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The sigma-1 antagonist BMY-14802 inhibits L-DOPA-induced abnormal involuntary movements by a WAY-100635-sensitive mechanism

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Abstract

Rationale—Levodopa (L-DOPA), the gold standard treatment for Parkinson's disease (PD), eventually causes L-DOPA-induced dyskinesia (LID) in up to 80% of patients. In the 6-hydroxydopamine (6-OHDA) rat model of PD, L-DOPA induces a similar phenomenon, which has

been termed abnormal involuntary movement (AIM). We previously demonstrated that BMY-14802 suppresses AIM expression in this model.

Objectives—Although BMY-14802 is widely used as a sigma-1 antagonist, it is also an agonist at serotonin (5-HT) 1A and adrenergic α -1 receptors. The current study was conducted to determine which of these mechanisms underlies BMY-14802's AIM-suppressing effect. This characterization included testing the 5-HT1A agonist buspirone and multiple sigma agents. When these studies implicated a 5-HT1A mechanism, we subsequently undertook a pharmacological reversal study, evaluating whether the 5-HT1A antagonist WAY-100635 counteracted BMY-14802's AIM-suppressing effects.

Results—Buspirone dose-dependently suppressed AIM, supporting past findings. However, no AIM-suppressing effects were produced by drugs with effects at sigma receptors, including BD-1047, finasteride, SM-21, DTG, trans-dehydroandrosterone (DHEA), carbetapentane, and opipramol. Finally, we show for the first time that the AIM-suppressing effect of BMY-14802 was dose-dependently prevented by WAY-100635 but not by the α -1 antagonist prazosin.

Conclusions—BMY-14802 exerts its AIM-suppressing effects via a 5-HT1A agonist mechanism, similar to buspirone. Other 5-HT1A agonists have failed clinical trials, possibly due to submicromolar affinity at other receptors, including D2, which may exacerbate PD symptoms. BMY-14802 is a promising candidate for clinical trials due to its extremely low affinity for the D2 receptor and lack of extrapyramidal effects during prior clinical trials for schizophrenia.

Keywords

BMY-14802; Buspirone; 5-HT1A; 6-hydroxydopamine; L-DOPA-induced dyskinesia; Parkinson's disease; Rat; Sigma

Introduction

Levodopa (L-DOPA) is the gold standard treatment for Parkinson's disease (PD), but it often induces side effects, which emerge as abnormal, involuntary movements, termed L-DOPA-induced dyskinesia (LID). LID may appear as soon as 2–3 years after initiating L-DOPA treatment and incidence increases with duration of treatment, varying from 30% to 80% after 5–10 years of treatment (Bhidayasiri and Truong 2008; Fabbrini et al. 2007; Chan et al. 2008). The appearance of LID and other motor complications has dampened enthusiasm to prescribe L-DOPA to patients, especially younger patients who seem more susceptible to these side effects (Halkias et al. 2007). Proposed treatments for LID include amantadine, which may lose efficacy after 8–12 months (Thomas et al. 2004), and dextromethorphan, which has the potential to be abused or psychotomimetic (Miller 2005). In the 6-hydroxydopamine (6-OHDA) rat model of PD, L-DOPA induces a similar phenomenon, termed abnormal involuntary movement (AIM). We recently demonstrated that the expression of AIM is prevented by BMY-14802, a widely used sigma-1 antagonist (Paquette et al. 2008). BMY-14802 has other notable mechanisms, including agonism at serotonin (5-HT) 1A and adrenergic α -1 receptors. The current study was conducted to determine which of these mechanisms underlies the AIM-suppressing effect of BMY-14802. We also tested the 5-HT1A agonist buspirone as well as several compounds with activity at sigma receptors.

A large body of clinical and preclinical literature supports the use of 5-HT1A agonists as pharmacotherapies for L-DOPA-induced complications. LID in humans is suppressed by buspirone (Bonifati et al. 1994), sarizotan (Olanow et al. 2004), and tandospirone (Kannari et al. 2002), while AIM in animal models is suppressed by 8-OH-DPAT (Dupre et al. 2007, 2008; Iravani et al. 2006; Tomiyama et al. 2005) and buspirone (Eskow et al. 2007; Lundblad et al. 2005). We chose to test buspirone in the current study because it is a parent compound

of BMY-14802 (Matthews et al. 1986). Similar to other 5-HT_{1A} agonists, BMY-14802 affects the firing of 5-HT_{1A} and catecholaminergic neurons (Matos et al. 1996; Vandermaelen and Braselton 1990; Zhang et al. 1993) and affects behaviors mediated by 5-HT (Bristow et al. 1991; Vanecek et al. 1998) in a 5-HT_{1A}-sensitive manner. Fortunately, despite sharing components of its chemical structure with buspirone, which has submicromolar affinity for the D₂ receptor, BMY-14802 is devoid of significant affinity for the D₂ receptor (Yevich et al. 1992). This is an important consideration because an AIM-suppressing agent would be of little use if it counteracted the dopamine (DA)-mediated therapeutic effects of L-DOPA, as would be expected with D₂ antagonists.

