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Differential effects of antipsychotic drugs on serotonin-1A receptor mediated disruption of prepulse inhibition

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Abbreviations:

5-HT_{1A} receptor = Serotonin-1A receptor

8-OH-DPAT = 8-hydroxy-di-propylaminotetralin

BA = Brodmann's Area

PPI = prepulse inhibition

ISI = Interstimulus interval

SEM = Standard error of the mean

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Abstract

Serotonin-1A (5-HT_{1A}) receptors have been implicated in the symptoms of schizophrenia. However, there is limited *in vivo* evidence for an interaction of antipsychotic drugs with 5-HT_{1A} receptor mediated behavioral effects. We therefore investigated in rats the action of several antipsychotic drugs on prepulse inhibition (PPI), a measure of sensorimotor gating which is deficient in schizophrenia. Disruption of PPI at the 100 msec interstimulus interval (ISI), but not the 30 msec ISI, was induced by treatment with 0.5 mg/kg of the 5-HT_{1A} receptor agonist, 8-hydroxy-di-propyl-aminotetralin (8-OH-DPAT). In rats pretreated with 0.25 mg/kg of haloperidol or raclopride, the disruption of PPI was no longer significant. Of the atypical antipsychotic drugs clozapine, olanzapine, risperidone, amisulpride and aripiprazole, only aripiprazole significantly reduced the effect of 8-OH-DPAT on PPI. This effect was mimicked by pretreatment with the 5-HT_{1A} receptor partial agonist, buspirone. On the other hand, some of the antipsychotic drugs and other pretreatments showed complex, prepulse-dependent effects on their own. These data show little *in vivo* interaction of several atypical antipsychotic drugs with the disruption of PPI mediated by 5-HT_{1A} receptor stimulation. The action of haloperidol and raclopride suggests a major involvement of dopamine D_2 receptors in this effect, possibly downstream from the initial serotonergic stimulation. The action of aripiprazole could be mediated by its partial agonist properties at 5-HT_{1A} receptors or its dopamine D_2 blocking properties.

While several studies have suggested a role for serotonin receptors in schizophrenia, most studies have focused on serotonin-2A (5-HT_{2A}) receptors. Recently, there has been increased interest in a possible role of 5-HT_{1A} receptors in schizophrenia as well. For example, some studies have suggested a link between a 5-HT_{1A} receptor C(-1019)G polymorphism and schizophrenia (Huang et al., 2004). Post-mortem research has shown changes in the density of the 5-HT_{1A} receptor, predominantly in the cortex from patients with schizophrenia. Thus, when using either homogenate binding or autoradiography, there was a 15 - 80% increase in 5-HT_{1A} receptor binding density in the frontal cortex, mostly in Brodmann's Area 10 (BA10, prefrontal cortex), but also in BA9, BA44 and BA46 (Bantick et al., 2001). There was a tendency for increased density of 5-HT_{1A} receptor binding in a number of other brain regions, but unlike the frontal cortex, findings have been less consistent (Bantick et al., 2001).

It is well established that atypical antipsychotics with combined D_2 and 5-HT_{2A} receptor antagonism are clinically effective in schizophrenia, however, the combination of D_2 receptor antagonism and 5-HT_{1A} receptor agonism has received less attention as an important receptor profile for antipsychotic treatment (Wadenberg and Ahlenius, 1991; Ichikawa and Meltzer, 1999; Bantick et al., 2001). Atypical antipsychotic drugs, such as aripiprazole, clozapine and ziprasidone, have a moderate affinity for 5-HT_{1A} receptors (Ichikawa and Meltzer, 1999; Bantick et al., 2001) and display a low incidence of extrapyramidal side-effects (Rollema et al., 2000; Cosi and Koek, 2001). Animal studies have shown that treatment with 5-HT_{1A} receptor agonists selectively increases dopamine release in the prefrontal cortex, while reducing or not affecting dopamine release in the striatum (for review see (Ichikawa and Meltzer, 1999; Bantick et al., 2001)). This is important for schizophrenia, as increasing cortical dopamine release may result in an improvement of the negative symptoms of schizophrenia, while the lack of such an effect in the striatum may

result in a low incidence of extrapyramidal side-effects (Ichikawa and Meltzer, 1999; Rollema et al., 2000). Furthermore, treatment with clozapine selectively increased dopamine release in the rat prefrontal cortex and ventral hippocampus, an effect at least partially mediated by 5-HT_{1A} receptors (Chung et al., 2004), potentially inhibiting serotonergic transmission via activation of 5-HT_{1A} autoreceptors (Bantick et al., 2001).

Several other of the proposed beneficial 5-HT_{1A} receptor components of antipsychotic drug action have been deduced from indirect and *in vitro* studies, such as in binding assays or cell cultures (Newman-Tancredi et al., 2005; Bruins Slot et al., 2006). Importantly, however, these atypical antipsychotics tend to have a rich pharmacology, including affinity for dopamine (e.g. D_2), 5-HT (e.g. 5-HT_{1A}, 5-HT_{2A}) and several other receptor sub-types, the combination of which is likely to be responsible for their clinical efficacy. Therefore, the specific importance of 5-HT_{1A} receptor agonist or antagonist properties in the antipsychotic profile of these drugs *in vivo* remains unclear.

In contrast to possible beneficial actions of 5-HT_{1A} receptor activation (see above), some of these effects resemble a schizophrenia-like state, rather than an antipsychotic action. For example, it is well described that administration of the prototypical 5-HT_{1A} receptor agonist, 8-hydroxy-di-propylaminotetralin (8-OH-DPAT) causes a disruption of prepulse inhibition (PPI) (Rigdon and Weatherspoon, 1992; Sipes and Geyer, 1995; Gogos and Van den Buuse, 2004), a measure of sensorimotor gating which is also deficient in schizophrenia (Braff and Geyer, 1989; Kumari and Sharma, 2002). The effect of 8-OH-DPAT on PPI could be blocked by pretreatment with the selective 5-HT_{1A} receptor antagonist, (+)WAY 100,135 (N-tert-butyl-3-(4-(2-methoxyphenyl)-piperazin-1-yl)-2-phenyl-propanamide) (Sipes and Geyer, 1995; Czyrak et al., 2003), confirming that this disruption is mediated by stimulation of 5-HT_{1A} receptors rather than 5-HT_7 receptors for which 8-OH-DPAT also has affinity (Shen et

al., 1993). However, there is limited information on the effect of antipsychotic drugs on 5-HT_{1A} receptor mediated disruptions of PPI. Therefore the aim of the present study was to compare six antipsychotic drugs, haloperidol, risperidone, clozapine, olanzapine, amisulpride and aripiprazole with respect to their ability to modulate the action of 8-OH-DPAT on PPI. We also tested the dopamine D_2 receptor antagonist, raclopride, as comparison for haloperidol, and the 5-HT_{1A} receptor partial agonists, MDL 73,005EF (8-[2-(2,3-dihydro-1,4-benzodioxin-2-yl-methylamino)ethyl]-8-azaspiro[4,5]decane-7,9-dione methyl sulphonate) and buspirone. We measured startle amplitude, as well as PPI at a short interstimulus interval (ISI, 30 msec) and a longer ISI (100 msec). The results show differential effects of antipsychotic drugs on 5-HT_{1A} receptor-mediated disruption of PPI with a major component of this interaction likely to be blockade of dopamine D_2 receptors.

Methods

Animals

Experiments were done on male Sprague-Dawley rats (body weight 300-400 g) which were obtained from the breeding colony at the Department of Pathology, University of Melbourne. After arriving at the institute, the rats were allowed at least one week of acclimation before testing commenced.

Protocol

Around 2-3 days before the start of the experiments, all rats were acclimated to the PPI procedure once without any treatments. After this 'pre-test', rats received two treatments per test (pretreatment with antipsychotic drug or saline vs. treatment with 8-OH-DPAT or saline) and were tested six times with 3-4 day intervals: saline/saline, antipsychotic drug low dose/saline, antipsychotic drug high dose/saline, saline/8-OH-DPAT, antipsychotic drug low dose/8-OH-DPAT, antipsychotic drug high dose/8-OH-DPAT. One separate cohort of 7-11 rats was used for each antipsychotic drug, except MDL 73,005EF and buspirone, which were tested at only one dose and were combined in one experiment. The sequence of treatment was pseudo-randomized so that at the end of the series of experiments, all rats in a cohort had received all treatment combinations. Injection volumes were 1 ml/kg body weight. Antipsychotic drugs or saline were injected intraperitoneally (i.p.) 30 min before injection of 0.5 mg/kg of 8-OH-DPAT or saline, which was injected subcutaneously (s.c.) about 5 min before the animals were placed in the PPI enclosures.

Drugs

8-OH-DPAT ((±)-8-hydroxy-2-dipropylaminotetralin hydrobromide) was obtained from Tocris (UK) and dissolved at 0.5 mg/ml in 0.9% saline. Haloperidol (4-[-4-(p-chlorophenyl)-4-hydroxypiperidino]-4-'fluoro butyrophenone) was obtained from Sigma (USA), dissolved in saline and injected at 0.05 mg/kg and 0.25 mg/kg. Raclopride (3,5-dichloro-N-(1-ethylpyrrolidin-2-ylmethyl)-2-hydroxy-6-methoxybenzamide tartrate) was obtained from Astra (Sweden), dissolved in saline and similarly injected at 0.05 and 0.25 mg/kg. Clozapine (8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]-diazepine) was obtained from BDG Synthesis (New Zealand), dissolved in a minimal amount of 0.1N HCl and diluted to the required 1 mg/kg or 5 mg/kg dose. For pretreatment with olanzapine (2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine), we used Zyprexa® Zydis® wafers (Lilly, USA), containing 5 mg or 15 mg of olanzapine each, which were dissolved in saline to prepare the required 1 mg/kg and 5 mg/kg doses. For pretreatment with risperidone 3-[2-[-4-(6-fluoro-1, 2-benzisoxazol-3-yl) piperidino] ethyl-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one), we used Risperdal® 1 mg/ml solution (Janssen-Cilag, Belgium) undiluted (1 mg/kg) or diluted in saline to obtain the required dose of 0.2 mg/kg. For pretreatment with amisulpride (4-amino-N-[(1-ethyl-2-pyrrolidinyl)methyl]-5-(ethylsulfonyl)-o-anisamide), we used Solian®400 tablets (Sanofi-Synthelabo, France), containing 400 mg amisulpride each, which were dissolved in saline to obtain the required doses of 10 mg/kg or 50 mg/kg. For pretreatment with aripiprazole (7-[4-[-4[-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyrilor 7-[4-[4-(2,3-dichlorophenyl) piperazin-1-yl]butoxy]-1,2,3,4,-tetrahydroquinolin-2-one), we used Abilify™ tablets (Bristol-Myers Squibb, UK), containing 15 mg aripiprazole each, which were dissolved in saline to obtain the required 1 and 5 mg/kg doses. MDL 73,005EF ((8-[2-(2,3-dihydro-1,4-

benzodioxin-2-yl-methylamino)ethyl]-8-azaspiro[4,5]decane-7,9-dione methyl sulphonate) and buspirone (N-[4-[4-(2-Pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4.5]decane-7,9-dione hydrochloride) were obtained from Sigma and dissolved in saline at 1 and 5 mg/kg, respectively. All drug doses were obtained from the literature or preliminary experiments in the laboratory.

