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The effects of BMY-14802 against L-DOPA- and dopamine agonist-induced dyskinesia in the hemiparkinsonian rat

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Abstract

Rationale—L-DOPA continues to be the primary treatment for patients with Parkinson's disease; however, the benefits of long-term treatment are often accompanied by debilitating side effects known as dyskinesias. In recent years, several 5-HT_{1A} receptor agonists have been found to reduce dyskinesia in clinical and experimental models of PD. The purported sigma-1 antagonist, BMY-14802 has been previously demonstrated to reduce L-DOPA induced dyskinesia in a 5-HT_{1A} receptor dependent manner.

Objective—In the present study, we extend these findings by examining the anti-dyskinetic potential of BMY-14802 against L-DOPA, the D_1 receptor agonist SKF81297 and the D_2 receptor agonist, Quinpirole, in the hemi-parkinsonian rat model. In addition, the receptor specificity of BMY-14802's effects was evaluated using WAY-100635, a 5-HT_{1A} receptor antagonist.

Results—Results confirmed the dose-dependent (20>10>5 mg/kg) anti-dyskinetic effects of BMY-14802 against L-DOPA with preservation of antiparkinsonian efficacy at 10 mg/kg. BMY-14802 at 10 and 20 mg/kg also reduced dyskinesia induced by both D_1 and D_2 receptor agonists. Additionally, BMY-14802's anti-dyskinetic effects against L-DOPA, but not SKF81297 or Quinpirole, were reversed by WAY-100635 (0.5 mg/kg).

Conclusion—Collectively, these findings demonstrate that BMY-14802 provides anti-dyskinetic relief against L-DOPA and direct DA agonist in a preclinical model of PD, acting via multiple receptor systems and supports the utility of such compounds for the improved treatment of PD.

Keywords

BMY-14802; Parkinson's disease; 6-hydroxydopamine; L-DOPA-induced dyskinesia; 5-HT_{1A}; D_1; D_2; Rat; DA agonist-induced dyskinesia

Introduction

L-DOPA continues to be the primary choice for symptomatic treatment of Parkinson's disease (PD) even though its chronic use leads to the development of debilitating side such as abnormal, involuntary movements (AIMs), widely known as L-DOPA-induced dyskinesias (LID) (Jankovic, 2008). The appearance of LID is observed in about 10% of patients in the first year of treatment and in nearly 90% of patients after 9 years of treatment

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(Ahlskog and Muenter, 2001, Fabbrini et al., 2007, Bhidayasiri and Truong, 2008, Chan et al., 2008). The preponderance of LID in most PD patients has necessitated the development of effective anti-dyskinetic adjuncts that neither hamper L-DOPA efficacy nor worsen parkinsonian symptoms.

Though the mechanisms underlying the development and expression of LID are complex, convergent evidence indicates that neuroplasticity within the serotonin (5-HT) system contributes to LID. For example, multiple studies have suggested that raphe-striatal serotonergic neurons take over the role of the deficient nigrostriatal dopamine (DA) system, actively converting exogenously administered L-DOPA into DA and releasing it into the striatum in a pulsatile, unregulated fashion (Arai et al., 1996, Maeda et al., 2003, Carta et al., 2007, Eskow et al., 2009, Rylander et al., 2010). Several 5-HT_{1A} receptor agonists, such as buspirone (Dekundy et al., 2007, Eskow et al., 2007), 8-OHDPAT (Iravani et al., 2006, Dupre et al., 2008b), piclozotan (Tani et al., 2010), tandospirone (Kannari et al., 2002) and sarizotan (Goetz et al., 2007) appear effective in reducing LID, in part, by dampening striatal DA efflux induced by L-DOPA.

In addition to the unregulated DA release after L-DOPA administration, aberrant striatal DA receptor signaling leading to dysregulated striatal output, is implicated in the expression of LID (Winkler et al., 2002, Cenci, 2007a, b, Cenci and Lindgren, 2007). This is supported by studies showing that both DA D_1 and D_2 receptor agonists produce dyskinesia in 6-OHDA models of PD and PD patients (Delfino et al., 2004, Dupre et al., 2007, Carta et al., 2008). Interestingly, 5-HT_1 agonists are able to reduce dyskinesias produced by DA receptor agonists (Dupre et al., 2007, Dupre et al., 2008a, Eskow et al., 2009, Jaunarajs et al., 2009). These findings suggest that 5-HT_{1A} agonists may act via mechanisms that are both pre- and post-synaptic to the striatum (Dupre et al., 2011; Ostock et al., 2011). Previous findings by Paquette and colleagues (2008, 2009) have established that BMY-14802, the purported sigma-1 receptor antagonist, provides relief against LID in a 5-HT_{1A}-dependent manner. The aims of this study were to extend this work by establishing an effective dose range for BMY-14802 that does not alter L-DOPA's antiparkinsonian actions, determine whether BMY-14802 reduces DA agonist-induced dyskinesias and finally examine whether the anti-dyskinetic effects of BMY-14802 are reversed by WAY-100635, a 5-HT_{1A} antagonist.

Materials and methods

Animals

Adult male Sprague-Dawley rats were used (225–250 g upon arrival; Taconic Farms, Hudson, NY, USA). Animals were housed in plastic cages (22 cm high, 45 cm deep and 23 cm wide) and had free access to food (Rodent Diet 5001; Lab Diet, Brentwood, MO, USA) and water. The colony room was maintained on a 12/12 h light/dark cycle (lights on at 0700 h) at a temperature of 22–23 °C. The guidelines of the Institutional Animal Care and Use Committee of Binghamton University and the "Guide for the Care and Use of Laboratory Animals" (8^{th} Ed., National Academies Press, 2011) were maintained throughout the study.

6-Hydroxydopamine lesion surgeries

One week after arrival, all rats received unilateral 6-hydroxydopamine (6-OHDA) lesions of the left medial forebrain bundle to destroy DA neurons. Desipramine HCl (25 mg/kg, ip; Sigma, St. Louis, MO, USA) was given 30 min prior to the 6-OHDA injection to protect norepinephrine (NE) neurons. Rats were anesthetized with inhalant isoflurane (2–3%; Sigma) in oxygen (2.5 l/min) and placed in a stereotaxic apparatus (David Kopf Instruments, Tujunga, CA, USA). The following coordinates relative to bregma were used for the site of injection: AP, −1.8 mm; ML,+2.0 mm; DV, −8.6 mm, with the incisor bar positioned at 3.3

mm below the interaural line (Paxinos and Watson, 1998). A Hamilton syringe attached to a 26-gauge needle was lowered into the target and 6-OHDA (12 μg; Sigma) dissolved in 0.9% NaCl + 0.1% ascorbic acid, was infused at a rate of 2 μL/min for a total volume of 4 μL. The needle was withdrawn 5 min later. Five min pre-surgery and 1 day post-surgery, rats received an injection of Buprenex (buprenorphine HCl; 0.03 mg/kg, ip.; Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA, USA) as analgesic treatment. Rats were allowed to recover for 3 weeks post-surgery before commencement of experimental manipulations.

