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The partial 5-HT$_{1A}$ agonist buspirone reduces the expression and development of l-DOPA-induced dyskinesia in rats and improves l-DOPA efficacy ☆

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Abstract

Dopamine (DA) replacement therapy with l-DOPA remains the standard pharmacotherapy for Parkinson's disease (PD). Unfortunately, chronic l-DOPA treatment is accompanied by development of motor fluctuations and l-DOPA-induced dyskinesia (LID). While serotonin (5-HT)$_{1A}$ agonists acutely reduce these complications, their prophylactic and long-term effects are not well-delineated. To test this, male Sprague–Dawley rats received unilateral 6-hydroxydopamine (6-OHDA) lesions. In experiment 1, l-DOPA-primed rats were pre-treated with Vehicle (0.9% NaCl), various doses of the partial 5-HT$_{1A}$ agonist, buspirone (0.25, 1.0 or 2.5 mg/kg, ip) or buspirone (2.5 mg/kg, ip)+the 5-HT$_{1A}$ antagonist, WAY100635 (0.5 mg/kg, ip) 5 min prior to l-DOPA (12 mg/kg+15 mg/kg benserazide, ip). Rats were tested for LID using the abnormal involuntary movements (AIMs) scale and motor performance using the forepaw adjusting steps test (FAS). In experiment 2, l-DOPA-naïve rats received co-administration of l-DOPA+buspirone (1.0 or 2.5 mg/kg, ip) for 2 weeks. AIMs and FAS were measured throughout. In l-DOPA-primed rats, buspirone dose-dependently reduced LID and improved l-DOPA-related motor performance due to action at the 5-HT$_{1A}$ receptor. In l-DOPA-naïve rats, buspirone delayed LID development while improving l-DOPA's anti-parkinsonian efficacy indicating the potential long-term benefits of 5-HT$_{1A}$ agonists for reduction of l-DOPA-related side effects.

Keywords: Rat; Serotonin; 6-Hydroxydopamine; Buspirone; Dyskinesia; Motor fluctuations; Parkinson's disease

1. Introduction

Dopamine (DA) replacement therapy with l-3,4-dihydroxyphenylalanine (l-DOPA) remains the standard pharmacotherapy for the treatment of movement deficit in patients with Parkinson's disease (PD; Obeso et al., 2000). Unfortunately, most PD patients eventually experience motor fluctuations, including "wearing off" and l-DOPA-induced dyskinesias (LID; Jankovic, 2005). The current necessity of DA replacement therapy and the debilitating nature of its side effects make non-dopaminergic adjunct treatments for the reduction of l-DOPA-induced motor complications indispensable for the health of PD patients.

One potential non-dopaminergic therapeutic target may prove to be the serotonin (5-HT) system. Following severe DA denervation, neuroadaptive changes in 5-HT raphestriatal projections and upregulated 5-HT receptors allow this system to more readily influence basal ganglia activity (Fox et al., 1998; Maeda et al., 2003; Bishop et al., 2004). Such findings have led to the suggestion that compounds targeting 5-HT neurotransmission may have therapeutic value for the reduction of problems that

Abbreviations: AIMs, Abnormal Involuntary Movements; benserazide, dl-Serine 2-(2,3,4-trihydroxybenzyl) hydrazide hydrochloride; DA, Dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; l-DOPA, l-3,4-dihydroxyphenylalanine methyl ester; 5-HIAA, 5-hydroxyindole-3-acetic acid; 5-HT, Serotonin; LID, l-DOPA-induced dyskinesia; NE, Norepinephrine; 6-OHDA, 6-hydroxydopamine hydrobromide; PD, Parkinson's disease; WAY100635, *N*-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinylcyclohexanecarboxamide maleate salt.

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accompany chronic l-DOPA treatment (Nicholson and Brotchie, 2002; Scholtissen et al., 2006). In support of this assertion, the 5-HT/DA releaser, 3,4-methylenedioxymethamphetamine and the 5-HT releaser, fenfluramine have been shown to convey both anti-parkinsonian and anti-dyskinetic effects in experimental models of PD (Iravani et al., 2003; Bishop et al., 2006). While multiple 5-HT receptor subtypes may have contributed to these beneficial effects, accumulating evidence suggests an integral role for the 5-HT_{1A} receptor.

In recent years, investigations into the beneficial effects of 5-HT_{1A} receptor stimulation have yielded encouraging, though occasionally conflicting results. In rats with unilateral DA lesions, acute administration of the full 5-HT_{1A} agonists, ±8-OH-DPAT and sarizotan was reported to reduce peak l-DOPA-induced rotations, but prolong response duration (Bibbiani et al., 2001; Ba et al., 2007). In MPTP-lesioned primates, acute administration of sarizotan was also shown to attenuate LID without affecting l-DOPA's efficacy (Bibbiani et al., 2001). These results were found to be specific to the drug's action at the 5-HT_{1A} receptor. In contrast, Iravani et al. (2006) reported that the more potent and selective enantiomer for the 5-HT_{1A} receptor, +8-OH-DPAT squelched LID, but worsened movement disability, likely reflecting induction of a 5-HT-like syndrome. Clinically, various 5-HT_{1A} agonists such as tandospirone (Kannari et al., 2002) and sarizotan (Olanow et al., 2004) have been employed with moderate success. For example, sarizotan has been reported to attenuate LID at low doses (Goetz et al., 2007) and prolong l-DOPA's efficacy in patients with advanced PD (Bara-Jimenez et al., 2005). However, similar to results in preclinical work, higher doses of these compounds can worsen parkinsonian features (Kannari et al., 2002; Goetz et al., 2007) and may have influenced the recent decision to halt the development of sarizotan as an l-DOPA adjunct therapy following Phase III clinical trials.