Support for sigma drugs as putative AIM-suppressing pharmacotherapies derives from the theory that the mechanisms underlying LID may be similar to those underlying sensitization to psychostimulants (Mura et al. 2002; Nutt 2000; for review, see Canales and Graybiel 2000). Therefore, medications reported to counteract behavioral sensitization to stimulants may be therapeutic in LID. The role of sigma-1 receptors in behavioral sensitization to psychostimulants, including cocaine and methamphetamine, has been clearly demonstrated (Romieu et al. 2000; Stefanski et al. 2004; Ujike et al. 1992a, b, c, 1996). Furthermore, sigma antagonists, including BMY-1802, rimcazole, and SR-31742A, have been shown to block the development of behavioral sensitization to cocaine (Ujike et al. 1996), and BMY-14802 has also been shown to block the development of behavioral sensitization to methamphetamine (Ujike et al. 1992a). Just as multiple sigma antagonists are effective in behavioral sensitization studies, they should be similarly effective in LID studies if BMY-14802's AIM-suppressing effects are mediated by a sigma-1 mechanism.

The current study investigated whether BMY-14802's AIM-suppressing effects are due to its known 5-HT_{1A}, sigma-1, and/or adrenergic α -1 actions. We first investigated the AIM-suppressing effects of the 5-HT_{1A} agonist buspirone and numerous agents acting at sigma receptors, including the sigma-1 antagonist BD-1047; the 5- α -reductase inhibitor finasteride, which causes accumulation of the potent sigma-1 antagonist progesterone; the sigma-2 antagonist SM-21; the sigma-1 and sigma-2 agonist DTG; and the sigma-1 agonists trans-DHEA, carbetapentane, and opipramol (see Table 1). Finally, to determine whether BMY-14802 mediates its AIM-suppressing effect via known 5-HT_{1A} or adrenergic α -1 agonism, we undertook a pharmacological reversal study: we investigated the efficacy of the 5-HT_{1A} antagonist WAY-100635 or the adrenergic α -1 antagonist prazosin to prevent BMY-14802's AIM-suppressing effect.

Materials and methods

Animals

A total of 80 (n=6–10/group) male Sprague–Dawley rats (Harlan, Indianapolis, IN, USA) weighing 300 gm at surgery were used. Rats were housed at 21 °C on a 12-h light-dark cycle (lights on at 0700 hours) and were given food and water ad libitum. Testing was conducted between 900 and 1500 hours. Procedures were conducted in accordance with the Institutional Animal Care and Use Committee, and the Portland VA Medical Center is AAALAC-certified.

Drugs

Rats were randomly assigned to receive up to three test compounds at least 5 days apart. L-DOPA methyl ester, benserazide hydrochloride, L-ascorbic acid, *d*-amphetamine sulfate, buspirone hydrochloride, opipramol dihydrochloride, prazosin hydrochloride, and *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinylcyclohexanecarboxamide maleate (WAY-100635) were obtained from Sigma–Aldrich (St. Louis, MO, USA). BD-1047 dihydrobromide, BMY-14802 hydrochloride, carbetapentane citrate, DTG, and SM-21

maleate were obtained from Tocris (Ellisville, MO, USA). DHEA was obtained from Fluka. Finasteride was obtained from Steraloids, Inc. BD-1047, BMY-14802, prazosin, SM-21, and WAY-100635 were dissolved in milliQ water. Buspirone, carbetapentane, and opipramol were dissolved in 0.9% saline. Finasteride was dissolved in 20% β -cyclodextrin, DTG was dissolved in 35% β -cyclodextrin, and DHEA was dissolved in 40% β -cyclodextrin; all β -cyclodextrin solutions were dissolved in saline. Drugs were administered i.p. at 1 ml/ 100 gm of body weight 30 min prior to L-DOPA, except for finasteride, which was administered 22 h prior to L-DOPA at 5 ml/100 gm of body weight to avoid acute motor-suppressant effects (Frye and Wolf 2002).

Whenever possible, doses of test compounds were chosen based on their efficacy to suppress behavioral effects of DA agonists without reducing basal activity levels. Buspirone doses (1, 4, or 10 mg/kg) were chosen based on previous experiments of L-DOPA-induced AIM in the 6-OHDA rat model (Dekundy et al. 2007; Eskow et al. 2007) and on doses known to suppress behavior induced by cocaine (Callahan and Cunningham 1997) and methylphenidate (Kleven et al. 1996). The BMY-14802 dose (15 mg/kg) has been shown to block the development of behavioral sensitization to methamphetamine (Ujike et al. 1996). The BD-1047 dose (3 mg/kg) has been shown to prevent reinstatement of conditioned place preference (CPP) to cocaine (Romieu et al. 2004). The finasteride dose (50 mg/kg) was shown to prevent progesterone-induced inhibition of orofacial dyskinesia (Bishnoi et al. 2008). The SM-21 dose (20 mg/kg) is within the antinociceptive dose range that does not impair spontaneous motor performance (Ghelardini et al. 1997). The DTG dose (3 mg/kg) has been shown to cause DA overflow in the striatum and to increase vacuous chewing movements (Patrick et al. 1993). The DHEA (15 mg/kg) dose is within the range that increases or reactivates cocaine CPP (Romieu et al. 2003, 2004). Carbetapentane and dextromethorphan are anticonvulsant at similar doses (Leander 1989); the dose of carbetapentane selected (45 mg/kg) is within the anticonvulsant range and is identical to the dose of dextromethorphan previously shown to suppress abnormal involuntary movements in the 6-OHDA rat (Paquette et al. 2008). The opipramol dose (10 mg/kg) has been shown to increase DA overflow and metabolism (Rao et al. 1990).

