Psychopharmacology (2002) 163:85–94
DOI 10.1007/s00213-002-1121-3

ORIGINAL INVESTIGATION

Laurence Mignon · William A. Wolf

Postsynaptic 5-HT_{1A} receptors mediate an increase in locomotor activity in the monoamine-depleted rat

Received: 20 December 2001 / Accepted: 5 April 2002 / Published online: 13 July 2002

Abstract *Rationale:* In animal models of reduced dopamine transmission, such as haloperidol-induced catalepsy or monoamine-depleted animals, serotonin (5-hydroxytryptamine; 5-HT) 5-HT_{1A} agonists appear to enhance motor activity. However, the exact mechanism remains unclear. *Objective:* The objective of the present study was to demonstrate that 5-HT_{1A} agonists can increase locomotor activity by activation of postsynaptic 5-HT_{1A} heteroreceptors without the involvement of somatodendritic 5-HT_{1A} autoreceptors which are known to regulate 5-HT neuronal activity. *Methods:* The effects of the 5-HT_{1A} full agonist *R*-(+)-8-hydroxy-2-(di-*n*-propylamino)tertralin (*R*-(+)-8-OHDPAT) on locomotor activity in reserpinized (i.e., monoamine-depleted) rats were studied. *Results:* The present data demonstrate that *R*-(+)-8-OHDPAT significantly increased locomotor activity in monoamine-depleted animals at a dose as low as 0.01 mg/kg. The partial 5-HT_{1A} agonist/D_2 antagonist buspirone (3 mg/kg) also elevated locomotor activity. The effects of these 5-HT_{1A} compounds were found to be similar to the locomotor-stimulating effect of the dopamine precursor 3,4-dihydroxyphenylalanine (150 mg/kg, 15 min after 50 mg/kg benserazide). The 5-HT_{1A} antagonist *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinyl-cyclohexanecarboxamide maleate (WAY 100635; 0.2 mg/kg) blocked the *R*-(+)-8-OHDPAT (0.03 mg/kg)-mediated increase in locomotion. Blockade of 5-HT synthesis with DL-*p*-chlorophenylalanine (pCPA), a tryptophan hydroxylase inhibitor, prior to reserpinization did not affect *R*-(+)-8-OHDPAT-induced locomotion. *Conclusions:* The present data indicate that *R*-(+)-8-OHDPAT can increase motor activity in monoamine-depleted rats through postsynaptic 5-HT_{1A} receptors and not necessarily through 5-HT_{1A} autoreceptor-mediated alterations in 5-HT synthesis and release. A potential mechanism of 5-HT_{1A}-mediated modulation of non-monoaminergic motor circuits in the brain is discussed. Taken together, the results suggest that 5-HT_{1A} agonists would provide a novel approach to the amelioration of antipsychotic-induced side effects and the symptomatic treatment of Parkinson's disease.

Keywords Basal ganglia · 5-HT_{1A} agonist · 8-OHDPAT · Rat · Locomotor activity · Reserpine · Parkinson's disease

L. Mignon · W.A. Wolf (✉)
Department of Pharmacology and Experimental Therapeutics, Loyola University, Stritch School of Medicine, Maywood, IL 60153, USA
e-mail: wwolf@luc.edu
Tel.: +1-708-2028387
Fax: +1-708-2162319

W.A. Wolf
Departments of Research and Biological Psychiatry, Research Service-151, Hines VA Hospital, Hines, IL 60141, USA

Introduction

Serotonin (5-hydroxytryptamine, 5-HT) -containing neurons which originate in the midbrain (dorsal and median) raphe nuclei innervate numerous basal ganglia, thalamic and cortical structures involved in motor control. Within each terminal field, a variety of 5-HT receptor subtypes exist, each of which subserve distinct functions. As a result, 5-HT has complex actions with respect to control of motor activity. One observed action is the ability of 5-HT_{1A} receptor agonists to ameliorate motor deficits associated with reduced dopaminergic transmission. For example, 5-HT_{1A} agonists such as (±)-8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OHDPAT) have been shown to reverse catalepsy caused by dopamine receptor blockade (Hicks 1990; Neal-Beliveau et al. 1993; Andersen and Kilpatrick 1996; Wadenberg 1996) and to increase locomotor activity in animals rendered akinetic by the monoamine-depleting agent reserpine (Ahlenius et al. 1993; Ahlenius and Salmi 1995). These observations suggest that 5-HT_{1A} agonists might be useful in reducing motor side effects caused by antipsychotic drugs and in the symptomatic treatment of Parkinson's disease (PD). However, studies have shown that systemic administration of 5-HT_{1A} agonists can also decrease ambulatory motor activity (Hillegaart et al. 1989; Mittman and Geyer 1989). Moreover, at relatively high doses, 8-OHDPAT

and other 5-HT_{1A} agonists elicit stereotypical motor behavior, such as forepaw treading and flat body posture, which could interfere with coordinated locomotion (Hjorth et al. 1982; Glennon and Lucki 1988).

The variability in motor response to 5-HT_{1A} agonists in experimental animals appears to depend, in part, on the experimental paradigm as well as the dose of agonist employed (Tricklebank et al. 1984; Mittman and Geyer 1989; Hillegaart et al. 1989; Evenden and Angeby-Moller 1990; Hillegaart 1990). For example, animals' habituation to the test environment appears to affect the response to 8-OHDPAT. Systemic 8-OHDPAT suppresses locomotor activity in rats unhabituated to the test environment when observations are limited to within 25–60 min post-injection; i.e., during a phase of heightened exploratory activity (Hillegaart et al. 1989; Mittman and Geyer 1989; Evenden and Angeby-Moller 1990; Hillegaart 1990). However, Evenden and Angeby-Moller (1990) demonstrated that, after several hours of observation, when activity in control animals decreases, 8-OHDPAT-injected animals exhibited hyperactivity. These same authors also demonstrated that 8-OHDPAT elicited only an increase in locomotor activity in rats that had been habituated to the test cage for 2 h prior to drug injection. In apparent contradistinction is the study of Mittman and Geyer (1989), in which 8-OHDPAT reduced locomotor activity regardless of whether animals were tested in a familiar or novel environment. However, in these studies, the injection of 8-OHDPAT always occurred prior to placing the animal in the test chamber, raising the possibility that on the test day these animals were not as habituated to the test chamber as those in the study of Evenden and Angeby-Moller (1990). Habituation appears to have a more profound effect on the motor response to 8-OHDPAT than the time of day of testing since similar results were found in unhabituated rats regardless of whether they were tested during the light phase of their light/dark cycle (Evenden and Angeby-Moller 1990) or during the dark phase (Hillegaart et al. 1989; Mittman and Geyer 1989; Hillegaart 1990).

