MDMA and fenfluramine reduce L-DOPA-induced dyskinesia via indirect 5-HT1A receptor stimulation

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Abstract
Chronic l-3,4-dihydroxyphenylalanine (L-DOPA) pharmacotherapy in Parkinson’s disease is often accompanied by the development of abnormal and excessive movements known as dyskinesia. Clinical and experimental studies indicate that indirect serotonergic agonists can suppress dyskinesia without affecting the efficacy of L-DOPA. While the mechanism by which these effects occur is not clear, recent research suggests that serotonin 5-HT1A receptors may play a pivotal role. To test this, male Sprague–Dawley rats with unilateral 6-hydroxydopamine medial forebrain bundle lesions received 1 week of daily treatment with L-DOPA (12 mg/kg, i.p.) plus benserazide (15 mg/kg, i.p.). Beginning on the 8th day of treatment and every 3rd or 4th day thereafter, rats were pretreated with vehicle (0.9% NaCl), the serotonin and dopamine releaser 3,4-methylenedioxymethamphetamine (MDMA; 0.25 or 2.5 mg/kg, i.p.) or the serotonin releaser fenfluramine (FEN; 0.25 or 2.5 mg/kg, i.p.) 5 min prior to L-DOPA, after which abnormal involuntary movements (AIMs) and rotations were quantified every 20th minute for 2 h. Pretreatment with 2.5 mg/kg of either MDMA or FEN reduced AIMs. To determine the contribution of the 5-HT1A receptor to these effects, another group of L-DOPA-primed 6-hydroxydopamine-lesioned rats were pretreated with the 5-HT1A antagonist WAY100635 (0.5 mg/kg, i.p.), MDMA + WAY100635 (2.5 + 0.5 mg/kg, i.p.) or FEN + WAY100635 (2.5 + 0.5 mg/kg, i.p.) 5 min prior to L-DOPA, after which abnormal involuntary movements and rotations were quantified every 20th minute for 2 h. Pretreatment with 2.5 mg/kg of either MDMA or FEN reduced AIMs. To determine the contribution of the 5-HT1A receptor to these effects, another group of L-DOPA-primed 6-hydroxydopamine-lesioned rats were pretreated with the 5-HT1A antagonist WAY100635 (0.5 mg/kg, i.p.), MDMA + WAY100635 (2.5 + 0.5 mg/kg, i.p.) or FEN + WAY100635 (2.5 + 0.5 mg/kg, i.p.) 5 min prior to L-DOPA and subsequent AIMs and rotation tests. The antidyskinetic effects of MDMA and FEN were reversed by cotreatment with WAY100635. These results suggest that 5-HT-augmenting compounds such as MDMA and FEN probably convey antidyskinetic properties in part via stimulation of 5-HT1A receptors.

Introduction
Dopamine (DA) replacement therapy with l-3,4-dihydroxyphenylalanine (L-DOPA) is the standard pharmacotherapy for treatment of Parkinson’s disease (PD; Tintner & Jankovic, 2002). Although L-DOPA initially alleviates motor impairment, chronic treatment can lead to L-DOPA-induced dyskinesia (LID), characterized by abnormal and excessive movements, which appears in 40% of PD patients within 4–6 years of treatment and in as many as 90% of patients by years 9–15 (Stocchi et al., 1997; Ahlskog & Muenter, 2001). Because it is unlikely that L-DOPA therapy will be replaced in the near future, a major challenge for basal ganglia researchers and clinicians is to identify nondopaminergic adjuncts to L-DOPA that attenuate LID while retaining antiparkinsonian efficacy.

Recent advances in understanding the role of serotonin (5-hydroxytryptamine; 5-HT) in PD and the generation of L-DOPA-induced side-effects have identified a number of serotonergic mechanisms that may constitute potential therapeutic targets (Nicholson & Brotchie, 2002). For example, following DA denervation, 5-HT exerts a more pronounced influence on the basal ganglia (Reader & Dewar, 1999; Maeda et al., 2003) and 5-HT receptors within the basal ganglia more readily mediate exaggerated movements in animal models of PD (Fox et al., 1998; Bishop et al., 2004; Jackson et al., 2004). Multiple lines of evidence now indicate that the amphetamine derivative 3,4-methylenedioxymethamphetamine (MDMA) or ‘ecstasy’ has antidyskinetic and antiparkinsonian properties (Schmidt et al., 2002; Iravani et al., 2003). MDMA is a compound with diverse pharmacological effects; it readily crosses the blood–brain barrier and preferentially binds to 5-HT transporters (Banks & Cunningham, 2001). MDMA administration causes a rapid increase in extracellular 5-HT via blockade of 5-HT reuptake, release of 5-HT from synaptic vesicles and inhibition of monoamine oxidase (Green et al., 2003). MDMA also acutely increases DA through similar mechanisms, though the long-term effects are less understood (Colado et al., 2004). It has been suggested that the pharmacological actions of MDMA on 5-HT function may mediate its purported antidyskinetic effects (Iravani et al., 2003).