Treatments and Procedures

Experiment 1. Effect of BMY-14802 administration on L-DOPA-induced dyskinesia and motor performance—All rats in experiment 1 (n = 14) received 3,4-dihydroxyphenylacetic acid methyl ester (L-DOPA; 12 mg/kg, sc; Sigma) + dl-Serine 2-(2,3,4-trihydroxybenzyl) hydrazide hydrochloride (benserazide; 15 mg/kg, sc; 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. This priming regimen with L-DOPA has been demonstrated to produce a maximal and stable response after 1 week of treatment (Bishop et al., 2009, Dupre et al., 2011). Rats were observed for Abnormal Involuntary Movements (AIMs; see below) on days 1, 5, and 7 of L-DOPA priming. Only rats displaying a cumulative axial, limb and orolingual (ALO) AIMs score, of ≥ 45 on day 7 of priming, derived from measures taken for 1 min every 10 min over 3 hours, were maintained for further study (n=14 of 14, 100%). Thereafter, rats were tested for AIMs every 3–4 days in a within-subjects, counterbalanced design, receiving a pre-treatment of VEH (dH_2O) or various doses of the 5-HT_{1A} partial agonist, BMY-14802 (5, 10 or 20 mg/kg, ip; Tocris) at 30 min prior to injection of L-DOPA (6mg/kg, sc) + benserazide (15 mg/kg, sc). Immediately following L-DOPA injections, rats were monitored for AIMs and rotations for 1 min every 10 min over 3 h.

In order to test the effects of BMY-14802 on the motor performance of L-DOPA-primed rats the Forelimb Adjusting Steps (FAS) test was employed. All rats received the following three treatments in a within subjects counterbalanced design: VEH + VEH, VEH + L-DOPA (6mg/kg, sc) + benserazide (15 mg/kg, sc) or BMY-14802 (10 mg/kg, ip) +L-DOPA (12 mg/kg, sc) + benserazide (15 mg/kg, ip). To allow for peak L-DOPA plasma levels (Sato et al., 1994), testing began 1 h after L-DOPA injection. FAS testing occurred every 3–4 days following termination of AIMs testing.

Experiment 2. Effect of BMY-14802 administration on D_1 or D_2 receptor induced dyskinesia—Three weeks after 6-OHDA lesions, all rats in experiment 2 (n=14) received injections of the D_1 receptor agonist R (+)-SKF-81297 hydrobromide (SKF81297; 0.8 mg/kg, sc; Sigma) on 3 separate occasions 2 to 3 days apart to sensitize both D_1 and D_2 receptors (Pollack and Yates, 1999). Contralateral rotations and AIMs were observed immediately after injections. Rats displaying ALO AIMs scores of ≥ 45 by the 3rd day of D_1 receptor agonist priming were retained for further study (n = 13 of 14, 93%). Thereafter, rats were tested for AIMs every 3–4 days in a within-subjects design, receiving a pre-treatment of VEH (dH_2O) or various doses of the 5-HT_{1A} partial agonist, BMY-14802 (5, 10 or 20 mg/kg, ip; Tocris) at 30 min prior to injection of vehicle (DMSO), a low dose of the D_1 receptor agonist SKF81297 (0.08 mg/kg, sc), or a low dose of the D_2 receptor agonist (±)-quinpirole dihydrochloride (quinpirole; 0.05 mg/kg, sc; Sigma). The doses for the direct DA receptor agonists were chosen with the aim of eliciting sub-maximal dyskinesia expression and were based on preliminary studies done in our lab (data not shown). Rats were monitored for AIMs and rotations for 1 min every 10 min over 3 h following the DA agonist injections. Given the time course of the agonists' effects, results were portrayed over a 2 h period.

Experiment 3. Effect of WAY-100635 administration on BMY-14802's anti-dyskinetic effects—Three weeks after 6-OHDA lesions, all rats in experiment 3 (n=8) received injections of L-DOPA (12 mg/kg, s.c.) + benserizide (15 mg/kg, sc) once daily for 7 days. Rats were observed for AIMs on days 1, 5, and 7 of L-DOPA priming. Only rats displaying a cumulative AIMs score, of ≥ 45 on day 7 of priming, derived from measures taken for 1 min every 10 min over 3 hours, were maintained for further study (n=8 of 8, 100%). Thereafter, rats were tested for AIMs every 3–4 days in a within-subjects, counterbalanced design, receiving a pre-treatment of WAY-100635 (0.5 mg/kg or VEH, ip) along with BMY-14802 (10 mg/kg or VEH, ip) at 30 min prior to injection of L-DOPA (6mg/kg, sc) + benserazide (15 mg/kg, sc). Immediately following L-DOPA injections, rats were monitored for AIMs and rotations for 1 min every 10 min over 3 h.

One week following the final L-DOPA injection, all rats (n=8) received injections of R (+)-SKF-81297 hydrobromide (SKF81297; 0.8 mg/kg, sc; Sigma) on 3 separate occasions 2 to 3 days apart to sensitize both D_1 and D_2 receptors. Thereafter, rats were tested for AIMs every 3–4 days in a within-subjects design, receiving a pre-treatment of WAY-100635 (0.5 mg/kg or VEH, ip) along with BMY-14802 (10 mg/kg or VEH, ip) at 30 min prior to injection of SKF81297 (0.08 mg/kg, sc), or (±)-quinpirole dihydrochloride (Quin; 0.05 mg/kg, sc; Sigma). Rats were monitored for AIMs and rotations for 1 min every 10 min over 3 h following the DA agonist injections.

High performance liquid chromatography

Rats from experiment 2 were killed by decapitation 1 week after the completion of the study, and striata were dissected out, flash-frozen, and stored at −80°C. Reverse-phase high performance liquid chromatography (HPLC) coupled to electrochemical detection was performed on striatal tissue, obtained from all rats, according to protocol of Kilpatrick et al. (1986). Detailed HPLC methods are described in Bishop et al. (2012); the present experiment differed only in the coulometric electrode potentials used: the guard cell was set to +700 mV, the two analytic electrodes were set at −150 mV and +250 mV. We examined tissue for levels of DA, 5-HT, 3,4-dihydroxyphenylacetic acid (DOPAC), and 5-hydroxyindole-3-acetic acid (5-HIAA). Monoamines and metabolites were expressed as picograms (pg) per milligram (mg) tissue (mean ± SEM).

