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The neurotensin-1 receptor agonist PD149163 inhibits conditioned avoidance responding without producing catalepsy in rats

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Abstract

Agonists for neurotensin (NT)-1 receptors have produced antipsychotic-like effects in many animals, including reversal of prepulse inhibition deficits and psychostimulant-induced increases in spontaneous activity. The present study sought to provide a basic assessment of the putative antipsychotic effects of PD149163 in rats using a two way conditioned avoidance response task, which is highly validated for screening antipsychotic drugs, and an inclined grid assessment, which is used to assess extrapyramidal side effect liability. PD149163 (0.0625–8.0 mg/kg) significantly suppressed conditioned avoidance responding (CAR) following administration of a 1.0 or 8.0 mg/kg dose. PD149163 failed to significantly increase catalepsy scores. The typical antipsychotic drug haloperidol (0.01–1.0 mg/kg) significantly suppressed CAR at a 0.1, 0.3, and 1.0 mg/kg dose, and a significant increase in catalepsy scores was found at the 1.0 mg/kg dose. The atypical antipsychotic drug clozapine (2.5–10.0 mg/kg) also produced a significant inhibition of CAR, which occurred following administration of a 10.0 mg/kg dose. Clozapine failed to significantly increase catalepsy scores. Finally, D-amphetamine (1.0 mg/kg), serving as a negative control, failed to suppress CAR or increase catalepsy scores. These data further suggest that PD149163 may have atypical antipsychotic-like properties.

1. Introduction

PD149163 is a brain penetrant neurotensin $(NT)_1$ receptor agonist (Petrie et al., 2004; Wustrow et al., 1995) that has been studied for several years as a putative atypical antipsychotic drug (APD). While the definition of an atypical APD has varied over the past several decades, due to different pharmacologic hypotheses (e.g., 5-HT_{2A}/D_2, D_2 "fast-off", D_2 receptor partial agonism) and differences in treatment efficacy (e.g., negative symptom and cognitive efficacy), a basic requirement remains an ability to reduce positive symptoms in schizophrenia without producing extrapyramidal side effects (EPS) at therapeutically effective doses (Gerlach, 2002; Goldstein, 2000).

These basic atypical APD properties have been thoroughly evaluated for many NT_1 receptor agonists. PD149163 (Feifel et al., 2008), as well as the NT_1 receptor agonists NT69L (Boules et al., 2001; Cusack et al., 2000), NT79 (Boules et al., 2010), and KH28 (Hadden et al., 2005), has reduced

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psychostimulant-induced increases in locomotion and other stereotypic behaviors in rodents, a common screen for APD effects. Moreover, PD149163 (Feifel et al., 2004), NT69L (Cusack et al., 2000), and KH28 (Hadden et al., 2005) have not been shown to exhibit catalepsy in rats, similar to the atypical APD clozapine, but not the typical APD haloperidol (Feifel et al., 2004). NT69L (Shilling et al., 2003), NT79 (Boules et al., 2010), and PD149163 (Feifel et al., 2008; Feifel et al., 2003; Feifel et al., 1999), also have been shown to prevent prepulse inhibition deficits produced by various psychotomimetic drugs, which might predict their efficacy for sensory gating deficits in schizophrenia.

The conditioned avoidance response task is another standard method for behaviorally screening putative APDs and offers few false positive results (Wadenberg and Hicks, 1999). In this task, animals, usually rats, are trained to avoid a floor grid shock when a warning stimulus, usually a tone or white noise, is activated. APD effects are represented as decreases in avoidance responses without failures to escape the foot shock. Atypicality may be inferred by an additional assessment of catalepsy at doses that produce decreases in avoidance responding. Intracerebroventricular injection of NT has produced decreases in conditioned avoidance responding (CAR) without producing escape failures in rats (Luttinger et al., 1982), although catalepsy has been reported in mice (Adams et al., 1997; Shibata et al., 1987; Snijders et al., 1982). Systemic administration of NT69L has been shown to inhibit CAR (Hertel et al., 2002) at doses that have not produced catalepsy in rats (Cusack et al., 2000; Sarhan et al., 1997).