Startle amplitude and PPI

PPI of the acoustic startle response was measured using 8 automated SR-Lab startle chambers (San Diego Instruments, San Diego, CA, USA). The startle chambers (38W x 41L x 58H cm) were isolated to minimize extrinsic sound sources, well-lit and ventilated. A speaker positioned centrally in the roof of the chamber presented all test sounds. Rats were placed in an acrylic Plexiglas cylinder of 8.8 cm in diameter, with a length of 19.5 cm, which were closed at either end. The Plexiglas cylinder was attached to a platform with a piezoelectric transducer to detect whole body movements within the cylinder. Presentation of sounds and the recording of responses were automated using SR-Lab software (San Diego Instruments), which was controlled by a computer in an adjacent room.

For all experiments, we used a PPI session which consisted of 104 trials with a variable intertrial interval of 12-28 sec (average 19 sec). The first three minutes of the session were a 70 dB background noise presentation, allowing further acclimation to the test environment. The session commenced and finished with eight 115 dB, 40 msec pulse-alone trials. Together with two blocks of eight pulse-alone trials from the main part of the session, these startle blocks were used to calculate average startle amplitude and startle habituation across the session. The main part of the session included eight of each of the following prepulse-pulse trials: PP2P115, PP4P115, PP8P115 and PP16P115 at 30 msec between the start of the 20

msec prepulse and start of the pulse, and at 100 msec between the start of the prepulse and the pulse. PP2, PP4, PP8 and PP16 indicates 2, 4, 8 or 16 dB above the 70 dB background, i.e. 72, 74, 78 and 86 dB prepulses. In addition to the pulse-alone and prepulse-pulse trials, the session included eight 'NOSTIM' trials, where no startle stimulus was presented, to check for non-specific movement artefacts. The sequence of trials within the session was pseudo-randomized and the same for all eight simultaneously tested rats and for all consecutive drug experiments.

Data analysis

All data are expressed as mean ± standard error of the mean (S.E.M.). Startle amplitudes were calculated as the average values of each of the four blocks of startle stimuli, allowing analysis of both startle magnitude and startle habituation. However, to simplify the data presentation, startle habituation will not be addressed here. Prepulse inhibition values were obtained and plotted for each of the prepulse levels for each ISI. Figures 1-8 show these results for each prepulse intensity, whereas figure 9 shows a summary of the results with only the average of all prepulse intensities included. First, analysis of variance (ANOVA) with repeated measures was used to assess main treatment effects on PPI. Within-animal repeated measures factors were antipsychotic dose effect (3 levels), 8-OH-DPAT effect (2 levels), and prepulse level (4 levels). Where appropriate, one-way ANOVA and Least-Significant Difference test (LSD) were then used to assess differences between treatments for individual prepulse intensities, i.e. to assess effects of antipsychotics or 8-OH-DPAT. When $P<0.05$, differences were considered statistically significant.

Results

Haloperidol (Fig. 1, Table 1)

Combined analysis of startle data for both haloperidol doses revealed a trend for a main effect of Dose ($F(2,12)=2.9$, $P=0.089$). Compared to saline, haloperidol at 0.25 mg/kg, but not 0.05 mg/kg, significantly reduced startle amplitudes ($F(1,6)=15.9$; $P=0.007$). 8-OH-DPAT treatment tended to cause an increase in startle responses, however this effect was not significant (Table 1).

While haloperidol had no effect on PPI at the 30 msec interval, there were significant main effects of 8-OH-DPAT treatment ($F(1,6)=31.0$, $P=0.001$) and of prepulse level ($F(3,18)=125.0$, $P<0.001$). However, there were no significant treatment effects at any of the individual prepulse intensities (Fig. 1).

Combined analysis of all haloperidol doses and all prepulse levels at the 100 msec interval showed significant main effects of Dose ($F(2,10)=17.7$, $P=0.001$), 8-OH-DPAT ($F(1,5)=35.0$, $P=0.002$) and Prepulse ($F(3,15)=113.0$, $P<0.001$). At PP2, the disruption of PPI by 8-OH-DPAT was significant after pretreatment with saline and 0.05 mg/kg of haloperidol, but was blocked after pretreatment with 0.25 mg/kg of haloperidol (Fig. 1). At PP4, the effect of 8-OH-DPAT was significant after pretreatment with 0.05 mg/kg of haloperidol, although not after saline pretreatment, and again was blocked after pretreatment with 0.25 mg/kg of haloperidol (Fig. 1). Similarly, at PP8 and PP16, the effect of 8-OH-DPAT was significant after pretreatment with saline and 0.05 mg/kg of haloperidol and was blocked after pretreatment with 0.25 mg/kg of haloperidol (Fig. 1). At none of the prepulse intensities did haloperidol treatment significantly alter PPI on its own.

Raclopride (Fig. 2, Table 1)

To confirm and extend the observation, that haloperidol pretreatment could block the action of 8-OH-DPAT on PPI, we also tested raclopride, another (putative) antipsychotic drug with a predominantly dopamine D_2 blocking mode of action.

Analysis of startle data showed that neither raclopride nor 8-OH-DPAT significantly affected startle (Table 1) although 8-OH-DPAT treatment tended to cause an increase in startle responses. Raclopride had no effect on PPI at the 30 msec interval, although there was a significant main effect of Prepulse level ($F(3,18)=110.4$, $P<0.001$). As with haloperidol, there were no significant treatment effects at any of the individual prepulse intensities (Fig. 2).

Combined analysis of all raclopride doses and all prepulse levels at the 100 msec interval showed significant main effects of 8-OH-DPAT ($F(1,6)=30.3$, $P=0.002$) and Prepulse ($F(3,18)=52.2$, $P<0.001$). In this cohort of rats, there were no treatment effects at PP2 (Fig. 2). Similar to the haloperidol experiment, at PP4 the disruption of PPI by 8-OH-DPAT was significant after pretreatment with 0.05 mg/kg of raclopride, although not after saline pretreatment, and was blocked after pretreatment with 0.25 mg/kg of raclopride (Fig. 2). At PP8, the effect of 8-OH-DPAT was significant after pretreatment with saline and 0.05 mg/kg of raclopride and was blocked after pretreatment with 0.25 mg/kg of raclopride (Fig. 2). At PP16, the effect of 8-OH-DPAT was significant only after saline pretreatment. At none of the prepulse intensities did raclopride pretreatment significantly alter PPI on its own.

Clozapine (Fig. 3, Table 1)

To assess if the blocking action of haloperidol and raclopride extended to atypical antipsychotic drugs, we also tested clozapine, olanzapine, risperidone, amisulpride and aripiprazole.

Clozapine significantly reduced startle responses ($F(2,16)=8.4$, $P=0.003$) and this effect was significant for both the 1 mg/kg dose ($F(1,8)=15.8$; $P=0.004$) and the 5 mg/kg dose ($F(1,8)=10.2$; $P=0.013$). 8-OH-DPAT treatment caused a slight, but significant increase of startle amplitude ($F(1,8)=6.0$, $P=0.040$) (Table 1).

At the 30 msec interval, ANOVA showed the expected main effects of 8-OH-DPAT ($F(1,8)=7.7$, $P=0.024$) and Prepulse level ($F(3,18)=110.4$, $P<0.001$). Moreover, ANOVA revealed that clozapine treatment resulted in complex modulation of PPI dependent on the prepulse intensity (Dose x Prepulse interaction $F(6,48)=3.3$, $P=0.009$). Further analysis at different prepulse intensities revealed that there was a clear tendency for 5 mg/kg of clozapine to reduce PPI at this ISI allowing an apparent enhancement of PPI by 8-OH-DPAT (Fig. 3). Thus, average PPI after saline- or 8-OH-DPAT treatment was 22±9% and 32±3%, respectively, after saline pretreatment, compared to -1±11% and 30±4%, respectively, after clozapine pretreatment. At PP2, there was no effect of 8-OH-DPAT after saline or 1 mg/kg of clozapine pretreatment, however after 5 mg/kg of clozapine, PPI tended to be reduced ($P=0.072$) revealing a significant PPI enhancing effect of 8-OH-DPAT (Fig. 3). At PP4, PPI was significantly reduced by 5 mg/kg of clozapine, again allowing a significant effect of 8-OH-DPAT (Fig. 3). At PP8, the effect of 5 mg/kg of clozapine was not significant, although again an apparent effect of 8-OH-DPAT appeared after this dose of the antipsychotic (Fig. 3). At PP16, there were no significant treatment effects, although the difference between 8-OH-DPAT after saline pretreatment and after 5 mg/kg of clozapine pretreatment reached trend level ($P=0.070$) (Fig. 3).