In order to examine the potential antidyskinetic effects of augmented extracellular 5-HT, the current study compared the effects of MDMA and the potent 5-HT-releasing agent fenfluramine [(+)-fenfluramine hydrochloride; FEN; Berger et al., 1992; Balcioglu & Wurtman, 1998a]. We hypothesized that if MDMA reduces dyskinesia...
via augmentation of 5-HT, and not DA, the specific 5-HT-releaser FEN should convey similar antidyskinetic effects. Because striatal 5-HT1A receptors have been shown to be up-regulated in the DA-depleted striatum (Frechilla et al., 2001) and compounds with agonist actions at 5-HT1A receptors have been shown to possess antidyskinetic properties (Bibbiana et al., 2001; Olanow et al., 2004; Bara-Jimenez et al., 2005), we further postulated that the effects of MDMA and FEN could be attenuated with the selective 5-HT1A receptor antagonist WAY100635 (Gozlan et al., 1995). To test these hypotheses we employed the abnormal involuntary movements (AIMs) model of LID (Cenci et al., 1998; Taylor et al., 2005), in which L-DOPA-primed 6-hydroxydopamine hydrobromide (6-OHDA)-lesioned rats were subject to various pharmacological manipulations. The present findings indicate that MDMA and FEN reduce LID via indirect stimulation of 5-HT1A receptors.

Materials and methods

Animals

Adult male Sprague–Dawley rats were used (225–250 g upon arrival; Charles River Laboratories, Wilmington, MA, 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; Laboratory Diet, Brentwood, MO, USA) and water. The colony room was maintained on a 12-h light–dark cycle (lights on at 07.00 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).

6-Hydroxydopamine lesion surgeries

One week after arrival, rats were subjected to a unilateral 6-OHDA lesion of the left medial forebrain bundle to destroy DA neurons. Desipramine HCl (25 mg/kg, i.p.; Sigma, St Louis, MO, USA) was given 30 min prior to the 6-OHDA injection to protect norepinephrine (NE) neurons. Rats were anaesthetized with ketamine (90 mg/kg, i.p.; Lloyd Laboratories, Shenendoah, IA, USA) and xylazine (15 mg/kg, i.p.; Lloyd Laboratories), then placed in a stereotaxic apparatus. The coordinates for 6-OHDA injections were AP, −2.5; ML, +2.0; DV, −9.0 mm relative to bregma with the incisor bar positioned 3.3 mm below the interaural line (Paxinos & 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 (two or three rats per cage). Fresh fruit and soft chow were provided as needed to facilitate recovery during the first week after surgery.

Pharmacological treatments

Beginning 3 weeks after the lesion surgery, all rats were primed with L-DOPA methyl ester (L-DOPA; 12 mg/kg, i.p.; Sigma) + dl-serine 2-(2,3,4-trihydroxybenzyl)hydrazide hydrochloride (benserazide; 15 mg/kg, i.p.; Sigma) once daily for 7 days. L-DOPA and benserazide were dissolved in vehicle (VEH; 0.9% NaCl containing 0.1% ascorbic acid) and administered at a volume of 1.0 mL/kg. Rats displaying a total AIMs score of ≥15 on the 5th day of L-DOPA priming were assigned to equal treatment groups and randomly tested with the pretreatments outlined below beginning on the 8th day. Thereafter, all rats were maintained on an intermittent schedule of L-DOPA + benserazide for 2 weeks (injections on the 11th, 15th, 18th and 22nd days).