While PD149163 has been thoroughly characterized in other APD models, only one report is available for the lack of cataleptic effects (Feifel et al., 2004). Moreover, there are no published studies on the effects of PD149163 on CAR. Thus, the present study was conducted to further evaluate the APD effects of PD149163 using the conditioned avoidance response task, which is highly predictive of APD effects, and using an inclined grip task to assess catalepsy, an indication of EPS liability. The effects of PD149163 were compared to the atypical APD clozapine and the typical APD haloperidol in both procedures. Finally, D-amphetamine was tested as a negative control.

2. Experimental procedures

2.1. Subjects

Ten male Sprague Dawley rats (Charles River, Portage, MI, USA) were used for all experiments. Animals were housed two per cage under stable laboratory conditions (21±2 °C, 55±5% relative humidity) under a 12 hour light/dark cycle (lights on at 07:00 am). All experiments were conducted at approximately the same time each day. Food and water was available ad libitum in the home cages. All procedures were approved by the Northern Michigan University Institutional Animal Care and Use Committee and performed in compliance with the Guide for the Care and Use of Laboratory Animals (National Research Council, 1996).

2.2. Apparatus

Two shuttlebox test chambers equipped with a tilting shock grid floor and white noise speakers in each compartment were used for these procedures (Med Associates Inc., St. Albans, VT, USA). The box was housed in a sound attenuating chamber equipped with a ventilation fan and masking noise. Data were collected using MedPC IV software (Med Associates Inc.). Catalepsy was assessed using a wire grid fastened to a frame that was inclined 60°.

2.3. Drugs

D-amphetamine hemisulfate salt (Sigma-Aldrich, St. Louis, MO, USA), clozapine (Sigma-Aldrich), and PD149163 (NIMH Drug Repository, Bethesda, MD, USA) were dissolved in 0.9% physiological saline. Haloperidol (Sigma-Aldrich) was dissolved in sterile water with a few drops of 85% lactic acid. All drugs were administered subcutaneously in a 1 ml/kg volume 30 min prior to a test session.

2.4. CAR training and testing

The procedures used to assess CAR were similar to those reported previously from this laboratory (Jacobson and Prus, 2010). Briefly, rats were trained once daily in 15 min sessions, which consisted of approximately 15–25 trials (separated by randomly selected intervals between 20 and 40 s) depending on performance. Each trial began with an 80-dB white noise followed 10 s later by electric shocks administered to the grid floor (0.6 mA of a 0.5 s duration, repeated every 1.5 s). Moving to the opposite compartment during this 10 s interval prevented onset of the shocks (avoidance response), whereas moving to the opposite compartment after onset of the shocks terminated the shocks (escape response). The white noise remained on until an animal emitted an avoidance or escape response. If an escape response failed to occur after 60 s (escape failure), the session was terminated.

Test sessions were conducted after animals produced avoidance responses for at least 90% of training session trials for 3 consecutive sessions. Test sessions were 10 min long, but otherwise, identical to training sessions. Thirty min prior to a test session, a 10 min pre-test was conducted to determine if animals were performing accurately, and subsequently, a rat was not tested that day if it failed to emit avoidance responses for 90% of the pre-test trials. Immediately following the pre-test session, drug or vehicle was given and a test session was conducted 30 min later.

Each rat was tested once with every dose. Test conditions were balanced so that every dose of a dose response curve, including vehicle, was assigned among the nine rats (one rat was removed from the study; see Results below), evaluated on the same test day. Otherwise, the dose assignments varied randomly for each animal. Rats were first tested with haloperidol, followed by PD149163, clozapine, and amphetamine. Tests sessions for each dose or vehicle for a drug were separated by at least 2 days. After a dose response curve for a drug was completed, rats were given at least 7 days off from experimental procedures before tests with the next drug were conducted.

2.5. Catalepsy

Immediately preceding a CAR test session, catalepsy was evaluated using an inclined grid. Rats were gently placed on a wire grid and the time to completely remove one paw was measured, excluding the first 30 s. Times were then scored according to the following scale: 0=0–0.08; 1=0.09–0.35; 2=0.36–0.80; 3=0.81–1.42; 4=1.43–2.25; 5≥2.25 min (Ahlenius and Hillegaart, 1986; Wadenberg et al., 2001).