Abnormal involuntary movements

The AIMs model of dyskinesia utilizes distinct behavioral measures and demonstrates face validity with known anti-dyskinetic compounds (Lundblad et al., 2002, Taylor et al., 2005). After treatment with L-DOPA, rats were placed in plastic cylinders and rated by trained observers blind to the experimental condition for 1 min every 10 min over a 180-min period. Individual dyskinesia severity scores ranging from 0 (not present) to 4 (severe and not interruptible) were recorded for axial, limb and orolingual (ALO) as detailed in Lindenbach et al. (2011) and Eskow et al. (2009). The three AIMs subtypes were sometimes combined to create a single ALO AIMs score for data analysis.

Forelimb adjusting steps

The effect of DA lesion and subsequent drug therapy on motor ability was assessed using the FAS test, which assesses akinesia, a cardinal symptom of PD (Chang et al., 1999, Olsson et al., 1995). Rats were held such that they had only one free forelimb; for each trial, rats were moved laterally across a table at a steady rate of 90 cm/10 s. Each stepping test consisted of six trials for each forepaw, alternating between directions (for more detail see Eskow et al., 2007). "Percent intact" stepping was derived by summing steps with the lesioned forelimb and dividing them by the sum of steps with the intact forelimb and multiplying by 100. Lower scores indicate a greater Parkinsonian impairment.

Data analyses

Monoamine and metabolite levels in the striatum were analyzed using paired *t*-tests (comparing intact vs. lesioned striata). Main effects of treatment for axial, limb and orolingual AIMs were analyzed using repeated measures non-parametric Friedman test (inset graphs for each corresponding figure) and Wilcoxon post hocs when appropriate. Individual time-point analyses for axial, limb and orolingual AIMs were performed using repeated-measures non-parametric Friedman test. Rotations were analyzed with 2-way (treatment X time) ANOVAs and LSD post hoc comparisons when appropriate. One-way ANOVAs followed by LSD post hoc tests were employed for analysis of FAS data. All analyses were performed with Statistica software '98 (Statsoft Inc., Tulsa, OK, USA). Alpha was set at 0.025.

RESULTS

Effect of 6-OHDA lesions on striatal monoamine and metabolite levels

The effects of 6-OHDA lesion on striatal monoamines (DA, 5-HT) and metabolites (DOPAC, 5-HIAA) were assessed by HPLC in the intact (right) and lesioned (left) hemispheres of the brain. Unilateral administration of 6-OHDA into the medial forebrain bundle resulted in severe depletion of DOPAC ($t_{12} = 7.66$, $p < 0.001$) and DA ($t_{12} = 12.88$, $p < 0.001$) from 9624 ± 750 & 4011 ± 517 in the intact striatum respectively, compared to 44 ± 17 & 50 ± 14 respectively in the lesioned striatum. There were no significant differences between intact and lesioned striata for 5-HT or 5-HIAA.

Effect of BMY-14802 on L-DOPA-induced Axial, Limb and Orolingual AIMs and Rotations

The anti-dyskinetic potential of BMY-14802 against LID was evaluated at 3 different doses (5, 10 and 20 mg/kg). As can be observed in Figure 1, BMY-14802 reduced axial, limb and orolingual AIMs and rotations, observed after L-DOPA (6 mg/kg) in a dose-dependent manner.

a) Axial AIMs—An overall main effect of treatment was observed upon analysis of Axial AIMs ($\chi^2 = 31.2$, $p<0.001$; Figure 1a, inset) and post hoc analysis revealed dose-dependent differences ($p<0.025$). Time point analysis revealed that the anti-LID efficacy of the highest dose of BMY-14802 (20 mg/kg) began at the 40 min time point and was maintained for up to 130 min after L-DOPA (all *p's* < 0.025). Lower doses of BMY-14802 (5 and 10 mg/kg) reduced AIMs from 40 to 50 min and 40 to 70 min after L-DOPA injection, respectively (*p's* < 0.025).

b) Limb AIMs—A significant main treatment effect was revealed following analysis ($\chi^2 = 34.5$, $p<0.001$) and post hoc analysis indicated that all 3 doses of BMY-14802 were effective. Similar effects occurred across multiple time-points after administration of L-DOPA (Figure 1b). Post hoc analyses confirmed that 5 mg/kg was effective beginning from 20–50 min and 80–90 min after L-DOPA (all *p's* < 0.025). Higher doses of BMY-14802 were effective for longer, such that 10 mg/kg was effective from 20–90 min and 110, 130 min after L-DOPA (all *p's* < 0.025), while 20 mg/kg was effective from 20–130 min after L-DOPA (all *p's* < 0.025).

c) Orolingual AIMs—BMY-14802, in a dose-dependent manner, was also effective in reducing orolingual dyskinesia produced by L-DOPA administration ($\chi^2 = 32.5$, $p < 0.001$; Figure 1c, inset). Time-point analysis revealed a significant suppression of orolingual dyskinesia at all doses of BMY-14802 examined. Further post hoc analysis confirmed that BMY-14802 at 5 mg/kg was able to significantly reduce orolingual dyskinesia at 50 and 70–90 min after L-DOPA (all *p's* < 0.025). BMY-14802 at a dose of 10 mg/kg was effective

from 30–80 and 130 min after L-DOPA (all p's < 0.025) and the effects of 20 mg/kg were observed from 30–130 and at 160 min post-L-DOPA (all p's < 0.025).

d) Rotations—Administration of L-DOPA resulted in the robust expression of rotations in the lesioned animals (Figure 1d). A repeated measures 2-way ANOVA revealed that there were main effects of treatment ($F_{(3,56)} = 3.04$, $p < 0.025$) and time ($F_{(17,952)} = 8.13$, $p < 0.025$); however, there was no significant interaction between treatment and time ($F_{(51,952)} = 1.26$, $p = 0.104$). Further analysis of the treatment effect indicated that only the highest dose of BMY-14802 reduced rotations produced by L-DOPA administration ($p < 0.025$).

Effect of BMY on L-DOPA effected improvement in FAS test

The FAS test was performed to confirm the anti-parkinsonian effects of L-DOPA on stepping performance and to assess the impact of BMY-14802 co-administration on L-DOPA efficacy. As seen in Figure 2, main effects of treatment were found ($F_{(3,42)} = 10.21$; $p < 0.001$) and post-hoc comparisons between the groups indicated that treatment with BMY (10 mg/kg) alone did not improve stepping. Importantly, L-DOPA at 6 mg/kg significantly improved stepping when compared to VEH-treated controls ($p < 0.025$) and co-administration of BMY-14802 with L-DOPA did not alter the improvement in stepping observed with L-DOPA administration.