6-OHDA Lesions

Rats underwent stereotaxic surgery under isoflurane anesthesia. A 30 gauge infusion cannula, attached via PE20 tubing to a 10 μ l Hamilton gastight syringe and driven by a microinfusion pump (Harvard Apparatus, Holliston, MA, USA) was used to infuse 6-OHDA (22.8 μ g/2 μ l of 0.9% saline with 0.02% ascorbic acid, 0.5 μ l/min) into each of two sites within the right medial forebrain bundle (AP-4.3 and AP-4.8, ML $\pm$ 1.2 mm, DV -8.6 mm). Rats then received an injection of buprenorphine analgesic (0.05 mg/kg, s.c.; Reckitt Benckiser Pharmaceuticals, Richmond, VA, USA) and supplemental soft food until regaining their presurgery weight.

Amphetamine-evoked rotational behavior

An a priori criterion of an average of ≥ 5 turns/min over ten consecutive min in response to amphetamine (5 mg/kg, i.p.) was used to select rats with significant hemi-Parkinsonism (Chang et al. 1999).

L-DOPA treatment

At least 3 days after rotational screening, all rats received L-DOPA methyl ester HCl (7.5 mg/kg, i.p.), combined with benserazide (15 mg/kg, i.p.) and ascorbic acid (2.6 mg/kg, i.p.), once daily for 21 consecutive days. Thereafter, rats received a maintenance regimen of 2 injections/week. All test drugs were administered during the maintenance phase to examine their efficacy to suppress AIM expression.

AIM assessment

AIM was assessed by an investigator blind to treatment, using an adaptation of the Abnormal Involuntary Movement Scale described by Cenci et al. (1998). The severity of limb, axial, and oral AIM, as well as contraversive rotational behavior (an index of L-DOPA's motor activating effects), were rated on a scale of 0–4 every 20th min for 3 h, beginning 20 min after L-DOPA. A sum of limb + axial + oral AIM was computed to reflect the total AIM score. Rats with low AIM scores (i.e., grade 0–1 on axial, limb, or oral AIM throughout the rating period) were infrequent and were not excluded from drug-testing studies.

Lesion size quantification

Brains were exposed to Western analysis to assess tyrosine hydroxylase (TH). Briefly, rats were killed by decapitation under anesthesia. Brains were removed, and whole neostriatum and ventral midbrain were dissected and frozen. Protein was extracted with lysis buffer (50 mM Tris, 10 mM EDTA, 1% Triton-X 100, 10 nM phenylmethylsulfonyl fluoride) containing complete protease inhibitor cocktail (Roche Diagnostics, Indianapolis, IN, USA), then quantified with a Pierce protein assay kit (Rockford, IL, USA). Samples (15 µg) were diluted 1:2 in Laemmli sample buffer (Sigma–Aldrich), heated at 100 °C for 5 min, then separated on a 10% Criterion Tris-HCl polyacryl-amide gel (Bio-Rad, Hercules, CA, USA; 200 V, 1 h). Proteins were transferred to polyvinylidene difluoride membranes (30 V, 13 h), then washed in Tris-buffered saline with 1% Tween-20 (pH7.4; 3×10 min) between steps: 5% nonfat dry milk for 1 h, monoclonal primary antibody (1:10,000 anti-TH; Immunostar, Hudson, WI, USA) for 2 h, and goat anti-mouse antibody (1:3,000; Bio-Rad) for 1 h. Proteins were visualized using a 15-min exposure to ECF (Amersham, Piscataway, NJ, USA) according to supplier's instructions, then scanned and quantified using the typhoon fluorescence detection system (Typhoon 9410 Variable Mode Imager, GE Healthcare, Piscataway, NJ, USA; Emission filter: 520 BP40, Laser: 488 Blue2).

Statistical analysis

Data were analyzed with SPSS (Chicago, IL, USA) with $p \leq 0.05$. A mixed design Time $\times$ Treatment ANOVA was used to analyze AIM over each 3-h session. ANOVAs or t tests, whichever was appropriate, were used to analyze the effect of treatment on summed scores for each of the AIM subscales, as well as for the sum of limb + axial + oral AIM scores, over the 3-h session and during the first hour after L-DOPA. When data violated homogeneity of variance assumptions, Greenhouse–Geisser corrections or t tests in which equal variance was not assumed were used for repeated or between-subjects data, respectively, yielding fractional degrees of freedom.