Given these challenges, essential questions remain concerning the utility of chronic 5-HT_{1A} adjunct therapy for the treatment of l-DOPA-related side effects. One understudied question in this area of research is the differential effects of adjunct treatments on induction (initial development) and subsequent expression (continued behavioral manifestation) of LID. While the effect of adjunct treatments on expression of LID has been extensive, effects on induction of LID have been relatively ignored. For example, 5-HT_{1A} agonists may have prophylactic utility on the development of motor fluctuations and subsequent LID expression (Tomiyama et al., 2005; Hauser et al., 2006). Moreover, partial 5-HT_{1A} agonists may convey greater benefit with less risk by reducing the likelihood of side effects related to potent 5-HT_{1A} receptor stimulation. To answer these questions, we systematically investigated the effects of 5-HT_{1A} receptor stimulation on l-DOPA-related side effects in both l-DOPA-primed and l-DOPA-naïve unilateral 6-hydroxydopamine (6-OHDA)-lesioned rats. We employed the partial 5-HT_{1A} agonist, buspirone, a common anxiolytic that has been used with some success as an experimental adjunct therapy with l-DOPA in humans (Kleedorfer et al., 1991; Bonifati et al., 1994). To measure LID, we utilized the well-validated abnormal involuntary movements procedure (Lundblad et al., 2002) and the forelimb adjusting steps test (Olsson et al., 1995; Chang et al., 1999) to quantify changes in motor performance. The current findings suggest that in this preclinical model, buspirone administration can reduce both the development and expression of l-DOPA-induced motor complications.

2. Materials and methods

2.1. Animals

Adult male Sprague–Dawley rats were used (225–250 g upon arrival; Taconic Farms, Hudson, NY, USA). Animals were housed in plastic cages (22 cm high, 45 cm deep and 23 cm wide) and had free access to standard lab chow (Rodent Diet 5001; Lab Diet, Brentwood, MO, USA) and water. The colony room was maintained on a 12/12 h light/dark cycle (lights on at 0700 h) at a temperature of 22–23 °C. Animals were maintained in strict accordance with the guidelines of the Institutional Animal Care and Use Committee of Binghamton University and the "Guide for the Care and Use of Laboratory Animals" (Institute of Laboratory Animal Resources, National Academic Press 1996; NIH publication number 85-23, revised 1996).

2.2. 6-Hydroxydopamine lesion surgeries

One week after arrival, rats received unilateral 6-hydroxydopamine (6-OHDA) lesions of the left medial forebrain bundle to destroy DA neurons. Desipramine HCl (25 mg/kg, ip; Sigma, St. Louis, MO, USA) was given 30 min prior to the 6-OHDA injection to protect norepinephrine (NE) neurons. Rats were anesthetized with inhalant isoflurane (2–3%; Sigma) in oxygen (2.5 l/min), then placed in a stereotaxic apparatus (David Kopf Instruments, Tujunga, CA, USA). The coordinates for 6-OHDA injections were AP: −1.8 mm, ML: +2.0 mm, DV: −8.6 mm relative to bregma with the incisor bar positioned 3.3 mm below the interaural line (Paxinos and Watson, 1998). Using a 10 µl Hamilton syringe attached to a 26 gauge needle, 6-OHDA (12 µg; Sigma) dissolved in 0.9% NaCl+0.1% ascorbic acid was infused through a small burr hole in the skull at a rate of 2 µl/min for a total volume of 4 µl. The needle was withdrawn 1 min later. Rats were placed in clean cages on warming pads to recover from the surgery, after which they were returned to group-housing (2 rats/cage). Soft chow was provided as needed to facilitate recovery during the first week after surgery.

2.3. Pharmacological treatments

All rats were allowed to recover 3 weeks after lesion surgery and were then assigned a priori to equal treatment groups based on forepaw adjusting steps (FAS) performance (Chang et al., 1999) and amphetamine-induced rotations (2.5 mg/kg, ip; Sigma) before pharmacological treatment commenced.

In order to test the effects of buspirone in l-DOPA-primed rats, all rats in the first study ($n=15$) received 3,4-dihydroxyphenylacetic acid methyl ester (l-DOPA; 12 mg/kg, ip; Sigma)+dl-Serine 2-(2,3,4-trihydroxybenzyl) hydrazide hydrochloride (benserazide; 15 mg/kg, ip; Sigma) once daily for 7 days.

l-DOPA and benserazide were dissolved in Vehicle (0.9% NaCl containing 0.1% ascorbic acid) and administered at a volume of 1.0 ml/kg. Rats were tested for abnormal involuntary movements (AIMs) on days 1, 5, and 7 of l-DOPA priming. Only rats displaying total AIMs of greater than 15 on day 5 of priming were included in the study, which corresponded with approximately 95% DA depletion upon HPLC analysis of striatal tissue samples. Thereafter, rats were tested for AIMs every 3–4 days in a within-subjects design, receiving a pre-treatment of buspirone Vehicle (dH_2O), various doses of the 5-HT_{1A} partial agonist, buspirone HCl (buspirone; 0.25, 1.0, or 2.5 mg/kg, ip; Sigma), the specific 5-HT_{1A} antagonist, *N*-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinylcyclohexanecarboxamide maleate salt (WAY100635; 0.5 mg/kg, ip; Sigma) or buspirone + WAY100635 (2.5 + 0.5 mg/kg, ip), 5 min prior to injection of l-DOPA (12 mg/kg, ip) + benserazide (15 mg/kg, ip) by random assignment. Immediately following l-DOPA injections, rats were monitored for AIMs and rotations for 2 h.