In the first study, one group of rats (n = 15) was assigned to receive a pretreatment of VEH or MDMA-HCl (0.25 or 2.5 mg/kg, i.p.; Sigma) 5 min prior to the 8th, 15th or 22nd day injection of L-DOPA (12 mg/kg, i.p.) + benserazide (15 mg/kg, i.p.). Another group (n = 14) was assigned to receive a pretreatment of VEH or FEN-HCl (0.25 or 2.5 mg/kg, i.p.; Sigma) 5 min before the 8th, 15th or 22nd day injection of L-DOPA + benserazide. Immediately following L-DOPA injections, rats were monitored for AIMs and rotations for 2 h. Rats were tested with pretreatments a maximum of twice.

A separate group of rats was employed (n = 24) for the antagonist study. In this study, rats were assigned to receive a pretreatment of VEH, the specific 5-HT1A antagonist N-[2-[4-(2-Methoxyphenyl)-1-piperazinyl][ethyl]-N-2-pyridinylcyclohexanecarboxamide maleate salt (WAY100635: 0.5 mg/kg, i.p.; Sigma), MDMA (2.5 mg/kg, i.p.), FEN (2.5 mg/kg, i.p.), MDMA + WAY100635 (2.5 + 0.5 mg/kg, i.p.) or FEN + WAY100635 (2.5 + 0.5 mg/kg, i.p.) 5 min prior to the 8th, 15th and 22nd day injection of L-DOPA (12 mg/kg, i.p.) + benserazide (15 mg/kg, i.p.). Immediately following L-DOPA injections, rats were observed for AIMs and rotations for 2 h. Rats were tested with pretreatments a maximum of three times.

Behavioural procedure

Rats were monitored for AIMs using a procedure slightly modified from that described in Lundblad et al. (2002) and Taylor et al. (2006). 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. On test days (09.00–14.00 h), rats were individually placed in plastic trays (60 × 75 cm) 5 min prior to pretreatments. 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 at the doses used. 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. ‘Limb’ 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 were considered abnormal as they occurred at times when the rats were 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 two consecutive minutes. Rats were rated for AIMs during the 1st min and rotational behaviour in the 2nd min. During the AIMs observation periods (beginning 20, 40, 60, 80, 100 and 120 min postinjection), a severity score of 0–4 was assigned for each AIMs category: 0, not present; 1, present for <50% of the observation period (i.e. 1–29 s); 2, present for >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 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.

High-performance liquid chromatography

One week after the completion of experiments, rats were killed by decapitation. The anterior striatum was dissected out, immediately frozen on dry ice and then stored at −80 °C. Reverse-phase high performance liquid chromatography coupled to electrochemical detection (HPLC-EC) was performed on striatal tissue, obtained from 20 randomly selected rats, according to the protocol of Kilpatrick et al. (1986), a method for semiautomated 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) with 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 analysed 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 sodium phosphate (monobasic, anhydrous), 100 mM; EDTA, 0.05 mM; octane sulphonic acid, 1.4 mM; and acetonitrile, 9%; adjusted to pH 3.0 with o-phosphoric acid. A coulometric detector configured with three electrodes (Model 5011; ESA) measured the content of monoamines and metabolites. An ESA model 5020 guard cell (+400 mV) was positioned prior to the WISP injector. The analytical cell (ESA model 501L; 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 analysed 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 nanograms (ng) of monoamine or metabolite per milligram (mg) protein (mean ± SEM).

Data analyses

Monoamine and metabolite levels in the anterior striatum were determined using paired t-tests. Non-parametric repeated-measures Friedman ANOVAs determined the development and stability of axial, limb, orolingual, locomotor and total AIMs (each of the aforementioned subcategories summed) over the course of treatment (days). Parametric repeated-measures ANOVAs were used to analyse rotations over the course of treatment. Acute treatment effects (expressed as means ± SE) for AIMs and rotations were analysed by employing Kruskal–Wallis and one-way ANOVAs, respectively. Significant differences between days and treatments were determined by Wilcoxon and Mann–Whitney post hoc comparisons for AIMs, respectively, and Newman–Keuls post hoc tests for rotations. Analyses were executed with the use of Statistica software’98 (Statsoft Inc., Tulsa, OK, USA). Alpha was set at P < 0.05.

Results

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 lesioned (left) vs. intact (right) striata are shown in Table 1. As anticipated, injection of 6-OHDA into the left medial forebrain bundle produced significant reductions in lesioned striatal DOPAC (t19 = 10.00, P < 0.001) and DA (t19 = 9.40, P < 0.001) levels, 85.6% and 96.3%, respectively, compared to control. 6-OHDA lesions also increased DOPAC/DA turnover by 394% in the lesioned striata compared to control (t19 = 7.25, P < 0.001). There were no significant differences between the lesioned and intact striata for NE, 5-HIAA, 5-HT or 5-HIAA/5-HT.