The effect of clozapine on PPI at the 100 msec ISI did not show the same reducing influence as seen at the 30 msec ISI, however there was a Dose x 8-OH-DPAT x Prepulse interaction ($F(6,48)=2.8$, $P=0.020$) again suggesting complex interacting effects of clozapine

and 8-OH-DPAT on PPI dependent on the prepulse intensity (Fig. 3). ANOVA also showed main effects of 8-OH-DPAT ($F(1,8)=11.5$, $P=0.009$) and of Prepulse intensity ($F(3,24)=36.3$, $P<0.001$). At PP2, the significant effect of 8-OH-DPAT was blocked by both the 1 and 5 mg/kg dose. On the other hand, no effect of clozapine at either dose was observed at PP4, while at PP8 and PP16, both doses appeared to enhance the effect of 8-OH-DPAT (Fig. 3).

Olanzapine (Fig. 4, Table 1)

Olanzapine significantly reduced startle responses ($F(2,14)=5.1$, $P=0.021$) at the 5 mg/kg dose ($F(1,7)=43.6$; $P<0.001$) but not the 1 mg/kg dose. 8-OH-DPAT treatment tended to cause an increase in startle amplitude, an effect which became significant when data for saline and 5 mg/kg of olanzapine were analyzed ($F(1,7)=8.1$, $P=0.025$) (Table 1).

PPI at the 30 msec ISI showed the expected effect of Prepulse intensity ($F(3,21)=102.6$, $P<0.001$) but was not significantly affected by either olanzapine or 8-OH-DPAT (Fig. 4).

PPI at the 100 msec ISI again showed the expected effect of Prepulse intensity ($F(3,21)=101.5$, $P<0.001$) and was significantly reduced by 8-OH-DPAT treatment ($F(1,7)=43.2$, $P<0.001$). In addition, there was a main effect of olanzapine of borderline significance ($F(2,14)=3.8$, $P=0.048$). At none of the prepulse intensities did olanzapine block the reducing effect of 8-OH-DPAT (Fig. 4). Thus, the effect of 8-OH-DPAT was significant at all prepulse intensities and all pretreatments, except after 1 mg/kg of olanzapine at PP2 and 5 mg/kg of olanzapine at PP8, which failed to reach significance (Fig. 4). At none of the prepulse intensities did olanzapine pretreatment significantly alter PPI on its own.

Risperidone (Fig. 5, Table 1)

Combined analysis of startle amplitudes revealed main effects of risperidone Dose ($F(2,12)=10.2$, $P=0.003$) and 8-OH-DPAT ($F(1,6)=13.6$, $P=0.010$). Pretreatment with risperidone slightly reduced startle amplitudes both at the 0.2 mg/kg dose ($F(1,6)=18.4$; $P=0.005$) and the 1 mg/kg dose ($F(1,6)=7.3$; $P=0.036$) while 8-OH-DPAT enhanced startle amplitude after both pretreatments ($F(1,6)=10.8$; $P=0.017$ and $F(1,6)=13.1$; $P=0.011$, respectively) (Table 1).

Analysis of PPI data at the 30 msec ISI revealed the expected main effects of 8-OH-DPAT ($F(1,6)=9.9$, $P=0.020$) and Prepulse level ($F(3,18)=109.6$, $P<0.001$). Moreover, ANOVA revealed that risperidone pretreatment, as with clozapine, resulted in complex modulation of PPI dependent on the prepulse intensity (Dose x Prepulse interaction $F(6,36)=2.6$, $P=0.035$; Dose x 8-OH-DPAT x Prepulse interaction $F(6,48)=2.8$, $P=0.023$). This was particularly clear at PP2, where 1 mg/kg of risperidone significantly reduced PPI on its own, unmasking significant enhancement of PPI by 8-OH-DPAT (Fig. 5). At other prepulse intensities, neither risperidone or 8-OH-DPAT affected PPI at the 30 msec ISI (Fig. 5).

Analysis of PPI at the 100 msec ISI revealed a main effect of risperidone dose ($F(2,12)=11.7$, $P=0.002$), reflecting a general tendency for PPI to be enhanced after risperidone treatment (Fig. 5). In addition, there was the expected disruption of PPI by 8-OH-DPAT ($F(1,6)=36.7$, $P=0.001$) and main effect of prepulse intensity ($F(3,18)=93.2$, $P<0.001$). At PP2, PP8 and PP16, 1 mg/kg of risperidone significantly increased PPI on its own while generally not blocking the disruption induced by 8-OH-DPAT (Fig. 5). Thus, the effect of 8-OH-DPAT was significant at all prepulse intensities and all pretreatment doses, except after 0.2 mg/kg of risperidone at PP2, after 1 mg/kg of risperidone at PP4 ($P=0.069$), and after saline pretreatment at PP8 and PP16 (Fig. 5).

Amisulpride (Fig. 6, Table 1)

Amisulpride had no effect on startle amplitude (Table 1), while 8-OH-DPAT significantly increased startle ($F(1,9)=13.6$, $P=0.005$).

Analysis of PPI at the 30 msec ISI showed the expected main effect of Prepulse intensity ($F(3,27)=48.8$, $P<0.001$). 8-OH-DPAT treatment tended to increase PPI, but only at lower prepulse intensities (8-OH-DPAT x Prepulse interaction $F(3,27)=6.5$, $P=0.002$). However, analysis of individual prepulse intensities did not reveal any significant effects of 8-OH-DPAT or amisulpride (Fig. 6).

Analysis of PPI at the 100 msec ISI revealed marked disruption by 8-OH-DPAT ($F(1,9)=60.6$, $P<0.001$) and a main effect of prepulse intensity ($F(3,27)=93.1$, $P<0.001$), however there was no effect of amisulpride (Fig. 6). As with clozapine, olanzapine and risperidone, amisulpride pretreatment did not block the action of 8-OH-DPAT on PPI (Fig. 6). Thus, the effect of 8-OH-DPAT was significant at all prepulse intensities and all pretreatment doses, except after 10 mg/kg of amisulpride at PP4 ($P=0.079$), PP8 and at PP16 (Fig. 6). At none of the prepulse intensities did amisulpride pretreatment significantly alter PPI on its own.

Aripiprazole (Fig. 7, Table 1)

8-OH-DPAT significantly enhanced startle amplitude ($F(1,7)=9.0$; $P=0.020$), however there were no effects of aripiprazole pretreatment (Table 1). PPI at the 30 msec ISI showed the main effect of Prepulse intensity ($F(3,21)=78.8$, $P<0.001$) but was not significantly affected by either aripiprazole or 8-OH-DPAT (Fig. 7).

Analysis of PPI data at the 100 msec ISI revealed a significant disruption by 8-OH-DPAT treatment ($F(1,7)=25.4$; $P<0.001$) and a main effect of prepulse intensity

(F(3,21)=103.1, P<0.001). At PP2, 8-OH-DPAT treatment tended to decrease PPI, except in animals which were pretreated with 5 mg/kg of aripiprazole, however these differences did not reach statistical significance (Fig. 7). In contrast, at PP4, 8-OH-DPAT significantly disrupted PPI and this effect was blocked by 5 mg/kg of aripiprazole (Fig. 7). Also at PP8 and PP16, 8-OH-DPAT significantly disrupted PPI, however this was not influenced by aripiprazole pretreatment (Fig. 7).

MDL 73,005EF and buspirone (Fig. 8, Table 1)

There were no significant main effects of MDL 73,005EF on startle amplitude (Table 1). PPI at the 30 msec ISI was slightly, but significantly increased by MDL 73,005EF treatment (F(1,16)=5.7, P=0.030) in addition to the main effect of prepulse intensity (F(3,48)=114.0, P<0.001) (Fig. 8). At PP2, 8-OH-DPAT significantly increased PPI, an effect which was not observed after pretreatment with MDL 73,005EF because of a significant increase in PPI induced by this pretreatment itself (Fig. 8). At PP4, a similar increase of PPI by MDL 73,005EF pretreatment was seen which was close to significance (P=0.065). At PP16, but not at PP8, there was again a slight, but significant increase of PPI after MDL 73,005EF pretreatment. 8-OH-DPAT had no significant effects at PP4, PP8 or PP16 (Fig. 8).

At the 100 msec ISI, again there was a main effect of prepulse intensity (F(3,48)=96.4, P<0.001) and the expected marked disruption of PPI by 8-OH-DPAT treatment (F(1,16)=14.8, P=0.001). There was also an overall increase in PPI induced by MDL 73,005EF pretreatment (F(1,16)=10.3, P=0.006) but no statistical interaction between the effects of MDL 73,005EF pretreatment and 8-OH-DPAT treatment (Fig. 8), similar to the result in risperidone-treated animals. At PP2, the effect of MDL 73,005EF on baseline PPI was close to significance (P=0.057). However, while PPI tended to be increased by MDL 73,005EF at other prepulse

intensities as well (Fig. 8), these effects did not reached significance. At PP4, 8-OH-DPAT significantly disrupted PPI after both saline pretreatment and MDL 73,005EF pretreatment. At PP8, a similar trend was observed (Fig. 8) although the effects only reached trend level ($P=0.091$ and $P=0.077$, respectively). At PP16, PPI was slightly, but significantly lower after 8-OH-DPAT treatment in saline controls only (Fig. 8).

Pretreatment with 5 mg/kg of buspirone did not significantly alter startle amplitude (Fig. 8). Neither buspirone pretreatment nor 8-OH-DPAT significantly affected PPI at the 30 msec ISI (Fig. 8) and only a main effect of prepulse intensity was observed ($F(3,48)=155.7$, $P<0.001$). On the other hand, analysis of PPI at the 100 msec ISI revealed main effects of prepulse intensity $F(3,48)=91.6$, $P<0.001$), buspirone pretreatment ($F(1,16)=6.7$, $P=0.020$), and of 8-OH-DPAT treatment ($F(1,16)=4.2$, $P=0.057$). There was also a significant interaction of buspirone pretreatment with the effect of 8-OH-DPAT ($F(1,16)=7.1$, $P=0.017$), reflecting blockade of the effect of 8-OH-DPAT treatment in buspirone-pretreated rats (Fig. 8). Thus, while buspirone pretreatment did not affect PPI on its own, it blocked the disruption of PPI by subsequent 8-OH-DPAT treatment at all prepulse intensities (Fig. 8).