Effect of BMY-14802 on Axial, Limb and Orolingual AIMs and Rotations produced by D1 and D2 agonists

In order to evaluate whether BMY-14802 acts upon DA receptor signaling, we evaluated the anti-dyskinetic efficacy of BMY-14802 (5, 10 and 20 mg/kg) against direct DA agonists. Previous studies have confirmed that the D_1 receptor agonist SFK81297 (0.08 mg/kg) and the D_2 receptor agonist quinpirole (0.05 mg/kg) produce dyskinetic behavior in 6-OHDA lesioned animals (Dupre et al., 2007). As shown in Figures 3, BMY-14802 also conveyed anti-dyskinetic relief against both D_1 and D_2 agonists.

a) Axial AIMs—Both DA agonists produced axial dyskinesia; however, it was observed that qualitatively quinpirole (Figure 3b) produced axial AIMs for a longer duration than SKF81297 (Figure 3a). Analyses revealed main effects of treatment for BMY-14802 against axial dyskinesia produced by SKF81297 ($\chi^2 = 21.5$, $p<0.001$) and quinpirole ($\chi^2 = 12.0$, $p<0.01$) (insets). Time point analyses revealed that 10 and 20 mg/kg of BMY-14802 effectively suppressed AIMs 40 min after the administration of SKF81297 (both p's < 0.025). Axial dyskinesia produced by quinpirole was attenuated by all the 3 doses of BMY-14802 at 30, 40 and 70 min after quinpirole and the higher doses were also effective at 20 min post-quinpirole (all p's < 0.025).

b) Limb AIMs—Overall, BMY14802 reduced limb dyskinesia produced by SKF81297 ($\chi^2 = 8.6$, $p < 0.025$; Figure 3c, inset) but not by quinpirole ($\chi^2 = 3.74$, $p < 0.25$; Figure 3d, inset). Focal analyses of time points revealed that 10 mg/kg of BMY14802 attenuated D_1 agonist-induced limb dyskinesia at the 10 and 50 min time points while the 20 mg/kg dose suppressed limb AIMs at 10, 20 and 40 min after SKF81297 injections (all p's < 0.025). BMY-14802 at 10 and 20 mg/kg similarly reduced limb AIMs 70–90 min after quinpirole administration ($p < 0.025$).

c) Orolingual AIMs—As shown in Figures 3e and 3f, BMY14802 also provided relief from orolingual AIMs induced by SKF81297 ($\chi^2 = 12.3$, $p < 0.025$) and quinpirole ($\chi^2 = 8.43$, $p < 0.025$) and further analysis revealed that both 10 and 20 mg/kg of BMY14802 significantly reduced this dyskinesia subtype. Time analyses indicated that BMY14802 at 20 mg/kg was effective from 10 min to 60 min after SKF81297 administration while 10 mg/kg

was effective at 10, 20 and 60 min time points (all p's < 0.025). In the case of quinpirole-induced orolingual dyskinesia, all the 3 doses of BMY-14802 were effective at 20 min, while 10 and 20 mg/kg were effective at 70 min, after administration of quinpirole (all p's < 0.025).

d) Rotations—Administration of both the direct DA agonists produced rotations in the lesioned animals (Figures 3g and 3h); however a main effect of treatment was only revealed with quinpirole ($F_{(3,36)} = 3.12$, $p < 0.025$). Two-way repeated measures ANOVA, for quinpirole, revealed a significant time effect ($F_{(17,799)} = 3.76$, $p < 0.025$) but no treatment effect; however, there was a significant interaction between time and treatment ($F_{(51,799)} = 1.44$, $p < 0.025$). Post hoc analyses revealed that the lowest dose of BMY-14802 suppressed rotations from 30–50 min and at 70–80 min after quinpirole administration. Higher doses of BMY14802 were effective from 40 to 90 min after quinpirole, except at 60 min where only 10 mg/kg had significant effects (all p's < 0.025).

Effect of WAY-100635 administration on BMY-14802's anti-dyskinetic effects

In order to evaluate the receptor specificity of BMY-14802, previously suggested to act in a 5-HT_{1A} dependent manner against LID (Paquette et al., 2009), we evaluated the effect of WAY-100635, a 5-HT_{1A} antagonist, on BMY-14802's anti-dyskinetic effects.

a) L-DOPA-induced dyskinesia—As demonstrated in experiment 1, BMY-14802 was able to attenuate LID (Figure 4a) from 40–120 min after L-DOPA administration (all p's < 0.025). Importantly, time analyses indicated that WAY-100635 reversed BMY-14802's anti-dyskinetic effects from 60 to 100 min after L-DOPA administration (all p's < 0.025).

b) Direct DA receptor agonist-induced dyskinesia—BMY-14802 attenuated dyskinesia produced by either SKF 81297 (Figure 4b) or Quinpirole (Figure 4c). Time analyses revealed that BMY-14802 attenuated dyskinesia at 10 and 30 min after SKF 81297 administration and at 20–40 min and 60 min after Quinpirole administration (all p's < 0.025). Unlike its effects on L-DOPA, WAY-100635 was unable to reverse the anti-dyskinetic effects of BMY-14802 when the source of the dyskinesia was either DA receptor agonist.

Discussion

The major findings from this study were: a) BMY-14802 dose-dependently reduced AIMs and contralateral rotations in 6-OHDA lesioned animals; b) BMY-14802, at an effective, anti-dyskinetic dose, did not alter L-DOPA's efficacy in improving stepping in lesioned animals; c) BMY-14802 attenuated dyskinesia produced by direct D_1 and D_2 receptor agonists, thereby indicating anti-dyskinetic efficacy against a broad spectrum of DA replacement therapies. Finally, d) BMY-14802's anti-dyskinetic effects against L-DOPA, but not direct DA receptor agonists, were reversed by the 5-HT_{1A} receptor antagonist, WAY-100635.

