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Iloperidone reduces sensorimotor gating deficits in pharmacological models, but not a developmental model, of disrupted prepulse inhibition in rats

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Abstract

Iloperidone is a novel atypical antipsychotic which acts as a broad spectrum dopamine/serotonin/norepinephrine receptor antagonist. To compare iloperidone behaviorally to other known antipsychotics, we evaluated the drug in three pharmacological models and one developmental model of disrupted prepulse inhibition (PPI) in rats. Firstly, 0.5 mg/kg apomorphine induced PPI deficits that were prevented by pretreatment with iloperidone (1 and 3 mg/kg). Secondly, treatment with the *N*-methyl-D-aspartate (NMDA)-receptor antagonist phencyclidine (PCP) produced robust deficits in PPI. Both doses of iloperidone (1 and 3 mg/kg) prevented the PPI-disruptive effects of treatment with 1 mg/kg PCP. Thirdly, treatment with the α_1-adrenoceptor agonist cirazoline (0.6 mg/kg) disrupted PPI, and produced a concurrent large increase in startle magnitude. A relatively low dose of iloperidone (0.3 mg/kg) prevented cirazoline-induced PPI deficits, independent of its effects on startle magnitude. Finally, iloperidone (1 mg/kg) did not reverse PPI deficits in the isolation-rearing model of schizophrenia. These results indicate that iloperidone exerts behavioral effects in pharmacological models of disrupted sensorimotor gating consistent with ''atypical'' antipsychotics, mediated by antagonism of dopaminergic and noradrenergic receptors. The absence of effect in isolation-reared rats may be due to the relatively small effect size of isolation rearing on PPI or dose of iloperidone.

Keywords: Animal model; Atypical antipsychotic; Isolation rearing; Prepulse inhibition; Psychosis; Schizophrenia

1. Introduction

Iloperidone (1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone) is a novel antipsychotic drug (Hesselink, 2002; Kelleher et al., 2002), currently in late Phase III trials (developed by Novartis Pharmaceuticals, presently under license by Vanda Pharmaceuticals (http://www.vandapharma.com/drug_dev_progress.html)). It was initially identified as the most promising in a large series of novel piperidinyl-benzisoxazoles, based on preclinical evidence that iloperidone demonstrated a 300-fold greater potency for mesolimbic dopaminergic compared to nigrostriatal activity in rodent behavioral paradigms (Strupczewski et al., 1995).

The receptor binding profile of iloperidone was confirmed in pharmacological studies (Strupczewski et al., 1995; Szewczak et al., 1995; Kongsamut et al., 1996; Szczepanik et al., 1996; Richelson and Souder, 2000). Iloperidone binds with a high affinity ($K_I < 10$ nM) to human α_1-adrenoceptors, serotonin (5-HT) 2A receptors and dopamine D_3 receptors, with a lower affinity ($K_I = 10-100$ nM) for dopamine D_{2A} and D_4 receptors, norepinephrine α_{2C}-adrenoceptors and serotonin 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2C} and 5-HT_6 receptors (Kalkman et al., 2001). Based on the influential explanatory hypothesis proposed by Meltzer and colleagues (Meltzer et al., 2003),

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in which atypical antipsychotics are characterized by a binding affinity approximately one order of magnitude greater for the 5-HT_{2A} over the D_2 receptor, it may be concluded that iloperidone exhibits an ''atypical'' pharmacological receptor binding profile. In addition, the compound also displays minimal affinity for receptors, including muscarinic and histamine H_1 receptors (Kalkman et al., 2001), that are typically associated with non-extrapyramidal side-effects characterizing neuroleptic or atypical antipsychotic treatment (Kroeze et al., 2003), such as salivation and sedation.

At present, the respective contributions of antagonism at individual receptors to the *in vivo* antipsychotic-like effects of iloperidone remain unknown. Iloperidone exhibits antagonism of 5-HT_2 receptors (Wettstein et al., 1999) and dopamine D_2 receptors (Strupczewski et al., 1995; Szewczak et al., 1995), although only in behavioral procedures with minimal cross-species homology, such as pharmacologically induced head-twitching or stereotypy. Fortunately, the advent of operationalized tasks for rodents that model specific psychophysiological symptoms associated with schizophrenia has allowed precise evaluation of the neurochemical bases for these behavioral changes and their relevance to antipsychotic drug activity. Sensorimotor gating tasks, such as prepulse inhibition (PPI) of the acoustic startle reflex, have proven to be important in determining the contribution of specific receptor antagonism on behavioral activity of antipsychotic drugs (Geyer et al., 2001; Barr et al., 2004a). Prepulse inhibition refers to the reduction in startle magnitude that occurs after the presentation of a brief, non-startling stimulus (Hoffman and Ison, 1980). Prepulse inhibition deficits are frequently observed in psychotic disorders, such as schizophrenia (Braff et al., 2001), and have been modeled in rodents after treatment with drugs, including the dopamine D_2 receptor agonist apomorphine (Geyer et al., 1999; Ellenbroek et al., 2001), the noradrenergic α-1 adrenoceptor agonist cirazoline (Carasso et al., 1998; Varty et al., 1999), and the NMDA receptor antagonist phencyclidine (PCP) (Bakshi and Geyer, 1995; Wiley and Kennedy, 2002). In addition, isolation-rearing of rats from weaning induces developmental aberrations that include reductions in PPI (Powell et al., 2003). Hence, in the present study, we evaluated the capacity of the novel antipsychotic iloperidone to reduce pharmacologically and developmentally induced disruptions of PPI in rats.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats (Harlan Laboratories, San Diego, CA), weighing 300 to 400 g, were used in these studies. Animals were housed in pairs in clear plastic cages located inside a temperature- and humidity-controlled animal colony and were maintained on a reversed day/night cycle (lights on from 19:00 to 07:00 h). Food (Harlan Teklad, Madison, WI) and water were available continuously except during behavioral testing, which occurred between 09:00 and 17:00 h. Upon arrival in the colony, all animals were handled gently by the experimenter in order to minimize stress during behavioral testing. Animal facilities were AAALAC-approved, and protocols were in accordance with the ''Guiding Principles in the Care and Use of Animals'' (provided by the American Physiological Society) and the guidelines of the National Institutes of Health.