Discussion

The aim of the present experiments was to investigate the *in vivo* interaction of several antipsychotic drugs with central 5-HT_{1A} receptor mechanisms in a behavioral animal model with relevance to schizophrenia. Thus we assessed the ability of antipsychotic drugs to modulate the effect of 8-OH-DPAT on PPI, a measure of sensorimotor gating, which is deficient in schizophrenia (Braff and Geyer, 1989; Kumari and Sharma, 2002). Figure 9 summarizes and compares the effect of the different antipsychotics on the action of 8-OH-DPAT. The main finding of our experiments was, that there does not seem to be an interaction of most atypical antipsychotic drugs with the effect of 8-OH-DPAT on PPI (Fig. 9). Only treatment with aripiprazole significantly inhibited this effect, although this effect was only seen at some prepulse intensities. It is possible that the partial agonist activity and high affinity of aripiprazole at 5-HT_{1A} receptors (Newman-Tancredi et al., 2005; Bruins Slot et al., 2006) is responsible for this interaction. Thus, the efficacy of aripiprazole at 5-HT_{1A} receptors may not be high enough to elicit a disruption of PPI, however its receptor occupancy is sufficient to block the effect of subsequently administered 8-OH-DPAT. This explanation is supported by the experiment with another partial agonist at 5-HT_{1A} receptors, buspirone. This compound did not disrupt PPI by itself, but blocked the action of subsequently administered 8-OH-DPAT. The result with the 5-HT_{1A} receptor partial agonist, MDL 73,005EF, was more complex as it tended to increase resting PPI by itself. Previous studies in other paradigms have also shown that pretreatment with partial 5-HT_{1A} receptor agonists may cause inhibition of the action of 8-OH-DPAT (Boddeke et al., 1992; Buisson-Defferier and Van den Buuse, 1992; Pauwels et al., 1993). Clozapine, olanzapine, risperidone and amisulpride all have

lower affinity at 5-HT_{1A} receptors than aripiprazole (Newman-Tancredi et al., 2005), which could explain their lack of effect on the disruption of PPI caused by 8-OH-DPAT treatment.

Surprisingly, pretreatment with haloperidol almost completely blocked the effect of the 5-HT_{1A} receptor agonist. This blockade was also observed with another dopamine D_2 receptor antagonist, raclopride. This effect of haloperidol is unlikely to be due to a direct action at 5-HT_{1A} receptors as the affinity of this drug for these receptors is low (Newman-Tancredi et al., 2005). Rather, it is likely that 5-HT_{1A} receptor activation elicits a chain of events in the brain, ultimately leading to 'downstream' dopamine D_2 receptor activation which, similar to treatment with dopaminergic drugs, leads to disruption of PPI. Previously, some behavioral effects of 8-OH-DPAT, such as lower lip retraction, could also be blocked by pretreatment with spiperone or haloperidol, confirming a possible dopaminergic 'link' in the behavioral effects of 5-HT_{1A} receptor activation (Berendsen et al., 1990). This complicates the explanation of the action of antipsychotic drugs on the effect of 8-OH-DPAT. Aripiprazole is reported to have an affinity for dopamine D_2 receptors only slightly lower than haloperidol (pKi = 8.59 vs. 9.01, respectively) (Newman-Tancredi et al., 2005). Aripiprazole is a partial agonist at these receptors (Burris et al., 2002; Shapiro et al., 2003) while in rats it is metabolized *in vivo* to a full D_2 receptor antagonist (Wood et al., 2006). Thus the effect of aripiprazole could be explained by its blocking action on dopamine D_2 receptors as well as or rather than an action on 5-HT_{1A} receptors. Even the effect of buspirone in blocking the 8-OH-DPAT induced disruption of PPI could have been mediated by its binding to dopamine D_2 receptors. Buspirone displays high affinity for these receptors and has been shown to act as a dopamine D_2 receptor antagonist in several behavioral models (Ryan et al., 1993; Protais et al., 1998). On the other hand, risperidone was reported to have an affinity at dopamine D_2 receptors of 8.70 (Newman-Tancredi et al., 2005) yet in our experiments there was no

statistical interaction of risperidone pretreatement with the disruption of PPI caused by 8-OH-DPAT treatment. This lack of interaction was mainly caused by an increase in resting PPI after risperidone pretreatment and it should be noted that PPI in animals treated with both risperidone and 8-OH-DPAT was similar to that in controls, which would further support the conclusion that dopamine D_2 receptor blockade is able to inhibit the effect of 5-HT_{1A} receptor activation on PPI.

In a recent study, several antipsychotics were tested against the disruption of PPI induced by treatment with the dopamine receptor agonist, apomorphine (Auclair et al., 2006). Of the antipsychotics we also included, pretreatment with haloperidol, risperidone and olanzapine blocked the effect of apomorphine, while clozapine and aripiprazole were less effective (Auclair et al., 2006). Interestingly, when pretreatment with mixed D_2/5-HT_{1A} ligands was combined with a 5-HT_{1A} receptor antagonist, the ability to block the action of apomorphine was enhanced. These results support our finding of a functional interaction of activation of D_2 and 5-HT_{1A} receptors in PPI regulation, but also emphasize the complexity of this interaction. It would be reasonable to assume that involvement of dopamine D_2 receptors in PPI is modulated both positively and negatively by 5-HT_{1A} receptor activation. Further experimentation, for example with local injections into the brain, is needed to elucidate such interactions.

Our experiments also showed effects of antipsychotic drugs by themselves. For example, olanzapine and risperidone pretreatement increased PPI at the 100 msec ISI, whereas clozapine and risperidone induced complex, prepulse-dependent effects at the 30 msec ISI. These results show that for the full interpretation of drug effects on PPI, an extended protocol, including multiple prepulse intensities and ISIs, is preferable. Particularly at the shorter ISIs, modulation of the startle responses is a mix of true PPI and of negative PPI or prepulse

facilitation (PPF) (Plappert et al., 2004; Swerdlow et al., 2004a; Swerdlow et al., 2004b). The regulation and functional significance of PPF is poorly understood. Men have been shown to display higher PPI than women, but women displayed higher PPF than men (Aasen et al., 2005). PPF was found to be reduced in patients with schizophrenia and their unaffected siblings (Wynn et al., 2004). Thus, the modulatory effects of antipsychotic drugs on PPF seen in the current study could have relevance for our understanding of the mechanism of action of these drugs in patients with schizophrenia. PPI at longer ISIs is susceptible to attentional mechanisms, whereas PPI at shorter ISIs is a more "automatic" mechanism (Filion et al., 1993; Bohmelt et al., 1999) and these components could be differentially affected in schizophrenia and by antipsychotic drugs. Thus, psychopharmacological effects on PPI need to be interpreted with caution as the results may represent multiple and separate startle modulation mechanisms. In our experiments, 8-OH-DPAT only disrupted PPI at the 100 msec ISI, making it likely that only PPI, not PPF mechanisms, are involved.

PPI reflects a gating mechanism for sensory information and, as such, could be involved in some of the cognitive deficits seen in patients with schizophrenia (Braff and Geyer, 1989; Kumari and Sharma, 2002). Antipsychotic drugs have been shown by some studies to reverse the disruption of PPI seen in patients with schizophrenia. For example, treatment with either olanzapine or amisulpride reversed PPI deficits in patients with schizophrenia (Quednow et al., 2006). Treatment with clozapine (Oranje et al., 2002) and risperidone (Kumari et al., 2002) similarly restored PPI deficits. In contrast, other studies have not found a reversal with antipsychotic treatment, for example treatment with risperidone (Mackeprang et al., 2002; Oranje et al., 2002) or haloperidol or olanzapine (Duncan et al., 2003). As the cause of PPI deficits in schizophrenia is unknown, the mechanism by which antipsychotic drugs potentially modulate this deficit, remains unclear. Therefore in the present

study, we used a clearly defined agonist treatment, 8-OH-DPAT, to induce a disruption of PPI in rats. Our experiments confirm that affinity and efficacy data obtained *in vitro* in cell lines or membrane assays are difficult to extrapolate into an *in vivo* situation. Firstly, in addition to being essentially a mix between PPI and PPF, modulation of startle is controlled by a multitude of brain areas and neurotransmitter systems (Koch, 1999; Geyer et al., 2001). But even with selective pharmacological stimulation by 8-OH-DPAT, multiple receptor systems appear to be involved in the behavioral response, in this case at least 5-HT_{1A} receptors and dopamine D_2 receptors. Clearly, for the interpretation of possible clinical effects of new antipsychotic drugs, pre-clinical *in vivo* testing is still crucial.

In conclusion, we have compared several antipsychotic drugs with respect to their ability to modulate the effect of 8-OH-DPAT on PPI. While 8-OH-DPAT consistently disrupted PPI at the 100 msec ISI, only haloperidol and aripiprazole were able to inhibit this effect. The action of these antipsychotics was mimicked by raclopride and buspirone. Our results provide new insight into the interaction of antipsychotic drugs with central mechanisms involved in PPI, a behavioral model with relevance to aspects of schizophrenia.

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Footnotes

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FIGURE LEGENDS

Figure 1

The effect of pretreatment with haloperidol on the action of 0.5 mg/kg of 8-OH-DPAT (filled symbols) vs. saline (open symbols) on PPI at a 30 msec interstimulus interval (ISI, top row) and PPI at a 100 msec ISI (bottom row). Rats were pretreated with saline (Sal), 0.05 mg/kg of haloperidol or 0.25 mg/kg of haloperidol. Separate panels depict data for prepulse intensities of 2, 4, 8 or 16 dB above baseline (PP2, PP4, PP8, PP16). * $P<0.05$ for difference between 8-OH-DPAT treatment and respective saline control. Data are mean ± SEM of 7 rats. Pretreatment with 0.25 mg/kg of haloperidol blocked the disruption of PPI at the 100 msec ISI caused by treatment with 8-OH-DPAT.