The FAS test was also employed throughout the study in order to test the effects of buspirone on the motor performance of l-DOPA-primed rats. All rats received the following three treatments by random assignment: Vehicle + Vehicle, Vehicle + l-DOPA (12 mg/kg, ip) + benserazide (15 mg/kg, ip) or buspirone (2.5 mg/kg, ip) + l-DOPA (12 mg/kg, ip) + benserazide (15 mg/kg, ip). To allow for peak l-DOPA plasma levels (Sato et al., 1994), testing began 1 h after l-DOPA injection. FAS testing occurred every 3–4 days following termination of AIMs testing.

In order to determine whether buspirone impacts the development of LID, all rats in the second study ($n = 30$) were l-DOPA naïve. Upon commencement of treatment, rats were assigned one of three daily pre-treatments: Vehicle + l-DOPA (12 mg/kg, ip) + benserazide (15 mg/kg, ip) or buspirone (1.0 or 2.5 mg/kg, ip) + l-DOPA (12 mg/kg, ip) + benserazide (15 mg/kg, ip) in a between-subjects design. AIMs measures were taken on days 1, 5, 8, 11, and 14 of treatment. Treatment was terminated on day 16. On day 19, all rats were injected with l-DOPA (12 mg/kg, ip) + benserazide (15 mg/kg, ip) alone and immediately monitored for AIMs and rotations to investigate post-treatment responsivity.

Rats in the second study were also tested for motor performance to investigate the effects of daily buspirone on l-DOPA efficacy. Baseline stepping measurements were obtained before initiation of the study (pre-test). On days 3, 9, and 15 following commencement of treatment, rats were treated with the following: Vehicle + l-DOPA (12 mg/kg, ip) + benserazide (15 mg/kg, ip) or buspirone (1.0 or 2.5 mg/kg, ip) + l-DOPA (12 mg/kg, ip) + benserazide (15 mg/kg, ip). Testing began 1 h after l-DOPA injection.

2.4. Abnormal involuntary movements

Rats were monitored for AIMs using a procedure similar to that described in Lundblad et al. (2002) and Bishop et al. (2006). On test days (0900–1400 h), rats were individually placed in plastic trays (60 cm × 75 cm) 5 min prior to pre-treatments. Following l-DOPA injection, a trained observer blind to treatment condition assessed each rat for exhibition of axial, limb, orolingual, and locomotor AIMs. In addition, contralateral rotations, defined as complete 360° turns away from the lesioned side of the brain, were tallied. No ipsilateral rotations, defined as complete 360° turns toward the lesioned side of the brain, were observed during testing. Dystonic posturing of the neck and torso, involving positioning of the neck and torso in a twisted manner directed toward the side of the body contralateral to the lesion, were referred to as "axial" AIMs. "Forelimb" AIMs were defined as rapid, purposeless movements of the forelimb located on the side of the body contralateral to the lesion. "Orolingual" AIMs were composed of repetitive openings and closings of the jaw and tongue protrusions. The movements are considered abnormal since they occur at times when the rats are not chewing or gnawing on food or other objects. Rats occasionally performed "locomotor" AIMs, in which they ambulated in a contralateral circular direction. Every 20th min for 2 h, rats were observed for 2 consecutive min. Rats were rated for AIMs during the 1st min and rotational behavior in the 2nd min. During the AIMs observation periods (beginning 20, 40, 60, 80, 100, and 120 min post-injection), a severity score of 0–4 was assigned for each AIMs category: 0 = not present, 1 = present for less than 50% of the observation period (i.e. 1–29 s), 2 = present for more than 50% or more of the observation period (i.e. 30–59 s), 3 = present for the entire observation period (i.e. 60 s) but interrupted by a loud stimulus (a tap on the wire cage lid), or 4 = present for the entire observation period and not interrupted by a loud stimulus. For each AIMs category, the scores were summed for the entire 2 h period. Thus, the theoretical maximum score for each type of AIM was 24 (4 × 6 periods) although observed scores were never this severe. Total AIMs (summing AIMs subcategories together, with a maximum potential of 96) and rotations were also tallied for the entire 2 h period.

2.5. Forelimb adjusting steps

Using a procedure slightly modified from that described in Olsson et al. (1995) and Chang et al. (1999), the number of adjusting steps taken by the forelimb in order to compensate for lateral movement was counted to determine the effects of lesion

Table 1
Effects of unilateral medial forebrain bundle (MFB) 6-OHDA lesions on concentrations of norepinephrine (NE), 3,4-dihydroxyphenylacetic acid (DOPAC), dopamine (DA), 5-hydroxyindoleacetic acid (5-HIAA), serotonin (5-HT) and their metabolites/monoamine ratios in the striatum

Side	NE	DOPAC	DA	DOPAC/DA	5-HIAA	5-HT	5-HIAA/5-HT
Intact (right)	0.15 ± 0.02	2.58 ± 0.33	11.2 ± 1.06	0.28 ± 0.03	0.54 ± 0.09	0.62 ± 0.09	1.14 ± 0.26
Lesion (left)	0.14 ± 0.02 (93.3%)	0.19 ± 0.03* (7.4%)	0.55 ± 0.10* (4.9%)	0.68 ± 0.05* (246%)	0.62 ± 0.08 (115%)	0.62 ± 0.07 (100%)	1.30 ± 0.25 (115%)

Values are nanogram monoamine or metabolite per milligram protein or ratios of metabolite to monoamine (mean ± S.E.) with percent of Vehicle group in parentheses. Differences between group means were determined by paired *t*-tests (*$p < 0.05$ compared to the intact side).