2.2. Drugs

Iloperidone (0.3–3.0 mg/kg) was generously donated by Novartis Pharma (Basel, Switzerland), while PCP (1.0–1.5 mg/kg), apomorphine (0.5 mg/kg), and cirazoline (0.3–0.6 mg/kg) were purchased from Sigma Chemical Co. (St. Louis, MO). PCP and cirazoline were dissolved in saline, apomorphine was dissolved in 0.1% ascorbic acid, and iloperidone was dissolved in 0.1 N HCl and 4% Tween and buffered with NaOH to a pH between 6 and 7. Injection volume was 1.0 ml/kg for all drugs except for iloperidone and its vehicle, which were administered in a volume of 3.0 ml/kg.

2.3. Isolation rearing

In experiment 5, iloperidone was tested against isolation rearing-induced PPI deficits. A total of 65 female Sprague–Dawley rats were used in this experiment. Ten timed-pregnant Sprague–Dawley (Harlan; San Diego, CA) dams were shipped to our facility on gestation day 18. On postnatal day 3, litters were culled to 11 in same-sex groups for a total of 65 rats. At the time of weaning (postnatal day 23), rats were assigned to either social housing ($n = 33$) or isolation housing ($n = 32$). Social housing consisted of 3 rats per standard polycarbonate cage ($25 \times 48 \times 20$ cm), and isolation housing consisted of one rat per cage. Rats were tested with 1 mg/kg iloperidone after 13 weeks of isolation or social housing.

2.4. Apparatus

All testing occurred in startle chambers from San Diego Instruments (San Diego, CA). Startle boxes consisted of clear non-restrictive Plexiglas cylinders resting on a platform inside a ventilated and illuminated chamber. A high-frequency loud-speaker inside the chamber produced both a continuous background noise of 65 dB and the various acoustic stimuli. As described previously (Mansbach et al., 1988), the whole-body startle response of the animal caused vibrations of the Plexiglas cylinder, which were then converted into analog signals by a piezoelectric unit attached to the platform. These signals were then digitized and stored by a microcomputer and interface unit. Monthly calibrations were performed on the chambers to ensure the accuracy of the sound levels and measurements. Sound levels were measured as described previously (Mansbach et al., 1988) using the dB(A) scale.

2.5. Behavioral testing

One week after arrival, all rats underwent a brief baseline startle/PPI session consisting of 120 dB PULSE − ALONE trials and PREPULSE + PULSE trials in which a 12 dB above background noise was presented 100 msec before the onset of the 120 dB pulse. In this session and the subsequent test session, the background noise (65 dB) was presented alone for 5 min and then continued throughout the remainder of the session. A total of 24 trials were presented in a pseudo-random order: 18 presentations of a 40 msec 120 dB broadband burst and 6 trials in which a 77 dB burst preceded the 120 dB burst by 100 msec. Treatment groups were established by using the mean startle response to the 120 dB PULSE − ALONE trial and the mean % PPI calculated from the PREPULSE + PULSE trials (see formula in data analysis section below), so that all groups had comparable baseline startle reactivity and PPI. Two to three days after the baseline session, drug testing began.

The test session utilized in all of the experiments contained four different trial types: a PULSE − ALONE trial in which a 40 msec, 120 dB broadband burst was presented; three PREPULSE + PULSE trials in which 20 msec noises (68, 71, 77 dB) were presented 100 msec before the onset of the 120 dB pulse. All trial types were presented several times in a pseudo-random order for a total of 54 trials (24 PULSE-ALONE trials, 10 each of the PREPULSE + PULSE trials). NO STIMULUS trials, which included only the background noise, were presented between each trial. In addition, four of the PULSE − ALONE trials, which were not included in the calculation of PPI values, were presented at the beginning of the test session to achieve a relatively stable level of startle reactivity for the reminder of the session (based on the observation that the most rapid habituation of the startle reflex

occurs within the first few presentations of the startling stimulus; (Geyer et al., 1990)). Another four of the PULSE-ALONE trials, which were also not included in the calculation of PPI values, were presented at the end of the test session to assess startle habituation. Between the two groups of PULSE − ALONE trials used to assess startle habituation, the remaining 46 trials were divided into two blocks of 23 trials each in which all the trial types were equally represented. An average of 15 s (ranging from 7 to 23 s) separated consecutive stimulus trials. The total duration of the session was approximately 20 min.

In experiment 4, an additional 32 trials were presented at the end of the session. These additional 32 trials were added in order to vary the startle magnitude. Two types of PULSE − ALONE trials (105 dB and 120 dB; 8 trials of each) and two types of PREPULSE + PULSE trials (77 dB followed by either 105 dB or 120 dB; 6 of each) were presented. In addition four NOSTIM trials were also incorporated into the session.

2.6. Experimental design

In experiments 1, 2, and 3, naïve rats without previous drug exposure were tested. In experiment 4, rats that had been tested previously in experiment 3 were used; a wash-out period of three weeks was allowed between tests. In experiment 5, isolate and socially housed rats were used that had been tested in a previous experiment with either vehicle or diazepam (data not included). A two week washout period was allowed between the two experiments (diazepam and iloperidone) and prior treatment history was balanced between the groups. In all experiments, iloperidone was administered intraperitoneally (i.p.) 30 min prior to being placed in the startle chambers. Apomorphine was administered subcutaneously (s.c.) immediately prior to being placed in the startle chamber. Because we have shown that apomorphine does not produce any carryover effects on PPI, the apomorphine experiment was run as a within subjects crossover design with a one week washout between treatment with saline and apomorphine. The order of apomorphine or saline treatment was balanced across groups and the vehicle or iloperidone pretreatment remained constant across the two weeks. PCP was administered s.c. 10 min prior to being placed in the startle chambers, and cirazoline was administered i.p. 5 min prior to being placed in the startle chambers. For a summary of different drug administration schedules for each experiment, see Table 1.