Figure 2

The effect of pretreatment with raclopride on the action of 0.5 mg/kg of 8-OH-DPAT (filled symbols) vs. saline (open symbols) on PPI at a 30 msec interstimulus interval (ISI, top row) and PPI at a 100 msec ISI (bottom row). Rats were pretreated with saline (Sal), 0.05 mg/kg of raclopride or 0.25 mg/kg of raclopride. Separate panels depict data for prepulse intensities of 2, 4, 8 or 16 dB above baseline (PP2, PP4, PP8, PP16). * $P<0.05$ for difference between 8-OH-DPAT treatment and respective saline control. Data are mean ± SEM of 7 rats. Pretreatment with 0.25 mg/kg of raclopride blocked the disruption of PPI at the 100 msec ISI caused by treatment with 8-OH-DPAT.

Figure 3

The effect of pretreatment with clozapine on the action of 0.5 mg/kg of 8-OH-DPAT (filled symbols) vs. saline (open symbols) on PPI at a 30 msec interstimulus interval (ISI, top row) and PPI at a 100 msec ISI (bottom row). Rats were pretreated with saline (Sal), 1 mg/kg of clozapine or 5 mg/kg of clozapine. Separate panels depict data for prepulse intensities of 2, 4, 8 or 16 dB above baseline (PP2, PP4, PP8, PP16). * $P<0.05$ for difference between 8-OH-DPAT treatment and respective saline control. + $P<0.05$ for difference with saline pretreatment. Data are mean ± SEM of 9 rats. 8-OH-DPAT treatment increased PPI at the 30 msec ISI after pretreatment with 0.25 mg/kg of clozapine. The disruption of PPI at the 100 msec ISI by treatment with 8-OH-DPAT was not blocked by clozapine, except at PP2.

Figure 4

The effect of pretreatment with olanzapine on the action of 0.5 mg/kg of 8-OH-DPAT (filled symbols) vs. saline (open symbols) on PPI at a 30 msec interstimulus interval (ISI, top row) and PPI at a 100 msec ISI (bottom row). Rats were pretreated with saline (Sal), 1 mg/kg of olanzapine or 5 mg/kg of olanzapine. Separate panels depict data for prepulse intensities of 2, 4, 8 or 16 dB above baseline (PP2, PP4, PP8, PP16). * $P<0.05$ for difference between 8-OH-DPAT treatment and respective saline control. Data are mean ± SEM of 8 rats. Olanzapine pretreatment had little effect on the action of 8-OH-DPAT.

Figure 5

The effect of pretreatment with risperidone on the action of 0.5 mg/kg of 8-OH-DPAT (filled symbols) vs. saline (open symbols) on PPI at a 30 msec interstimulus interval (ISI, top

row) and PPI at a 100 msec ISI (bottom row). Rats were pretreated with saline (Sal), 0.2 mg/kg of risperidone or 1 mg/kg of risperidone. Separate panels depict data for prepulse intensities of 2, 4, 8 or 16 dB above baseline (PP2, PP4, PP8, PP16). * $P<0.05$ for difference between 8-OH-DPAT treatment and respective saline control. + $P<0.05$ for difference with saline pretreatment. Data are mean ± SEM of 7 rats. At PP2 at the 30 msec ISI, 1 mg/kg of risperidone reduced PPI and 8-OH-DPAT caused an increase after this pretreatment. At the 100 msec ISI, risperidone pretreatment generally increased PPI but did not prevent a significant disruption by 8-OH-DPAT.

Figure 6

The effect of pretreatment with amisulpride on the action of 0.5 mg/kg of 8-OH-DPAT (filled symbols) vs. saline (open symbols) on PPI at a 30 msec interstimulus interval (ISI, top row) and PPI at a 100 msec ISI (bottom row). Rats were pretreated with saline (Sal), 10 mg/kg of amisulpride or 50 mg/kg of amisulpride. Separate panels depict data for prepulse intensities of 2, 4, 8 or 16 dB above baseline (PP2, PP4, PP8, PP16). * $P<0.05$ for difference between 8-OH-DPAT treatment and respective saline control. Data are mean ± SEM of 10 rats. Amisulpride pretreatment had little effect on the action of 8-OH-DPAT.

Figure 7

The effect of pretreatment with aripiprazole on the action of 0.5 mg/kg of 8-OH-DPAT (filled symbols) vs. saline (open symbols) on PPI at a 30 msec interstimulus interval (ISI, top row) and PPI at a 100 msec ISI (bottom row). Rats were pretreated with saline (Sal), 1 mg/kg of aripiprazole or 5 mg/kg of aripiprazole. Separate panels depict data for prepulse intensities

of 2, 4, 8 or 16 dB above baseline (PP2, PP4, PP8, PP16). * P<0.05 for difference between 8-OH-DPAT treatment and respective saline control. Data are mean ± SEM of 8 rats. Pretreatment with 5 mg/kg of aripiprazole blocked the action of 8-OH-DPAT at the 100 msec ISI, particularly at lower prepulse intensities.

Figure 8

The effect of pretreatment with MDL 73,005EF (MDL) or buspirone (Busp) on the action of 0.5 mg/kg of 8-OH-DPAT (filled symbols) vs. saline (open symbols) on PPI at a 30 msec interstimulus interval (ISI, top row) and PPI at a 100 msec ISI (bottom row). Rats were pretreated with saline (Sal), 1 mg/kg of MDL 73,005EF or 5 mg/kg of buspirone. * P<0.05 for difference between 8-OH-DPAT treatment and respective saline control. + P<0.05 for difference with saline pretreatment. Data are mean ± SEM of 9 rats. MDL 73,005EF pretreatment increased PPI at the 30 msec ISI. Buspirone pretreatment blocked the action of 8-OH-DPAT on PPI at the 100 msec ISI.

Figure 9

Summary of the effect of pretreatment with haloperidol, raclopride, clozapine, olanzapine, risperidone, amisulpride, aripiprazole, MDL 73,005EF or buspirone on the disruption of PPI mediated by treatment with 8-OH-DPAT. PPI was assessed using a 30 msec interstimulus interval (ISI, first and third row) or a 100 msec ISI (second and fourth row). White bars depict values obtained after saline treatment and black bars depict values obtained after 8-OH-DPAT treatment. Doses of pretreatment drugs (mg/kg) are shown on the horizontal axes. PPI data are plotted as the average of all four prepulse intensities used (PP2, PP4, PP8,

PP16). For analysis of individual prepulse intensity results, see figures 1-8. * indicates a significant effect of 8-OH-DPAT as analyzed after either saline-, low-dose- or high-dose pretreatment. Data are mean ± SEM.

Table 1:

Average startle and PPI of rats treated with 8-OH-DPAT after pretreatment with various other drugs, including antipsychotics.

Pretreatments	Average startle	
Treatments:	Saline	8-OH-DPAT
Haloperidol (n=7)		
Saline	382 ± 34	485 ± 63
0.05 mg/kg	371 ± 34	400 ± 35
0.25 mg/kg	320 ± 29	426 ± 58
Raclopride (n=7)		
Saline	239 ± 37	324 ± 37
0.05 mg/kg	271 ± 40	315 ± 43
0.25 mg/kg	229 ± 47	271 ± 32
Clozapine (n=9)		
Saline	409 ± 79	539 ± 75
1 mg/kg	285 ± 56	382 ± 47
5 mg/kg	200 ± 33^{+}	455 ± 79*
Olanzapine (n=8)		
Saline	363 ± 70	498 ± 48
1 mg/kg	325 ± 54	352 ± 57
5 mg/kg	223 ± 40	351 ± 69
Risperidone (n=7)		
Saline	298 ± 28	587 ± 113*
0.2 mg/kg	219 ± 26	436 ± 79*
1 mg/kg	181 ± 15	537 ± 116*
Amisulpride (n=10)		
Saline	408 ± 60	826 ± 142*

10 mg/kg	473 ± 93	752 ± 108
50 mg/kg	353 ± 68	660 ± 137
Aripiprazole (n=8)		
Saline	231 ± 32	587 ± 120*
1 mg/kg	242 ± 17	695 ± 164*
5 mg/kg	234 ± 19	511 ± 97*
MDL 73,005EF/Buspirone (n=9)		
Saline	294 ± 48	355 ± 51
MDL 73,005EF 1 mg/kg	313 ± 60	339 ± 46
Buspirone 5 mg/kg	330 ± 71	264 ± 31

Data are mean ± SEM and were analyzed with ANOVA with repeated measures (for main effects see text). Further between-group analysis was done with one-way ANOVA and post-hoc Least-Significant-Difference comparisons. * $P<0.05$ for difference between 8-OH-DPAT treatment and respective saline control treatment. $^{+}$ $P<0.05$ for difference with saline pretreatment.

