marked motor disability (Figs. 1, A and B, 2, A and B), including bradykinesia and akinesia, poor coordination, abnormal posture, reduced alertness, and reduced head checking movements. Vocalization was absent.

Administration of L-DOPA plus carbidopa (both 12.5 mg/kg p.o.) significantly increased locomotor activity and decreased motor disability (Figs. 1, A and B, 2, A and B). The improvement in motor function occurred within 30 min of drug administration and lasted for approximately 4 h (data not shown).
shown). The locomotor response to l-DOPA was continuous and the animals seemed driven with stereotypy evident at the time of peak drug action.

**Effect of BTS 74 398 on Locomotor Deficits and Motor Disability.** BTS 74 398 (5.0, 10.0, or 20.0 mg/kg) dose-dependently increased locomotor activity and reduced motor disability compared with vehicle-treated animals (Figs. 1A and 2A). Peak effect was reached within the first 30 min after drug administration and lasted for approximately 10 h. The locomotor activity seemed natural and was intermittent rather than continuous and the animals did not seem driven. No stereotypy was observed. Alertness was improved and head checking movements were seen. Vocalization remained absent.

**Effect of GBR 12909 on Locomotor Deficits and Motor Disability.** GBR 12909 (2.5, 5.0, and 10.0 mg/kg p.o.) only increased locomotor activity at the highest dose examined relative to vehicle-treated animals (Fig. 1B). Peak activity occurred after 120 min and lasted for approximately 10 h (data not shown). In contrast, GBR 12909 (2.5, 5.0, and 10.0 mg/kg) significantly decreased motor disability at all doses tested (Fig. 2B). Alertness, head checking movements, posture, reactions, balance, and coordination were all improved. Substantial vomiting was observed with the highest dose. Therefore, no higher doses were evaluated.

**Effect of Bupropion on Locomotor Deficits and Motor Disability.** Bupropion (6.0, 12.5, 18.0, and 25.0 mg/kg p.o.) did not significantly increase locomotor activity or decrease motor disability compared with vehicle-treated animals (Figs. 1C and 2C). Some minor improvements in alertness and posture accompanied by head checking movements were observed at the two higher doses.

**Effect of Nomifensine on Locomotor Deficits and Motor Disability.** Nomifensine (1.0, 5.0, 10.0, 20.0, or 25.0 mg/kg p.o.) only produced a significant increase in locomotor activity at the highest dose tested (Fig. 1D). Peak activity occurred 90 min after drug administration and lasted for approximately 6 h (data not shown). Nomifensine reduced motor disability at the 20.0- and 25.0-mg/kg dose level but not at lower doses (Fig. 2D). Effective doses increased alertness and improved head checking movements, posture, balance, and coordination with both floor and perch activities being observed.

**Effect of Nisoxetine on Locomotor Deficits and Motor Disability.** Nisoxetine (0.3, 1.0, 3.0, and 5.0 mg/kg p.o.) did not increase locomotor activity compared with vehicle-treated animals (Fig. 3A). In fact, locomotor activity was significantly depressed after administration of 3.0 and 5.0 mg/kg, although this effect was small (Fig. 3A). Significant reductions in motor disability were produced by the two lower doses (0.3 and 1.0 mg/kg) but these were not apparent at the higher doses (Fig. 3B). Increased alertness and head checking movements were observed especially at the two lower doses.

**Effect of Sertraline on Locomotor Deficits and Motor Disability.** Sertraline (1.0, 5.0, and 10.0 mg/kg p.o.) further depressed locomotor activity and increased motor disability relative to vehicle-treated animals at a single dose (Fig. 3, C and D). The administration of 5.0 and 10.0 mg/kg sertraline reduced reactions, hindered balance, and worsened posture.