Results

The average TH loss ipsilateral to the 6-OHDA-infused side, relative to the contralateral side, was determined to be $90.92 \pm 1.04\%$ in striatum and $81.11 \pm 2.99\%$ in ventral midbrain. All rats expressed AIM, as shown by a significant effect of the repeated factor Time [$F \geq 3.47$, $p < 0.05$], though levels of AIM were variable among different cohorts of animals. Similarly, all rats expressed L-DOPA-induced contraversive rotation [$F \geq 6.58$, $p < 0.001$], though rotation was also variable.

As expected, the 5-HT_{1A} agonist buspirone suppressed AIM. The time $\times$ treatment interaction effect was significant [$F(5.29, 190.43) = 7.49$, $p < 0.001$], and the effect of treatment was significant [$F(3, 36) = 6.62$, $p \leq 0.001$], as shown in Fig. 1a. Post hoc tests revealed that 10 mg/kg buspirone significantly reduced AIM relative to vehicle over the 3-h test session. The treatment effect was especially apparent during the first hour after L-DOPA [$F(2, 31) = 12.6$, $p < 0.001$], when post hoc tests revealed that 1–10 mg/kg buspirone suppressed AIM relative to

vehicle, as shown in Fig. 1b. The AIM-suppressing effect of buspirone was apparent for the limb, axial, and oral subscales over the 3-h test session, as indicated by significant time $\times$ treatment interaction effects [$F \geq 3.04$, $p < 0.001$], and significant treatment effects [$F(3, 36) \geq 4.24$, $p \leq 0.01$], as shown in Fig. 1c–e. Post hoc tests revealed that 10 mg/kg buspirone suppressed limb, axial, and oral AIM relative to vehicle. The time $\times$ treatment interaction was also significant for L-DOPA-induced rotation [$F(5.80, 208.64) = 5.94$, $p < 0.001$], as shown in Fig. 1f. The treatment effect for rotation showed a trend toward significance [$F(3, 36) = 2.54$, $p = 0.072$]. Post hoc tests revealed that 10 mg/kg buspirone suppressed L-DOPA-induced rotation. In the first hour after L-DOPA, the treatment effect was even more pronounced [$F(2, 31) = 9.81$, $p < 0.001$], and post hoc tests revealed that 4–10 mg/kg buspirone suppressed rotation (data not shown).

Conversely, none of the sigma agents had any effect on AIM, including the sigma-1 antagonist BD-1047 (3 mg/kg), elevation of the sigma-1 antagonist progesterone by finasteride (50 mg/kg), the sigma-2 antagonist SM-21 (20 mg/kg), the sigma-1 and sigma-2 agonist DTG (3 mg/kg), and the sigma-1 agonists DHEA (15 mg/kg), carbetapentane (45 mg/kg), and opipramol (10 mg/kg). For each of these compounds, the time $\times$ treatment interaction effect over the 3-h test session was not significant [$F \leq 1.76$, n.s.] nor was the effect of the treatment significant [$F \leq 1.27$, n.s.], as shown in Table 2. The effect of treatment was also not significant during the first hour [$t \leq 1.08$, n.s.] (data not shown). No effects were apparent for the limb, axial, or oral subscales over the 3-h test session, as indicated by nonsignificant time $\times$ treatment interaction effects [$F \leq 1.85$, n.s.] and treatment effects [$F \leq 2.90$, n.s.] (data not shown). No significant effects on rotation were observed over the 3-h session, including the time $\times$ treatment interaction effects [$F \leq 1.69$, n.s.] or treatment effects [$F \leq 1.75$, n.s.], and no significant treatment effect on rotation was observed over the first hour [$t \leq 1.27$, n.s.] (data not shown).