L-DOPA-induced AIMs remained stable

AIMs and rotation data following L-DOPA (days 1 and 5) and VEH + L-DOPA (days 8 and 22) were compiled in a subset of randomly selected animals from the entire study (n = 16 of 53) to assess the development and stability of L-DOPA-induced behaviours over the course of testing. Repeated-measures ANOVAs revealed significant time effects on axial (χ² = 11.16, P < 0.01), limb (χ² = 19.97, P < 0.001), locomotor (χ² = 17.02, P < 0.001) and total (χ² = 10.56, P < 0.02) AIMs as well as rotations (F3,45 = 8.19, P < 0.01). As depicted in Fig. 1, post hoc tests of these significant effects indicated that AIMs and rotations on days 5, 8 and 22 were higher than those observed on day 1 (all P < 0.05) and did not differ from one another. Exceptions were day 22 of locomotor AIMs and day 22 of rotations, which did not differ from day 1.

MDMA and FEN dose-dependently reduced AIMs

Various doses of MDMA and FEN were tested in 6-L-DOPA-primed rats to determine their effects on AIMs and rotations. As shown in Fig. 2, significant treatment effects were observed on measures of axial, limb, orolingual and total AIMs. On measures of axial AIMs,
both MDMA ($H = 7.20, P < 0.03$) and FEN ($H = 7.83, P < 0.02$) altered behaviour. Post hoc tests revealed that 2.5 mg/kg of MDMA and FEN reduced axial dyskinesia (both $P < 0.05$). A similar pattern of treatment effects were observed for limb AIMs (MDMA: $H = 11.20, P < 0.004$; FEN: $H = 8.35, P < 0.02$), with post hoc tests demonstrating reduced limb AIMs to 2.5 mg/kg of each compound (both $P < 0.05$). A treatment effect of MDMA was also observed upon analysis of orolingual AIMs ($H = 8.91, P < 0.02$); this effect was not observed following FEN administration. Further analysis revealed that again the 2.5 mg/kg dose of MDMA significantly reduced orolingual dyskinesia ($P < 0.05$). Finally, total AIMs were affected by both MDMA ($H = 6.99, P < 0.04$) and FEN ($H = 6.96, P < 0.03$), with post hoc tests revealing that 2.5 mg/kg of MDMA and FEN reduced total dyskinesia (both $P < 0.05$). No significant treatment effects were observed on measures of locomotor AIMs or rotations.
Significant differences were established with L-DOPA (12 mg/kg) treatment. It is noteworthy that neither locomotor AIMs nor rotations were affected by MDMA or FEN pretreatment. This pharmacological distinction between classic dyskinetic behaviours (Hagell & Widner, 1999; Cenci et al., 2002) and rotations further demonstrates the functional differences that may exist between the AIMS and rotational behaviours. While the antidyskinetic effects of the 5-HT- and DA-releasing agent MDMA in rodents support anecdotal reports in humans and experimental evidence in primates (Durrif et al., 1995; Bibbiana et al., 2001; Olanow et al., 2004; Bara-Jimenez et al., 2005). The unilateral 6-OHDA-lesioned rat model of PD has been useful for the study of movement deficits and compensatory processes that occur following DA depletion (Ungerstedt, 1971; Miller & Beninger, 1991; Schallert et al., 2000). Traditionally, rotational behaviour has been interpreted to indicate potential antiparkinsonian and antidyskinetic properties of various pharmacological manipulations. However, in recent years the usefulness and applicability of rotational behaviour has been challenged (Cenci et al., 2002; Castaneda et al., 2005). While more recent rodent models of dyskinesia (Cenci et al., 1998; Steece-Collier et al., 2003) also utilize the unilateral DA-depleted rat, they employ discrete behavioural measures that resemble the clinical manifestations of LID (Hagell & Widner, 1999; Cenci et al., 2002) and display face validity with known antidyskinetic compounds (Lundblad et al., 2002).

Another advantage of the AIMS model, as demonstrated in Fig. 1 and others (Lundblad et al., 2002; Taylor et al., 2005), is that AIMS behaviour remains stable for a number of weeks and can be maintained with regular L-DOPA treatment. It is noteworthy that, in the present study, rotations and locomotor AIMS declined somewhat on the final test day (day 22). These effects, while not significantly different from days 5 or 8, may indicate a rotation-specific reduction in response duration to L-DOPA (Bibbiana et al., 2001; Oh et al., 2002).