These findings are an extension of previous studies (Paquette et al., 2008, Paquette et al., 2009) that established the anti-dyskinetic potential of BMY-14802 against LID. In the current study, we confirmed a dose-range that is effective in reducing LID and contralateral rotations and more importantly, demonstrated anti-dyskinetic efficacy for BMY-14802 in attenuating dyskinesia produced by direct DA receptor agonists, SKF81297 and quinpirole. BMY-14802 previously used in clinical settings to treat schizophrenia, is known to be a sigma receptor antagonist (Gewirtz et al., 1994). However, recent work has indicated that the anti-LID effect of BMY-14802 is likely mediated by 5-HT_{1A} receptors, as it has been

shown to have high affinity for 5-HT_{1A} receptors and its behavioral effects can be reversed by a selective 5-HT_{1A} receptor antagonist (Paquette et al., 2009). In this regard, the anti-dyskinetic properties of BMY-14802 are in agreement with other 5-HT_{1A} agonists, like buspirone (Lundblad et al., 2002, Olanow et al., 2004, Dekundy et al., 2007), 8-OHDPAT (Tomiyama et al., 2005, Iravani et al., 2006, Dupre et al., 2008b, Bishop et al., 2009), tandospirone (Kannari et al., 2002) and piclozotan (Tani et al., 2010) that have been shown to be effective in reducing dyskinesia in patients and in experimental animal models. Despite the early success of several 5-HT_{1A} agonists, this class of compounds has not always favorably translated to PD patients or has been associated with worsening of extrapyramidal PD symptoms (Kannari et al., 2002, Goetz et al., 2007). It has been suggested that the high affinity of 5-HT_{1A} agonists, like sarizotan, for the D_2 receptor is responsible for the exacerbation of extra-pyramidal symptoms (Bartoszyk et al., 2004). Fortunately, it has been firmly established that BMY-14802 does not bind with high affinity to the D_1 or D_2 receptor (IC50s > 1,000 and 6,430 nM, respectively; Yevich et al., (1992).

To exclude the possibility that the anti-dyskinetic efficacy of BMY-14802 was due to an attenuation of L-DOPA's efficacy we examined the effect of BMY-14802 on motor improvement provided by L-DOPA administration using the FAS test. In this test, DA-lesioned animals exhibit significant deficits in stepping that are reversed by L-DOPA administration (Chang et al., 1999, Winkler et al., 2002). In the present study it was observed that DA-lesioned animals exhibited a 65% reduction in performance with their lesioned forelimb compared to the intact side and stepping improved when rats were treated with L-DOPA. While BMY-14802 treatment alone did not alter stepping, it did not significantly worsen motor performance compared to vehicle treated animals. Most importantly, BMY-14802, when co-administered with L-DOPA, did not hinder the improvement in stepping produced by L-DOPA.

Our results suggest that BMY-14802 at the dose tested provides anti-dyskinetic relief without reducing anti-parkinsonian efficacy. The FAS test measures the ability to initiate movement in response to a somatosensory stimulus. Since we did not measure spontaneous movement in this study, we cannot exclude the possibility that BMY-14802 might have affected unsolicited movement; however, previous research in mice found that 10 mg/kg BMY-14802 did not affect movement in motion chambers (Kamei et al., 1994). Additionally, doses up to 30 mg/kg did not cause catalepsy in rats (Matthews et al., 1986) suggesting that our lower doses of BMY-14802 were not precipitating parkinsonian features. This said, it is important to be cautious when employing 5-HT agonists since this class of compounds are known to be produce "serotonin-syndrome"-like symptoms (Kaneda et al., 2001, Bijl, 2004). This was observed in the current study at the highest dose of BMY-14802 (20 mg/kg) where rats transiently (~30 min) exhibited flat-body posture.

Another important goal of this study was to characterize the effect of BMY-14802 on dyskinesias produced by direct DA receptor agonists. Experimental evidence suggests that stimulation of 5-HT_{1A} receptors may influence dyskinetic behavior produced by activation of downstream DA receptors, independent of raphe striatal mechanisms (Iravani et al., 2006, Matsubara et al., 2006, Marin et al., 2009). To evaluate potential anti-dyskinetic efficacy of BMY-14802 against DA agonists, we employed SKF81297 and quinpirole, direct D_1 & D_2 agonists respectively, at doses known to produce equivalent AIMs (Dupre et al., 2007). Both D_1 and D_2 receptors have been implicated in development and expression of LID (Boyce et al., 1990, Elliott et al., 1992), and the administration of D_1 or D_2 antagonists have been demonstrated to block LID (Grondin et al., 1999, Taylor et al., 2005). Most importantly, both D_1 and D_2 agonists are known to produce dyskinesia in both clinical and experimental models of PD (Rascol et al., 2001, Monville et al., 2005, Delfino et al., 2007, Dupre et al., 2007). In the current study, it was observed that BMY-14802 reduced all the types of

dyskinesias, namely axial, limb and orolingual, produced by both D1 and D2 agonists in a dose-dependent manner. Interestingly, contralateral rotations produced by the D1 agonist, SKF82197, were not affected by BMY-14802, whereas, BMY-14802 was able to block contralateral rotations produced by the D2 agonist, quinpirole. The meaning of contralateral rotations remains a matter of debate. Drug-induced rotations are highly-variable between subjects and are not necessarily correlated with striatal DA depletion (Chang et al., 1999). Some research suggests that rotations are a reasonable, though perhaps less useful, proxy of dyskinesia (Cenci & Lundblad, 2007). This is supported by findings that, relative to a therapeutic dose of L-DOPA, a high L-DOPA dose produces increased ALO AIMs, rotations and striatal Δ-fosB expression (a molecular marker of dyskinesia) even while providing the same level of antiparkinsonian benefit (Smith et al., 2012). Other research indicates that rotations reflect antiparkinsonian efficacy (Lane et al., 2006) as some compounds that relieve PD symptoms produce contralateral rotations without dyskinesia (e.g. bromocriptine: Lundblad et al., 2002). The present findings support the former hypothesis that rotations are a better indicator of dyskinesia since both ALO AIMs and rotations evoked by L-DOPA or quinpirole were strongly suppressed by BMY-14802. By contrast, in the SKF81297 experiment where BMY-14802 had only a small impact on AIMs, there was no significant reduction in contralateral rotations.

In accordance with previous findings by Paquette and colleagues (2009), the anti-dyskinetic effects of BMY-14802 against LID were reversed by the 5-HT_{1A} antagonist, WAY-100635. Interestingly, WAY-100635 was unable to reverse BMY-14802 mediated reduction of dyskinesias produced by direct DA receptor agonists, SKF81297 and quinpirole, suggesting that these anti-dyskinetic effects are at least in part 5-HT_{1A} receptor independent. While the mechanism(s) of BMY-14802's anti-dyskinetic action against direct DA agonists remains unclear, it also acts as a D4 receptor antagonist (Newman-Tancredi et al., 1997). This property of BMY-14802 could have contributed towards its anti-dyskinetic effects against direct DA receptor agonist induced dyskinesias (Huot et al., 2012). Additionally, BMY-14802 exhibits affinity for sigma receptors where it is known to act as an antagonist (Paquette et al., 2008).

