

Serotonin 2A receptor antagonist treatment reduces dopamine D1 receptor-mediated rotational behavior but not L-DOPA-induced abnormal involuntary movements in the unilateral dopamine-depleted rat

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Abstract

Previous experiments have demonstrated that serotonin (5-HT) 2A receptor antagonists suppress hyperkinetic behaviors associated with dopamine (DA) D1 receptor supersensitivity in rats with 6-hydroxydopamine (6-OHDA) lesions. Since L-DOPA induced dyskinesia (LID) may be mediated by oversensitive D1-mediated signaling, the present study examined the effects of the selective 5-HT_{2A} antagonist M100907 on LID behaviors in DA-depleted rats. Adult male Sprague–Dawley rats with unilateral 6-OHDA lesions received daily L-DOPA treatments to produce dyskinetic behaviors as measured by abnormal involuntary movements (AIMs) testing. In these animals, M100907 (0.01, 0.1 or 1.0 mg/kg, ip) given 30 min before L-DOPA did not alter the appearance or intensity of AIMs behaviors. Because L-DOPA induced AIMs in rats are dependent upon D1 and D2 receptor activation, a second study was performed to determine if M100907 could suppress D1- or D2-mediated rotational behaviors. Contralateral rotations induced by the D1 agonist SKF82958 were significantly reduced by pre-treatment with M100907. However, M100907 was ineffective in reducing rotations induced by the D2 agonist quinpirole. The finding that M100907 suppresses rotations induced by D1, but not D2, agonists may provide a partial explanation for the lack of effect of a selective 5-HT_{2A} antagonist on L-DOPA-induced AIMs behaviors.

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1. Introduction

Dopamine (DA) replacement therapy with L-DOPA is the common treatment for the alleviation of motor impairments

associated with Parkinson's Disease (PD). Unfortunately, prolonged L-DOPA treatment leads to L-DOPA-induced dyskinesia (LID) characterized by abnormal and excessive movements in 40% of patients within 4–6 years of treatment and as much as 90% by 9–15 years (Ahlskog and Muenter, 2001). One factor hypothesized to underlie LID is the development of supersensitive DA D1 receptors – a mechanism suggested to contribute to the problem of LID in PD patients, MPTP-treated primates, and 6-hydroxydopamine-lesioned rats (Pifl et al., 1992; Cai et al., 2002; Gerfen et al., 2002;

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Corvol et al., 2004; Aubert et al., 2005; Taylor et al., 2005). As such, methods for reducing abnormal D1 signaling may also decrease the problem of LID and enhance the therapeutic efficacy of L-DOPA treatment.

Recent studies suggest that 5-HT_{2A} receptor-mediated signaling may contribute to hyperkinetic behaviors and abnormal striatal gene expression patterns observed in DA-depleted rats treated with D1 agonists. D1 and 5-HT₂ agonist treatments produce a synergistic induction of striatonigral gene expression in the DA-lesioned rat while no such effect is observed in the intact animal (Gresch and Walker, 1999b; Campbell et al., 2001). This observation is consistent with behavioral studies showing hyperlocomotion following combined D1 and 5-HT₂ agonist infusion into the DA-depleted striatum at low doses that had no effect on behavior when administered separately (Bishop and Walker, 2003). More recently, the selective 5-HT_{2A} receptor antagonist M100907 was found to suppress hyperactive locomotor behaviors induced by intrastriatal infusion of the D1 agonist SKF82958 (Bishop et al., 2005). Interestingly, both experimental and clinical studies suggest that LID is reduced by atypical antipsychotics with 5-HT_{2A} receptor antagonist abilities (Meco et al., 1998; Grondin et al., 1999; Oh et al., 2002; Durif et al., 2004), as well as the 5-HT₂ receptor antagonist ritanserin (Maertens de Noordhout and Delwaide, 1986; Meco et al., 1988). Thus, it is possible that 5-HT_{2A} receptor antagonist treatment may also have LID suppressing effects in L-DOPA-treated rats since LID behaviors have been shown to be dependent, at least in part, upon D1 receptor activation (Taylor et al., 2005). To address this question, the present studies examined the effects of 5-HT_{2A} antagonist treatment with M100907 on L-DOPA-induced abnormal involuntary movements (AIMs) in adult rats with unilateral DA lesions. In addition, experiments also measured the effects of M100907 on contralateral rotational behavior induced by selective D1- and D2-receptor agonists to determine if 5-HT_{2A} antagonist treatment was differentially effective in blocking supersensitive effects at one or both receptors.