Differences in methodology may result in the differential involvement of somatodendritic 5-HT_{1A} autoreceptors and postsynaptic 5-HT_{1A} receptors. 5-HT_{1A} autoreceptors are located on the 5-HT cell soma and dendrites in the midbrain raphe nuclei where they act to reduce 5-HT synthesis and neuronal activity, thereby reducing serotonergic transmission in terminal fields of these neurons. Postsynaptic 5-HT_{1A} receptors are located on neurons in 5-HT terminal fields throughout the forebrain. Regions involved in motor control which express moderate density of postsynaptic 5-HT_{1A} receptors in the forebrain include the cerebral cortex (especially layer V), reticular thalamic nucleus and centromedial thalamic nucleus (Pompeiano et al. 1992; Wright et al. 1995).

Given this information, an important question to answer is whether the motor-activating effects of 5-HT_{1A} agonists in DA deficient animals are mediated via activation of 5-HT_{1A} somatodendritic autoreceptors which would reduce 5-HT neurotransmission throughout the brain or via stimulation of postsynaptic 5-HT_{1A} receptors. Micro-injection of the 5-HT_{1A} agonist 8-OHDPAT into the median (and possibly dorsal) raphe has been shown to reverse catalepsy caused by DA D_2 receptor blockade by either haloperidol or raclopride (Invernizzi et al. 1988; Elliott et al. 1990; Wadenberg and Hillegaart 1995). These data would suggest a presynaptic site of action. However, the ability of 8-OHDPAT to reverse haloperidol-induced catalepsy in animals which have had 5-HT synthesis inhibited by the tryptophan hydroxylase inhibitor *p*-chlorophenylalanine (pCPA) led Neal-Beliveau et al. (1993) to suggest that postsynaptic 5-HT_{1A} receptors are also involved. In the reserpinized or "monoamine-depleted" rat, 8-OHDPAT can increase locomotor activity (Ahlenius et al. 1993; Ahlenius and Salmi 1995), but there has been no attempt to determine whether this effect is pre- or postsynaptically mediated. This question is relevant for two reasons. First, Kuhn et al. (1985) have shown that a functional pool of newly synthesized 5-HT remains available for release in reserpinized animals. Thus, the motor effects of 8-OHDPAT could be mediated by alterations in 5-HT transmission. Second, the direct involvement of postsynaptic 5-HT_{1A} receptors in mediating increased motor activity in the "monoamine-depleted" rat may provide further insight into non-monoaminergic neurochemical pathways involved in motor control and suggest potential avenues for symptomatic treatment of PD and reducing the motor side effects of antipsychotic agents.

The present study examined the effects of the full 5-HT_{1A} agonist *R*-(+)-8-OHDPAT on locomotion in the monoamine-depleted rat model to determine whether motor effects elicited by this drug were mediated by stimulation of presynaptic (i.e., somatodendritic) 5-HT_{1A} receptors or postsynaptic 5-HT_{1A} receptors. The results indicate that the locomotor-stimulating effects of *R*-(+)-8-OHDPAT are mediated by postsynaptic 5-HT_{1A} receptors and are not the result of altered 5-HT synthesis and release. The significance of these results with respect to 5-HT_{1A}-mediated modulation of activity within non-monoaminergic motor circuits of the brain is discussed.

Materials and methods

Animals and animal treatment

Adult male Sprague-Dawley rats (250–300 g; Harlan Sprague-Dawley, Indianapolis, Ind.) were used throughout the study. The animals were acclimated to the animal facility at least 7 days before use. They were housed three per cage and maintained on a 12-h/12-h light/dark cycle (lights on at 0600 hours). Food and water were available ad libitum. All behavioral testing took place between 0900 hours and 1200 hours under normal laboratory lighting. Prior to drug challenge and assessment of locomotor activity, all animals were allowed to acclimate to the test cage for 1 h. Following subcutaneous injection of test drugs, locomotor activity was measured for 1 h.

In the first experiment, a dose–response of the motor effects of *R*-(+)-8-OHDPAT was established in reserpinized rats. All animals

received 5 mg/kg reserpine subcutaneously. The locomotor activity of animals was measured 16–20 h post-reserpine treatment following a challenge injection with either vehicle (physiological saline containing 0.02% ascorbate) or *R*-(+)-8-OHDPAT (0.01–0.1 mg/kg). As the onset of 5-HT_{1A} agonist action was apparent within several minutes (by observing lower-lip retraction), assessment of locomotor activity began 2 min following *R*-(+)-8-OHDPAT. Two identical dose–response experiments were carried out approximately 4 months apart (representing the first and next-to-last study of the project) in order to verify that seasonal and animal-lot variation did not influence the data. Seven rats per group were originally employed and a two-way analysis of variance (ANOVA; treatment × month) following rank-order transformation of the data established that there were no significant differences in motor response to *R*-(+)-8-OHDPAT between the two experiments (treatment × month interaction F=0.379, P=0.77). Thus, the data were pooled, re-analyzed using one-way ANOVA and presented as one dose–response experiment (n=12–14 animals per group).

For comparison, in a separate experiment, the dose–response of the motor effects of *R*-(+)-8-OHDPAT was established in non-reserpinized rats. The dose range (0.03–1.0 mg/kg) was chosen from the literature. These animals were administered vehicle (0.5 M citric acid) 16–20 h prior to testing. On the day of testing, animals were allowed to acclimate for 1 h and then challenged with either vehicle (physiological saline containing 0.02% ascorbate) or *R*-(+)-8-OHDPAT (0.03–1.0 mg/kg). Two minutes after injection, locomotor activity was scored for 1 h. Five animals per group were employed.