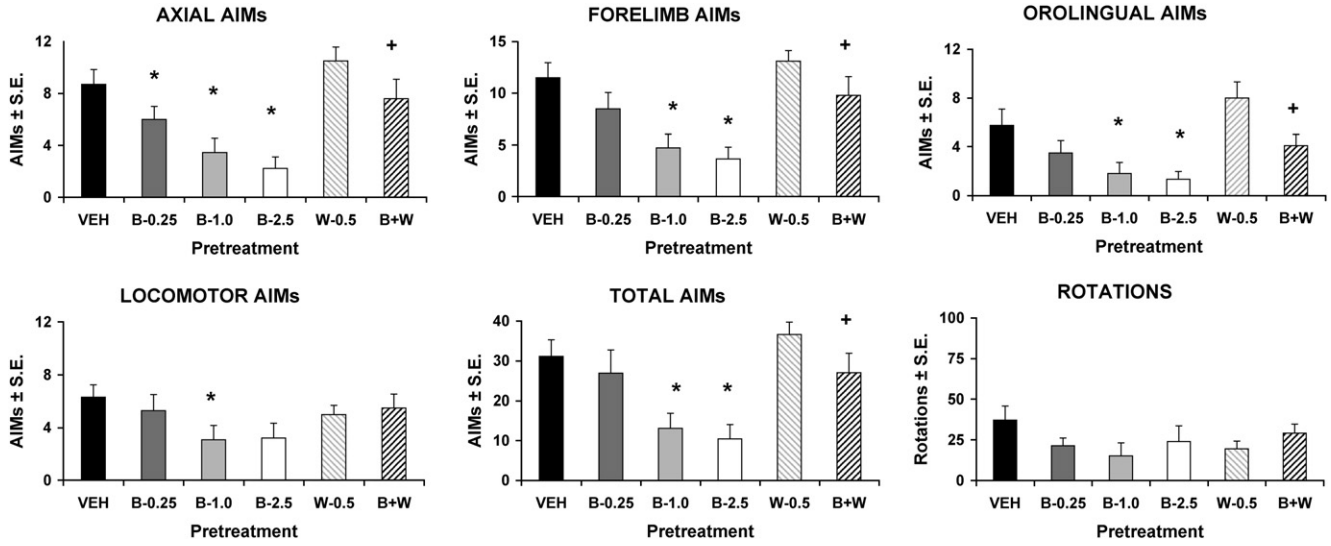

Fig. 1. Effects of buspirone on AIMs and rotations in l-DOPA (12 mg/kg)+benserazide (15 mg/kg)-primed rats. Bars show the acute effects of the following treatments: Vehicle (dH_2O; VEH), buspirone (0.25, 1.0, 2.5 mg/kg; B-0.25, B-1.0, B-2.5, respectively), the specific 5-HT_{1A} receptor antagonist WAY100635 (0.5 mg/kg; W-0.5), or buspirone+WAY 100635 (2.5 mg/kg and 0.5 mg/kg; B+W) pre-treatment on axial, forelimb, orolingual, locomotor, total AIMs and rotations induced by l-DOPA treatment (*$p<0.05$) and between B-2.5 and B+W ($^{+}p<0.05$) were established by post hoc comparisons.

and drug treatment on motor performance. Rats were moved laterally across a table at a steady rate of 90 cm/10 s. The rear part of the torso and the hindlimbs were lifted from the table and one forepaw was held by the experimenter so as to bear weight on the other forepaw. Each stepping test consisted of six trials for each forepaw, alternating between directions both forehand (defined as compensating movement toward the body) and backhand (defined as compensating movement away from the body) on the table. Data was derived by summing steps (forehand and backhand) of the lesioned forelimb and dividing them by the sum of steps (forehand and backhand) of the intact forelimb and multiplying by 100. This calculation yields a percentage of the intact side indicating the degree of forepaw disability.

2.6. High performance liquid chromatography

One week after the completion of experiments, rats were sacrificed by decapitation. The striatum was dissected, immediately frozen on dry ice, and then stored at −80 °C. Reverse-phase high performance liquid chromatography coupled to electrochemical detection was performed on striatal tissue obtained from 24 randomly selected rats (14 from the first study, 10 from the second study) according to the protocol of Kilpatrick et al. (1986), a method for semi-automated catecholamine and indoleamine analysis with coulometric detection. The system included an ESA autoinjector (Model 542), an ESA solvent delivery system (1582), an external pulse dampener (ESA), an ESA Guard-Pak column, and a C-18 (100×4.6 mm, 5 μm packing) column (ESA). Samples were homogenized in ice-cold perchloric acid (0.1 M), 1% ethanol, and 0.02% EDTA. The homogenates were spun for 30 min at 16,100 *g* with the temperature maintained at 4 °C. Aliquots of supernatant were then analyzed for abundance of DA, 5-HT, NE, 3,4-dihydroxyphenylacetic acid (DOPAC) and 5-hydroxyindole-3-acetic acid (5-HIAA). Samples were separated using a mobile phase composed of 90 mM sodium dihydrogen phosphate (monobasic, anhydrous), 0.05 mM EDTA, 1.7 mM octane sulfonic acid, and 10% acetonitrile, adjusted to pH 3.0 with *o*-phosphoric acid. A coulometric detector configured with 3 electrodes (Coulochem III, ESA) measured content of monoamines and metabolites. An ESA model 5020 guard cell (+350 mV) was positioned prior to the autoinjector. The analytical cell (ESA model 5011A; first electrode at −100 mV, second electrode at +250 mV) was located immediately after the column. The second analytical electrode emitted signals that were recorded and analyzed by EZChrom Elite software via a Scientific Software, Inc. (SS420χ) module. The final oxidation current values were plotted on a standard curve of known concentrations from 10^{-5} M to 10^{-9} M and adjusted to striatal tissue