Figure 1

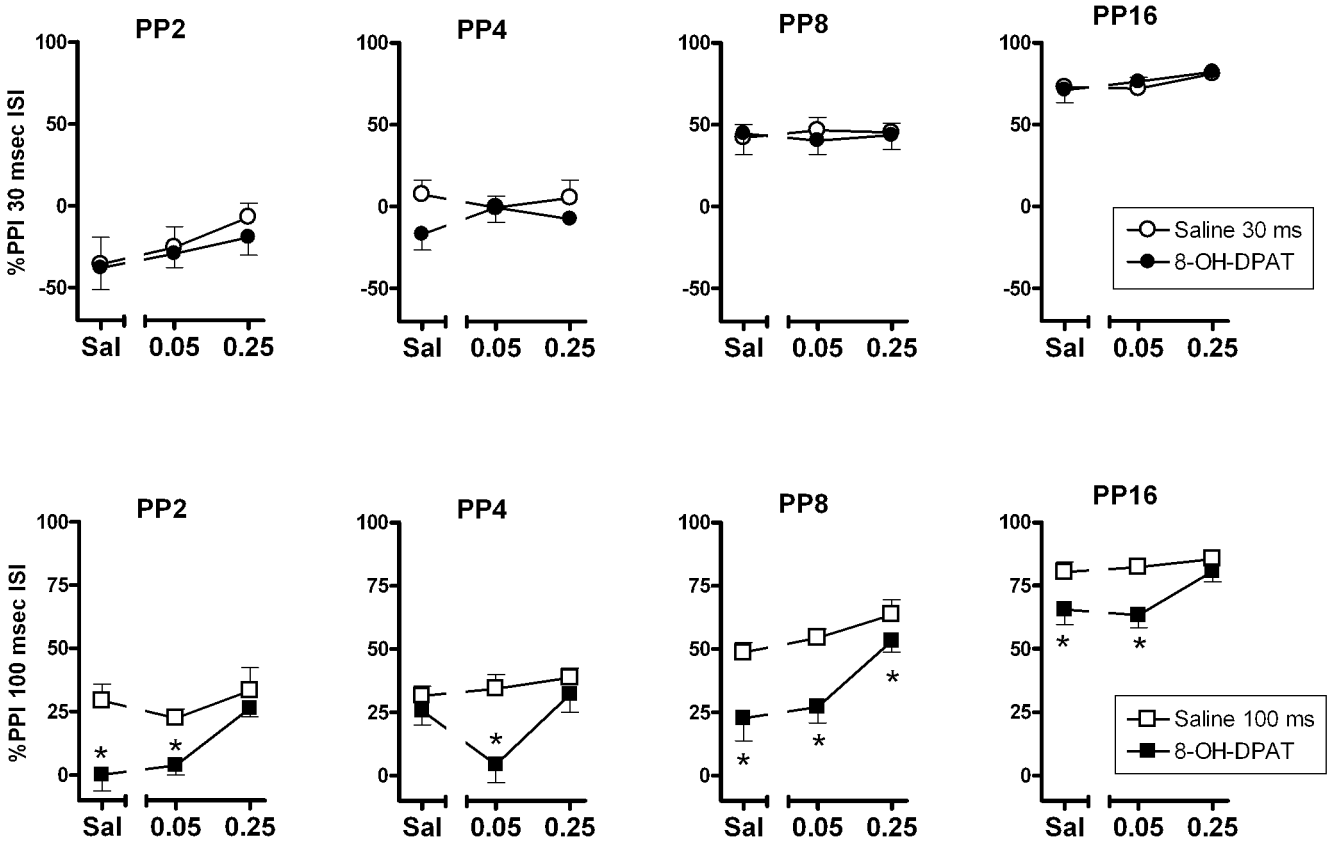

PP2
PP4
PP8
PP16
%PPI 30 msec ISI
%PPI 100 msec ISI
100
50
0
-50
75
25
Sal
0.05
0.25
Saline 30 ms
8-OH-DPAT
Saline 100 ms
8-OH-DPAT
*
Dose haloperidol pretreatment (mg/kg)

Figure 2

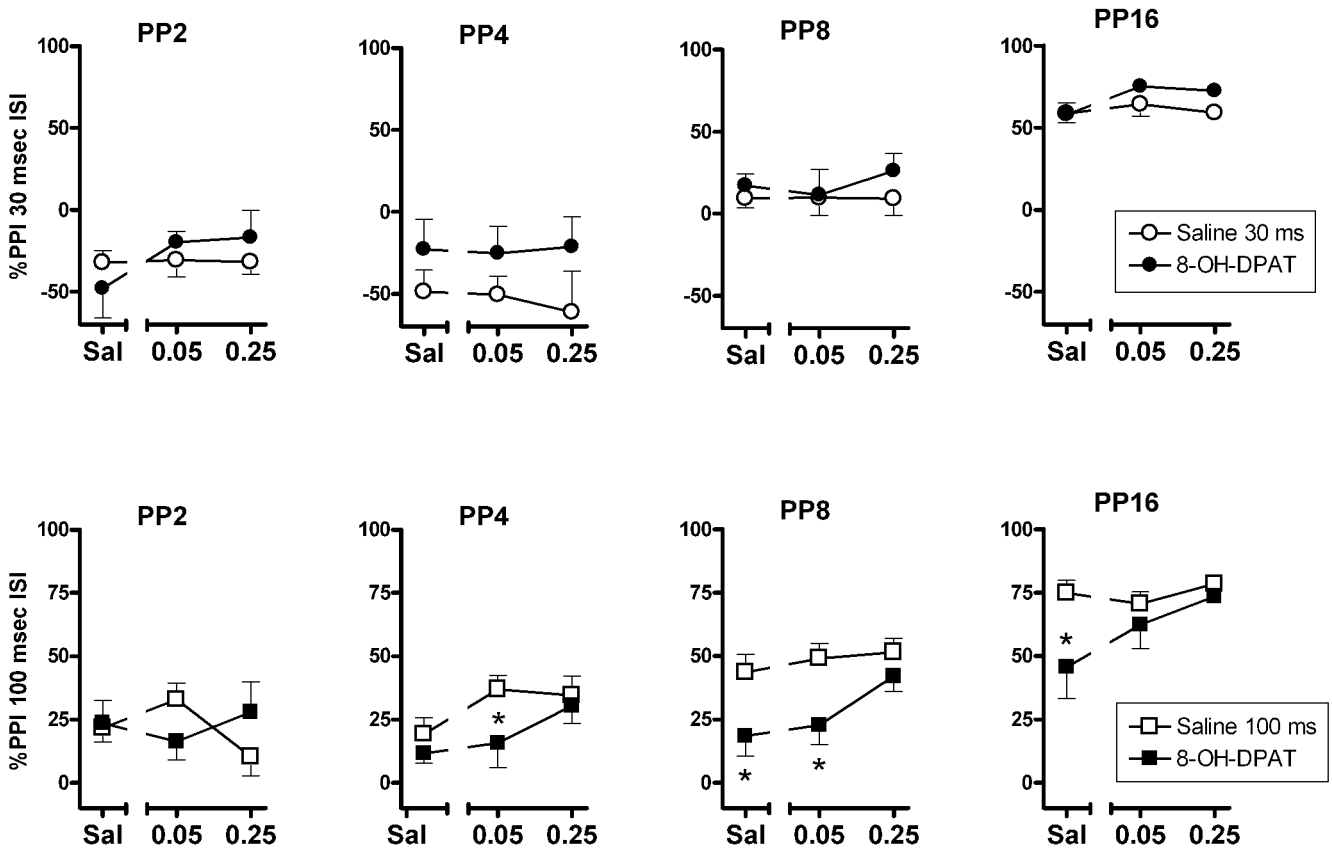

PP2
PP4
PP8
PP16
%PPI 30 msec ISI
%PPI 100 msec ISI
100
50
0
-50
75
25
Sal
0.05
0.25
Saline 30 ms
8-OH-DPAT
Saline 100 ms
8-OH-DPAT
*
Dose raclopride pretreatment (mg/kg)

Figure 3

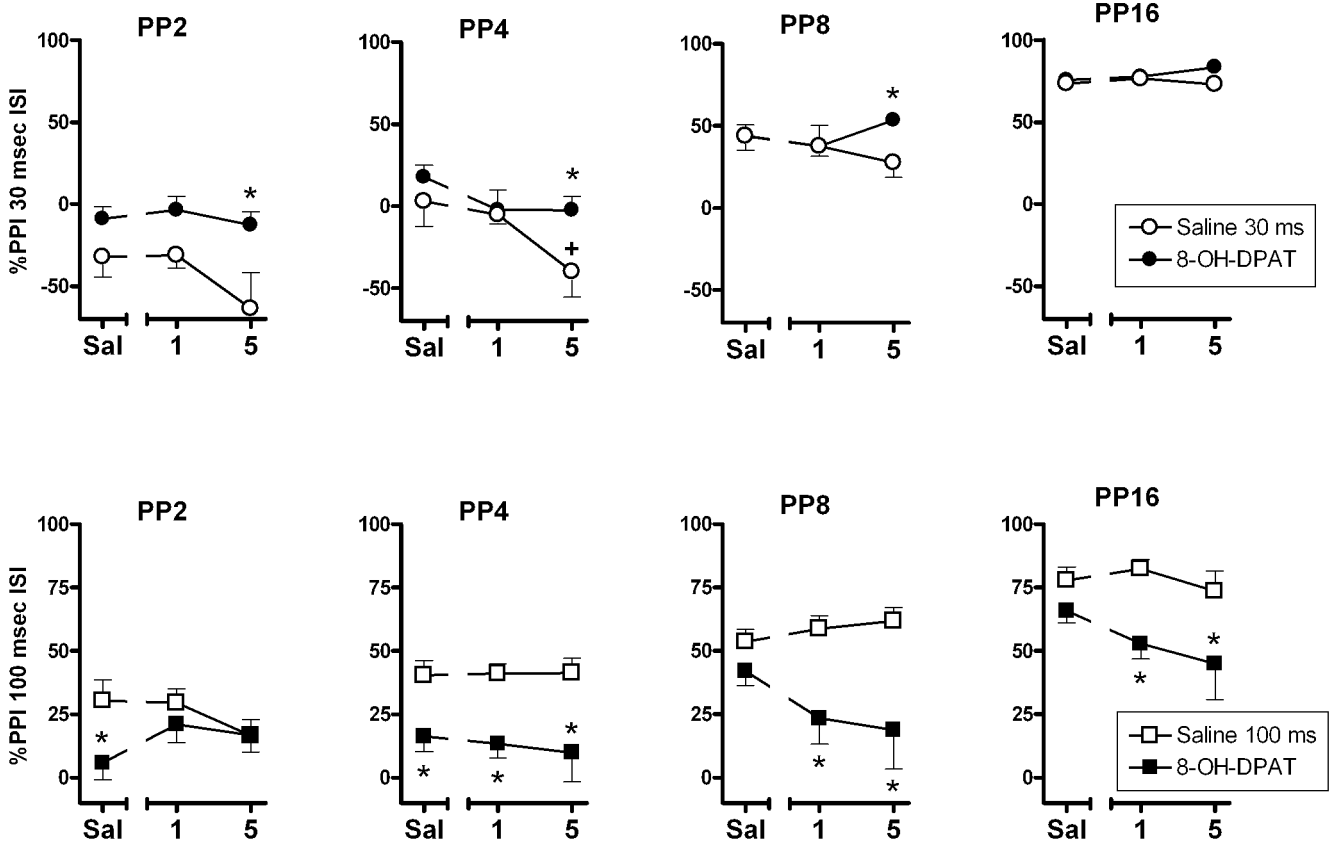

PP2
PP4
PP8
PP16
%PPI 30 msec ISI
%PPI 100 msec ISI
100
50
0
-50
75
25
Sal
1
5
*
+
Saline 30 ms
8-OH-DPAT
Saline 100 ms
8-OH-DPAT
Dose clozapine pretreatment (mg/kg)