In the next set of experiments, two other compounds were independently tested for their motor effects in reserpinized rats. All animals received 5 mg/kg reserpine subcutaneously. The locomotor activity of animals was measured 16–20 h post-reserpine treatment following challenge injection with active drug or vehicle. Following 1 h of acclimation, the 5-HT_{1A} agonist buspirone (3 mg/kg) or vehicle (physiological saline) was administered. As the onset of 5-HT_{1A} agonist actions was apparent within several minutes (by observing lower-lip retraction), assessment of locomotor activity began 2 min following buspirone. Five animals per group were employed. In a separate experiment, the dopamine precursor L-dihydroxyphenylalanine (L-DOPA; 150 mg/kg, 15 min following 50 mg/kg benserazide) was tested as a reference compound since its locomotor effects in reserpinized rats have been widely studied (Klockgether and Turski 1990; Skuza et al. 1994; Starr et al. 1997; Fisher et al. 2000). Benserazide is an inhibitor of L-aromatic amino acid decarboxylase and, at the dose employed, is used to block peripheral conversion of L-DOPA to dopamine. Animals were allowed to acclimate for 1 h and were then administered benserazide or vehicle (saline containing 0.02% ascorbate). Fifteen minutes later, L-DOPA or vehicle (saline containing 0.02% ascorbate) was administered. As the onset of L-DOPA-mediated locomotion has been observed to occur more slowly (Lotti and Porter 1970), assessment of locomotor activity commenced 30 min post-L-DOPA injection and lasted 1 h. In this experiment, six animals per group were used. Data from these two experiments were analyzed independently using the Mann-Whitney rank sum test.

In the next experiment, the ability of the 5-HT_{1A} antagonist *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinyl-cyclohexanecarboxamide maleate (WAY 100635; 0.2 mg/kg) to block the motor effects of a maximal dose of *R*-(+)-8-OHDPAT (0.03 mg/kg) was tested in reserpinized animals. Animals received 5 mg/kg reserpine subcutaneously. The locomotor activity of animals was measured 16–20 h post-reserpine treatment. Four groups of animals receiving either vehicle + vehicle, WAY 100635 + vehicle, vehicle + *R*-(+)-8-OHDPAT, or WAY 100635 + *R*-(+)-8-OHDPAT were tested. In all groups, physiological saline containing 0.02% ascorbate served as vehicle. WAY 100635 (or vehicle) was administered after 1 h of acclimation and 15 min prior to *R*-(+)-8-OHDPAT. Two minutes after *R*-(+)-8-OHDPAT injection, assessment of locomotor activity commenced and lasted for 1 h. Five animals per group were employed.

In the last experiment, 36 animals (9 animals per group) were employed. Half of the animals were pretreated with the tryptophan hydroxylase inhibitor pCPA (250 mg/kg) 2 days prior to reserpine treatment. The other half of the animals were given vehicle (saline containing 0.02% ascorbate) in place of pCPA followed by reserpine 2 days later. All animals received 5 mg/kg reserpine. The locomotor activity of these rats was tested 16–20 h post-reserpine following an injection of 0.03 mg/kg *R*-(+)-8-OHDPAT or vehicle (saline containing 0.02% ascorbate) essentially as described above for the dose–response experiment. For biochemical assessment of the effects of pCPA, animals were killed by decapitation after the behavioral tests. Their brains were quickly removed and dissected on a chilled alumina plate. Frontal cortex was obtained by making a coronal cut just rostral to the caudate [3 mm anterior to bregma according to Paxinos and Watson (1986)]. The cortical lobes were then dissected free from the remainder of the brain. Striatum was obtained by free dissection from the remainder of the brain. Tissues were immediately frozen on dry ice and stored at –80°C until processed. All animal care and experimentation were carried out in accordance with the NIH *Guide for the Care and Use of Laboratory Animals* and were approved by the Hines/Loyola Institutional Animal Care and Use Committee.

Drugs

Reserpine, DL-*p*-chlorophenylalanine hydrochloride methylester (pCPA), *R*-(+)8-hydroxy-2-(di-*n*-propylamino)tetralin HBr (8-OHDPAT), *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinyl-cyclohexanecarboxamide maleate (WAY-100635 maleate), L-dihydroxyphenylalanine methyl ester hydrochloride (L-DOPA), buspirone and benserazide were purchased from Sigma Chemical Co. (St. Louis, Mo.). Reserpine was dissolved in 0.5 M citric acid. *R*-(+)-8-OHDPAT was first dissolved in a 2% ascorbic acid/saline solution to make up a 1-mg/ml solution. This solution was then diluted as required to obtain solutions of 0.01–1.0 mg/ml. WAY 100635 and pCPA were dissolved in a 2% ascorbic acid/saline solution. All other drugs were dissolved in physiological saline. All drugs and appropriate vehicle solutions were administered subcutaneously in a 1-ml/kg volume, except pCPA which was given as 2 ml/kg. All doses refer to the free compound.

HPLC assessment of 5-HT and 5-hydroxyindoelacetic acid

The frontal cortex and the striatum were homogenized in approximately ten volumes of homogenization buffer [0.16 M $HClO_4$, 0.5 mM ethylene diamine tetraacetic acid (EDTA), 0.04 ng/µl 2,3-dihydroxybenzoic acid (DHBA) as internal standard]. Homogenates were then centrifuged for 10 min at 18,000 *g*. The supernatant of each sample was diluted twofold with deionized water and 50 µl injected on the high-performance liquid chromatography (HPLC) machine. Chromatographic conditions and electrochemical detection were carried out using a method adapted from Wolf and Bobik (1989). The mobile phase consisted of 25 mM trisodium citrate, 25 mM monobasic sodium phosphate containing 250 µM EDTA, 6% acetonitrile, 4 mM heptane sulfonic acid and was brought to pH 3.4 with phosphoric acid. The stationary phase was an Ultrasphere ODS 5-µm column (25 cm×4.6 mm i.d.; Beckman Instruments, Calif.). The flow rate was set at 0.9 ml/min. A glassy carbon electrode set at a working potential of +0.675 against a Ag/AgCl reference electrode was used for detection (LC-4C detector; Bioanalytical Systems, Ind.). Quantification was carried out by comparing peak heights in samples with standard peak heights.