2. Methods

2.1. Animals

Adult male Sprague–Dawley rats were used (225–250 g upon arrival; Charles River Laboratories, Wilmington, MA). 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; LabDiet, Brentwood, MO) and water. The colony room was maintained on a 12-h light/dark cycle (lights on at 0700 hrs) 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 Wayne State 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 ($n = 67$) were subjected to a unilateral 6-OHDA lesion to the right or left medial forebrain bundle to destroy DA neurons. Desipramine HCl (25 mg/kg, ip) was given 30 min prior to the 6-OHDA

injection to protect norepinephrine neurons. Rats were anesthetized with ketamine (30–90 mg/kg, ip) and xylazine (5–15 mg/kg, ip), then placed in a stereotaxic apparatus. The coordinates for the 6-OHDA injections were AP: –2.5 mm, ML: ± 2.0 mm, and DV: –9.0 mm relative to bregma with the incisor bar positioned –3.3 mm below the interaural line (Paxinos and Watson, 1998). Using a 10- μ l Hamilton syringe attached to a 26-gauge needle, 6-OHDA (12 μ g; dissolved in 0.9% sodium chloride and 0.1% ascorbic acid) was infused through a small burr hole in the skull at a rate of 2 μ l/min for a total volume of 4 μ l. The needle was withdrawn 1 min later. Upon recovery from surgery, rats were returned to group-housing (2–4 rats/cage).

2.3. L-DOPA-induced AIMs

The “L-DOPA AIMs” group of rats ($n = 23$) was primed with L-DOPA (6 mg/kg, ip) plus the peripheral amino acid decarboxylase inhibitor benserazide (15 mg/kg, ip; dissolved in 0.9% NaCl and 0.1% ascorbic acid) once daily for 10 consecutive days. Rats retained for antagonist tests had a minimum total AIMs score of 20 during the 120-min period following L-DOPA (6 mg/kg; $n = 10$). AIMs were maintained by administering the same priming dose of L-DOPA (6 mg/kg) plus benserazide (15 mg/kg, ip) up to 3 times per week. Rats were given each dose of the 5-HT_{2A} antagonist M100907 (0.01, 0.1, or 1.0 mg/kg, ip) or vehicle (100% DMSO, ip) 1 time, followed 30 min later by L-DOPA (6 mg/kg, ip) plus benserazide (15 mg/kg, ip). A within-subjects design was used with antagonist treatments counterbalanced to avoid order effects.

Rats were monitored for AIMs using a procedure slightly modified from that described in Lundblad et al. (2002). Specifically, rats were observed for a 2-h time period rather than a 3-h time period, as L-DOPA-induced AIMs were near baseline levels by 2 h after the injection. Additionally, rats were not disturbed during the observation period in the current study. Rats were individually placed in plastic cages of the same style as those used to house the animals for the observation of AIMs. A trained observer blind to treatment condition assessed each rat for exhibition of axial, limb, orolingual, and locomotor AIMs. Dystonic posturing of the neck and torso, which involves positioning of the neck and torso in a twisted manner directed toward the side of the body contralateral to the lesion is referred to as “axial” AIMs. Rats will often exhibit the dystonic posture while in a bipedal position or when they have lost their balance and are laying on their backs. “Limb” AIMs involve rapid, purposeless movements of the forelimb located on the side of the body contralateral to the lesion and can occur in multiple body positions, but are not counted while the rat ambulates. “Orolingual” AIMs are composed of repetitive openings and closings of the jaw and tongue protrusions, which do not seem to depend on the position of the body. 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 perform “locomotor” AIMs, in which they ambulate in a contralateral circular direction. Each rat was observed every 20th minute to provide a sampling of the dyskinetic behavior over the 2-h period following the L-DOPA injection. During each of these 1-min observation periods (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) and interrupted by a loud stimulus (a tap on the wire cage lid), or 4 = present for the entire observation period but 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 is 24 (4 \times 6 periods) although observed scores were never this severe.

2.4. D1 and D2 agonist-induced rotational behavior

Priming treatments began at least 3 weeks after the lesion surgery. All rats used for the rotation studies were given 2–3 priming doses of the D1 agonist SKF82958 (0.5 mg/kg, ip; O’Boyle et al., 1989) at least 1 day apart to enhance rotations induced by the test doses of agonists (Pollack and Yates, 1999). After the priming period, the “D1 rotation” group ($n = 30$) was observed for

rotations to the test dose of SKF82958 (0.2 mg/kg, ip), while the “D2 rotation” group ($n = 14$) was observed for rotations to the test dose of quinpirole (0.2 mg/kg, ip; Tsuruta et al., 1981). Rats retained for the D1 study ($n = 16$) averaged 9 or more contralateral rotations/min in response to SKF82958 (0.2 mg/kg). Rats retained for the D2 study ($n = 7$) averaged 4 or more contralateral rotations/min in response to quinpirole (0.2 mg/kg).