**Effect of Administration of GBR 12909 Alone and in Combination with Nisoxetine and/or Sertraline on Locomotor Deficits and Motor Disability.** GBR 12909 (10.0 mg/kg p.o.) increased locomotor activity and decreased motor disability compared with vehicle-treated animals (Fig. 4). Nisoxetine and sertraline given alone (both 1.0 mg/kg p.o.) did not increase locomotor activity but decreased motor disability compared with GBR 12909 alone (Fig. 4). Nisoxetine (1.0 mg/kg p.o.) with GBR 12909 (10.0 mg/kg p.o.) significantly reduced the reversal in locomotor activity and caused a small nonsignificant reduction in motor disability compared with GBR 12909 alone (Fig. 4). Coadministration of sertraline (1.0 mg/kg p.o.) and GBR 12909 (10.0 mg/kg p.o.) completely abolished the improvement in locomotor activity and reduced the reversal of motor disability by GBR 12909 alone (Fig. 4). Nisoxetine, sertraline (each at 1.0 mg/kg p.o.), and GBR 12909 (10.0 mg/kg p.o.) together also abolished the increase in locomotor activity and diminished the reversal in motor disability observed after GBR 12909 (Fig. 4).

**Discussion**

Agents that inhibit DA reuptake (BTS 74 398, GBR 12909, and nomifensine) reversed the locomotor deficits and motor disability in MPTP-treated common marmosets but to varying degrees. BTS 74 398 was the most effective because the reversal of motor deficits was similar to that produced by l-DOPA, although with a significantly longer duration of action. GBR 12909 was less effective and only approached the level seen with l-DOPA at the highest dose evaluated. Substantial vomiting was also observed with this dose, and therefore no higher doses were evaluated, hence we were unable to determine whether GBR 12909 could attain the same maximal effect as BTS 74 398. Nomifensine produced a weak reversal of motor symptoms. Bupropion was without effect. The efficacy of the compounds was entirely consistent.
uptake inhibitor nisoxetine (Wong et al., 1975) and the selective 5-HT reuptake inhibitor sertraline (Koo et al., 1983) for their ability to reverse motor deficits in the MPTP-treated primate. Neither nisoxetine nor sertraline caused any improvement in locomotor activity, but interestingly both produced some reduction in motor disability, although the effects of sertraline were not robust. It is unknown whether this preferential improvement in motor disability versus locomotor deficits is indicative of some role of NE and 5-HT systems in the treatment of PD, although to date there is no clinical evidence that this is the case. It suggests that NE and 5-HT reuptake inhibition are unlikely to play a major role in the effects of nonselective monoamine reuptake blockers, such as BTS 74 398, on motor activity in MPTP-treated primates, although pharmacokinetic factors cannot be excluded. One caveat to this argument is that in MPTP-treated primates, there is no decrease in brain NE or 5-HT content as opposed to the situation in PD because the locus coeruleus and raphe nuclei are largely unaffected by MPTP toxicity (Burns et al., 1983; Langston et al., 1984). Consequently, enhancement of NE or 5-HT transmission might be more efficacious in human than in this primate model. However, the effect of nisoxetine and/or sertraline on the reversal of motor dysfunction produced by GBR 12909 suggests that blockade of NE or 5-HT reuptake might adversely affect dopaminergic manipulation of PD.