Locomotor activity measurements

Locomotor activity was measured in a rectangular Plexiglas cage (25×45×20 cm) outfitted with a bank of 15 infrared emitters and sensors spaced 3 cm apart and situated 3 cm above the floor of the cage (Opto-Varimex Mini, Columbus, Ohio). With this apparatus,

ambulatory activity represents the number of photobeam interruptions exclusive of repeated interruptions of a single photobeam. Thus, repetitive stereotyped behavior by an animal sitting in place is not counted in the ambulatory activity. The locomotor measurements were performed under normal laboratory lighting in a ventilated and sound-attenuating room between 0900 hours and 1400 hours.

Data analysis

Ambulatory activity data were statistically analyzed using non-parametric statistical tests due to the non-homogeneity of variance around the different treatment means (i.e., vehicle-treated animals did not move). For experiments with more than two treatment groups (e.g., dose–response data), Kruskal-Wallis one-way ANOVA on ranks was performed. Post-hoc comparisons against control were performed using Dunnett's test (or Dunn's test in the case of unequal sample sizes). For analysis of two treatment groups, a Mann-Whitney rank sum test was performed. To determine the significance of drug pretreatment (e.g., WAY 100635 or PCPA) on the motor response to *R*-(+)-8-OHDPAT a two-way ANOVA was performed following rank-order transformation of the data.

Results

Effects of *R*-(+)-8-OHDPAT on locomotor activity in reserpinized animals

The hypokinetic state induced by reserpine was significantly reversed by the full 5-HT_{1A} agonist *R*-(+)-8-OHDPAT (Fig. 1A). At doses ranging between 0.01 mg/kg and 0.1 mg/kg (s.c.), *R*-(+)-8-OHDPAT significantly increased locomotor activity in monoamine-depleted animals when compared with vehicle ($P<0.05$). Maximal locomotor activity was seen at 0.03 mg/kg with no further increase evident at 0.1 mg/kg *R*-(+)-8-OHDPAT. Other behavioral signs of 5-HT_{1A} receptor activation, such as flat body posture and lower-lip retraction, were evident in reserpinized animals at all doses, although these were not quantified. At 0.1 mg/kg, *R*-(+)-8-OHDPAT also elicited discontinuous forepaw treading which may have interfered with ambulatory activity. The time course for the *R*-(+)-8-OHDPAT-mediated increase in locomotion showed that, at all doses, the greatest locomotor stimulation occurred within the first 10 min and remained significantly elevated relative to vehicle throughout the 30 min post-injection (Fig. 1B). Moreover, activity in animals receiving 0.03 mg/kg or 0.1 mg/kg *R*-(+)-8-OHDPAT was significantly elevated throughout the 60 min of observation.

Effects of *R*-(+)-8-OHDPAT on locomotor activity in non-reserpinized animals

A dose–response relationship of *R*-(+)-8-OHDPAT was also performed in non-reserpinized animals in order to compare the potency and efficacy of this drug on locomotion between reserpinized and non-reserpinized animals. A significant increase in locomotor activity was seen at 0.3 mg/kg and 1.0 mg/kg (s.c.) *R*-(+)-8-OHDPAT (Fig. 2A). These doses are 30- to 100-fold higher than the dose required to significantly increase activity in reserpinized animals (Fig. 1A). It should be noted that the absolute magnitude of motor response in non-reserpinized animals is greater than that observed for reserpinized animals (Fig. 2A and Fig. 1A). In non-reserpinized animals, locomotor activity was significantly elevated by all doses of *R*-(+)-8-OHDPAT within the first 10 min of observation. In contrast to reserpinized animals, locomotor activity was no longer significantly elevated by any dose of *R*-(+)-8-OHDPAT by 60 min (Fig. 2B). All animals exhibited lower-lip retraction within the first 2 min following *R*-(+)-8-OHDPAT injection while flat body posture as well as forepaw treading was most evident at the higher doses of *R*-(+)-8-OHDPAT (0.3 mg/kg and 1.0 mg/kg).

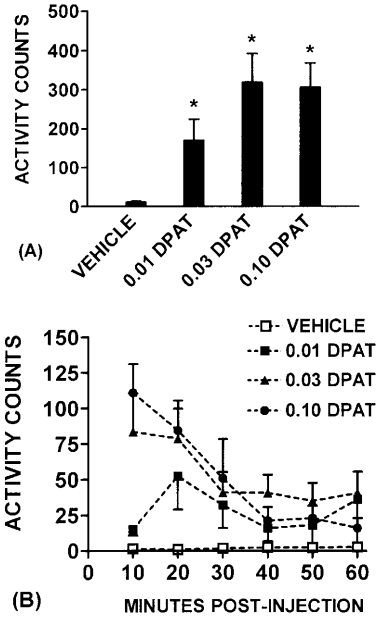

Fig. 1A, B Effects of *R*-(+)-8-hydroxy-2-(di-*n*-propylamino)tertralin (*R*-(+)-8-OHDPAT) on ambulatory locomotor activity in reserpinized rats. **A** Total ambulatory activity during the 60-min observation period. Doses of *R*-(+)-8-OHDPAT (*DPAT*; mg/kg) were administered 2 min prior to start of observation. Data represent the mean±SEM of 12–14 animals per group. Data were analyzed using Kruskal-Wallis one-way ANOVA on ranks with post-hoc comparison against control (*vehicle*) using Dunn's test. (* significantly different from vehicle, $P<0.05$). **B** Time course of R-(+)-8-OHDPAT (*DPAT*) effects on locomotor activity. Data represent the activity counts observed in each 10-min interval during the 60-min period represented in **A** above. Data were analyzed using two-way ANOVA (treatment × time) following rank order transformation of data. Significant treatment ($P<0.001$), time ($P<0.001$) and interaction ($P=0.003$) effects were found. Post-hoc comparisons against control (*vehicle*) were carried out using Dunnett's test. 0.03 mg/kg DPAT and 0.1 mg/kg DPAT were significantly greater than vehicle at all time points ($P<0.05$). 0.01 mg/kg DPAT was significantly greater than vehicle at 10, 20, and 30 min ($P<0.05$)