Antagonists or vehicle were given every 2–4 days in a randomized order using a within-subjects design for each group. On test days, rats were given the D1 receptor antagonist SCH23390 (0.1 or 1.0 mg/kg, ip; Hyttel, 1983), the D2 receptor antagonist eticlopride (0.1 or 1.0 mg/kg, ip; Hall et al., 1985), the 5-HT_{2A} receptor antagonist M100907 (0.1 or 1.0 mg/kg, ip; Ullrich and Rice, 2000), or vehicle (100% DMSO, ip). Rats were removed from their home cages, given antagonist pre-treatments, and then individually placed in plastic trays (60 cm × 75 cm). Five minutes later, rats were given SKF82958 (D1 rotation group; 0.2 mg/kg) or quinpirole (D2 rotation group; 0.2 mg/kg) and immediately returned to the trays. Rotational behavior over the 90-min period following the agonist injection was sampled for each rat by manually tallying the number of contralateral turns (360°) performed every 5th minute. The average number of rotations/min was then calculated. Rats had previously been acclimated to the trays on several occasions during the priming period.

2.5. Drugs

6-Hydroxydopamine hydrobromide (6-OHDA); desipramine HCl; (±)-6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide (SKF82958 or chloro-APB); *trans*-(±)-4,4a,5,6,7,8,8a,9-Octahydro-5-propyl-1H-pyrazolo[3,4-g]quinoline dihydrochloride (quinpirole); 3-methyl-1-phenyl-2,3,4,5-tetrahydro-7-chloro-8-hydroxy-(1H)-3-benzazepine (SCH23390); *S*-(−)-3-chloro-5-ethyl-N-[(1-ethyl-2-pyrrolidinyl)methyl]-6-hydroxy-2-methoxybenzamide hydrochloride (eticlopride); L-3,4-dihydroxyphenylalanine methyl ester hydrochloride (L-DOPA); DL-serine 2-(2,3,4-trihydroxybenzyl)hydrazide hydrochloride (benserazide); and dimethyl sulfoxide (DMSO) were purchased from Sigma (St. Louis, MO). Ketamine and xylazine were produced by Lloyd Laboratories (Shenandoah, IA). (R)-(+)-±-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidine-methanol (M100907) was synthesized at NIH according to the methods of Ullrich and Rice (2000).

2.6. High performance liquid chromatography

After the completion of experiments, rats were sacrificed by decapitation. The anterior striatum was dissected, immediately frozen on dry ice, and then stored at -80°C . Reverse-phase high performance liquid chromatography coupled to electrochemical detection (HPLC-ED) was performed on samples of the intact and lesioned striata obtained from 10 randomly selected rats according to the protocol of Kilpatrick et al. (1986) – a method for semi-automated catecholamine and indoleamine analysis with coulometric detection. The system included a Waters WISP autoinjector, a BAS solvent delivery system (PM-80), an external pulse dampener (Rainin), a Waters Guard-Pak column, and a C-18 (100 × 4.6 mm, 5 μm packing) column (Perkin–Elmer). 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 3,4-dihydroxyphenylacetic acid (DOPAC) and DA. Samples were separated using a mobile phase composed of 100 mM sodium phosphate (monobasic, anhydrous), 0.05 mM EDTA, 1.4 mM octane sulfonic acid, and 9% acetonitrile, adjusted to pH 3.0 with *o*-phosphoric acid. A coulometric detector configured with 3 electrodes (Model 5011, ESA) measured content of DOPAC and DA. An ESA model 5020 guard cell (+400 mV) was positioned prior to the WISP injector. The analytical cell (ESA model 5011; first electrode at -40 mV, second electrode at $+500$ mV) was located immediately past the column. The second analytical electrode emitted signals that were recorded and analyzed by a Waters Baseline 810 Chromatography Workstation via a Waters Interface Module. The final oxidation current values were adjusted to protein amounts determined by Lowry assay (Lowry et al., 1951) and expressed as nanogram (ng) of DOPAC or DA per milligram (mg) protein (mean ± SE).

2.7. Data analyses

HPLC data were analyzed by independent *t*-tests. For behavioral measures, significant main effects of pre-treatment were determined by repeated measures 1-way ANOVA tests. Newman–Keuls post hoc tests were performed to detect significant differences between antagonist and vehicle pre-treatments. When a significant main effect of M100907 was found, a 2-way repeated measures ANOVA was used to determine whether a significant treatment by time interaction was present. Neuman–Keuls post hoc tests were then used to detect differences between M100907 and vehicle pre-treatments at the same time points after the L-DOPA injection. Statistica software '98 was used (Statsoft Inc., Tulsa, OK, USA). Alpha was set at $p < 0.05$.