Although BMY-14802's sigma receptor-mediated contribution towards LID was refuted (Paquette et al., 2009) it still remains to be known if BMY-14802's actions at the sigma receptor play a role in its attenuation of dyskinesias induced by direct DA agonists. Interestingly, recent research indicates that activation of sigma receptors results in amplification of D1 receptor agonist induced signaling (Fu et al., 2010), a known aberrant mechanism underlying dyskinesia. Finally, stimulation of sigma receptors is known to modulate the release of glutamate (Lu et al., 2012), a neurotransmitter system involved with the expression of dyskinesia. How this contributed to BMY-14802 remains an open question.

In conclusion, BMY-14802 demonstrated anti-dyskinetic efficacy across a 4-fold dose range against LID and was also effective in reducing D_1 and D_2 receptor agonist-induced dyskinesias. Importantly, at anti-LID doses, BMY-14802 did not affect the efficacy of L-DOPA against lesion-induced akinesia. Additionally, advanced PD patients suffer from psychosis, and BMY-14802 is known to be an antagonist at the sigma-receptor, a receptor known to be involved in psychosis. In fact, BMY-14802 has been shown to be effective in animal models to treat psychosis suggesting that it may have value for treatment of non-motor PD symptoms as well. Taken together, through its actions at multiple receptor systems, BMY-14802 and similar compounds appear to be reasonable approaches towards improvement of DA replacement therapy in PD patients.

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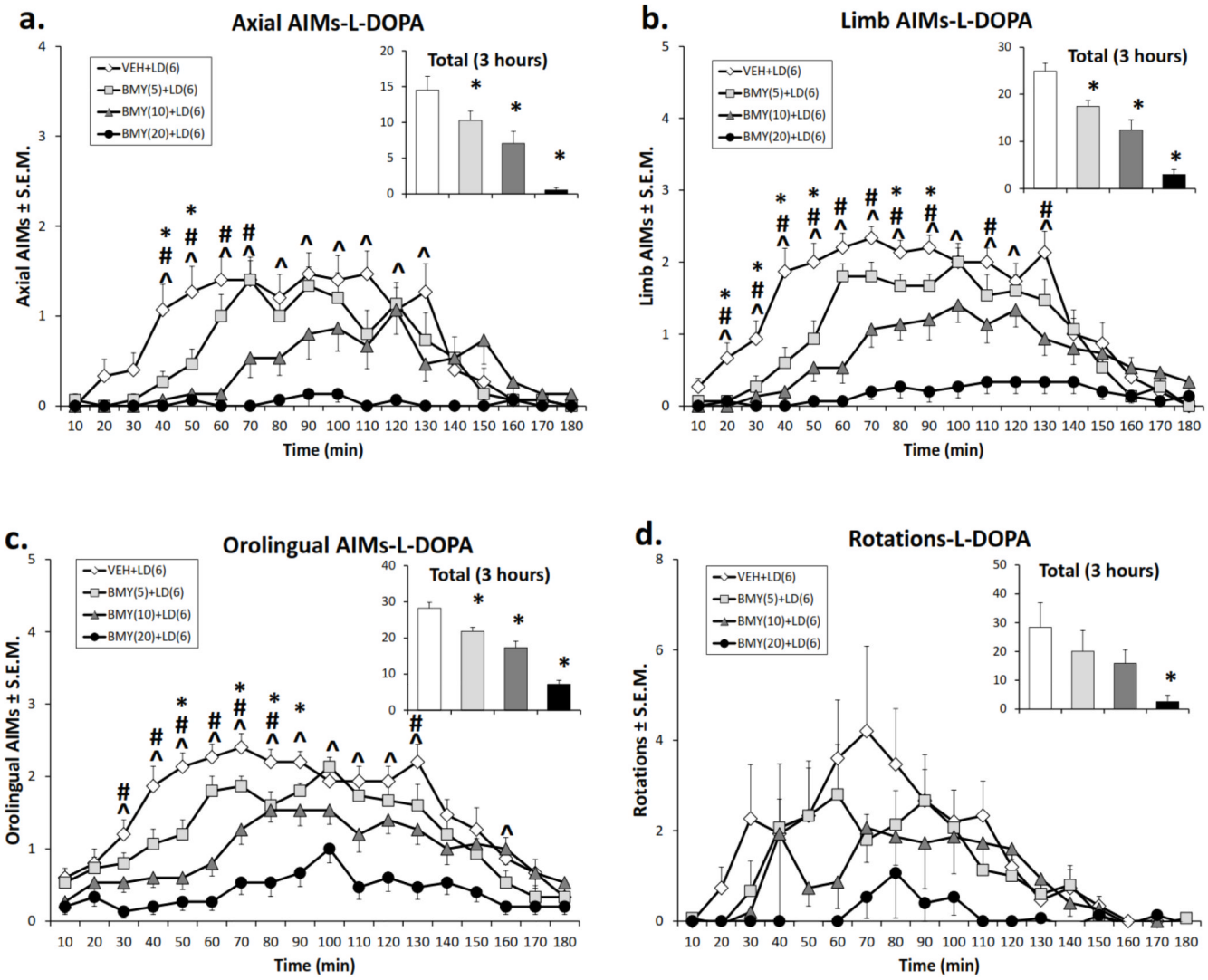

Fig. 1.

Effects of BMY 14802 on L-DOPA-induced a) axial, b) limb and c) orolingual Abnormal Involuntary Movements (AIMs), as well as d) rotations. Thirty minutes min after pretreatments with BMY-14802 (BMY; 5, 10, 20 mg/kg or VEH), rats (n = 13) received treatments with the L-DOPA (LD; 6 mg/kg, sc) Symbols demonstrate mean axial, limb and orolingual AIMs and rotations ± S.E.M. every 10 min over the 3 h sampling period immediately after LD. *p < 0.025 for BMY(5) + LD vs. VEH+LD, # p < 0.025 for BMY(10)+ LD vs. VEH+LD, ^p < 0.025 for BMY(20) vs. VEH+LD. For the inset graphs in panels a-d, bars denote the average axial, limb and orolingual AIMs and rotations ± S.E.M. for unilateral 6-OHDA-lesioned rats for the entire 3 h period after the L-DOPA injection. *p < 0.025 when compared vs.VEH+LD