As expected, BMY-14802 suppressed AIM. Interestingly, this AIM-suppressing effect was dose-dependently prevented by the 5-HT_{1A} antagonist WAY-100635. The time $\times$ treatment interaction effect was significant [$F(3.84, 226.50) = 6.03$, $p < 0.001$], and the effect of treatment was significant [$F(5, 59) = 11.43$, $p < 0.001$], as shown in Fig. 2a. Post hoc tests revealed that 15 mg/kg BMY-14802 significantly reduced AIM relative to vehicle over the 3-h test session, while 0.5 mg/kg WAY-100635 slightly increased AIM relative to vehicle. At 0.5 mg/kg, but not 0.1 mg/kg, WAY-100635 prevented the AIM-suppressing effect of BMY-14802, demonstrating levels of AIM similar to vehicle, as shown in Fig. 2a. The treatment effect was especially apparent during the first hour after L-DOPA, when a two-way ANOVA revealed main effects for BMY-14802 [$F(9, 50) = 6.49$, $p < 0.001$] and WAY-100635 [$F(18, 102) = 2.58$, $p \leq 0.001$], as well as an interaction effect [$F(18, 102) = 1.75$, $p < 0.05$], as shown in Fig. 2b. During this first hour, BMY-14802 suppressed AIM, while 0.1–0.5 mg/kg WAY-100635 alone had no effect on LID, and 0.5 mg/kg WAY-100635 prevented BMY-14802's AIM-suppressing effect. The limb, axial, and oral subscales showed significant time $\times$ treatment interaction effects [$F \geq 2.64$, $p < 0.001$], and treatment effects [$F(5, 59) \geq 8.85$, $p < 0.001$], as shown in Fig. 2c–e. Post hoc tests revealed that BMY-14802 significantly suppressed limb, axial, and oral AIM. Furthermore, 0.5 mg/kg WAY-100635 prevented BMY-14802's effects on limb and oral AIM and showed a trend to prevent BMY-14802's effects on axial AIM ($p = 0.065$). L-DOPA-induced rotation also showed significant effects, including a time $\times$ treatment interaction effect [$F(5.10, 300.85) = 4.53$, $p < 0.001$] and treatment effect [$F(5, 59) = 8.13$, $p < 0.001$], as shown in Fig. 2f. Post hoc tests revealed that BMY-14802 suppressed L-DOPA-induced rotation, and 0.5 mg/kg WAY-100635 showed a trend to prevent BMY-14802's effect on rotation ($p = 0.072$). In the first hour after L-DOPA, this treatment effect was even more pronounced [$F(5, 64) = 11.69$, $p < 0.001$]. Post hoc tests revealed that BMY-14802 suppressed rotation, and 0.5 mg/kg WAY-100635 prevented this effect.

Conversely, prazosin administered at a dose known to antagonize adrenergic α -1 receptor function (Sánchez et al. 1989; Solomon et al. 1989; Yen et al. 1996) did not prevent BMY-14802's AIM-suppressing effect. The time $\times$ treatment interaction effect was significant [$F(3.93, 164.91)=10.49, p<0.001$], and the effect of treatment was significant [$F(3, 42)=14.07, p<0.001$], as shown in Fig. 3a. Post hoc tests revealed that 15 mg/kg BMY-14802 significantly reduced AIM relative to vehicle over the 3-h test session, while 0.1 mg/kg prazosin had no effect on AIM. Rats treated with prazosin + BMY-14802 showed levels of AIM similar to those treated with BMY-14802 alone, as shown in Fig. 2a. The treatment effect was especially apparent during the first hour after L-DOPA, when a two-way ANOVA revealed a main effect for BMY-14802 [$F(8, 35)=5.97, p<0.001$] but no significant main effect for prazosin [$F(8, 35)=0.64, n.s.$] or interaction effect [$F(8, 35)=1.35, n.s.$]. During this first hour, BMY-14802 suppressed AIM, while prazosin had no effect on AIM by itself or when combined with BMY-14802, as shown in Fig. 3b. Higher doses of prazosin were not tested in combination with BMY-14802, as 1-3 mg/kg of prazosin alone was observed to reduce general activity, including AIM (data not shown). The limb, axial, and oral subscales showed significant time $\times$ treatment interaction effects [$F\geq 2.64, p<0.001$], and treatment effects [$F(3, 45)\geq 17.26, p<0.001$], as shown in Fig. 3c–e. Post hoc tests revealed that BMY-14802 significantly suppressed limb, axial, and oral AIM, and prazosin had no effect by itself or when combined with BMY-14802. L-DOPA-induced rotation also showed significant effects, including a time $\times$ treatment interaction effect [$F(5.68, 238.57)=6.52, p<0.001$], and treatment effect [$F(3, 42)=7.66, p<0.001$], as shown in Fig. 3f. Post hoc tests revealed that BMY-14802 suppressed L-DOPA-induced rotation, and prazosin had no effect by itself or when combined with BMY-14802. In the first hour after L-DOPA, the treatment effect was even more pronounced [$F(3, 45)=17.26, p<0.001$]. Post hoc tests revealed that BMY-14802 suppressed rotation and prazosin had no effect by itself or when combined with BMY-14802.

Discussion

We previously demonstrated that BMY-14802 reduces AIM expression in the 6-OHDA rat model of PD (Paquette et al. 2008). The aim of this study was to determine which of BMY-14802's known mechanisms of action might underlie its AIM-suppressing effect. The current data support the involvement of the 5-HT_{1A} receptor, but not sigma or α -1 receptors in regulating AIM expression. Specifically, the 5-HT_{1A} agonist buspirone suppresses AIM expression in our model, supporting past research for AIM-suppressing effects of 5-HT_{1A} agonists, as discussed below. Conversely, despite the AIM-suppressing effects of BMY-14802, seven other compounds with sigma action failed to reduce AIM, suggesting that sigma receptors may not be effective targets for antidyskinesia pharmacotherapies. Furthermore, the 5-HT_{1A} antagonist WAY-100635, but not the adrenergic α -1 antagonist prazosin, dose-dependently prevented BMY-14802's AIM-suppressing effect, suggesting that BMY-14802's action involves agonism of the 5-HT_{1A} receptor but not the α -1 receptor.