3. Results

3.1. DOPAC and DA levels

Unilateral 6-OHDA injections into the medial forebrain bundle caused a 96% reduction in DA levels in the ipsilateral lesioned (0.45 ± 0.31 ng DA per mg protein) versus contralateral intact (10.95 ± 1.94 ng DA per mg protein) striatum ($t_{18} = -5.64$, $p < 0.05$). Additionally, DOPAC levels were 93% lower in the ipsilateral (0.11 ± 0.02 ng DOPAC per mg protein) compared to the contralateral (1.51 ± 0.22 ng DOPAC per mg protein) striatum ($t_{18} = -6.66$, $p < 0.05$).

3.2. L-DOPA-induced AIMs

L-DOPA (6 mg/kg) + benserazide (15 mg/kg) induced the expression of axial, limb, orolingual and locomotor AIMs. Pre-treatment with the 5-HT_{2A} antagonist M100907 did not alter any category of L-DOPA-induced AIMs, as no significant main effects of treatment were found for axial ($F_{(3,27)} = 0.24$; NS; Fig. 1A), limb ($F_{(3,27)} = 0.12$; NS; Fig. 1B), orolingual ($F_{(3,27)} = 0.06$; NS; Fig. 1C), or locomotor ($F_{(3,27)} = 1.13$; NS; Fig. 1D) AIMs. These data suggested that acute M100907 may not reduce L-DOPA-induced AIMs in rats with established dyskinesia.

3.3. D1 receptor agonist-induced rotation

The D1 agonist SKF82958 (0.2 mg/kg) caused contralateral rotations that were altered by the various pre-treatments. A significant main effect of treatment was observed with the D1 antagonist SCH23390 ($F_{(2,30)} = 171.42$; $p < 0.05$; Fig. 2A). Rats pre-treated with either the 0.1 or 1.0 mg/kg dose of SCH23390 made fewer contralateral rotations than those pre-treated with vehicle ($p < 0.05$). There was not a significant main effect of treatment for the D2 antagonist eticlopride ($F_{(2,30)} = 2.16$; NS; Fig. 2B). These results suggested that the stimulatory effects of SKF82958 were primarily due to D1 rather than D2 receptor activation. Pre-treatment with the 5-HT_{2A} antagonist M100907 also led to a significant main effect of treatment ($F_{(2,30)} = 6.83$; $p < 0.05$; Fig. 2C). Pre-treatment with the 0.1 or the 1.0 mg/kg doses of M100907 reduced the average number of rotations elicited by SKF82958 ($p < 0.05$), which indicated that the 5-HT_{2A} receptor antagonist reduced D1 supersensitivity. Further analysis indicated that the suppressive effect of M100907