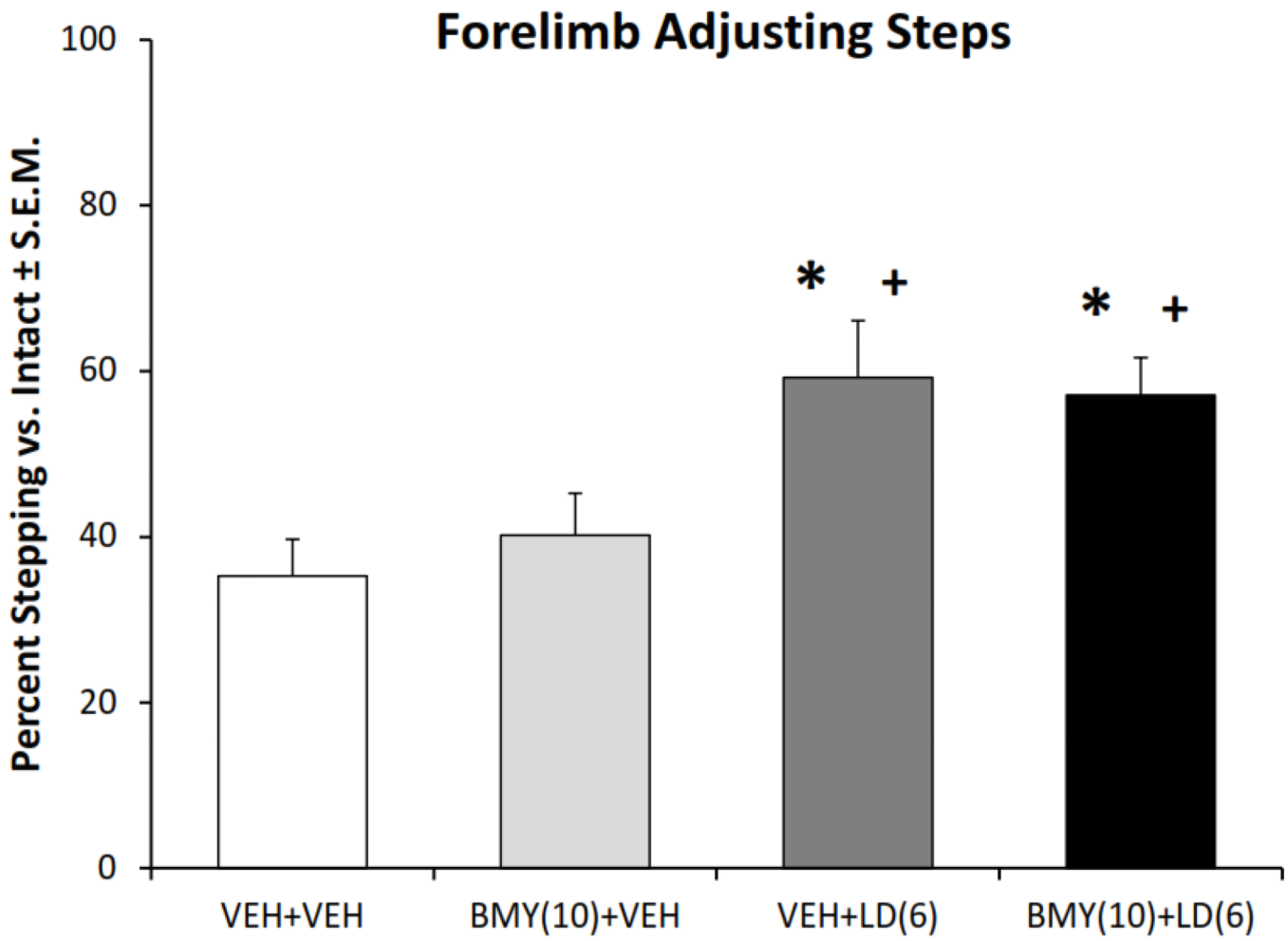

Fig. 2.

Effects of BMY-14802 and L-DOPA on forelimb adjusting steps at 30 min after pretreatments with BMY-14802 (BMY; 10 mg/kg or VEH) in a randomized within subjects design. Rats (n = 14) received treatments of L-DOPA (LD; 6 mg/kg, sc. or VEH) + benserizide (15 mg/kg, sc), leading to 4 treatment conditions (VEH+VEH, BMY-10+VEH, VEH+LD(6) and BMY-10+LD(6). Bars denote the average percent stepping in the lesioned forelimb compared to the intact forelimb ± S.E.M. for unilateral 6-OHDA-lesioned rats 60 min after the second injection. * $p < 0.025$ when compared with VEH+VEH; +$p < 0.025$ vs. BMY-10+VEH