The effects of nisoxetine and sertraline were assessed in conjunction with GBR 12909, the most selective dopamine reuptake blocker among the compounds used in this study. The ability of nisoxetine to partially inhibit the improvement in locomotor activity and motor disability produced by GBR 12909 implies that enhancement in NE transmission does not contribute to the antiparkinsonian actions of nonselective monoamine reuptake blockers and might potentially impede their ability to reverse motor deficits. Similarly, ipsilateral turning provoked by monoamine reuptake inhibitors in 6-OHDA-lesioned rats is attenuated in the presence of α2 adrenergic receptor antagonists and these antagonists alone fail to produce any rotational response (Mavridis et al., 1991). However, there is little or no information available on the manner in which noradrenergic mechanisms contribute to the reversal of motor deficits in MPTP-treated primates. The inhibition of motor function by blockade of NE reuptake may explain the poor efficacy of nomifensine, which is a more potent inhibitor of the NE transporter (Table 1; Heikkila and Manzino, 1984; Jackson et al., 1984). The effects of sertraline were even more marked, causing a complete inhibition of the actions of GBR 12909 on motor disability in the MPTP-treated primate. This also suggests that inhibition of 5-HT reuptake does not contribute to the potential antiparkinsonian actions of nonselective monoamine reuptake blocking drugs. In the light of the marked improvements in motor function produced by brasofensine and BTS 74398, these data were surprising. Inhibition of both NE and 5-HT reuptake by combined administration of nisoxetine and sertraline also totally abolished the motor response to GBR 12909. The marked effect of enhancing 5-HT reuptake was expected because sertraline and other selective serotonin reuptake inhibitors were previously shown to induce parkinsonism or worsen or not improve parkinsonian symptoms in human and to reduce levels of extracellular DA derived from L-DOPA (Korsgaard et al.,...
creased extracellular NE levels after nisoxetine treatment increases the rotational response to indirect DA agonists, inactivate rodent 5-HT2c receptors because 5-HT2C receptor activation is responsible for the potential antiparkinsonian actions of monoamine reuptake inhibitors. Sertraline may affect antiparkinsonian response to L-DOPA therapy in PD patients coadministered with fluoxetine; and 2) reduced nerve activity, whereas 5-HT2C antagonists alone produce rotational activity and can potentiate quinpirole-induced circling behavior in 6-OHDA-lesioned rats (Fox et al., 1998; Gobert et al., 2000). However, 5-HT2c receptors may also be involved because this subtype has been implicated in 1) the reduced antiparkinsonian response to L-DOPA therapy in PD patients coadministered with fluoxetine; and 2) reduced nerve terminal release of 5-HT after systemic administration of 5-HT reuptake inhibitors, including sertraline (Rutter et al., 1995; Yamato et al., 2001). More specific studies are required.

The potent actions of mixed reuptake blockers, such as BTS 74 398, in MPTP-treated marmosets require some explanation given the conflicting effects of NE and 5-HT reuptake inhibition. An immediate explanation may lie in the high affinity of BTS 74 398 to inhibit [3H]DA uptake compared with GBR 12909 (Table 1; Heikkila and Manzino, 1984; Cheetham et al., 1998) but is not totally compelling and further exploration is required to understand how such drugs work at the mechanistic rather than the behavioral level. Indeed, the anatomical site at which monoamine reuptake blockers act to produce an antiparkinsonian response is debatable. Because MPTP treatment of primates results in almost complete destruction of striatal dopaminergic terminals (Burns et al., 1983), it seems improbable that monoamine reuptake blockers act at this site to produce an antiparkinsonian response. Rather, we have argued previously that such drugs act preferentially to alter mesolimbic or mesocortical DA function (Pearce et al., 2002). This may indirectly influence basal ganglia function through the cortico-striatal glutamate pathway. DA reuptake blockers have greater in vivo activity in the nucleus accumbens versus the caudate putamen (Cass et al., 1993, and references cited therein). So this region may be responsible for the interaction between DA reuptake blockade and effects on motor function mediated by inhibition of the NE and 5-HT transporter. The extrastriatal actions of monoamine reuptake blockers may also explain the ability of these drugs to enhance motor function in MPTP-treated primates without evoking established dyskinesia (M. J. Hansard, L. A. Smith, M. J. Jackson, S. C. Cheetham, and P. Jenner, unpublished observations; Pearce et al., 2002).

In summary, inhibition of the DA transporter seems responsible for the potential antiparkinsonian actions of monoamine reuptake blockers, whereas blockade of NE and/or 5-HT reuptake does not impart any antiparkinsonian potential and may adversely influence DA-mediated motor impairment. Monoamine reuptake blockers may represent an important means of controlling the symptoms of PD and may do so in a manner that differs from L-DOPA and DA agonists by avoiding established dyskinesia. Why high-efficacy, mixed monoamine reuptake inhibitors are so effective despite their potent actions on NE and 5-HT reuptake remains a mystery.

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