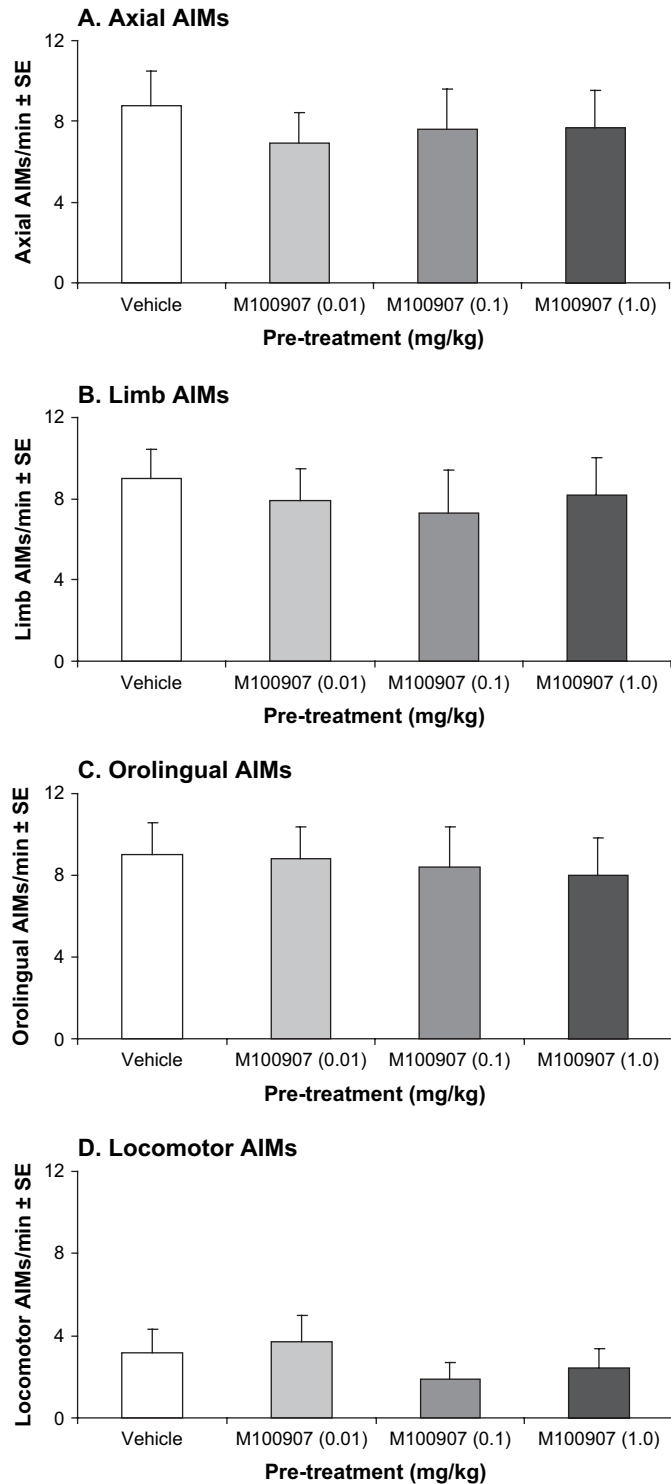


Fig. 1. L-DOPA-induced abnormal involuntary movements (AIMs). Graphs show the effects of pre-treatment with the 5-HT_{2A} antagonist M100907 (0.01, 0.1, and 1.0 mg/kg) on (A) axial, (B) limb, (C) orolingual, and (D) locomotor AIMs elicited by L-DOPA (6 mg/kg) + benserazide (15 mg/kg). 1-Way ANOVA tests did not reveal significant main effects of treatment.

was significant from 45 to 70 min post-injection for the 0.1 mg/kg dose and 40–70 min post-injection for the 1.0 mg/kg dose ($p < 0.05$; Fig. 3). Administration of antagonists alone had no effect on rotation (data not shown).

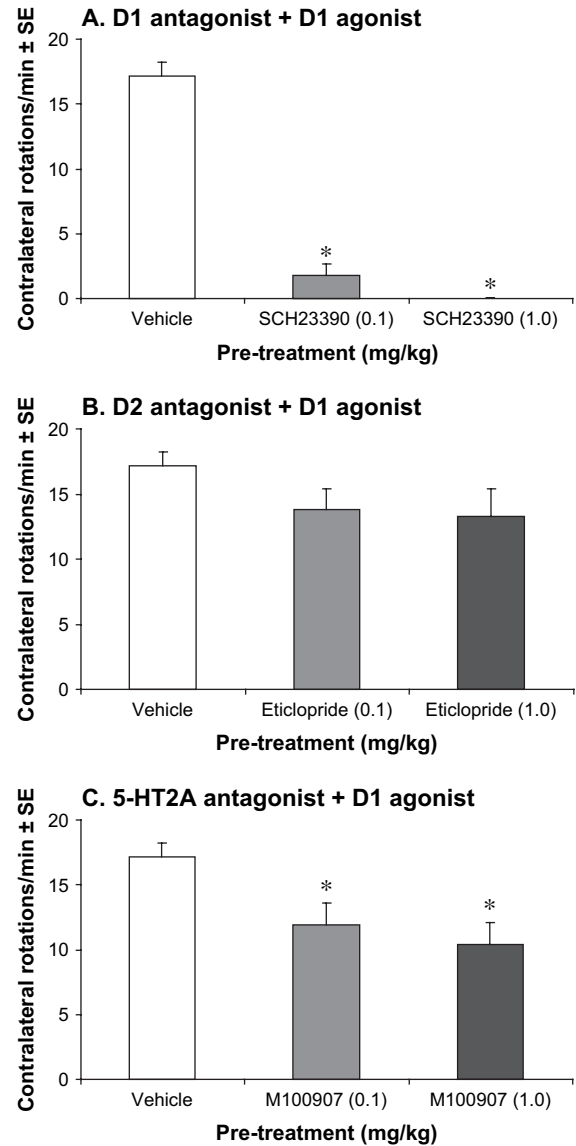


Fig. 2. D1 agonist-induced contralateral rotations. Graphs show the effects of pre-treatment with (A) the D1 antagonist SCH23390 (0.1 and 1.0 mg/kg), (B) the D2 antagonist eticlopride (0.1 and 1.0 mg/kg), and (C) the 5-HT_{2A} antagonist M100907 (0.1 and 1.0 mg/kg) on rotations elicited by the D1 agonist SKF82958 (0.2 mg/kg). Main effects of treatment were analyzed for significance by 1-way ANOVA tests. Group differences for each dose of antagonist versus vehicle were determined by Newman–Keuls post hoc tests and are indicated by * ($p < 0.05$).