2.7. Statistical analyses

The startle response to the 120 dB burst was recorded for each PULSE − ALONE and PREPULSE + PULSE trial. For each rat, two independent measures were calculated from these data. First, the amount of PPI was calculated as a percentage score: %PPI = 100 − {[(startle response for PREPULSE + PULSE trial)/(startle response for PULSE − ALONE trial)] × 100}. Second, startle magnitude was calculated as the average response of all the PULSE − ALONE trials, minus the first and last four PULSE − ALONE trials. PPI data were analyzed in each experiment by using three-way ANOVA, with antipsychotic drug pretreatment (iloperidone or vehicle), PPI-disruptive treatment (apomorphine/PCP/cirazoline/isolation or vehicle), and prepulse intensity as main factors. Separate ANOVAs were performed on startle magnitude (i.e., PULSE − ALONE) values to assess the effects on baseline startle reactivity and startle habituation. Where appropriate, specific comparisons were made using Tukey's posthoc test. ANOVAs were performed with BMDP7D or BMDP2V software.

Table 1
Summary of experimental manipulations designed to impair PPI, with corresponding treatment doses of the atypical antipsychotic iloperidone, for all experiments

	Experimental manipulation used to impair PPI	Iloperidone (dose)
Exp 1	Apomorphine (0.5 mg/kg)	1.0, 3.0 mg/kg
Exp 2	Phencyclidine (1.0 mg/kg)	1.0 mg/kg
	Phencyclidine (1.25 mg/kg)	1.0 mg/kg
Exp 3	Cirazoline (0.6 mg/kg)	0.3, 1.0 mg/kg
Exp 4	Cirazoline (0.3 mg/kg)	0.3 mg/kg
	Cirazoline (0.6 mg/kg)	0.3 mg/kg
Exp 5	Isolation rearing	1.0 mg/kg

3. Results

3.1. Experiment 1 − iloperidone vs apomorphine

Results of the ANOVA indicated that there was no significant effect of pretreatment with iloperidone or apomorphine on startle reactivity (Table 2), and no effect on startle habituation. With respect to PPI, there were significant main effects of pretreatment with iloperidone [$F_{(2,27)} = 11.86$; $P < 0.001$] and treatment with 0.5 mg/kg apomorphine [$F_{(2,27)} = 18.30$; $P < 0.001$]. In confirmation of the main hypothesis, there was a significant interaction of pretreatment with iloperidone × treatment with apomorphine [$F_{(2,27)} = 9.27$; $P < 0.001$]. There was also a significant effect of prepulse intensity [$F_{(2,54)} = 14.07$, $P < 0.001$] and significant interactions between prepulse intensity × pretreatment with iloperidone [$F_{(4,54)} = 2.98$, $P < 0.05$], prepulse intensity × treatment with apomorphine [$F_{(2,54)} = 14.25$, $P < 0.001$], and prepulse intensity × pretreatment with iloperidone × treatment with apomorphine [$F_{(4,54)} = 4.49$, $P < 0.01$]. Further analysis of these results (Fig. 1) with one-way paired t-tests (alpha set at $P = 0.025$) by prepulse intensity indicated that treatment with vehicle-apomorphine, as expected, produced an overall decrease in PPI, which was significantly different from vehicle-vehicle treated rats at the 71 and 77 dB prepulse levels. Post-hoc tests by drug treatment (saline and apomorphine) indicated that pretreatment with both doses of iloperidone (1.0 and 3.0 mg/kg) completely prevented this effect, as PPI with both doses of iloperidone-apomorphine was significantly greater than vehicle-apomorphine treated rats at all prepulse levels. Interestingly, PPI was significantly greater in the 3.0 mg/kg dose of iloperidone-vehicle treated rats than vehicle-vehicle treated rats at the 77 dB prepulse level, indicating that higher doses of the antipsychotic increase PPI, at particular prepulse levels, even compared to rats whose PPI has not been decreased by pharmacological means.

3.2. Experiment 2 − iloperidone vs PCP

Analysis indicated that there was no significant effect of pretreatment with iloperidone or treatment with PCP on startle reactivity (Table 2). The ANOVA revealed a significant main effect on PPI of pretreatment with a single 1.0 mg/kg dose of iloperidone [$F_{(1,53)} = 9.88$; $P < 0.005$] and a significant main effect of treatment with both doses (1.0 and 1.25 mg/kg) of PCP [$F_{(2,53)} = 26.64$; $P < 0.0001$], which reduced PPI across all prepulse intensities (Fig. 2). There was also a significant main effect of prepulse intensity [$F_{(2,106)} = 58.6$, $P < 0.001$] but no interaction between prepulse intensity and pretreatment with iloperidone or treatment with PCP. Further analysis of the effects of the 1.0 mg/kg dose PCP with a separate ANOVA indicated a significant main effect of

Table 2
Startle amplitude in Experiments 1–3 with 120 dB acoustic stimuli (VEH = vehicle, ILO = iloperidone, APO = apomorphine, PCP = phencyclidine, CIR = cirazoline; see Section 2 for details)

EXP 1	VEH	VEH	VEH	APO	APO 0.5	APO 0.5
	SAL	ILO 1.0	ILO 3.0	0.5 SAL	ILO 1.0	ILO 3.0
STARTLE (±SEM)	349 ± 36	252 ± 63	210 ± 38	290 ± 96	104 ± 17	232 ± 67
EXP 2	VEH	VEH	VEH	ILO 1.0	ILO 1.0	ILO 1.0
	SAL	PCP 1.0	PCP 1.25	SAL	PCP 1.0	PCP 1.25
STARTLE (±SEM)	321 ± 58	462 ± 62	384 ± 42	275 ± 23	348 ± 85	444 ± 80
EXP 3	VEH	VEH	VEH	CIR	CIR	CIR
	SAL	ILO 0.3	ILO 1.0	VEH	ILO 0.3	ILO 1.0
STARTLE (±SEM)	313 ± 60	311 ± 49	107 ± 32	680 ± 118**	316 ± 54	207 ± 28

**$P < 0.01$ vs all other groups.

pretreatment with 1.0 mg/kg iloperidone [$F_{(1,35)} = 9.46$; $P < 0.005$] and a significant main effect of treatment with 1.0 mg/kg PCP [$F_{(1,35)} = 24.13$; $P < 0.0001$]; there was also a significant interaction of pretreatment with iloperidone × treatment with PCP [$F_{(1,35)} = 6.36$; $P < 0.05$]. Posthoc analysis revealed that iloperidone prevented the disrupting effects of the 1.0 mg/kg dose of PCP on PPI, as levels were significantly greater in iloperidone-PCP than vehicle-PCP rats at both the 68 and 77 dB prepulse intensities, and were not significantly different from vehicle-vehicle rats at any prepulse intensity. Treatment with the 1.0 mg/kg dose of iloperidone did not significantly reduce the disruptive effects of 1.25 mg/kg PCP. Similar unsurmountable effects of PCP on PPI were also observed with a 1.5 mg/kg dose of PCP and 3.0 mg/kg dose of iloperidone (data not shown).