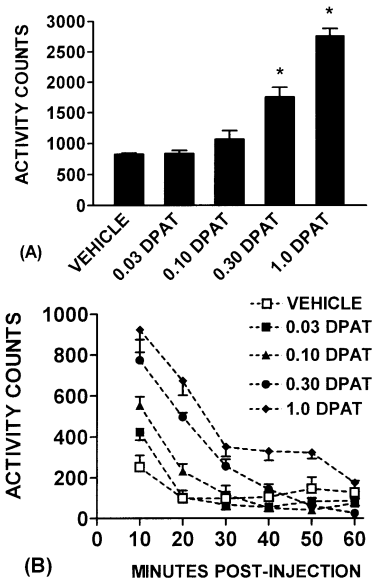

Fig. 2A, B Effects of *R*-(+)-8-hydroxy-2-(di-*n*-propylamino)tertralin (*R*-(+)-8-OHDPAT) on ambulatory locomotor activity in non-reserpinized rats. **A** Total ambulatory activity during the 60-min observation period. Doses of *R*-(+)-8-OHDPAT (*DPAT*; mg/kg) were administered 2 min prior to the start of observation. Data represent the mean±SEM of five animals per group. Data were analyzed using the Kruskal-Wallis one-way ANOVA on ranks with post-hoc comparison against control (*vehicle*) using Dunnett's test. (* significantly different from vehicle, $P<0.05$). **B** Time course of *R*-(+)-8-OHDPAT (*DPAT*) effects on locomotor activity. Data represent the activity counts observed in each 10-min interval during the 60-min period represented in **A** above. Data were analyzed using two-way ANOVA (treatment × time) following rank order transformation of data. Significant treatment ($P<0.001$), time ($P<0.001$) and interaction ($P<0.001$) effects were found. Post-hoc comparisons against control (*vehicle*) were carried out using Dunnett's test (significance set at $P<0.05$). Activity following 0.03 mg/kg DPAT was significantly greater than vehicle at 10 min only. Activity following 0.1 mg/kg DPAT was significantly greater than vehicle at 10 min and 20 min. Activity following 0.3 mg/kg DPAT was significantly greater than vehicle at 10, 20, and 30 min. Activity following 1.0 mg/kg DPAT was significantly greater than vehicle at 10, 20, 30, 40, and 50 min

Effect of buspirone and L-DOPA on locomotor activity in reserpinized animals

The partial 5-HT_{1A} agonist buspirone was also tested for its ability to increase locomotor activity in reserpinized rats. Buspirone (3 mg/kg, s.c.), significantly increased locomotor activity in reserpinized animals relative to vehicle-challenged reserpinized animals ($P<0.05$; Fig. 3A). The extent of activity was somewhat less than the maximal effect seen with *R*-(+)-8-OHDPAT (Fig. 1A). By comparison, treatment of reserpinized rats with L-DOPA (150 mg/kg, s.c., 15 min following 50 mg/kg benserazide) elicited locomotor activity to a similar extent as seen with 0.03 mg/kg *R*-(+)-8-OHDPAT (Fig. 3B and Fig. 1A).

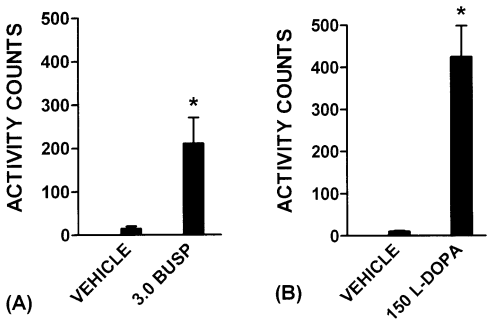

Fig. 3A, B Effects of buspirone or 3,4-dihydroxyphenylalanine (L-DOPA) on ambulatory locomotor activity in reserpinized rats. **A** Total ambulatory activity during the 60-min observation period following buspirone. Buspirone (3 mg/kg) was administered 2 min prior to the start of observation. Data represent the mean±SEM of five animals per group. Data were analyzed using the Mann-Whitney rank sum test (* significantly different from vehicle, $P=0.008$). **B** Total ambulatory activity during the 60-min observation period following L-DOPA. Benserazide (50 mg/kg) was administered 45 min prior to the start of observation and L-DOPA (150 mg/kg) was administered 30 min prior to the start of observation. Data represent the mean±SEM of six animals per group. Data were analyzed using the Mann-Whitney rank sum test (* significantly different from vehicle, $P=0.002$)

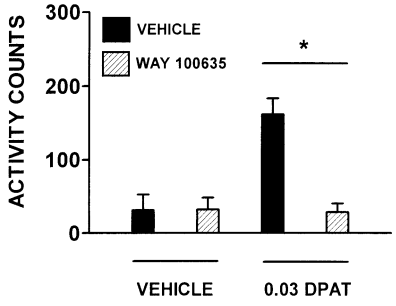

Fig. 4 Effects of the 5-HT_{1A} antagonist *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinyl-cyclohexanecarboxamide maleate (WAY 100635) on *R*-(+)-8-hydroxy-2-(di-*n*-propylamino)tertralin (*R*-(+)-8-OHDPAT)-induced ambulatory locomotor activity in reserpinized rats. Total ambulatory activity during the 60-min observation period. WAY 100635 (0.2 mg/kg) or vehicle was administered 15 min prior to *R*-(+)-8-OHDPAT (0.03 mg/kg) or vehicle. Observation was started 2 min following *R*-(+)-8-OHDPAT. Data represent the mean±SEM of five animals per group. Data were analyzed using two-way ANOVA following rank order transformation of data with post-hoc comparison among treatment groups using the Student Newman-Keuls test (* significantly different from vehicle, $P<0.05$)

Effects of 5-HT_{1A} antagonism on *R*-(+)-8-OHDPAT-induced locomotor activity in reserpinized animals

The 5-HT_{1A} antagonist WAY 100635 (0.2 mg/kg, s.c.) by itself had no effect on locomotor activity in reserpinized rats (Fig. 4). However, WAY 100635 completely blocked the increase in locomotor activity caused by *R*-(+)-8-OHDPAT (0.03 mg/kg, s.c.; Fig. 4).