2.6. Data analysis

Percent avoidance was calculated by dividing the number of trials where avoidance occurred over the total number of trials for the session. Then, this value was multiplied by 100. These percentage values were expressed as medians (+/−semi-interquartile range).

These and other data were analyzed using a Friedman one-way analysis of variance (ANOVA) by ranks, followed by the Wilcoxon matched-pairs signed ranks test, as appropriate, using GraphPad Prism v. 5.01 (GraphPad Software, Inc., La Jolla, California, USA).

3. Results

3.1. CAR training

Of the 10 rats used in this study, one was removed from the study due to failure to maintain training criteria. The remaining nine rats were trained within a mean of 15.11 days (+/−standard error of the mean = 1.67 days).

3.2. Percent CAR

Percent CAR data are shown in Fig. 1.

PD149163 produced a significant reduction of CAR ($\chi^2 = 36.67$, DF = 6, $p < 0.0001$) (left panel). Percent avoidance at the 1.0 and 8.0 mg/kg doses was significantly lower than vehicle. No escape failures occurred.

Clozapine also significantly reduced CAR ($\chi^2 = 24.36$, DF = 3, $p < 0.0001$), which was found for the 10.0 mg/kg dose versus vehicle control (center panel). No escape failures occurred for clozapine.

Haloperidol produced a significant suppression of CAR ($\chi^2 = 43.29$, DF = 6, $p < 0.0001$), which occurred at the 0.1, 0.3, and 1.0 mg/kg doses compared to vehicle (right panel). Escape failures occurred at the 0.05, 0.1, 0.3 and 1.0 mg/kg doses (data not shown).

No statistically significant effects on CAR were observed after amphetamine administration (data not shown).

3.3. Catalepsy

Catalepsy scores are shown in Fig. 2.

Neither PD149163 (left panel) nor clozapine (center panel) produced a statistically significant increase in catalepsy scores. However, haloperidol produced a statistically significant increase in catalepsy scores ($\chi^2 = 28.91$, DF = 6, $p < 0.0001$), which occurred at the 1.0 mg/kg dose compared to vehicle (right panel).

No statistically significant effects on catalepsy were observed after amphetamine administration (data not shown).

4. Discussion

In the present study, PD149163 significantly decreased CAR without producing increases in catalepsy. These effects on CAR were observed at a 1.0 mg/kg dose, which has been shown to be an effective dose in many APD behavioral models in rats, including a reversal of amphetamine-, MK801- (Feifel et al., 1999), DOI- (Feifel et al., 2003; Shilling et al., 2004), and cirazoline-induced (Shilling et al., 2004) prepulse inhibition deficits, of inherent prepulse deficits in Brattleboro rats (Feifel et al., 2004; Feifel et al., 2009), and of amphetamine-induced increases in locomotion (Feifel et al., 2008). Moreover, a 1.0 mg/kg dose of PD149163 inhibited fear potentiated startle responses (Shilling and Feifel, 2008), suggesting potential anxiolytic effects. An inhibition of CAR, but no increase in catalepsy, was found at an 8.0 mg/kg dose, well beyond the behaviorally effective doses of PD149163 described above.

In the present study, the atypical APD clozapine produced full inhibition of CAR and failed to produce increases in catalepsy scores at up to a 10.0 mg/kg dose. Clozapine inhibition of CAR has been demonstrated in numerous studies in rats using similar doses (Hertel et al., 1999; Olsen et al., 2006; Wadenberg et al., 1998), and an inability to induce catalepsy has been evaluated at much higher doses. For example, clozapine has failed to increase catalepsy values in rats at 15 mg/kg (Feifel et al., 2004), 17 mg/kg (Bartoszyk et al., 1996), and 40 mg/kg (Millan et al., 1998) doses. Furthermore, clozapine has been shown to prevent catalepsy induced by a 1.0 mg/kg dose of haloperidol (Bartoszyk et al., 1996; Millan et al., 1998). Similar increases in catalepsy measures by haloperidol were found in the present study using a 0.3 and 1.0 mg/kg dose, although a potential reversal of these effects by clozapine or PD149163 was not evaluated. However, the NT_1 receptor agonist NT69L, which appears to have a potency similar to PD149163 in several APD animal models (e.g., Boules et al., 2001; Cusack et al., 2000), is also without cataleptic effects. Further, NT69L has been shown to prevent catalepsy induced by a 1.0 mg/kg dose of haloperidol (Cusack et al., 2000).