3.3. Experiment 3 – iloperidone vs. cirazoline

The ANOVA indicated that there was a significant main effect of treatment with the 0.6 mg/kg cirazoline dose on startle magnitude [$F_{(1,56)} = 10.11$; $P < 0.005$], as levels in cirazoline-vehicle treated rats were more than twice those of vehicle-saline treated rats (Table 1). There was also a significant interaction of pretreatment with iloperidone × treatment with cirazoline [$F_{(2,56)} = 4.94$; $P < 0.05$], as both the 0.3 and

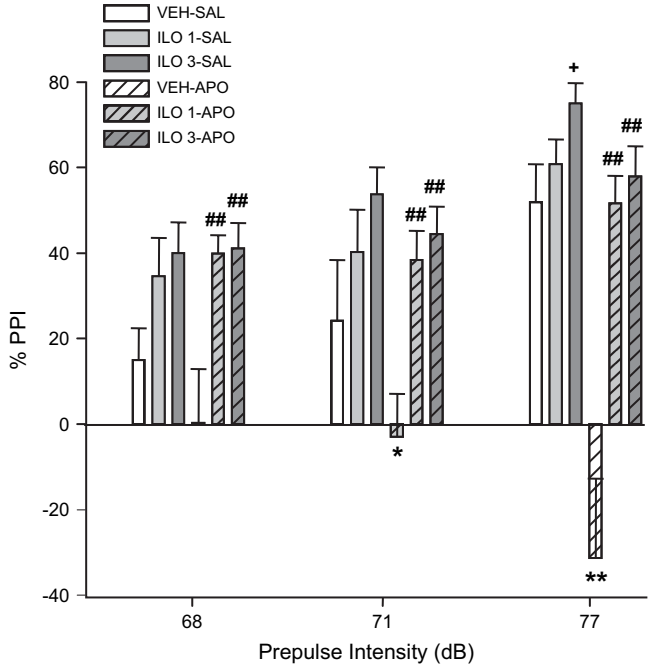

Fig. 1. Effects of two different doses of the antipsychotic drug iloperidone on apomorphine (0.5 mg/kg)-induced PPI deficits in rats (ILO = iloperidone, APO = apomorphine, VEH = vehicle, SAL = saline). Apomorphine disrupted PPI at the 71 and 77 dB prepulse intensities (* = $P < 0.025$; ** = $P < 0.01$ vs. VEH = SAL). Both doses of iloperidone significantly prevented PPI deficits at all prepulse intensities (68, 71, and 77 dB; i.e., 3, 6, and 12 dB above background noise level) (## = $P < 0.01$ vs VEH-APO). Iloperidone significantly increased PPI at the 77 dB prepulse intensity; + = $P < 0.05$ vs VEH-SAL). Data represent group means ± SEM, $n = 10$ per group.

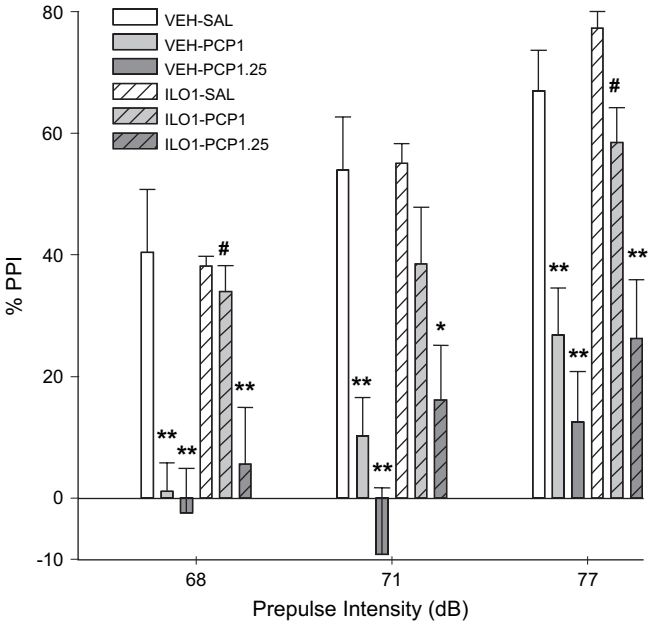

Fig. 2. Effects of the antipsychotic drug iloperidone (1 mg/kg) on PCP (1.0, 1.25 mg/kg)-induced PPI deficits in rats (ILO = iloperidone, PCP = phencyclidine, VEH = vehicle, SAL = saline). Both doses of PCP produced significant PPI deficits across all prepulse intensities (68, 71, and 77 dB; i.e., 3, 6, and 12 dB above background noise level) (* = $P < 0.05$ vs VEH-SAL, ** = $P < 0.01$ vs VEH-SAL; # = $P < 0.05$ vs VEH-PCP 1 mg/kg). Iloperidone reduced PPI deficits in rats treated with 1.0 mg/kg PCP at prepulse intensities of 68 and 77 dB (i.e., 3 and 6 dB above background noise level) (# = $P < 0.05$ vs VEH-PCP 1.0). Data represent group means ± SEM, $n = 10$ per group.

1.0 mg/kg iloperidone doses selectively normalized startle magnitude in cirazoline-treated rats to levels similar to vehicle-vehicle treated rats.