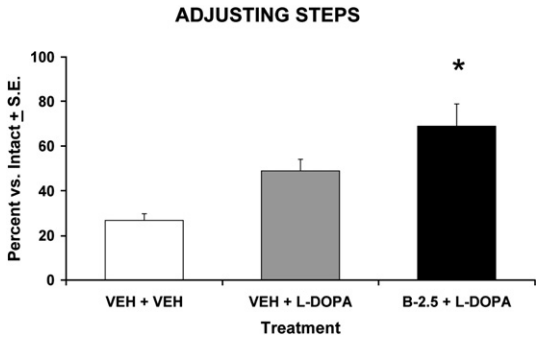

Fig. 2. Effects of buspirone and l-DOPA (12 mg/kg)+benserazide (15 mg/kg) on motor performance in FAS tests in l-DOPA-primed rats. Bars show the acute effects of the following treatments on motor performance in the FAS test expressed as a percentage of intact forepaw adjusting steps: Vehicle+Vehicle (dH_2O+0.9% NaCl; VEH+VEH), Vehicle+l-DOPA and benserazide (dH_2O+12 mg/kg and 15 mg/kg; VEH+l-DOPA), or buspirone+l-DOPA and benserazide (2.5 mg/kg+12 mg/kg and 15 mg/kg; B-2.5+l-DOPA). Main effects were determined by one-way ANOVAs. Significant differences from VEH+VEH were established by post hoc comparisons (*$p<0.05$).

weights and expressed as nanogram (ng) of monoamine or metabolite per milligram (mg) tissue (mean±S.E.).

2.7. Data analyses

Monoamine and metabolite levels in the striatum were analyzed using paired *t*-tests. Non-parametric Chi-squared median tests determined treatment effects (expressed as means±S.E.) for axial, limb, orolingual, locomotor, and total AIMs (each of the aforementioned subcategories summed). Significant differences between treatments were examined by Mann–Whitney post hoc comparisons. One-way ANOVAs and least significant differences (LSD) post hoc tests were employed for analyses of rotations and FAS results in both acute and chronic treatments. Alpha was set at $p<0.05$. Statistical analyses were conducted with Statistica Software '98 (Statsoft, Inc., Tulsa, OK, USA).

3. Results

3.1. Monoamine and metabolite levels

The effects of the 6-OHDA lesion on concentrations of monoamine and metabolite levels and turnover ratios (metabolite/monoamine) in the intact (right) versus lesioned (left) striata are shown in Table 1. As anticipated, unilateral 6-OHDA injection into the medial forebrain bundle produced significant reductions in lesioned striatal DOPAC ($t_{23}=7.72$, $p<0.05$) and DA levels ($t_{23}=10.32$, $p<0.05$), 92.6% and 95.1% respectively, compared to intact striatum. The denervated side also showed an increased DOPAC/DA turnover rate (246%) compared to control ($t_{23}=7.97$, $p<0.05$). There were no significant differences between intact and lesioned striata for any other monoamine measures.

3.2. Buspirone dose-dependently reduced AIMs expression

Various doses of buspirone were tested in l-DOPA-primed rats to determine their effects on AIMs and rotations. As shown in Fig. 1, significant treatment effects were observed on measures of axial ($\chi^2=24.08$, $p<0.05$), forelimb ($\chi^2=31.61$, $p<0.05$), orolingual ($\chi^2=19.93$, $p<0.05$), locomotor ($\chi^2=11.35$, $p<0.05$), and total AIMs ($\chi^2=20.01$, $p<0.05$). Post hoc analyses demonstrated that the 0.25 mg/kg dose of buspirone diminished axial AIMs ($p<0.05$). The 1.0 mg/kg dose of buspirone reduced AIMs on all significant measures (all $p<0.05$) and the 2.5 mg/kg buspirone dose attenuated AIMs in every category (all $p<0.05$) with the exception of locomotor AIMs.

3.3. 5-HT_{1A} receptor antagonism reversed buspirone's anti-dyskinetic effects

As shown in Fig. 1, rats also received a pre-treatment with either the 5-HT_{1A} antagonist WAY100635 (1.0 mg/kg) or buspirone (2.5 mg/kg)+WAY100635 in order to investigate the contribution of 5-HT_{1A} receptors to the anti-dyskinetic effects of buspirone. On measures of axial, forelimb, orolingual, and total AIMs, post hoc analyses revealed that co-administration of WAY100635 significantly reversed the anti-dyskinetic effects of buspirone (all $p<0.05$). In each case, AIMs rebounded to levels similar to those in the Vehicle pre-treatment group.