3.4. D2 receptor agonist-induced rotation

The D2 agonist quinpirole (0.2 mg/kg) also elicited contralateral rotations. No significant main effect of treatment with the D1 antagonist SCH23390 was observed ($F_{(2,12)} = 0.40$; NS; Fig. 4A). Since a significant main effect of pre-treatment occurred when rats were given the D2 antagonist eticlopride prior to quinpirole ($F_{(2,12)} = 20.33$; $p < 0.05$; Fig. 4B), the quinpirole-induced contralateral rotation likely was primarily due to D2 rather than D1 receptor stimulation. Both the 0.1 mg/kg and the 1.0 mg/kg doses of eticlopride significantly reduced quinpirole-induced rotation ($p < 0.05$). Pre-treating

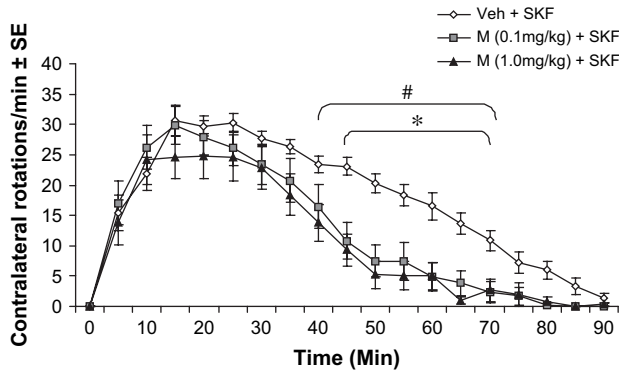


Fig. 3. Time course of D1 agonist-induced contralateral rotations. Graph shows time course of effect of pre-treatment with the 5-HT2A antagonist M100907 (M; 0.1 and 1.0 mg/kg) on rotations elicited by the D1 agonist SKF82958 (SKF; 0.2 mg/kg). A significant treatment by time interaction was determined by a 2-way ANOVA test. Significant differences ($p < 0.05$) for antagonist versus vehicle (Veh) pre-treatment at each time point were determined by Newman–Keuls post hoc tests and are indicated by * (0.1 mg/kg dose) and # (1.0 mg/kg dose).

rats with the 5-HT2A antagonist M100907 did not significantly alter quinpirole-induced rotation ($F_{(2,30)} = 2.21$; NS; Fig. 4C). Thus, it is unlikely that M100907 reduced D2 supersensitivity.

4. Discussion

Experimental destruction of nigrostriatal DA neurons in a model of PD leads to significant plasticity of striatal function. One such alteration is the emergence of D1 receptor supersensitivity, which refers to greater D1 agonist-induced molecular and behavioral responses in DA-depleted versus intact animals (Kostrzewa, 1995). This plasticity is evidenced by larger increases in DA-stimulated adenylate cyclase activity (Cai et al., 2002), D1 agonist-induced MAPK phosphorylation (Gerfen et al., 2002), and D1 agonist-induced gene expression (Berke et al., 1998) in the striatum ipsilateral to the 6-OHDA injection. Enhanced coupling of *G α /olf* to GTP γ S or D1 receptors has also been observed in the lesioned striatum and may underlie the above-mentioned supersensitive responses (Cai et al., 2002). Other consequences of D1 supersensitivity include the facilitation of D1 agonist-induced motoric behaviors such as stereotypy and locomotion in rats with bilateral 6-OHDA lesions (Breese et al., 1985, 1987; Bishop and Walker, 2003; Bishop et al., 2005) as well as contralateral rotations in rats with unilateral 6-OHDA lesions (Schwartz and Huston, 1996).