Analysis of PPI data revealed a significant main effect of pretreatment with iloperidone [$F_{(2,56)} = 34.06$; $P < 0.0001$] and a significant main effect of treatment with cirazoline [$F_{(1,56)} = 12.32$; $P < 0.001$]. There was also a highly significant interaction of pretreatment with iloperidone × treatment with cirazoline [$F_{(2,56)} = 18.36$; $P < 0.0001$]. The amount of PPI increased with increasing prepulse intensity, as indicated by a main effect of prepulse intensity [$F_{(2,112)} = 81.11$, $P < 0.001$]. There were also interactions of prepulse intensity × pretreatment with iloperidone [$F_{(4,112)} = 3.42$, $P < 0.05$] and prepulse intensity × treatment with cirazoline [$F_{(2,112)} = 5.10$, $P < 0.01$]. Posthoc analysis indicated that PPI was uniformly decreased by cirazoline, and that this was significantly prevented by pretreatment with either 0.3 mg/kg or 1.0 mg/kg iloperidone doses (Fig. 3).

3.4. Experiment 4 — iloperidone vs. cirazoline

While the results from Experiment 3 confirmed that cirazoline-induced PPI deficits could be reduced by iloperidone, it was unclear whether this effect was due to the capacity of iloperidone to prevent increases in startle magnitude caused by a 0.6 mg/kg dose cirazoline. To clarify this issue, we tested animals again with 0.6 mg/kg cirazoline, but also with an additional, lower (0.3 mg/kg) dose of cirazoline, on the assumption that PPI may be disrupted by this dose, without effects on startle magnitude. The ANOVA on PPI indicated significant main effects of pretreatment with iloperidone [$F_{(1,55)} = 16.00$; $P < 0.001$], treatment with cirazoline [$F_{(2,55)} = 13.07$; $P < 0.0001$], and a significant interaction of pretreatment with iloperidone × treatment with cirazoline [$F_{(2,55)} = 10.44$; $P < 0.001$]. The posthoc analysis indicated that iloperidone (0.3 mg/kg) prevented PPI deficits in rats treated with 0.6 mg/kg of cirazoline, reconfirming the results of Experiment 3. However, there was no significant effect of treatment on PPI with the lower, 0.3 mg/kg dose of cirazoline, leaving open the question as to whether the antagonistic effects of iloperidone on cirazoline-induced PPI deficits are mediated through its effects on startle.

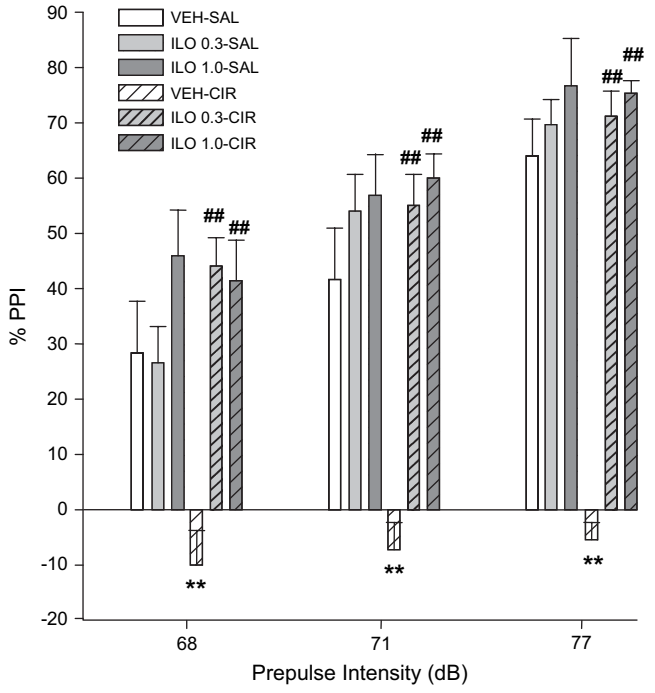

Fig. 3. Effects of the antipsychotic drug iloperidone (0.3 & 1.0 mg/kg) on cirazoline (0.6 mg/kg)-induced PPI deficits in rats (ILO = iloperidone, CIR = cirazoline, VEH = vehicle, SAL = saline). Cirazoline produced significant PPI deficits across all three prepulse intensities (68, 71, and 77 dB; i.e., 3, 6, and 12 dB above background noise level) (** = $P < 0.01$ vs VEH-SAL). Both doses of iloperidone reduced PPI deficits in rats treated with cirazoline at all prepulse intensities (## = $P < 0.001$ vs VEH-CIR). Data represent group means ± SEM, $n = 10$ per group.

To address this issue further, we modified the PPI test session to include additional trials that tested startle reactivity in response to a lower intensity startle stimulus of 105 dB, and compared PPI and startle on these trials to those with the standard 120 dB startle stimulus. A separate analysis of startle magnitude for these trials indicated a significant interaction of pretreatment with iloperidone × stimulus intensity level (i.e. 105 dB vs 120 dB) [$F_{(1,55)} = 6.12$; $P < 0.05$], and a significant interaction of treatment with cirazoline × stimulus intensity level [$F_{(2,55)} = 7.18$; $P < 0.01$]. Subsequent posthoc analysis demonstrated that startle magnitude with the 120 dB stimulus was significantly greater in the 0.6 mg/kg cirazoline-vehicle treated rats than vehicle-vehicle treated animals, similar to data from Experiment 3 (Fig. 4A). However, interestingly, there was no significant difference in startle magnitude between the 0.6 mg/kg cirazoline-vehicle treated rats and the vehicle-vehicle treated animals at the lower intensity 105 dB startle stimulus. Iloperidone (0.3 mg/kg) prevented the increase in startle magnitude with the 0.6 mg/kg cirazoline-vehicle treated rats at 120 dB, but there was no significant effect of iloperidone on startle magnitude with the 0.6 mg/kg cirazoline-vehicle treated rats at 105 dB.

Given equivalent levels of startle magnitude with the lower intensity startle stimulus, we compared PPI in different treatment groups (Fig. 4B). The ANOVA on PPI indicated significant main effects of pretreatment with iloperidone [$F_{(1,55)} = 45.94$; $P < 0.0001$], treatment with cirazoline [$F_{(2,55)} = 25.39$; $P < 0.0001$], and a significant interaction of pretreatment with iloperidone × treatment with cirazoline [$F_{(2,55)} = 18.21$; $P < 0.0001$]. Posthoc analysis indicated that treatment with 0.6 mg/kg cirazoline decreased PPI compared to vehicle-vehicle treated rats at both startle stimulus intensities, and iloperidone was equally effective in preventing these deficits at both stimulus intensity levels. These latter results strongly indicate that iloperidone can antagonize cirazoline-induced PPI deficits independent of its effects on startle magnitude.