Effect of *R*-(+)-8-OHDPAT on levels of 5-HT and 5-hydroxyindoelacetic acid in reserpinized animals

There is evidence that release of newly synthesized cytoplasmic 5-HT can occur in reserpinized animals (Kuhn et al. 1985). Thus, it would be possible for *R*-(+)-8-OHDPAT to modulate 5-HT synthesis and release even in reserpinized animals. In order to determine whether *R*-(+)-8-OHDPAT influenced 5-HT synthesis and turnover in terminal fields, the levels of 5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) were measured in the frontal cortex and striatum in reserpinized rats 60 min after either *R*-(+)-8-OHDPAT (0.03 mg/kg; n=5) or vehicle (n=8). *R*-(+)-8-OHDPAT did not alter the levels of 5-HT in frontal cortex (30±4 pg/mg wet weight after vehicle and 28±2 pg/mg wet weight after *R*-(+)-8-OHDPAT) or striatum (57±7 pg/mg wet weight after vehicle and 54±5 pg/mg wet weight after *R*-(+)-8-OHDPAT). Similarly, 5-HIAA levels were unchanged following *R*-(+)-8-OHDPAT in reserpinized rats in frontal cortex (345±20 pg/mg wet weight after vehicle and 342±18 pg/mg wet weight after *R*-(+)-8-OHDPAT) and striatum (730±30 pg/mg wet weight after vehicle and 750±20 pg/mg wet weight after *R*-(+)-8-OHDPAT).

Effects of 5-HT synthesis inhibition on *R*-(+)-8-OHDPAT-induced locomotor activity in reserpinized animals

Pretreatment with the tryptophan hydroxylase inhibitor pCPA was carried out to block 5-HT synthesis and preclude any actions of *R*-(+)-8-OHDPAT on 5-HT neuronal activity and release via 5-HT_{1A} somatodendritic autoreceptors. Analysis of 5-HT and 5-HIAA was carried out in pCPA pretreated, reserpinized animals given vehicle and *R*-(+)-8-OHDPAT. Levels of 5-HT in all pCPA pretreated, reserpinized animals fell to undetectable levels (<0.8 pg/mg wet weight) in frontal cortex and striatum (n=8 per group). Levels of 5-HIAA were undetectable in frontal cortex (<0.8 pg/mg wet weight). In the striatum, 5-HIAA levels were detected in six animals and averaged 15.6±6.0 pg/mg wet weight. Despite blocking 5-HT synthesis and further depleting animals of 5-HT, pCPA pretreatment had no effect on *R*-(+)-8-OHDPAT-mediated activity (Fig. 5).

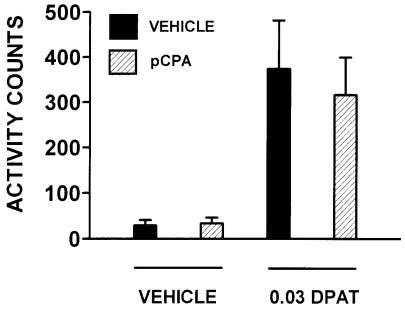

Fig. 5 Effects of the tryptophan hydroxylase inhibitor DL-*p*-chlorophenylalanine (pCPA) on *R*-(+)-8-hydroxy-2-(di-*n*-propylamino)tertralin (*R*-(+)-8-OHDPAT)-induced ambulatory locomotor activity in reserpinized rats. Total ambulatory activity during the 60-min observation period. pCPA (250 mg/kg) or vehicle was administered 48 h prior to reserpine (5 mg/kg). *R*-(+)-8-OHDPAT (0.03 mg/kg) or vehicle was administered 16–20 h following reserpine administration. Observation was started 2 min following *R*-(+)-8-OHDPAT. Data represent the mean±SEM of 7–9 animals per group. Data were analyzed using two-way ANOVA following rank order transformation of data

Discussion

The present results extend previous work by demonstrating that the full agonist *R*-(+)-8-OHDPAT increases locomotor activity in monoamine-depleted rats by activation of postsynaptic 5-HT_{1A} receptors. *R*-(+)-8-OHDPAT was used in place of the commonly used racemic (±)-8-OHDPAT to study the effects of 5-HT_{1A} agonists on motor activity in monoamine-depleted rats, because the (+)-isomer is reported to act as a full agonist at 5-HT_{1A} receptors whereas the (–)-isomer has been reported to have less than full efficacy (Cornfield et al. 1991; Yu et al. 1996; Lejeune et al. 1997). In addition, the partial agonist buspirone was tested and found to increase locomotor activity in monoamine-depleted rats although to a somewhat lesser degree. The specific involvement of 5-HT_{1A} receptors in mediating the locomotor response to *R*-(+)-8-OHDPAT was established through the use of the highly selective 5-HT_{1A} antagonist WAY 100635. The lack of involvement of somatodendritic 5-HT_{1A} autoreceptors regulating 5-HT neurotransmission was established by demonstrating that neither intact 5-HT stores nor newly synthesized 5-HT mediated the locomotor effects of *R*-(+)-8-OHDPAT.

In the present study, locomotor activity was significantly increased in monoamine-depleted rats at the lowest dose of *R*-(+)-8-OHDPAT tested (0.01 mg/kg) and appeared to reach a maximal level by 0.03 mg/kg (Fig. 1A). The high potency of *R*-(+)-8-OHDPAT to increase locomotor activity observed in the present study contrasts somewhat with the dose–response observed by Ahlenius and Salmi (1995) who employed the racemic (±)-8-OHDPAT in a dose range of 0.04 mg/kg–2.4 mg/kg (based on free compound). Racemic (±)-8-OHDPAT in the milligram per kilogram range has been shown to elicit behavioral and electrophysiological effects through direct activation of dopamine D_2 or D_3 receptors (Yu et al. 1996; Lejeune et al. 1997). Thus, a relatively high dose of racemic (±)-8-OHDPAT could increase locomotor activity by activating D_2 or D_3 receptors, especially if they were rendered supersensitive by reserpine-induced dopamine depletion. Ahlenius and Salmi (1995) appeared to rule out the involvement of D_2-like receptors by demonstrating that the D_2/D_3 antagonist raclopride did not alter the locomotor effects of 0.6 mg/kg (±)-8-OHDPAT in monoamine-depleted rats. In the present study, the potent effects of *R*-(+)-8-OHDPAT to increase locomotor activity suggest a lack of involvement of D_2/D_3 receptors since

radioligand binding studies have shown that *R*-(+)-8-OHDPAT exhibits selectivity for the 5-HT_{1A} receptor over the D_3 receptor and D_2 receptor of 400-fold and 2000-fold, respectively (Ki approximately 0.5 nM, 200 nM, 1100 nM for 5-HT_{1A}, D_3, D_2, respectively; Lejeune et al. 1997). Moreover, direct confirmation of a role for 5-HT_{1A} receptors was provided by the observation that the selective 5-HT_{1A} antagonist WAY 100635 completely blocked the motor effects of *R*-(+)-8-OHDPAT (Fig. 4).