Figure 4

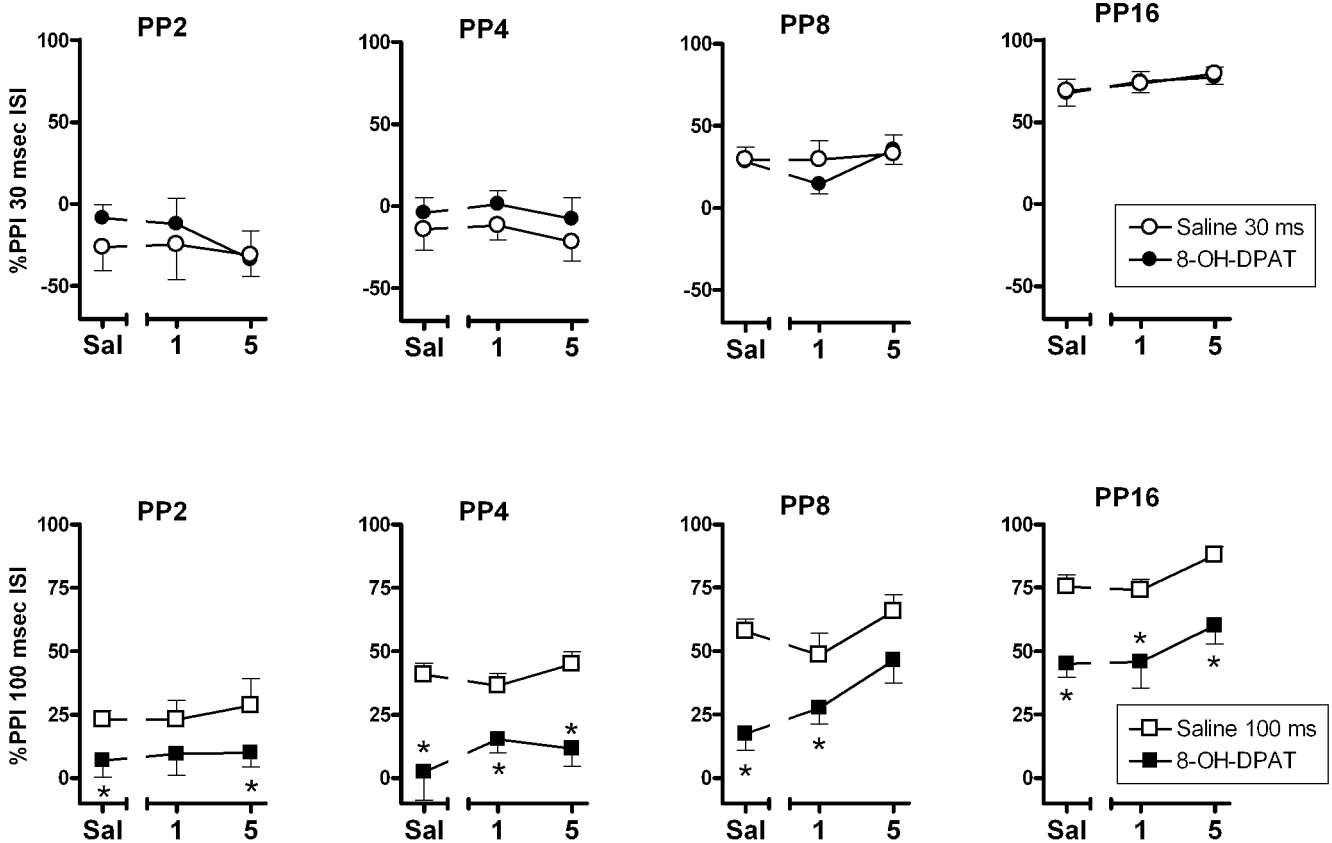

PP2
PP4
PP8
PP16
%PPI 30 msec ISI
%PPI 100 msec ISI
100
50
0
-50
75
25
Sal
1
5
Saline 30 ms
8-OH-DPAT
Saline 100 ms
8-OH-DPAT
*
Dose olanzapine pretreatment (mg/kg)

Figure 5

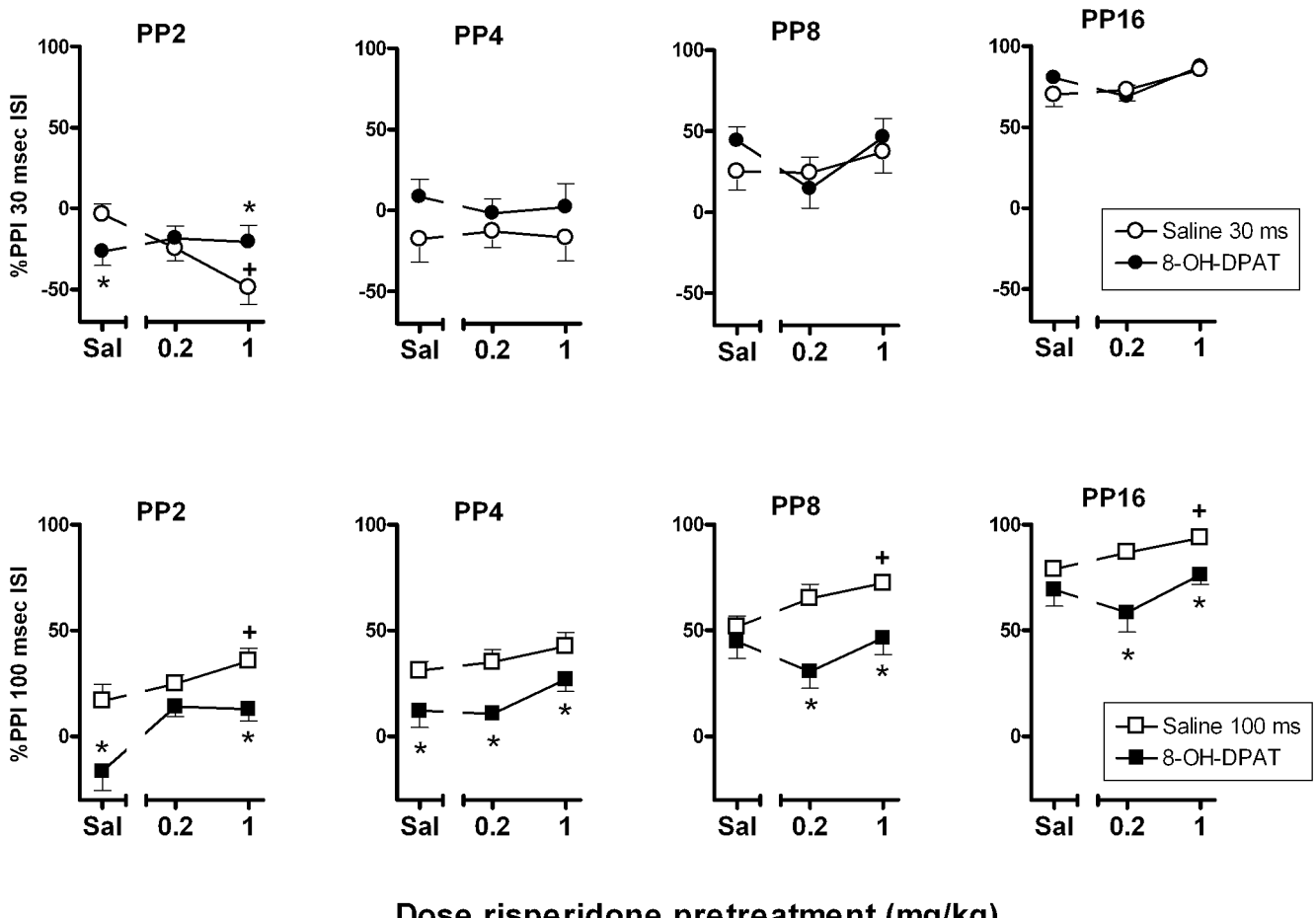

PP2
PP4
PP8
PP16
%PPI 30 msec ISI
%PPI 100 msec ISI
100
50
0
-50
Sal
0.2
1
Saline 30 ms
8-OH-DPAT
Saline 100 ms
8-OH-DPAT
Dose risperidone pretreatment (mg/kg)