The first goal of the present study was to determine whether pretreatment with either MDMA or FEN altered LID expression in the L-DOPA-primed 6-OHDA-lesioned rat. As demonstrated in Fig. 2, both compounds reduced axial and limb AIMS in a dose-dependent manner. The higher dose of MDMA also blunted the expression of orolinguinal AIMS. It is noteworthy that neither locomotor AIMS nor rotations were affected by MDMA or FEN pretreatment. This pharmacological distinction between classic dyskinetic behaviours (Hagell & Widner, 1999; Cenci et al., 2002) and rotations further demonstrates the functional differences that may exist between the AIMS and rotational behaviours. While the antidyskinetic effects of the 5-HT- and DA-releasing agent MDMA in rodents support anecdotal reports in humans and experimental evidence in primates (Irvani et al., 2003), we also demonstrate for the first time that the 5-HT-releasing agent FEN reduces AIMS in rodents.

Pharmacologically, MDMA and FEN share many similarities, most notably their effects on 5-HT. Both are potent 5-HT releasers via active carrier-mediated processes (Berger et al., 1992; Crespi et al., 1997) and increase 5-HT by blocking its reuptake and reducing the activity of monoamine oxidase (Berger et al., 1992; Irvani et al., 2000; Colado et al., 2004). While FEN and MDMA can induce striatal DA release indirectly via 5-HT-related mechanisms (Koch & Galloway, 1997; Balcioglu & Wurtman, 1998b), only MDMA induces a 5-HT-
independent release of DA from neurons (Bankson & Cunningham, 2001; Colado et al., 2004). Although substituted amphetamines can exhibit agonist properties, neither MDMA nor FEN at the doses employed (0.25 or 2.5 mg/kg) were likely to act as direct agonists at either 5-HT or DA receptors (Battaglia et al., 1988; Porter et al., 1999; Esteban et al., 2001). As such, it is probable that FEN and MDMA reduced dyskinetic behaviours through indirect pharmacological mechanisms as a result of elevated 5-HT and/or DA.

While the pharmacological effects of MDMA and FEN have been well-documented in the intact brain, their actions under conditions of DA depletion have not. Maeda et al. (2003) reported that unilateral medial forebrain bundle 6-OHDA lesions induce 5-HT hyperinnervation in the ipsilateral striatum of adult rats. Such 5-HT neuroplasticy may increase available 5-HT for release by MDMA and FEN in the DA-depleted striatum. Our HPLC-EC analysis did not reveal a lesion-induced increase in basal striatal 5-HT tissue concentrations, indicating that striatal 5-HT hyperinnervation may not have been necessary to produce the effects of MDMA and FEN. More probably these compounds reduced LID by augmenting 5-HT release and blocking 5-HT reuptake, leading to enhanced stimulation of 5-HT receptors. This is supported by previous work in MPTP-treated primates showing that the antidyskinetic effects of MDMA can be attenuated by pretreatment with the selective 5-HT reuptake inhibitor fluvoxamine (Iravani et al., 2003). Alternatively, there is evidence that, following 6-OHDA lesions, raphe-striatal 5-HT neurons can compensate for lost nigrostriatal DA neurons by converting L-DOPA to DA and releasing it via reverse 5-HT transport (Tanaka et al., 1999; Maeda et al., 2005). Thus, DA derived from exogenous L-DOPA and released by 5-HT neurons in response to MFDMA or FEN administration may have contributed to their antidyskinetic properties. While such effects may account for the reported antiparkinsonian effects of MDMA (Schmidt et al., 2002; Iravani et al., 2003), enhanced striatal DA release in L-DOPA-primed rats would be predicted to worsen, not attenuate, LID.