The ability of the partial 5-HT_{1A} agonist buspirone (3 mg/kg), which is structurally different from *R*-(+)-8-OHDPAT, to also increase ambulatory locomotor activity in monoamine-depleted rats reinforces the potential for 5-HT_{1A} receptor agonists to stimulate locomotor activity in monoamine-depleted animals. In addition to being a partial 5-HT_{1A} agonist, buspirone has moderate affinity for the D_2 receptor where it functions as an antagonist (Cimino et al. 1983). Thus, at the dose employed (3 mg/kg), buspirone can be expected to stimulate 5-HT_{1A} receptors while antagonizing dopamine D_2 receptors (Rijnders and Slangen 1993; Piercey et al. 1994; Kleven et al. 1996). The magnitude of locomotor response to buspirone is somewhat lower than what was seen following *R*-(+)-8-OHDPAT. This could be due to the partial agonist properties of buspirone at 5-HT_{1A} receptors or the fact that a full dose–response was not carried out to determine maximal effect. That notwithstanding, the ability of buspirone, a 5-HT_{1A} agonist/D_2 antagonist, to increase locomotor activity in monoamine-depleted rats supports the conclusion that stimulation of 5-HT_{1A} receptors can increase ambulatory locomotion in the absence of dopaminergic (at least D_2-mediated) activity. Consistent with this conclusion is the well-documented observation that 5-HT_{1A} agonists reverse catalepsy induced by D_2 blockade (Hicks 1990; Neal-Beliveau et al. 1993; Andersen and Kilpatrick 1996; Wadenberg 1996).

For comparative purposes, the ambulatory locomotor activity-enhancing effect of the dopamine precursor L-DOPA (150 mg/kg) combined with benserazide (50 mg/kg; to block peripheral decarboxylase activity) was also tested. Consistent with previous studies using this dose regimen in reserpinized rats (Skuza et al. 1994; Starr et al. 1997; Fisher et al. 2000), L-DOPA significantly increased locomotor activity in reserpinized animals when compared with reserpinized animals given vehicle (Fig. 3B). The increase in ambulatory locomotion elicited by L-DOPA was similar in magnitude to what was observed following a maximal dose of *R*-(+)-8-OHDPAT (Fig. 1A and Fig. 3B). The comparable response magnitude observed following *R*-(+)-8-OHDPAT and L-DOPA suggests that 5-HT_{1A} agonists may have potential utility in the symptomatic treatment of PD.

In the present study, non-reserpinized rats were also tested for their response to *R*-(+)-8-OHDPAT. No significant effects on locomotor activity were seen in habituated, non-reserpinized animals at doses of 0.1 mg/kg or below (Fig. 2A). However, consistent with previous reports in habituated, non-reserpinized animals, doses of *R*-(+)-8-OHDPAT of 0.3 mg/kg and 1 mg/kg did significantly elevate locomotor activity (Fig. 2A, Evenden and Angeby-Moller 1990). Despite the apparent lower potency of *R*-(+)-8-OHDPAT to increase locomotion in non-reserpinized rats relative to reserpinized rats, it is apparent that the absolute increase in motor activity is greater in non-reserpinized animals (Fig. 2A and Fig. 1A). This may indicate that intact stores of dopamine and/or norepinephrine contribute to *R*-(+)-8-OHDPAT-induced motor activity in normal animals. The higher sensitivity of reserpinized animals to the locomotor enhancing effects of *R*-(+)-8-OHDPAT relative to non-reserpinized animals may be the result of 5-HT_{1A} receptor supersensitivity caused by reserpine-induced depletion of 5-HT (Renyi 1986). However, at least one previous study has shown that the locomotor-enhancing ability of 8-OHDPAT was actually suppressed following reserpine administration 24 h prior to testing (Tricklebank et al. 1984). It remains to be determined whether acute reserpine treatment can upregulate postsynaptic 5-HT_{1A} function. Alternatively, this increased sensitivity to *R*-(+)-8-OHDPAT in reserpinized animals may reflect the increased importance of non-monoaminergic pathways for mediating locomotor activity which may be modulated by 5-HT_{1A} receptors. As will be discussed later, substantial evidence supports the potential involvement of excitatory amino acid (EAA) pathways. Finally, it is possible that in non-reserpinized animals 5-HT_{1A} autoreceptor regulation of 5-HT neurotransmission functionally antagonizes the locomotor effects of postsynaptic 5-HT_{1A} receptor activation.

Although 8-OHDPAT increases locomotor activity in non-reserpinized animals, it is unclear as to whether such motor effects occur as the result of 5-HT_{1A}-induced modulation of 5-HT neuronal activity (via somatodendritic autoreceptors) or via direct actions at 5-HT_{1A} receptors postsynaptically located in 5-HT terminal fields. Along these lines, it has been shown that local application of 8-OHDPAT into the dorsal raphe suppresses spontaneous locomotor activity, while median raphe injections increase spontaneous locomotor activity in non-reserpinized animals (Hillegaart 1990). Thus, activation of 5-HT_{1A} autoreceptors in the dorsal raphe in non-reserpinized animals might mitigate the locomotor-enhancing effects of postsynaptic 5-HT_{1A} receptors, as suggested above. However, in rats rendered cataleptic by D_2 blockade (e.g., with haloperidol) micro-injection of 8-OHDPAT or 5-HT into the median raphe (and dorsal raphe) reverses catalepsy (Invernizzi et al. 1988; Elliott et al. 1990; Wadenberg and Hillegaart 1995; Wadenberg et al. 1999). Taken together, these studies would suggest that the motor activating effects of a 5-HT_{1A} agonist, especially in an animal in which D_2 function is diminished, are mediated at the level of the 5-HT cell body. Furthermore, these data are consistent with the present observation that following disruption in dopaminergic transmission 5-HT_{1A} agonists tend to increase locomotor activity.