These data are consistent with a large body of literature supporting 5-HT_{1A} agonists as LID- and AIM-suppressing agents. AIM-suppressing effects of the selective 5-HT_{1A} agonist 8-OH-DPAT have been demonstrated in the unilateral 6-OHDA rat (Dupre et al. 2007, 2008; Tomiyama et al. 2005) and MPTP monkey (Iravani et al. 2006) models of PD. Likewise, the 5-HT_{1A} agonist buspirone has been demonstrated to suppress AIM development (Eskow et al. 2007) and expression in the 6-OHDA rat (Dekundy et al. 2007; Lundblad et al. 2002), AIM expression in the 6-OHDA mouse (Lundblad et al. 2005), and LID expression in PD patients in open-label (Olanow et al. 2004) and double-blind crossover studies (Bonifati et al. 1994). The 5-HT_{1A} agonist tandospirone has also been demonstrated to suppress LID in PD patients (Kannari et al. 2002).

The predictive validity of the preclinical models is supported by data showing that medications known to modulate clinical LID, including amantadine (Del Dotto et al. 2001; Verhagen-Metman et al. 1998a, b), buspirone (Bonifati et al. 1994), and dextromethorphan (Verhagen-Metman et al. 1998a, b) have comparable effects on preclinical AIM (amantadine, Blanchet et al. 1997; Lundblad et al. 2002, 2005; buspirone, Eskow et al. 2007; Dekundy et al. 2007; Lundblad et al. 2002; dextromethorphan, Paquette et al. 2008). However, not all agents that have shown promise in the animal model have translated favorably to human PD patients. Clinical evaluation of the 5-HT_{1A} agonist sarizotan ended in failure despite AIM-suppressing effects in animal models (Bibbiani et al. 2001). Sarizotan improved LID at the expense of exacerbating PD symptomatology or increasing “off” time (Olanow et al. 2004; Goetz et al. 2007). We suggest that this profile may be explained by the affinity of sarizotan for D₂-family receptors (Kuzhikandathil and Bartoszyk 2006).

Likewise, adverse extrapyramidal effects of 5-HT_{1A} agonists (Iravani et al. 2006; Kannari et al. 2002) are likely due to activity at receptors other than 5-HT_{1A}, including the DAergic D₂ receptor. Both sarizotan and buspirone have comparatively high affinity for the D₂ receptor (Abou-Gharbia et al. 1988, 1989; Kuzhikandathil and Bartoszyk 2006; Perrone et al. 1994; Peroutka 1985). Sarizotan failed clinical trials, while buspirone showed promise to suppress LID (Bonifati et al. 1994). The lack of extrapyramidal side effects of buspirone despite its relatively high affinity for the D₂ receptor may be due to its 5-HT_{1A} agonist profile. Similarly, 5-HT_{1A} agonism is believed to contribute to the lack of extrapyramidal side effects of another class of drugs, atypical antipsychotic medications (Bardin et al. 2006; Kleven et al. 2005).

The 5-HT_{1A} agonist ($\pm$) 8-OH-DPAT may have activity at D₁ and D₂ receptors (Ahlenius et al. 1990; Hajos-Korcsok and Sharp 1996; Matuszewich et al. 1999), as well as 5-HT₇ receptors (Eglen et al. 1997) and 5-HT transporters (Schoemaker and Langer 1986). While the (+) enantiomer of 8-OH-DPAT lacks DAergic receptor activity, partial agonist activity at 5-HT₇ receptors (Tsou et al. 1994; Wood et al. 2000) may be responsible for its exacerbation PD symptoms in the MPTP monkey model (Iravani et al. 2006). Therefore, selection of 5-HT_{1A} agonists for clinical trials in human PD patients with L-DOPA complications must carefully consider the binding profile of the test drug to minimize the chance of worsening PD symptoms.

BMY-14802 has affinity for the 5-HT_{1A} receptor (IC₅₀=320 nM, Yevich et al. 1992), but unlike other 5-HT_{1A} agonists, BMY-14802 does not bind with high affinity to the D₁ or D₂ receptor (IC₅₀s>1,000 and 6,430 nM, respectively; Yevich et al. 1992) and does not appear to have the adverse clinical effects of a DA antagonist (Gewirtz et al. 1994; Matthews et al. 1986). BMY-14802's other sites of action, sigma-1 and adrenergic α -1 receptors (IC₅₀'s of 112 and 460 nM, respectively; Yevich et al. 1992), are unlikely to worsen PD symptoms or cause adverse side effects. BMY-14802's affinity for α -1 is much lower than the μ M affinity of vasopressors and noradrenaline (Bevilacqua et al. 1991; Feldstein et al. 1986; McPherson and Summers 1982). In fact, adrenergic α -1 agonists may improve frontal lobe function in PD (Bedard et al. 1998), and α -1 agonists have been shown to enhance amphetamine-induced rotation in the 6-OHDA rat model (Mavridis et al. 1991), suggesting that these drugs facilitate motor activity controlled by the nigrostriatal pathway. Furthermore, BMY-14802 and other sigma antagonists have been demonstrated to be safe in clinical trials of schizophrenia (Gewirtz et al. 1994; Modell et al. 1996). An exception to this rule is the sigma antagonist EMD 57445 (panamesine), which has been shown to increase extrapyramidal symptoms in some studies (Huber et al. 1999; Müller et al. 1999) but not others (Frieboes et al. 1997), likely due to anti-DAergic activity (Bartoszyk et al. 1996; Skuza et al. 1998). Therefore, we believe that BMY-14802 is a good candidate for clinical development as an antidyskinesia pharmacotherapy.