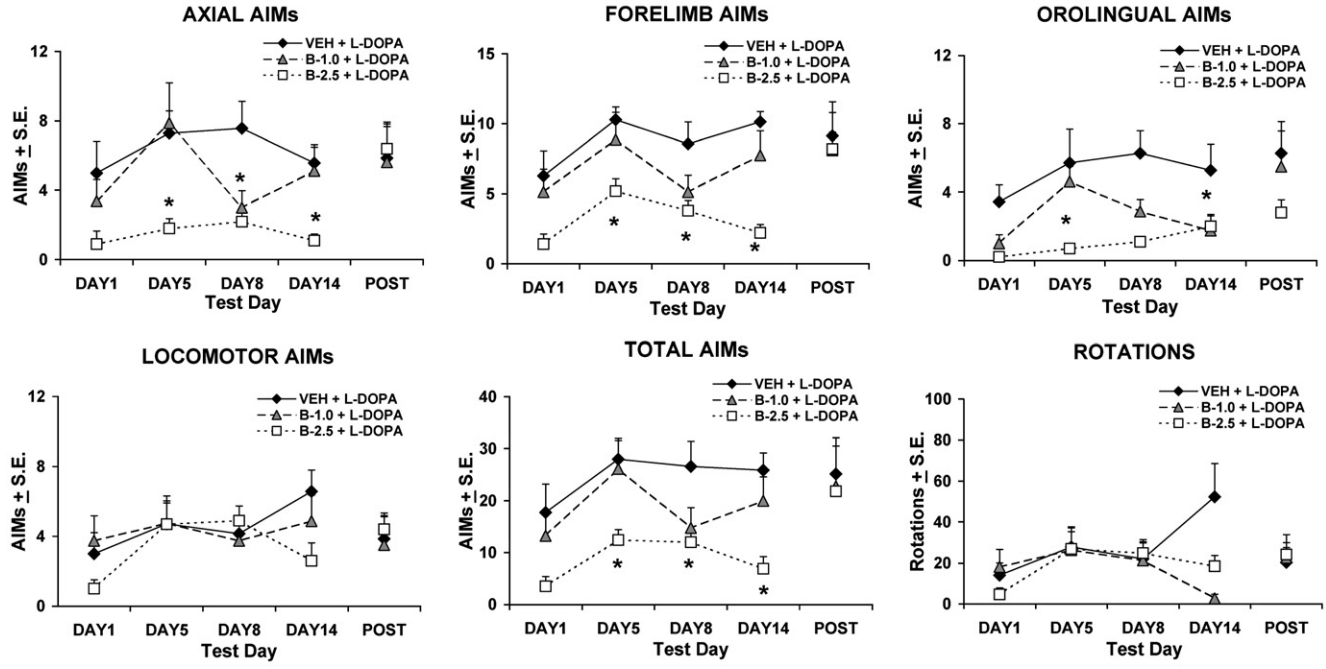

Fig. 3. Effects of buspirone (1.0 and 2.5 mg/kg) and l-DOPA (12 mg/kg)+benserazide (15 mg/kg) on the development of AIMs and rotations. Symbols demonstrate the chronic effects of Vehicle (dH_2O, VEH) and buspirone (1.0 and 2.5 mg/kg; B-1.0 and B-2.5, respectively) pre-treatment on axial, limb, orolingual, locomotor, total AIMs and rotations induced by l-DOPA (12 mg/kg)+benserazide (15 mg/kg) treatment on test days 1, 5, 8, 14 after initiation of treatment (*$p<0.05$ vs. VEH+l-DOPA).

3.4. Buspirone treatment improved l-DOPA efficacy on the FAS test

In order to ascertain whether administration of buspirone affects l-DOPA's efficacy, l-DOPA-primed rats were tested for motor performance using the FAS test. Results are shown in Fig. 2. One-way ANOVA indicated a significant effect of treatment ($F_{2,30}=8.56$; $p<0.05$). Post hoc analyses revealed that co-administration of buspirone (2.5 mg/kg)+l-DOPA, but not Vehicle+l-DOPA improved stepping of the lesioned forepaw of l-DOPA-primed rats ($p<0.05$).

3.5. Co-administration of buspirone with l-DOPA reduced AIMs development

As demonstrated in Fig. 3, various doses of buspirone were co-administered with l-DOPA to l-DOPA-naïve rats to determine their effects on the development of AIMs and rotations. On days 5, 8, and 14, significant treatment effects were observed on measures of axial ($\chi^2=6.81$, 7.21, and 13.82, respectively; all $p<0.05$), forelimb ($\chi^2=6.81$, 7.21, and 13.82, respectively; all $p<0.05$), and total AIMs ($\chi^2=6.59$, 6.78 and 8.31, respectively; all $p<0.05$). An effect of treatment was also observed for orolingual AIMs on days 5 and 14 ($\chi^2=8.31$ and 7.21, respectively; both $p<0.05$). Post hoc analyses revealed a reduction of AIMs in every significant category following co-administration of 2.5 mg/kg buspirone+l-DOPA versus l-DOPA alone (all $p<0.05$).

3.6. Buspirone maintained the efficacy of l-DOPA on the FAS test

In order to investigate whether buspirone maintains the efficacy of l-DOPA, motor performance was measured throughout the development study. Results are shown in Fig. 4. Co-administration of Vehicle ($F_{3,17}=6.27$, $p<0.05$), buspirone (1.0 mg/kg; $F_{3,23}=4.44$, $p<0.05$), and buspirone (2.5 mg/kg; $F_{3,29}=6.05$, $p<0.05$) with l-DOPA improved motor performance compared to pre-test levels. Post hoc analyses showed that while Vehicle +l-DOPA proved efficacious on days 3 and 15 (both $p<0.05$), there was a distinct reduction in stepping to pre-test levels on day 9. Co-administration of either dose of buspirone maintained the beneficial effects of l-DOPA on all days tested (all $p<0.05$).

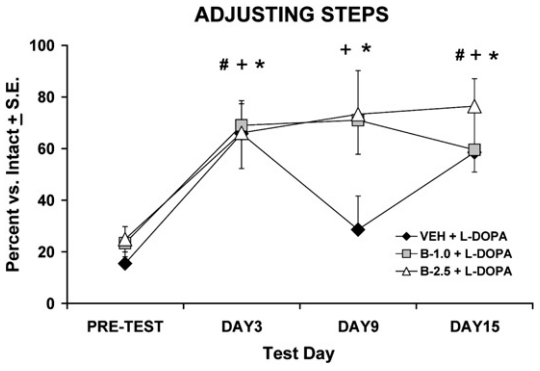

Fig. 4. Chronic effects of buspirone and l-DOPA (12 mg/kg)+benserazide (15 mg/kg) on motor performance in FAS tests. Bars show the chronic effects of the following treatments on motor performance in the FAS test: Vehicle+l-DOPA and benserazide (dH_2O+12 mg/kg and 15 mg/kg; VEH+l-DOPA), buspirone+l-DOPA and benserazide (1.0 mg/kg+12 mg/kg and 15 mg/kg; B-1.0+l-DOPA), or buspirone+l-DOPA and benserazide (2.5 mg/kg+12 mg/kg and 15 mg/kg; B-2.5+l-DOPA) expressed as a percentage of intact forepaw adjusting steps. Main effects were determined by one-way ANOVAs of each treatment. Significant differences from pre-test levels were established by post hoc comparisons of VEH+l-DOPA, B-1.0+l-DOPA, B-2.5+l-DOPA ($^{\#}p<0.05$, $^{+}p<0.05$, and $^{*}p<0.05$, respectively).