Although D1 supersensitivity may provide a compensatory mechanism for reduced nigrostriatal DA transmission, stimulation of supersensitive D1 receptors by DA converted from exogenous L-DOPA has been hypothesized to be one underlying factor for excessive, aberrant movements associated with LID in PD (Nutt, 1990). In primate studies, dyskinetic animals exhibited greater D1 agonist-stimulated striatal GTP γ S binding, Cdk-5, and DARPP-32 expression than non-dyskinetic primates (Aubert et al., 2005). Additional studies have shown that D1 agonist treatment promotes similar dyskinetic

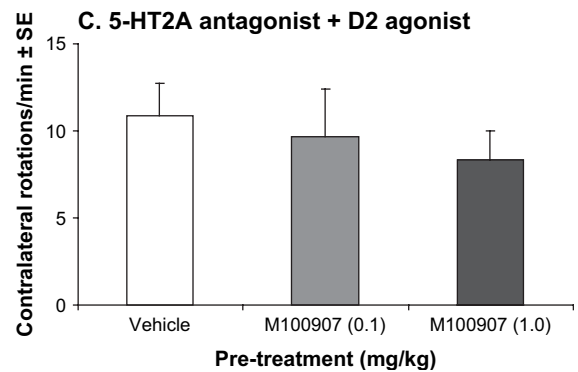
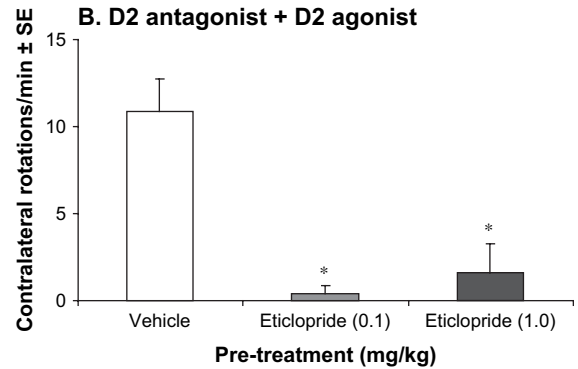
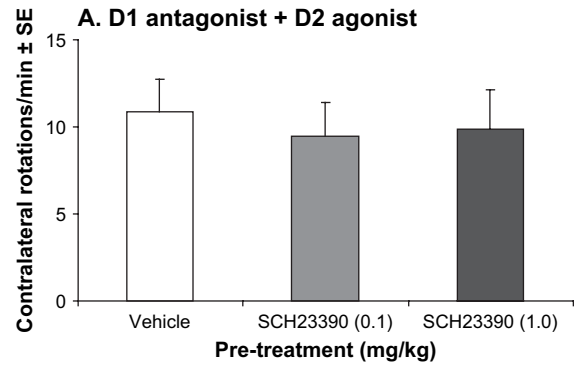


Fig. 4. D2 agonist-induced contralateral rotations. Graphs show the effects of pre-treatment with (A) the D1 antagonist SCH23390 (0.1 and 1.0 mg/kg), (B) the D2 antagonist eticlopride (0.1 and 1.0 mg/kg), and (C) the 5-HT2A antagonist M100907 (0.1 and 1.0 mg/kg) on rotations elicited by the D2 agonist quinpirole (0.2 mg/kg). Main effects of pre-treatment were analyzed for significance by 1-way ANOVA tests. Significant differences for each dose of antagonist versus vehicle were determined by Newman–Keuls post hoc tests and are indicated by * ($p < 0.05$).

behaviors as L-DOPA (Rascol et al., 2001) while D1 antagonists were found to reduce LID symptoms (Grondin et al., 1999; Taylor et al., 2005). However, D1 antagonist treatment would also be expected to reduce the beneficial effects of L-DOPA treatment in PD. The present study examined the 5-HT2A antagonist M100907 as a potential adjunct treatment that could reduce LID by suppressing excessive D1-mediated signaling with minimal negative influences on the beneficial effects of L-DOPA treatment.

M100907 was developed as a potential atypical antipsychotic with high potency at 5-HT2A receptors and far less affinity for DA receptors (Kehne et al., 1996a,b; Dekeyne et al.,

2003). In the intact rat, there is evidence that 5-HT₂ antagonist treatment causes a reduction in stimulated striatal DA release without altering basal DA levels (Lucas and Spampinato, 2000; Porrás et al., 2002). Such a mechanism may be impulse-dependent or reliant upon alterations in DA synthesis (Schmidt et al., 1992, 1994). However, neither acute nor chronic M100907 alters the spontaneous activity of nigrostriatal neurons (Sorensen et al., 1993). Moreover, M100907 does not reduce hyperactivity elicited by the D1 agonist SKF82958 in normosensitive (intact) mice (O'Neill et al., 1999).