The current study replicated our earlier findings that BMY-14802 suppresses not only AIM but also L-DOPA-induced rotation (Paquette et al. 2008), generally considered to reflect the motor-activating effects of L-DOPA. This could be due to a nonspecific motor suppressant effect. While sigma antagonists lack sedative effects (Gewirtz et al. 1994; Matthews et al. 1986), 5-HT_{1A} agonists can induce odd body posture and sedation reminiscent of the “serotonin syndrome” (Iravani et al. 2006). These effects could interfere with expression of AIM as well as normal motor behavior, which is cause for concern, as this might worsen PD symptoms and/or prevent L-DOPA-mediated motoric improvement. However, BMY-14802 did not evoke Parkinsonian side effects in clinical trials for schizophrenia (Gewirtz et al. 1994), and it has been shown to counteract haloperidol-induced dystonia in preclinical experiments (Okumura et al. 1996). In addition, ongoing studies in our laboratory demonstrate that BMY-14802 does not interfere with L-DOPA-mediated improvement of PD symptoms in the 6-OHDA rat (unpublished observations). Lacking significant D₂ antagonism, it is unlikely that BMY-14802 will exacerbate PD to a similar extent as the 5-HT_{1A} agonist sarizotan, which failed clinical trials of LID.

While the mechanism(s) underlying LID are not known, dyskinesias are generally thought to arise from overstimulation of supersensitive post-synaptic DA receptors. In support of this hypothesis, D₁ and D₂ antagonists have been demonstrated to reduce AIM (Taylor et al. 2005). However, evidence has been accumulating to support a role for the 5-HT₂ system, which is well-situated to modulate DA neurotransmission (see Alex and Pehek 2007 for a review). Specifically, 5-HT_{1A} receptors are upregulated in the striatum in animal models of PD (Frechilla et al. 2001), and 5-HT_{1A} agonists affect midbrain DAergic activity (Cobb and Abercrombie 2003; Kelland et al. 1990) and reduce L-DOPA-mediated DA overflow (Kannari et al. 2001).

In addition to directly regulating DA neurotransmission, the 5-HT system may also affect LID indirectly by altering glutamate neurotransmission within the cortico-striatal pathway. 5-HT₂ fibers innervate glutamatergic regions of the basal ganglia circuitry, including the cortex, subthalamic nucleus, and thalamus (Di Giovanni et al. 2006). Direct infusion of sarizotan into the motor cortex (Antonelli et al. 2005) or systemic injection of 8-OH-DPAT (Mignon and Wolf 2005) reduces striatal glutamate overflow. Furthermore, 8-OH-DPAT has been shown to decrease phosphorylation of the glutamate-1 receptor (Ba et al. 2006). Glutamate receptors, especially NMDA, have been thought to mediate LID for many years (Blanchet et al. 1997; Papa and Chase 1996). Recently, evidence has emerged to support a role for the metabotropic glutamate receptor group 5 (mGluR5) in dyskinesia (Dekundy et al. 2006; Mela et al. 2007; Levandis et al. 2008). Thus, it seems reasonable to conclude that 5-HT could mediate LID by affecting glutamate neurotransmission.

5-HT could also affect LID by its known effects in other regions of the basal ganglia circuitry, including the globus pallidus (Hashimoto and Kita 2008) and subthalamic nucleus (Chen et al. 2008; Stanford et al. 2005; Temel et al. 2007; Xiang et al. 2005). Based on the many potential mechanisms through which 5-HT may modulate basal ganglia circuitry, it seems likely that 5-HT plays an integral role in motor function and LID, though that role is not yet clearly understood.

In conclusion, the current study replicated the AIM-suppressing effect of BMY-14802 (Paquette et al. 2008) and its parent compound buspirone (Bonifati et al. 1994; Dekundy et al. 2007; Eskow et al. 2007; Lundblad et al. 2002, 2005). For the first time, we demonstrated that other agents acting at sigma-1 and sigma-2 receptors have no effect on AIM and that the AIM-suppressing action of BMY-14802 is dependent on 5-HT_{1A} but not adrenergic α -1 receptors, as this effect is prevented by the 5-HT_{1A} antagonist WAY-100653 but not the α -1 antagonist prazosin. Therefore, we conclude that BMY-14802 suppresses AIM via a 5-HT_{1A} agonist

effect. Based on the known pharmacological profile of BMY-14802, as well as the lack of DAergic side effects in previous clinical trials, we suggest that BMY-14802 is a promising candidate for clinical trials of LID in PD patients.