3.5. Experiment 5 — iloperidone vs. isolation rearing

Analysis of the data indicated that there was a significant main effect of housing condition on levels of startle reactivity

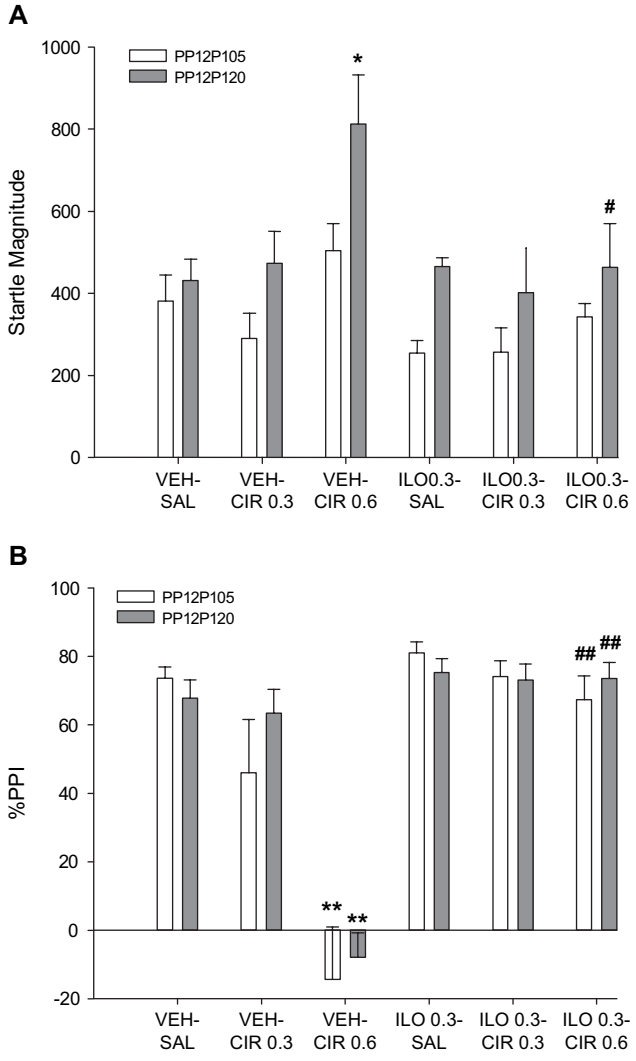

Fig. 4. (A) Effects of iloperidone (0.3 mg/kg) and cirazoline (0.3, 0.6 mg/kg) on startle magnitude (arbitrary units) in rats (ILO = iloperidone, CIR = cirazoline, VEH = vehicle, SAL = saline). Data indicate startle levels with two different startle intensities, at either 105 dB or 120 dB. The 0.6 mg/dose of cirazoline produced a significant increase in startle magnitude only with the higher startle intensity (* = $P < 0.05$ vs VEH-SAL). Iloperidone only prevented increased startle in the 0.6 mg/kg cirazoline treated rats at the higher startle intensity (# = $P < 0.05$ vs VEH-CIR 0.6). Data represent group means ± SEM, $n = 10$ per group. (B) Effects of iloperidone (0.3 mg/kg) and cirazoline (0.3, 0.6 mg/kg) on PPI in rats. Data indicate PPI levels with two different startle intensities, at either 105 dB or 120 dB. The 0.6 mg/dose of cirazoline produced significant decreases in PPI at both startle intensities (** = $P < 0.01$ vs VEH-SAL). Iloperidone blocked PPI deficits in the 0.6 mg/kg cirazoline-treated rats at both startle intensities (## = $P < 0.05$ vs VEH-CIR 0.6). These data strongly suggest that the effects of iloperidone on cirazoline-induced PPI deficits are independent of its effects on startle magnitude, as evident in (A). Data represent group means ± SEM, $n = 10$ per group.

$[F_{(1,61)} = 21.95,\ P < 0.001]$, as levels were significantly increased in isolation-reared rats compared to group-reared animals. The ANOVA also revealed a strongly significant effect of antipsychotic drug treatment $[F_{(1,61)} = 68.79,\ P < 0.001]$, as well as a housing × drug interaction $[F_{(1,61)} = 21.65,\ P < 0.001]$ on startle reactivity. Further analysis of these data with posthoc tests indicated that isolation rearing significantly increased startle reactivity. Although iloperidone decreased startle overall, the decrease in startle reactivity in group-reared iloperidone-treated rats did not reach statistical significance. Treatment with iloperidone restored levels of startle in isolation-reared rats to those of group-reared vehicle-treated rats (i.e., isolation-reared rats treated with iloperidone did not differ from group-reared rats treated with vehicle; Fig. 5A).

Analysis of PPI by ANOVA indicated a significant main effect of housing condition $[F_{(1,61)} = 8.25,\ P < 0.01]$. Post-hoc analysis showed that PPI levels were significantly decreased