The second goal of the present study was to determine whether 5-HT1A receptors mediate the antidyskinetic effects of MDMA and FEN. It is known that, subsequent to DA denervation, 5-HT1A receptors contribute to the antidyskinetic effects of MDMA and FEN. As demonstrated in Fig. 3, coadministration of WAY100635 resulted in a complete attenuation of the antidyskinetic effects of MDMA and FEN on measures of axial, limb and total AIMS. It is worth noting that MDMA did not reduce orolingual AIMS in this second experiment. The cause of this discrepancy is unclear but may have been a result of fluctuating baseline effects that orolingual AIMS seem especially susceptible to with L-DOPA treatment (see Fig. 1). Nonetheless, taken with previous research, these results strongly implicate the 5-HT1A receptor as a primary mechanism by which these compounds attenuate their effects. It is possible that other 5-HT receptors may have contributed to the observed antidyskinetic actions of MDMA and FEN. The 5-HT1B/1D agonist SKF-91101-H reduces LID, but at the expense of the beneficial effects of L-DOPA (Jackson et al., 2004). Indirect stimulation of 5-HT2C receptors in the substantia nigra may also reduce excessive movements in the DA-depleted brain (Fox et al., 1998; Fox & Brotchie, 2000), though this has not been directly tested. 5-HT2A receptors are unlikely to have contributed to the effects of MDMA and FEN given that 5-HT2A stimulation may actually exacerbate exaggerated movements (Bishop & Walker, 2003; Bishop et al., 2004).

Convergent evidence, including the present results, indicates that 5-HT1A receptor stimulation diminishes LID. For example, the partial 5-HT1A receptor agonist sarizotan reduces LID in MPTP-treated primates (Bibbiana et al., 2001) and humans (Olanow et al., 2004; Bara-Jimenez et al., 2005). Despite these findings, the mechanism(s) by which these effects occur are not readily known. 5-HT1A receptors are located most notably on soma and dendrites of the dorsal raphe which has 5-HT-utilizing afferents to the basal ganglia (Knobelman et al., 2000). These receptors are also found on cortical neurons that send glutamatergic projections to the striatum (Cela et al., 2001; Kelly & Strick, 2004). While it was initially suggested that 5-HT1A receptors were absent in the striatum, Frechilla et al., 2001) demonstrated strong [3H]-5-OH-DPAT binding in striatal striosomes of MPTP-treated primates. As such, activating 5-HT1A receptors may alter basal ganglia function and reduce LID in a number of ways. First, stimulation of raphe 5-HT1A receptors reduces 5-HT release in the striatum (Hjorth & Sharp, 1991; Martín-Ruiz & Ugedo, 2001) and may dampen 5-HT contributions to excessive movements. Second, stimulation of cortical or striatal 5-HT1A receptors may reduce the activity of glutamatergic inputs to the striatum (Antonelli et al., 2005; Mignon & Wolff, 2005), a potential underlying contributor to LID (Picconi et al., 2003). Finally, it has been suggested that, following DA depletion, raphe-striatal neurons usurp the role previously held by DA neurons by storing and releasing DA (Kannari et al., 2001; Yamato et al., 2001). Thus, stimulation of 5-HT1A receptors may act to regulate 5-HT neuron release of L-DOPA-derived DA (Maeda et al., 2005). Further study will be necessary to reveal the contributions of these potential mechanisms.

While it is unlikely that chronic administration of MDMA, which has been shown to damage to 5-HT nerve endings (for review see Green et al., 2003) or FEN, which is linked to valvular heart disease (for review see Connolly et al., 1997) has clinical utility for the treatment of LID in humans, the findings of the present report are instructive. We demonstrate that the antidyskinetic actions of MDMA and FEN are mediated, in part, through indirect pharmacological actions on 5-HT1A receptors. Such effects, though not well understood, support continued work with 5-HT compounds in particular 5-HT1A receptor agonists that may demonstrate clinical utility for the reduction of LID in PD patients.

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Abbreviations

5-HIAA, 5-hydroxyindole-3-acetic acid; 5-HT, serotonin or 5-hydroxytryptamine; 6-OHDA, 6-hydroxydopamine hydrobromide; AIMS, abnormal involuntary movements; benzazide, di-serine 2-(2,3,4-trihydroxybenzyl) hydrazide hydrochloride; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; FEN, (+)-fenfluramine hydrochloride; HPLC-EC, high performance liquid chromatography coupled to electrochemical detection; L-DOPA, l-3,4-dihydroxyphenylalanine methyl ester; LID, L-DOPA-induced dyskinesia; MDMA, (+)/−)-3,4-methylenedioxymethamphetamine hydrochloride; MPTP, 1-methyl-1-phenyl-1,2,3,6-tetrahydropyridine; NE, norepinephrine; PD, Parkinson’s disease; VEH, vehicle; WAY100635, N-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinylcyclohexanecarboxamide maleate salt.
References