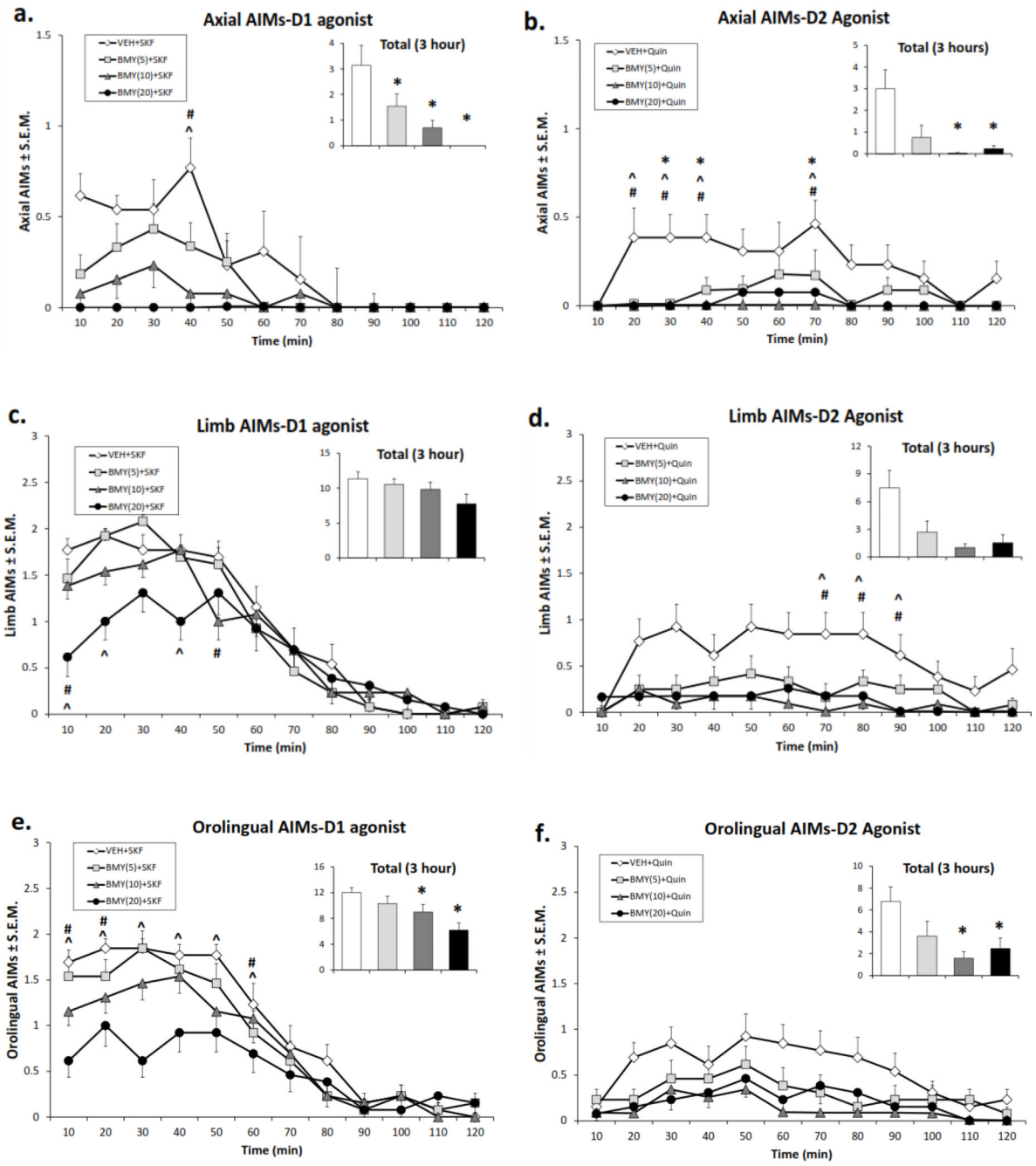

Fig. 3.

Effects of BMY-14802 on direct DA agonist-induced a) axial (a,b) b) limb (c,d) and c) orolingual (e,f) Abnormal Involuntary Movements (AIMs), as well as d) rotations (g,h). Thirty min after pretreatments with BMY-14802 (BMY; 5, 10, 20 mg/kg or VEH), rats (n = 13) received treatments with either the D1 receptor agonist SKF81297 (SKF; 0.08 mg/kg, sc) or the D2 receptor agonist quinpirole (Quin; 0.08 mg/kg, sc). Symbols demonstrate mean axial, limb and orolingual AIMs and rotations ± S.E.M. every 10 min over the 2 h sampling period immediately after SKF or Quin *$p < 0.025$ for BMY (5) + SKF vs. VEH+SKF or BMY (5) + Quin vs. VEH+Quin, # $p < 0.025$ for BMY (10) + SKF vs.VEH+SKF or BMY (10) + Quin vs.VEH+Quin, ^$p < 0.025$ for BMY (20) vs. VEH+SKF or BMY (20)+Quin vs.

VEH+Quin. For the inset graphs in panels a-h, bars denote the average axial, limb and orolingual AIMs and rotations ± S.E.M. for unilateral 6-OHDA-lesioned rats for the entire 3 h period after the SKF injection. *$p < 0.025$ when compared vs. VEH+SKF or VEH+Quin.

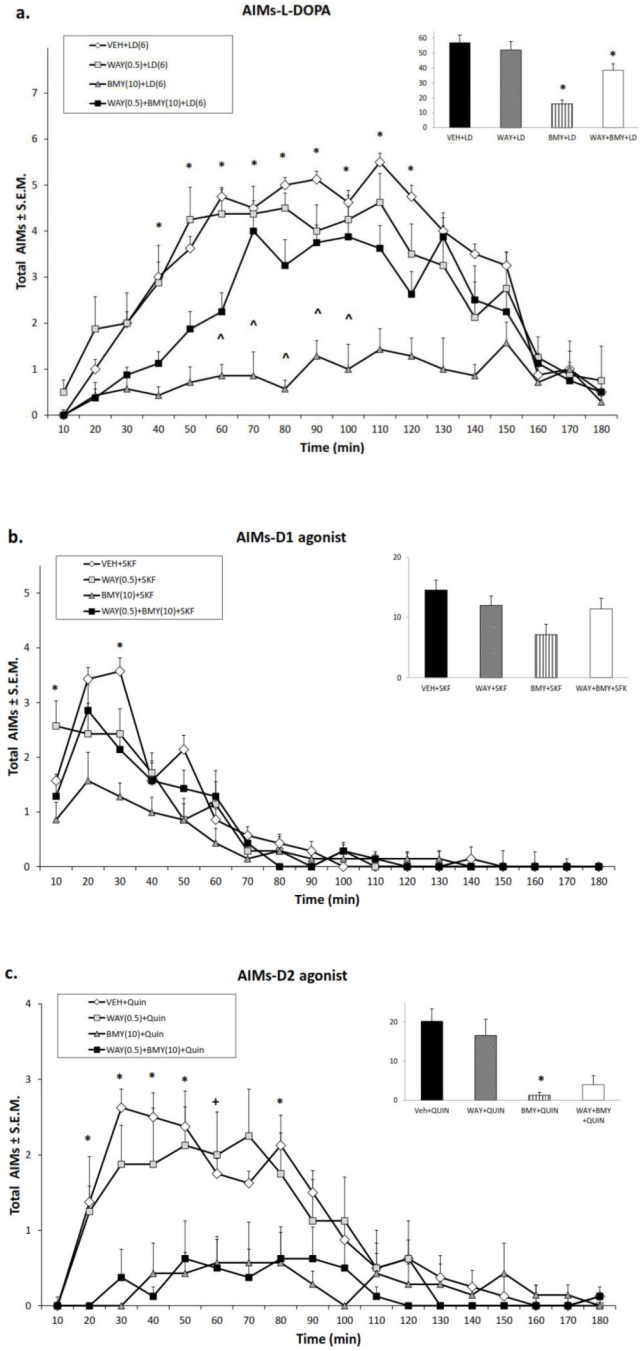

Fig. 4.

Effects of WAY-100635 on BMY-14802's anti-dyskinetic effects on a) L-DOPA b) D1 receptor agonist and c) D2 receptor agonist-induced Abnormal Involuntary Movements (AIMs). Thirty min after pretreatments with WAY-100635 (WAY; 0.5 mg/kg or VEH, sc), along with BMY-14802 (BMY; 10 mg/kg or VEH, sc), rats (n=8) received treatments with L-DOPA (LD; 6 mg/kg, sc. or VEH) + benserizide (15 mg/kg, sc), the D1 receptor agonist SKF81297 (SKF; 0.08 mg/kg, sc) or the D2 agonist quinpirole (Quin; 0.08 mg/kg, sc). Symbols demonstrate mean ALO AIMs ± S.E.M. every 10 min over the 3 h sampling period immediately after drug treatments. For the inset graphs in panels a-c, bars denote the average ALO AIMs ± S.E.M. for unilateral 6-OHDA-lesioned rats for the entire 3 h period.

*p < 0.025 for VEH+LD vs. BMY+LD; VEH+SKF vs BMY+SKF and VEH+Quin vs BMY +Quin. ^p < 0.025 for BMY+LD vs WAY+BMY+LD.