While the inhibition of CAR by PD149163 is qualitatively similar to the effects found with clozapine and haloperidol, PD149163 did not produce the same magnitude of inhibition. Clozapine and haloperidol produced a median of 0% CAR at the highest doses tested, while PD149163 only produced a median of approximately 50% and 60% CAR at the two highest doses tested, 1.0 and 8.0 mg/kg,

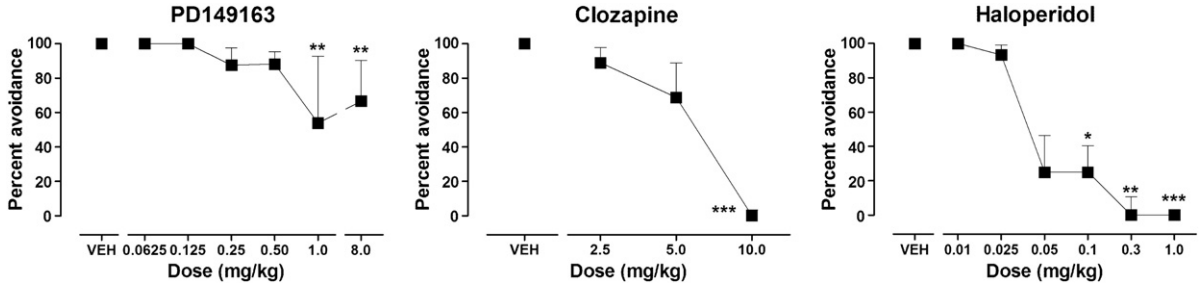

Figure 1 The effects of PD149163 (left), clozapine (center), and haloperidol (right) on median percent conditioned avoidance responding (+/−semi-interquartile range; N = 9 for each drug). ***$p < 0.001$, **$p < 0.01$, and *$p < 0.05$ versus vehicle (VEH). N = 9.

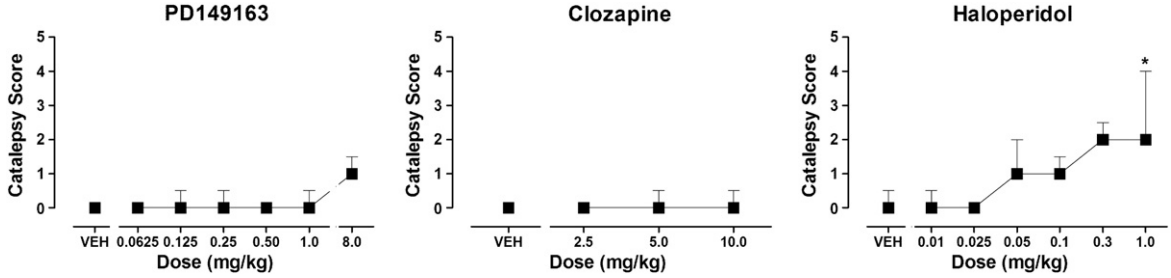

Figure 2 The effects of PD149163 (left), clozapine (center), and haloperidol (right) on median catalepsy scores (+/−semi-interquartile range; N = 9 for each drug). *$p < 0.05$ versus VEH.

respectively. Although it is possible that still higher doses of PD149163 may have achieved a greater inhibition of CAR, PD149163 was evaluated at a dose (8.0 mg/kg) that was far higher than those demonstrated to be behaviorally effective in other APD models (discussed above). There was also not a trend toward greater CAR inhibition between the 1.0 and 8.0 mg/kg doses.