It was important in the present study to ascertain whether 5-HT_{1A} autoreceptor-mediated alterations in 5-

HT neuronal activity were responsible for the changes in locomotor activity in the monoamine-depleted rats. Reserpine prevents the storage of 5-HT (as well as dopamine and norepinephrine) and depletes brain 5-HT levels to approximately 5% of control. However, neurotransmitter synthesis and turnover is intact, as indicated by 5-HIAA levels which are actually increased over values seen in non-reserpinized animals (Kuhn et al. 1985; Wolf et al. 1985). This increase is presumably due, in part, to the loss of vesicular 5-HT storage which results in greater accessibility of monoamine oxidase to newly synthesized 5-HT. The 5-HT and 5-HIAA levels in the reserpinized rats of the present study are similar to what Wolf et al. (1985) and Kuhn et al. (1985) observed. Despite such drastic 5-HT depletion, extracellular levels of 5-HT measured by means of in vivo microdialysis are only reduced to 32% of control (Heslop and Curzon 1994). Moreover, behavioral and in vivo microdialysis studies indicate that neurotransmitter release can still occur from the pool of newly synthesized cytoplasmic 5-HT (Kuhn et al. 1985; Adell et al. 1989). Thus, it would be possible for *R*-(+)-8-OHDPAT to reduce the synthesis and release of 5-HT which remains intact even in reserpinized animals. The present results indicate that *R*-(+)-8-OHDPAT did not affect the synthesis and turnover of 5-HT in reserpinized animals, as evidenced by the lack of change in levels of 5-HT and its metabolite 5-HIAA in striatum or frontal cortex following drug administration (see Results). In non-reserpinized rats, a similar dose of 8-OHDPAT has been shown to reduce striatal 5-HT synthesis (as measured by 5-hydroxytryptophan accumulation following L-aromatic amino acid decarboxylase inhibition) and turnover (as measured by the ratio of 5-HIAA/5-HT) by 45% and 20%, respectively, 60 min after injection (Hjorth and Magnusson 1988). In the present study the contribution of newly synthesized 5-HT in the locomotor response to *R*-(+)-8-OHDPAT was assessed by treating rats with the tryptophan hydroxylase inhibitor pCPA prior to reserpinization. pCPA blocked 5-HT synthesis and brought 5-HT and 5-HIAA to near-undetectable levels, similar to the results of Kuhn et al. (1985). However, blockade of 5-HT synthesis did not affect the *R*-(+)-8-OHDPAT-mediated increase in locomotion in reserpinized animals (Fig. 5), indicating that the motor-enhancing effect was postsynaptically mediated.

The data presented herein indicate that in a monoamine-depleted animal, 5-HT_{1A} agonists can increase locomotor activity through direct stimulation of postsynaptic 5-HT_{1A} receptors. The question remains as to how this can occur. One possibility is through a reduction in overactive EAA transmission in the basal ganglia that has been caused by dopamine deficiency. It is widely held that increased EAA activity in the basal ganglia contributes to the motor deficits seen in PD (Greenamyre 1993). In vivo microdialysis studies have shown that acute reserpine pretreatment, haloperidol administration, or 6-OHDA lesions of the substantia nigra increase glutamate release in basal ganglia regions such as the striatum and entopeduncular nucleus, the rodent homologue of the internal globus pallidus (Yamamoto and Cooperman 1994; Meshul et al. 1996; Biggs et al. 1997). Moreover, MK-801 and other *N*-methyl-D-aspartate antagonists have been shown to increase locomotor activity in reserpinized animals to a level similar to what was presently observed with *R*-(+)-8-OHDPAT (Klockgether and Turski 1990; Starr 1995). Several studies have indicated that nerve terminal release of glutamate can be inhibited by 5-HT_{1A} receptor activation (Maura et al. 1988; Raiteri et al. 1991; Dijk et al. 1995). Finally, a recent study has suggested that 5-HT has a tonic inhibitory influence on striatal glutamate neurotransmission (Di Cara et al. 2001).

Based on the distribution of 5-HT_{1A} mRNA and receptor expression one can speculate on several neuroanatomical sites for 5-HT_{1A}–EAA interaction. 5-HT_{1A} receptors have been shown to be localized on EAA-containing cortical pyramidal neurons of layer V (Francis et al. 1992; Wright et al. 1995) which send projections to the striatum (Bellomo et al. 1998). The effect of 5-HT_{1A} receptor stimulation is to hyperpolarize and inhibit pyramidal cell activity in the cortex (Araneda and Andrade 1991; Tanaka and North 1993). It is tempting to speculate that activation of postsynaptic 5-HT_{1A} receptors on EAA-containing corticostriatal projections would inhibit EAA release in the striatum which could result in increased locomotor activity. In addition, 5-HT_{1A} receptors exist in moderate density in thalamic nuclei (Pompeiano et al. 1992; Wright et al. 1995). Thus, it is possible that 5-HT_{1A} receptor stimulation could serve to reduce EAA input to the striatum from the thalamus as well. The possibility that 5-HT_{1A} agonists can reduce glutamate release in various regions of the basal ganglia is currently under investigation. To this end, in vivo microdialysis studies underway in this lab indicate that *R*-(+)-8-OHDPAT can reduce extracellular striatal glutamate (unpublished observations).

The present data suggest that 5-HT_{1A} agonists can enhance motor activity through non-monoaminergic mechanisms and could provide a novel approach to the symptomatic management of PD and the motor side effects of antipsychotic drugs.

Acknowledgements The authors would like to thank Gerald Bieganski, Department of Research at Hines VA Hospital, for excellent technical assistance in HPLC analyses and binding assays. This work was supported by PHS grant NS36410 (W.A.W.)and VA Merit Award (W.A.W.). This research represents work carried out in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the Department of Pharmacology, Loyola University Chicago Stritch School of Medicine (L.M).

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