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Fig. 1.

a Buspirone dose-dependently suppressed AIM over the 3-h test session. Specifically, 10 mg/kg, but not lower doses, reduced AIM relative to vehicle. **b** In the first hour of the test, 1-10 mg/kg buspirone suppressed AIM relative to vehicle. **c-f** Effects on the limb, axial, and oral subscales, as well as on L-DOPA-induced rotation, were similar to the summed AIM score (compare to **a**). Buspirone was administered i.p. 30 min prior to L-DOPA at 1 ml/100 gm body weight. * $p < 0.001$ relative to vehicle

Fig. 2.

a Relative to vehicle, BMY-14802 suppressed AIM, while WAY-100635 (0.5 mg/kg) slightly but significantly increased AIM over the 3-h test session. WAY-100635 prevented BMY-14802's AIM-suppressing effect at 0.5 mg/kg, but not 0.1 mg/kg. **b** In the first hour of the test, BMY-14802 suppressed AIM relative to vehicle, while WAY-100635 (0.1-0.5 mg/kg) had no effect. BMY-14802's AIM-suppressing effect was prevented by WAY-100635 at 0.5 mg/kg, but not 0.1 mg/kg. **c-f** Effects on the limb, axial, and oral subscales, as well as on L-DOPA-induced rotation were similar to the summed AIM score (compare to panel **a**). Test compounds were administered i.p. 30 min prior to L-DOPA at 1 ml/100 gm body weight.

* $p < 0.001$ relative to vehicle; + $p < 0.01$ relative to BMY-14802

Fig. 3.

a Relative to vehicle, BMY-14802 suppressed AIM, while prazosin (0.1 mg/kg) had no effect by itself or in combination with BMY-14802. **b** In the first hour of the test, BMY-14802 suppressed AIM relative to vehicle, while prazosin had no effect by itself or in combination with BMY-14802. **c-f** Effects on the limb, axial, and oral subscales, as well as on L-DOPA-induced rotation were similar to the summed AIM score (compare to panel **a**). Test compounds were administered i.p. 30 min prior to L-DOPA at 1 ml/100 gm body weight. * $p < 0.01$ relative to vehicle

Table 1

Receptor binding profiles of sigma agents

Drug	Sigma-1	Sigma-2	Selectivity (sigma-1/sigma-2)	Reference
BD-1047	0.93	47	0.02	Matsumoto et al. 1995
Carbetapentane	41	894	0.05	Calderon et al. 1994
DHEA	706	N/A	N/A	Waterhouse et al. 2007
DTG	35.45	39.87	1.1	Lever et al. 2006
Opipramol	7	56	0.13	Holoubek and Muller 2003
Progesterone	36	N/A	N/A	Waterhouse et al. 2007
SM-21	1050	145	7.24	Matsumoto et al. 2007

Binding affinities at sigma-1 and sigma-2 receptors are shown in nM. All values represent K_i , except for opipramol, where values represent IC_{50} .

N/A not available

Table 2

Effect of sigma agents of L-DOPA-induced dyskinesia

Drug'	Limb + axial + oral dyskinesia over 3h	Effect of drug
Vehicle	44.18±6.60	
BD-1047	45.50±9.19	<i>F</i> (1, 18)=0.08, n.s.
Vehicle	59.56±2.96	
Finasteride	64.56±3.31	<i>F</i> (1, 16)=1.27, n.s.
Vehicle	48.00±6.35	
SM-21	55.40±8.92	<i>F</i> (1, 18)=0.46, n.s.
Vehicle	52.22±5.29	
DTG	63.83±9.55	<i>F</i> (1, 10)=0.06, n.s.
Vehicle	45.70±6.51	
DHEA	51.90±7.60	<i>F</i> (1, 17)=0.001, n.s.
Vehicle	60.17±11.14	
Carbetapentane	56.40±6.28	<i>F</i> (1, 18)=1.40, n.s.
Vehicle	65.30±2.70	
Opipramol	60.80±3.28	<i>F</i> (1, 18)=1.12, n.s.

None of the sigma agents tested reduced LID over the 3-h test session. All test drugs were administered i.p. 30 min prior to L-DOPA at 1 ml/100 gm body weight, except finasteride, which was administered i.p. 22 h prior to L-DOPA at 5 ml/100 gm body weight. Doses used were: BD-1047 (3 mg/kg), finasteride (50 mg/kg), SM-21 (20 mg/kg), DTG (3 mg/kg), DHEA (15 mg/kg), carbetapentane (45 mg/kg), and opipramol (10 mg/kg).