However, the lack of further CAR inhibition does not appear unique to PD149163. The NT_1 receptor agonist NT69L, at a 0.32 mg/kg dose, produced a mean maximum inhibition of CAR of approximately 50% (Hertel et al., 2001). Further, intracerebroventricular administration of NT into the lateral ventricle, at amounts ranging from 0.2 to 17.0 nmol, only reduced mean percent CAR to approximately 85%, and similar to the present findings, there was no discernable trend toward further inhibition beyond 0.6 nmol (Luttinger et al., 1982). PD149163 has also exhibited a varying degree of reversal of prepulse inhibition deficits in rats. PD149163, at doses up to 1.0 mg/kg, has been shown to fully reverse prepulse inhibition deficits produced by amphetamine, but only partially reverse prepulse inhibition deficits produced by MK-801 (Feifel et al., 1999). However, PD149163, again using doses up to 1.0 mg/kg, has also fully reversed innate PPI deficits in Brattelboro rats, using Long Evans rats as controls (Feifel et al., 2009).

The lack of effect of PD149163 on escape failures is similar to the Luttinger et al. (1982) findings, described earlier, which failed to find escape failures by intracerebroventricular administration of neurotensin. In a further comparison, systemic administration of NT69L (0.08–0.31 mg/kg) also did not induce escape failures during CAR testing (Hertel et al., 2001). Whereas clozapine generally does not produce escape failures in this task (Olsen et al., 2006; Wadenberg et al., 1998), haloperidol did produce an increase in escape failures at doses ranging from 0.05 to 1.0 mg/kg, replicating findings reported previously (e.g., Hertel et al., 2001).

Studies that have evaluated the neuropharmacological mechanisms that mediate suppression of CAR are too numerous to cover here. However, in a comprehensive review on the utility of CAR for APD screening, Wadenberg and Hicks (1999) concluded that inhibition of CAR is mediated by the mesocorticolimbic dopamine pathway, and moreover, that the inhibition of CAR produced by "false positives" (e.g., LSD, morphine) might also be due to effects on this pathway. NT closely interacts with dopamine along this and the nigrostriatal pathway. NT is released from dopamine neurons in these pathways, and NT_1 receptors, which PD149163 is highly selective for (Petrie et al., 2004), are co-localized with D_2 receptors. Activation of NT_1 receptors causes an allosteric inhibition of D_2 receptor binding, which may mediate the APD-like effects of NT and NT receptor agonists (for review, see Binder et al., 2001).

The present study provides further evidence for the putative atypical APD effects of the NT_1 receptor agonist PD149163, providing additional support for NT analogs as a novel class of atypical APDs. While there is strong evidence for the mesocorticolimbic dopamine mediation of NT_1 receptor agonist effects in APD models, the implications of close interactions between NT and other monoamines, for example serotonin (Jolas and Aghajanian, 1997), and a remaining controversy surrounding a possible tolerance to NT_1 receptor agonists after repeated administration (Elliott and Nemeroff, 1986; Feifel et al., 2010; Feifel et al., 2008; Hertel et al., 2001; Hertel et al., 2002), requires further evaluation of the utility of NT_1 receptor agonists for the treatment of schizophrenia and possibly other mental disorders. Moreover, other properties of NT_1 receptor agonists need to be assessed as well. Importantly, neurotensin appears to enhance malignant pancreatic tumor growth, and is otherwise associated with breast, colorectal, lung, prostate, and various other cancers (for review, see Mark Evers, 2006). Thus, these and potential other limitations of neurotensin receptor agonists must be addressed as the utility of these compounds for the treatment of schizophrenia and other mental disorders are evaluated.

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Contributors

Elizabeth Holly and Bree Ebrecht both conducted data collection, managed literature searches, and contributed writing to the first draft of this manuscript for this study. Dr. Adam Prus designed and supervised the study, conducted the statistical analyses, and completed the final draft of this manuscript.

Conflict of interest

Dr. Adam Prus received an NIMH grant (1R15MH083241-01) to study the effects of neurotensin receptor agonists for the treatment of schizophrenia. All other authors declare that they have no conflicts of interest.

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