4. Discussion

In the present study, we demonstrate several findings that support exploration of partial 5-HT_{1A} receptor agonists as adjuncts to l-DOPA pharmacotherapy. First, in corroboration with other preclinical models, acute administration of the partial 5-HT_{1A} receptor agonist buspirone conveyed anti-dyskinetic effects in l-DOPA-primed rats that were specific to the 5-HT_{1A} receptor. Second, acute buspirone improved the efficacy of l-DOPA on measures of motor performance. Most importantly, we demonstrated that co-administration of buspirone with l-DOPA to l-DOPA-naïve rats prophylactically suppressed AIMs development and expression while improving l-DOPA efficacy.

The 6-OHDA rat model of PD has proven extremely useful for the study of PD and the side effects of l-DOPA treatment (Ungerstedt, 1971; Miller and Beninger, 1991; Schallert et al., 2000). Traditionally, investigations using this model have measured l-DOPA-induced rotations as an indication of the anti-dyskinetic efficacy of various pharmacological treatments (Carey, 1991). In recent years, the pertinence of rotational behavior has been called into question (Castaneda et al., 2005) and alternative methods that resemble clinical manifestations of LID have been developed (Hagell and Widner, 1999; Lundblad et al., 2002). The AIMs procedure used in the present study employs discrete behavioral measures, displays face validity with known anti-dyskinetic compounds, and shows consistency throughout treatment in l-DOPA-primed rats (Lundblad et al., 2002; Taylor et al., 2005; Bishop et al., 2006).

While examining the anti-dyskinetic properties of potential l-DOPA adjuncts remain the paramount goal of most preclinical studies, the modulation of l-DOPA efficacy by these compounds is often overlooked. In order to fully characterize the effects of buspirone in the l-DOPA-treated hemiparkinsonian rat, we also employed the FAS test (Olsson et al., 1995; Chang et al., 1999; Schallert et al., 2000). The FAS test has been extensively utilized as a measure of forelimb akinesia, demonstrating sensitivity to DA loss and reversal of deficit by DA replacement therapy, stem cell transplantation, and surgical intervention (Chang et al., 1999; Cho et al., 2006). In this study, the FAS test facilitated the investigation of 6-OHDA-induced motor deficit and the recovery of motor function upon treatment with l-DOPA alone or in conjunction with buspirone.

In the first experiment we were interested in determining the acute anti-dyskinetic effects and pharmacological specificity of buspirone on AIMs in the l-DOPA-primed rat. As demonstrated in Fig. 1, buspirone dose-dependently reduced AIMs

expression, but did not significantly alter l-DOPA-induced rotations. Since rotations were not affected by buspirone administration, the effect of buspirone on locomotor AIMs was also weak. More importantly, co-administration of the 5-HT_{1A} antagonist, WAY100635 completely reversed the anti-dyskinetic effects of buspirone treatment. While extant reports indicate that adjunct buspirone therapy lessens LID symptoms in human patients (Kleedorfer et al., 1991; Bonifati et al., 1994), we demonstrate that the anti-dyskinetic effects of buspirone are primarily due to its action on the 5-HT_{1A} receptor. These results corroborate earlier studies in which the effects of direct or indirect 5-HT agonists with anti-dyskinetic properties were blocked by administration of selective 5-HT_{1A} antagonists (Bibbiani et al., 2001; Iravani et al., 2003; Bishop et al., 2006; Ba et al., 2007).

While the acute anti-dyskinetic effects of 5-HT_{1A} receptor stimulation have been shown in both preclinical (Bibbiani et al., 2001; Bishop et al., 2006) and clinical investigations (Olanow et al., 2004; Bara-Jimenez et al., 2005; Goetz et al., 2007), to date the prophylactic anti-dyskinetic efficacy of these compounds remains largely unknown. Preliminary results have suggested that 5-HT_{1A} agonists may have some utility in this role since Tomiyama et al. (2005) observed that chronic pretreatment with the full 5-HT_{1A} agonist, ±8-OH-DPAT reduced the development of l-DOPA-induced rotational behavior. However, rotations are a controversial measure of l-DOPA-related side effects and have limited face validity with the actual human disorder (Cenci et al., 2002; Castaneda et al., 2005). Therefore, in the second experiment we investigated whether buspirone co-administration prophylactically reduces the development of l-DOPA-induced AIMs. As shown in Fig. 3, the high dose of buspirone both reduced the development of AIMs and maintained these effects when chronically co-administered with l-DOPA over a 2 week period. Interestingly, when rats were re-tested for AIMs after a 4 day wash-out period, all groups displayed similar levels of dyskinesia. These results suggest that while buspirone may decrease the expression of LID, the underlying mechanism may be perpetuated. This corroborates an anecdotal report by Bonifati et al. (1994), who reported that one individual who discontinued adjunct buspirone treatment suffered a complete resurfacing of previous LID.

l-DOPA treatment in humans is often beneficial to motor performance for a time until the therapeutic window shrinks resulting in progressive motor fluctuations (Obeso et al., 2000). Optimal adjunct treatment should prolong the beneficial aspects of DA replacement therapy while concurrently reducing deleterious side effects, such as LID and wearing off (Jankovic, 2005). The present study shows that buspirone exerts some promise in this dual role, as demonstrated by the results on the FAS test. In l-DOPA-primed rats, treatment with l-DOPA alone produced a non-significant increase in lesioned forelimb stepping compared to control forelimb (see Fig. 2). Acute co-administration of buspirone with l-DOPA resulted in significantly improved lesion-side stepping. More importantly, we show that chronic adjunct treatment with buspirone may also convey beneficial motor effects (see Fig. 4). While l-DOPA administration alone reversed stepping deficit, this effect was variable which is consistent with motor fluctuations often seen in PD patients receiving chronic l-DOPA therapy (Jankovic, 2005). Buspirone consistently improved motor fluctuations at both doses tested.