In response to DA depletion, the relationship between 5-HT_{2A} and D1 receptor-mediated signaling changes dramatically. Several studies have found that 5-HT_{2A} receptors are elevated in the DA-depleted striatum (Radja et al., 1993; Numan et al., 1995; Basura and Walker, 1999) particularly within neurons of the direct output pathway also known to express D1 receptors (Gerfen et al., 1990; Harrison et al., 1990; Laprade et al., 1996). A functional consequence of this plasticity is that 5-HT_{2A} receptor stimulation was found to normalize preprotachykinin gene expression within the direct striatal output pathway following DA depletion similar to D1 receptor agonist treatment (Gerfen et al., 1990; Gresch and Walker, 1999a; Basura and Walker, 2001). Furthermore, 5-HT₂ receptor stimulation potentiated the effects of a D1 agonist on striatal preprotachykinin gene expression in lesioned, but not intact, rats (Gresch and Walker, 1999b; Campbell et al., 2001). Such observations signified the emergence of a novel facilitatory 5-HT_{2A} and D1 receptor interaction following DA depletion. At the behavioral level, striatal 5-HT_{2A} receptors also modulated hyperactivity elicited by the stimulation of supersensitive striatal D1 receptors in rats with bilateral 6-OHDA lesions (Bishop et al., 2003, 2005; Bishop and Walker, 2003). For instance, intrastriatal infusions of M100907 reduced the supersensitive increases in D1 agonist-induced locomotion and stereotypy in DA-depleted rats (Bishop et al., 2005). These data suggested that M100907 could potentially reduce L-DOPA-induced AIMs observed in rats with unilateral 6-OHDA lesions since dyskinetic behaviors were previously shown to be partially dependent upon D1 receptor stimulation (Taylor et al., 2005).

At the clinical level, there is also evidence that 5-HT_{2A} antagonist treatment may be effective in reducing LID in PD. Chronic administration of ritanserin, a 5-HT_{2A/2C} antagonist, reduced LID in a small number of PD patients (Maertens de Noordhout and Delwaide, 1986; Meco et al., 1988). Parkinson's patients who experience drug-induced psychosis may be given atypical antipsychotic drugs (Friedman and Factor, 2000) such as clozapine and quetiapine with higher affinity for 5-HT_{2A} over D2 receptors (Meltzer et al., 2003). Interestingly, several of these drugs have recently been shown to reduce LID (Meco et al., 1998; Grondin et al., 1999; Oh et al., 2002; Durif et al., 2004). Clozapine also has been reported to reduce L-DOPA-induced AIMs in DA-depleted rats (Lundblad et al., 2002). It is also worthy to note that stimulation of 5-HT_{1A} receptors by atypical antipsychotics may also be important since 5-HT_{1A} agonists have been shown to reduce LID (Bara-Jimenez et al., 2005).

Even with compelling evidence in support of a positive outcome with M100907, the results of the present study do not indicate that 5-HT_{2A} receptor antagonist treatment offers effective suppression of LID behaviors in rats with severe unilateral DA lesions. In fact, no dose of M100907 provided a significant reduction L-DOPA-induced AIMs. The range of M100907 doses employed has been reported to decrease DOI-induced head-twitch behavior or stimulant-induced locomotion in intact rats without altering basal locomotion (Kehne et al., 1996a,b; Moser et al., 1996; McMahon and Cunningham, 2001; Vickers et al., 2001; Filip et al., 2004). In addition, the middle and high (0.1 and 1.0 mg/kg) doses of M100907 reduced D1 agonist-induced rotation in the current study. However, D2 receptor-mediated rotations induced by quinpirole treatments were not prevented by M100907. This finding is important since D2 receptor stimulation has been shown to elicit dyskinesia or AIMs in several other studies (Gomez-Mancilla and Bedard, 1991; Rascol et al., 2000; Delfino et al., 2004). In addition, we recently found that L-DOPA-induced AIMs behaviors are mediated by the combined signaling effects of both D1 and D2 receptors (Taylor et al., 2005). Thus, it is possible that compounds that reduce oversensitive signaling at D1 or D2 receptors, but not both, may be ineffective in suppressing LID behaviors in PD.

In conclusion, the selective 5-HT_{2A} receptor antagonist M100907 significantly reduced contralateral rotations induced by the D1 agonist SKF82958 in rats with severe unilateral DA lesions. M100907, however, did not suppress L-DOPA-induced AIMs behaviors that are suggested to model the problem of LID in PD. A possible explanation for this discrepancy stems from the additional finding that M100907 had no effect on contralateral rotations induced by the D2 agonist quinpirole. Thus, agents that suppress both D1 and D2 receptor-mediated contralateral rotation would be predicted to have significant LID-reducing capabilities. However, such compounds may also negatively affect motor recovery induced by L-DOPA necessitating the incorporation of behavioral tests that assess the effects of adjunct treatments on L-DOPA-induced functional recovery in addition to LID blocking potential.

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