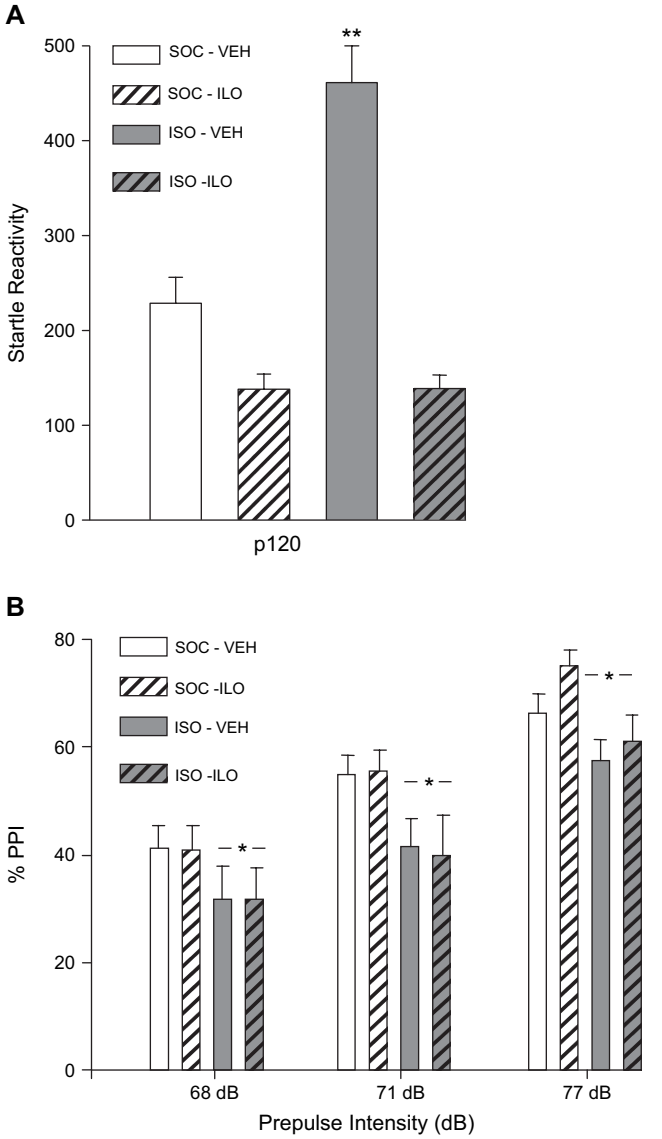

Fig. 5. (A) Effects of 1 ml/kg iloperidone (ILO) versus vehicle (VEH) on startle magnitude (arbitrary units) in group-reared (SOC) and isolation-reared (ISO) rats. The isolation-reared rats exhibited a significant increase in startle magnitude compared to group-reared animals. This effect was reversed by treatment with iloperidone (** = $P < 0.01$ vs all other groups). Data represent group means ± SEM, $n = 10$ per group. (B) Effects of 1 ml/kg iloperidone (ILO) versus vehicle (VEH) on isolation-rearing induced PPI deficits. Isolation rearing (ISO) induced a significant reduction of PPI across all prepulse intensities relative to group-reared animals (SOC) (* = $P < 0.05$ vs SOC). Treatment with iloperidone did not reverse isolation-induced PPI deficits. Data represent group means ± SEM, $n = 10$ per group.

in isolation-reared rats compared to group-reared animals across all three prepulse intensities (Fig. 5B). However, there was no effect of antipsychotic drug treatment nor was there a housing × drug interaction. Although there was a main effect of prepulse intensity [$F_{(2,122)} = 112.6$, $P < 0.001$], there were no interactions with intensity. Thus, the dose of 1 mg/kg iloperidone used in the present study did not reverse isolation-rearing induced loss of PPI.

4. Discussion

In the present study, we confirmed previous findings from our laboratory that PPI in rats is reduced by pharmacological treatment with apomorphine (Mansbach et al., 1988; Swerdlow et al., 1998; Geyer et al., 1999), PCP (Mansbach and Geyer, 1989; Bakshi and Geyer, 1995; Geyer et al., 1999), or cirazoline (Carasso et al., 1998; Varty et al., 1999). Both apomorphine and PCP were without effect on levels of startle reactivity, whereas the higher (0.6 mg/kg) dose of cirazoline produced a significant increase in startle magnitude, consistent with one prior report (Varty et al., 1999). Our findings indicate that doses of the putative antipsychotic drug iloperidone, that do not alter startle magnitude, prevented the PPI-disruptive effects of a 0.5 mg/kg dose of apomorphine. Iloperidone also prevented a dose-dependent disruption of PPI by PCP, whereby PPI deficits were reduced after treatment with a 1.0 mg/kg dose of PCP, although treatment with higher PCP doses (1.25, 1.5 mg/kg) produced insurmountable PPI deficits. Furthermore, iloperidone prevented PPI deficits induced by treatment with a 0.6 mg/kg cirazoline, which also significantly increased startle magnitude. While iloperidone significantly prevented both PPI deficits and startle magnitude increases in cirazoline-treated rats, it is unlikely that the former effect was due to the latter, because iloperidone also prevented cirazoline-induced PPI deficits with a lower intensity startle stimulus that produced equivalent levels of startle in rats treated with vehicle or cirazoline. We and other groups have previously demonstrated that PPI and acoustic startle are independent measures, e.g. (Bakshi et al., 1998; Cilia et al., 2001). Unexpectedly, 1 mg/kg iloperidone did not reverse PPI deficits in the isolation-rearing paradigm, although the drug reduced the elevated startle reactivity in isolation-reared rats to control levels.

The current behavioral findings are consistent with the known pharmacological activity of the drugs used in this study and the reported pharmacological binding profile of iloperidone for recombinant receptors. Iloperidone exhibits high affinity *in vitro* for human receptors that have traditionally been associated with antipsychotic activity, including high affinity ($K_I < 10$ nM) for norepinephrine α_1-adrenoceptors, 5-HT_{2A}, and dopamine D_3 receptors. Iloperidone also displays moderate affinity ($K_I = 10–100$ nM) for dopamine D_{2A} and D_4 receptors, norepinephrine α_{2C}-adrenoceptors and serotonin 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2C}, and 5-HT_6 receptors (Kalkman et al., 2001, 2003). Hence, the capacity of iloperidone to block the PPI-disruptive effects of the direct dopamine receptor agonist apomorphine, which exerts its effects on sensorimotor gating in rats primarily through activity at the D_2 receptor – and perhaps in part through the D_3 receptor (Varty and Higgins, 1998) – is consistent with the relatively high affinity of iloperidone for these dopamine receptors. Apomorphine also acts as a partial agonist at the D_4 receptor (Chabert et al., 1994), and while the affinity of iloperidone is greater for the D_2 and D_3 receptors than the D_4 receptor (21.4 and 7.1 nM vs 25.0 nM), it should be noted that at the current doses, iloperidone may exert part of its behavioral effects through this latter receptor.