This augmentation of l-DOPA efficacy supports previous work in rodents showing an attenuation of shortened rotational motor response duration in chronic l-DOPA-treated rats co-administered the full 5-HT_{1A} receptor agonists, sarizotan (Bibbiani et al., 2001) and ±8-OH-DPAT (Ba et al., 2007). Kannari et al. (2001) observed that 5-HT_{1A} stimulation with ±8-OH-DPAT augmented the half-life of DA concentration in the striatum of 6-OHDA-treated rats. Prolonging optimal DA levels may lead to rehabilitation of motor performance and amelioration of the pulsatile stimulation of DA receptors that leads to motor fluctuations (Jankovic, 2005). Additionally, these results may reflect primary effects of 5-HT_{1A} receptor stimulation since previous studies have reported 5-HT_{1A} receptor stimulation alone can convey anti-parkinsonian effects (Mignon and Wolf, 2002, 2007; Bezard et al., 2006).

In the present investigation, we employed the partial 5-HT_{1A} agonist, buspirone (Tunnicliff, 1991). This decision was made based on previous research showing the obvious detriments of engaging full 5-HT_{1A} receptor occupation, including immobility and stereotyped movements (Kannari et al., 2001; Iravani et al., 2006). These drawbacks may have been due to the induction of serotonin syndrome characterized by lower lip retraction, hindlimb abduction and flat body posture caused by an overstimulation of 5-HT_{1A} receptors (Goodwin et al., 1987). However, buspirone displays affinity for additional receptor subtypes in addition to 5-HT_{1A} receptors. For example, buspirone also has moderate affinity for D_2 receptors acting as an antagonist at high doses (McMillen et al., 1983; McCall et al., 1994; Gobert et al., 1999). We do not believe the current results reflect actions at this receptor. First, based on current models of dyskinesia, antagonism of corticostriatal D_2 autoreceptors would most likely promote LID by disinhibiting glutamatergic output to the striatum of these neurons. Second, antagonism of striatal postsynaptic D_2 receptors with eticlopride causes a reduction in AIMs behaviors but most likely at the expense of l-DOPA efficacy (Taylor et al., 2005). Neither of these effects was observed in the current study confirming that buspirone was not likely acting by antagonism of D_2 receptors to affect the development and expression of AIMs. While the 5-HT_{1A} antagonist, WAY100635 also purportedly exhibits antagonistic properties at D_2 receptors at high doses (Ahlenius et al., 1999), the dose employed in the current study was too low to exhibit noticeable effects at the D_2 receptor. There are reports that WAY100635 and its metabolite can act as D_4 agonists (Chemel et al., 2006). In the present study there was no evidence that WAY100635 produced any behavioral effects of its own via action at either of these DA receptors. Collectively, these data suggest that buspirone's effects on l-DOPA-induced motor complications were unique to its pharmacological profile as a partial agonist at the 5-HT_{1A} receptor.

Despite this knowledge, the mechanisms by which 5-HT_{1A} receptor agonists convey their effects are largely unknown. Buspirone's anti-dyskinetic action may be the result of 5-HT_{1A}

receptor stimulation at one or more areas that impact movement. For example, 5-HT_{1A} receptors are found postsynaptically within the motor cortex on corticostriatal glutamate projections (Antonelli et al., 2005; Saigal et al., 2006). There is also evidence of an upregulated 5-HT_{1A} receptor population within striatal striosomes following MPTP lesions in primates (Frechilla et al., 2001; Bezard et al., 2006). Furthermore, 5-HT_{1A} receptors also densely populate the dorsal raphe nucleus, where they act as somatodendritic autoreceptors (Hjorth and Sharp, 1991; Knobelman et al., 2000). 5-HT_{1A} receptor populations in these three areas may modulate DA output in several different ways. First, stimulation of postsynaptic 5-HT_{1A} receptors in the glutamatergic corticostriatal pathway may assuage dyskinesia by reducing excessive glutamate release in the striatum (Mignon and Wolf, 2002, 2007). Antonelli et al. (2005) observed that microinfusion of sarizotan into the motor cortex reduced glutamate levels in the striatum via this pathway. Alternatively, presynaptic 5-HT_{1A} receptors within striatal striosomes may squelch glutamate release into the striatum, where they may act to curb pathological striatal output that is responsible for dyskinetic movements. Recent studies further indicate that following extensive DA depletion, serotonergic raphestriatal neurons may usurp the role previously held by the nigrostriatal pathway, converting exogenous l-DOPA into DA and releasing it into the striatum (Tanaka et al., 1999; Maeda et al., 2005). 5-HT_{1A} receptor stimulation in the dorsal raphe nucleus may modulate output of l-DOPA-derived DA into the striatum, thereby prolonging DA half-life in the Parkinsonian brain (Tanaka et al., 1999; Olanow and Obeso, 2000; Kannari et al., 2001). Understanding of the mechanism(s) that underlie these effects is urgently needed.

In conclusion, the current preclinical findings further implicate the 5-HT_{1A} receptor as a promising therapeutic target for the reduction of LID and motor fluctuations. As important, these results suggest that partial 5-HT_{1A} receptor agonists may be employed prophylactically to reduce both the induction and expression of motor complications that may arise with continued DA replacement therapy, without a loss in l-DOPA efficacy as seen upon more complete 5-HT_{1A} receptor occupation. Such findings collectively support continued investigations with 5-HT_{1A} agonists that may improve the health of the PD patient. In future studies, we hope to look more closely at the prophylactic effects of 5-HT_{1A} receptor agonists and their benefits in a wider array of behavioral motor performance tests.

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