Cirazoline is an agonist at noradrenergic α_1-adrenoceptors, and the reduction of cirazoline-induced PPI deficits is in agreement with *in vitro* studies that confirm the antagonistic properties of iloperidone at the norepinephrine α_1-adrenoceptor (Kalkman et al., 2001). It is unlikely that iloperidone prevents PCP-induced sensorimotor gating deficits by direct activity at the NMDA receptor, as the drug displays minimal binding affinity for this receptor. Rather, it has been hypothesized that PCP disrupts PPI through its indirect effects on alternate neurotransmitter systems (Bakshi and Geyer, 1997; Geyer et al., 2001), and PCP-induced disruptions in PPI in rats can be blocked specifically by prazosin, a selective norepinephrine α_1-adrenoceptor antagonist (Bakshi and Geyer, 1997). This finding led to the hypothesis that most atypical antipsychotics which are effective in reversing PCP-induced PPI deficits may do so partly as a function of their antagonistic properties at the α_1-adrenoceptor (Geyer and Ellenbroek, 2003). Given the high affinity of iloperidone for this receptor, it is therefore likely that the capacity of iloperidone to prevent PCP-induced PPI deficits, as well as PPI disruption produced by more selective NMDA-receptor antagonists (Hans Neijt, personal communication), is mediated in part through antagonism of the α_1-adrenoceptor.

The present results provide strong evidence that the *in vitro* pharmacological profile of iloperidone that was demonstrated in earlier studies extends to ''atypical'' properties *in vivo* in a behavioral paradigm. While both typical and atypical antipsychotic drugs are effective in blocking PPI deficits induced by pharmacological treatment with direct or indirect dopamine receptor antagonists, such as apomorphine or *d*-amphetamine, there is a general consensus that atypical antipsychotics are relatively more effective in preventing NMDA-receptor antagonist-induced PPI deficits (Zhang et al., 1999; Geyer et al., 2001; Geyer and Ellenbroek, 2003), consistent with the manner in which iloperidone blocked PCP-induced PPI deficits. Although there are a few exceptions to the above rule, the overall pharmacological and behavioral profile of iloperidone thus suggests that it may be ascribed ''atypical'' status. According to Meltzer and colleagues, most atypical antipsychotic drugs, as exemplified by the prototypical drug clozapine, exhibit a high affinity for both the 5-HT_{2A} and the D_2 receptor (Meltzer et al., 1989, 2003), with the affinity of the former usually one order of magnitude greater than the latter. In the present study, we confirmed the efficacy of iloperidone against the D_2 receptor agonist apomorphine. Pilot studies from our laboratory also suggest that iloperidone is effective in preventing decreases in PPI caused by treatment with the 5-HT_{2A} receptor agonist 2, 5-dimethoxy-4 iodophenyl-isopropylamine

(DOI), while a previous study showed that iloperidone was behaviorally effective in another animal model of 5-HT_{2A} receptor activity, by blocking DOI-induced body shakes, forepaw tapping, and skin-jerks (Wettstein et al., 1999). Although high affinity for the α_1-adrenoceptor has not traditionally been considered a requirement for atypical antipsychotic drugs, most such compounds nevertheless exhibit a high binding affinity for this receptor, leading to the suggestion that this property may contribute to blockade of psychotic symptoms in humans (Svensson, 2003).

Given the above findings regarding the capacity of iloperidone to prevent pharmacologically induced PPI deficits, it is surprising that the drug did not reverse isolation rearing-induced PPI deficits. Postweaning social isolation of rats has been posited as a developmental animal model of schizophrenia (Powell and Geyer, 2002; Powell et al., 2003; Barr et al., 2004b), and PPI deficits in this model are typically responsive to second generation or ''atypical'' antipsychotic drugs (Bakshi et al., 1998). Several explanations for this discrepancy may be considered. Firstly, the single 1 mg/kg dose of iloperidone may have been insufficient to reverse PPI deficits in isolation-reared rats, despite the capacity of the drug to reverse startle reactivity increases in these animals. However, we were disinclined to use a higher dose of iloperidone, as the results of the apomorphine study revealed an effect on PPI with the 3 mg/kg dose even in vehicle-treated rats. Alternatively, the relatively smaller effect size of isolation rearing on PPI compared to pharmacological disruption may have reduced our statistical power to observe a significant reversal of PPI deficits by iloperidone. Additional future studies are required to address these possibilities, as well as in alternative models of sensorimotor gating loss, such as psychostimulant-induced sensitization (Barr et al., 2002; Sawada et al., 2005; Tenn et al., 2005) early lesion paradigms (Zhang et al., 1999) and drug withdrawal paradigms (Barr and Markou, 2005; Peleg-Raibstein et al., in press). It will also be informative to assess the behavioral effects of iloperidone in rodents with ''naturally'' low levels of PPI, such as in the DBA/2J strain of mice (Olivier et al., 2001) or the Brown Norway rat (Palmer et al., 2000), as well as in chronic administration studies and across a wider dose range.

In addition to the potent effects of iloperidone in the present investigation on drug-induced manipulation of sensorimotor gating, the drug has also been shown to be effective in other preclinical pharmacological models of antipsychotic activity. Earlier studies with iloperidone demonstrated that the compound prevented dopamine-related behavioral changes in rodents, including apomorphine-induced climbing behavior in mice and pole climb avoidance and self-stimulation behavior in rats (Szewczak et al., 1995). Importantly, iloperidone exhibited minimal activity in tasks predictive of extrapyramidal side effect liability (Strupczewski et al., 1995; Szewczak et al., 1995). Evidence that iloperidone is effective in serotonergic-related paradigms came from studies showing that iloperidone effectively reduced 5-HT-induced head twitch in rats (Szewczak et al., 1995) and also increased the social interaction of rats with unknown conspecifics (Strupczewski et al., 1995). Iloperidone also displayed anxiolytic-like properties in the elevated plus maze in rodents (Szewczak et al., 1995), which is consistent with our present observations that the compound is effective in reversing elevated acoustic startle in both cirazoline-treated and isolation-reared rats; elevated acoustic startle has been associated with a generalized anxiety-like state (Anisman et al., 2000). Interestingly, a more recent study indicated that iloperidone was able to selectively increase the working memory performance of rats on a longer-delay matching paradigm (Gemperle et al., 2003). Given that schizophrenia is associated with working memory deficits (Howard et al., 2002), and that pharmacological treatments for the pre-attentive and memory-related cognitive symptoms of schizophrenia are a priority for clinical development (Meltzer, 2004), the present results suggest that iloperidone merits further investigation, in both human and preclinical studies, as a drug for the treatment of psychotic disorders.

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