Figure 6

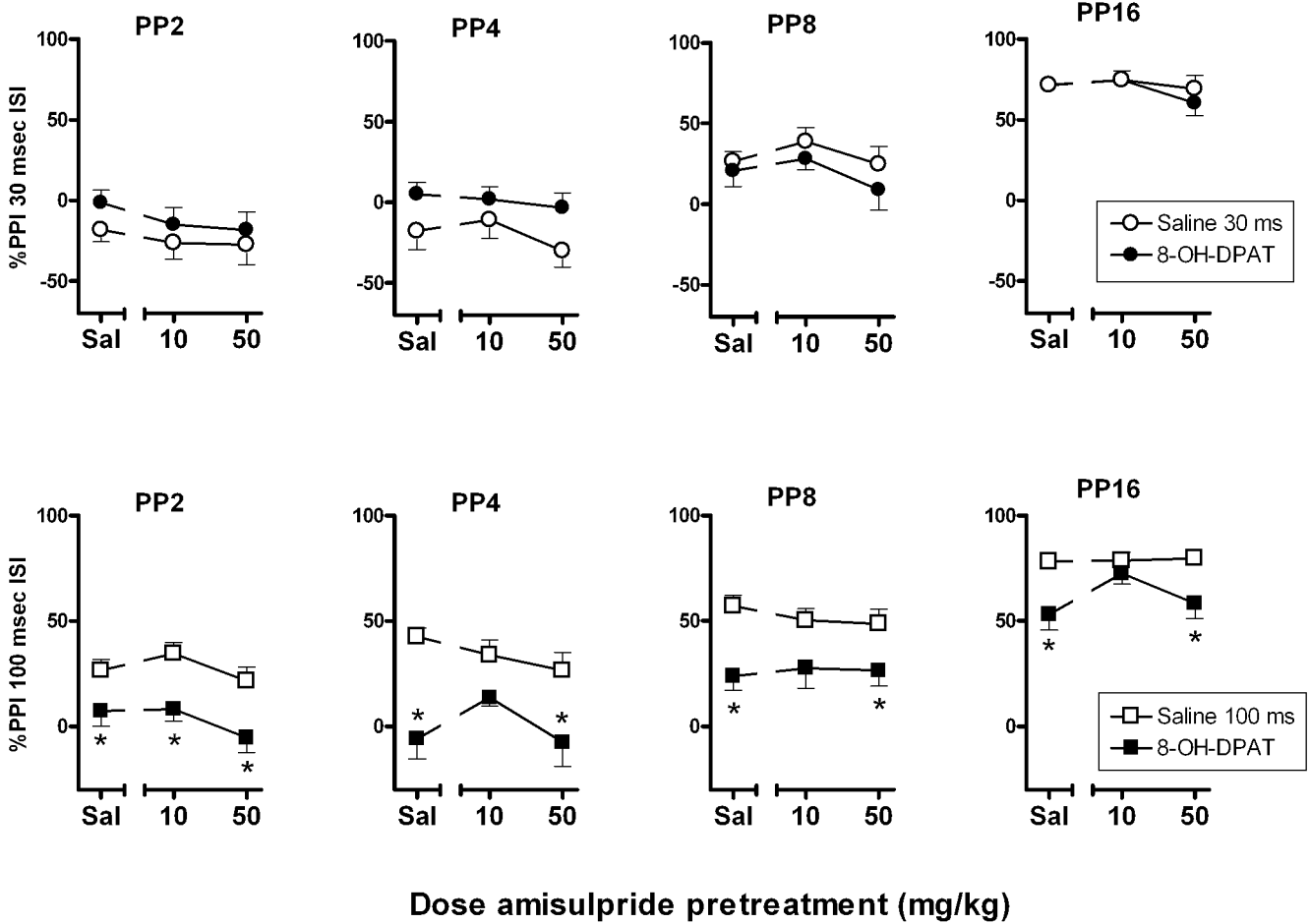

PP2
PP4
PP8
PP16
%PPI 30 msec ISI
%PPI 100 msec ISI
100
50
0
-50
Sal
10
50
Saline 30 ms
8-OH-DPAT
Saline 100 ms
*
Dose amisulpride pretreatment (mg/kg)

Figure 7

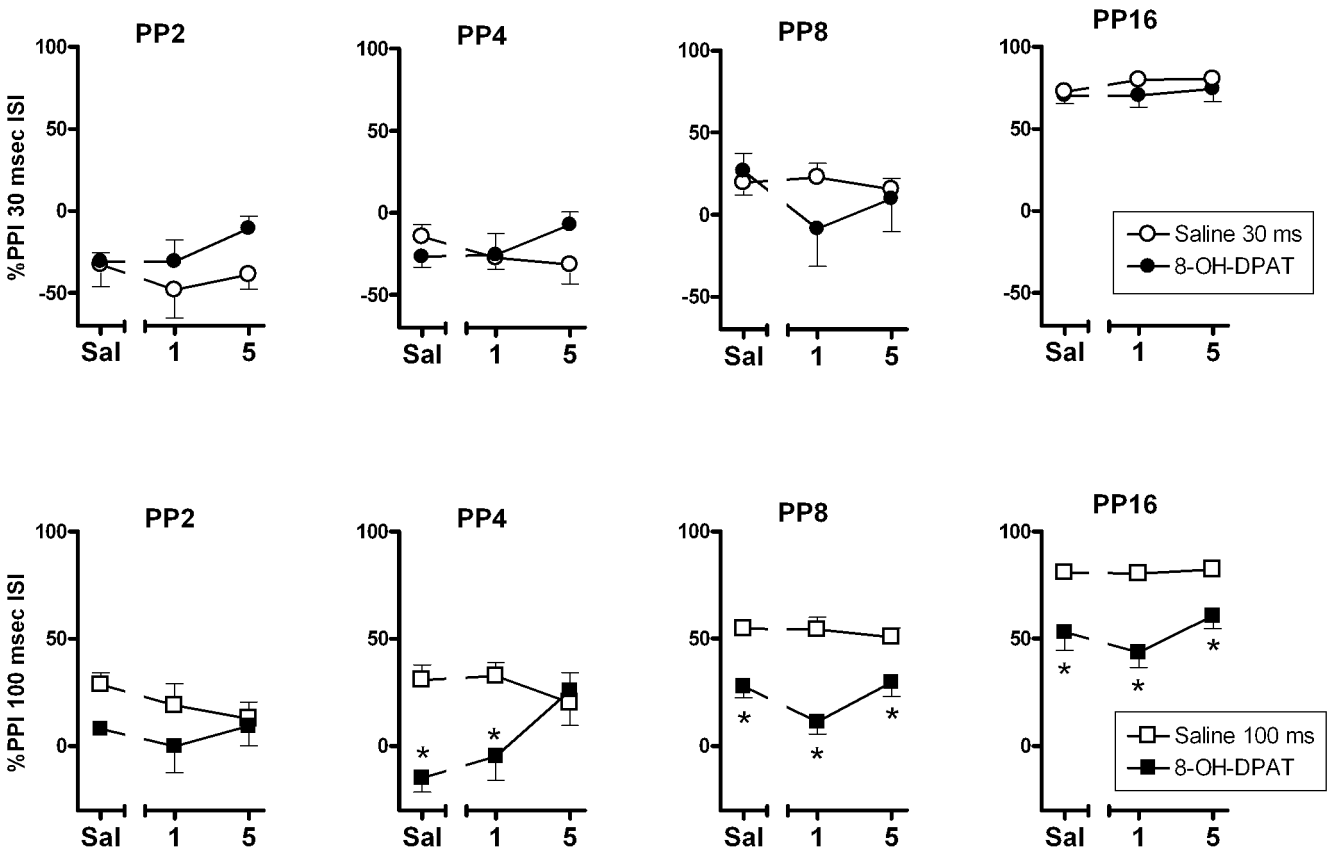

PP2
PP4
PP8
PP16
%PPI 30 msec ISI
%PPI 100 msec ISI
100
50
0
-50
Sal
1
5
Saline 30 ms
8-OH-DPAT
Saline 100 ms
8-OH-DPAT
*
Dose aripiprazole pretreatment (mg/kg)

Figure 8

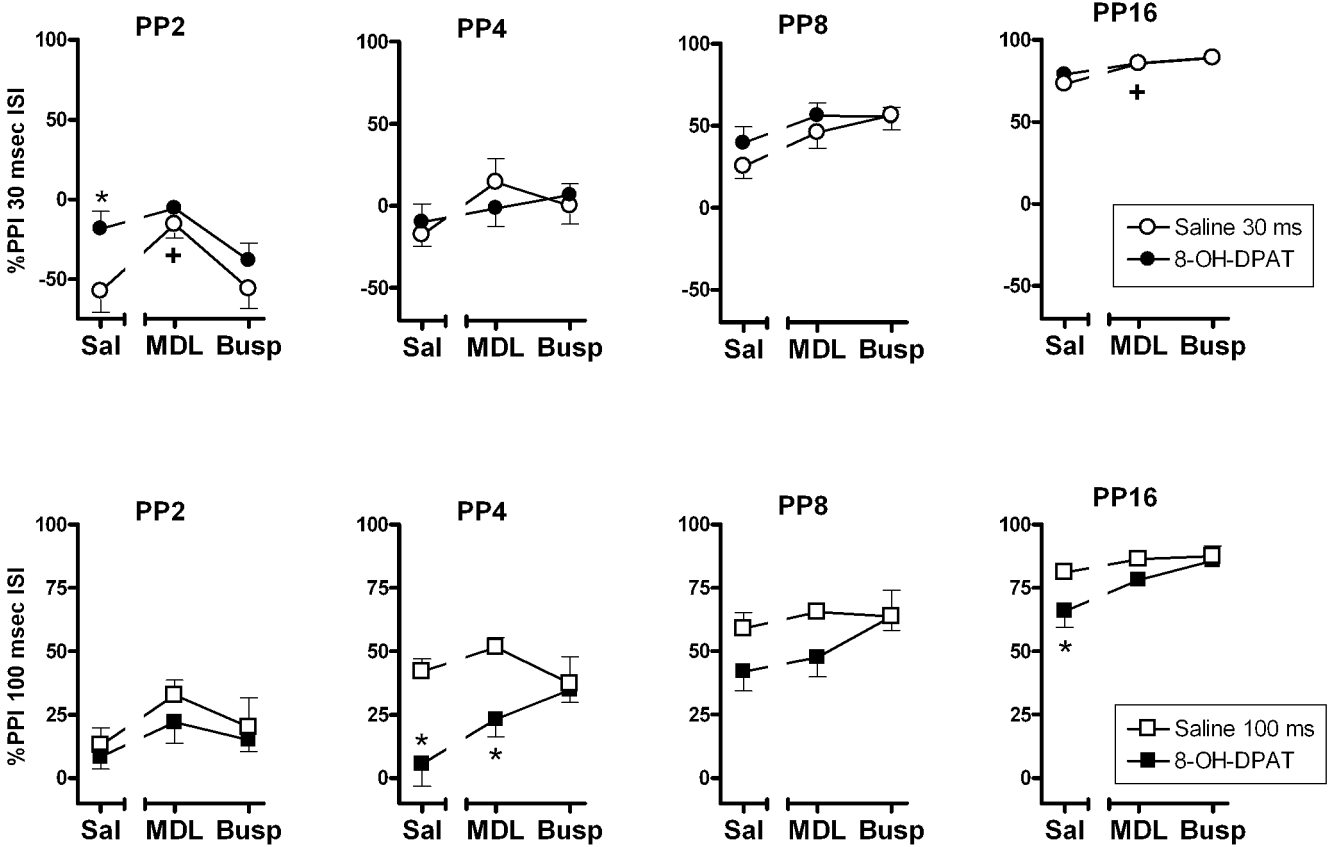
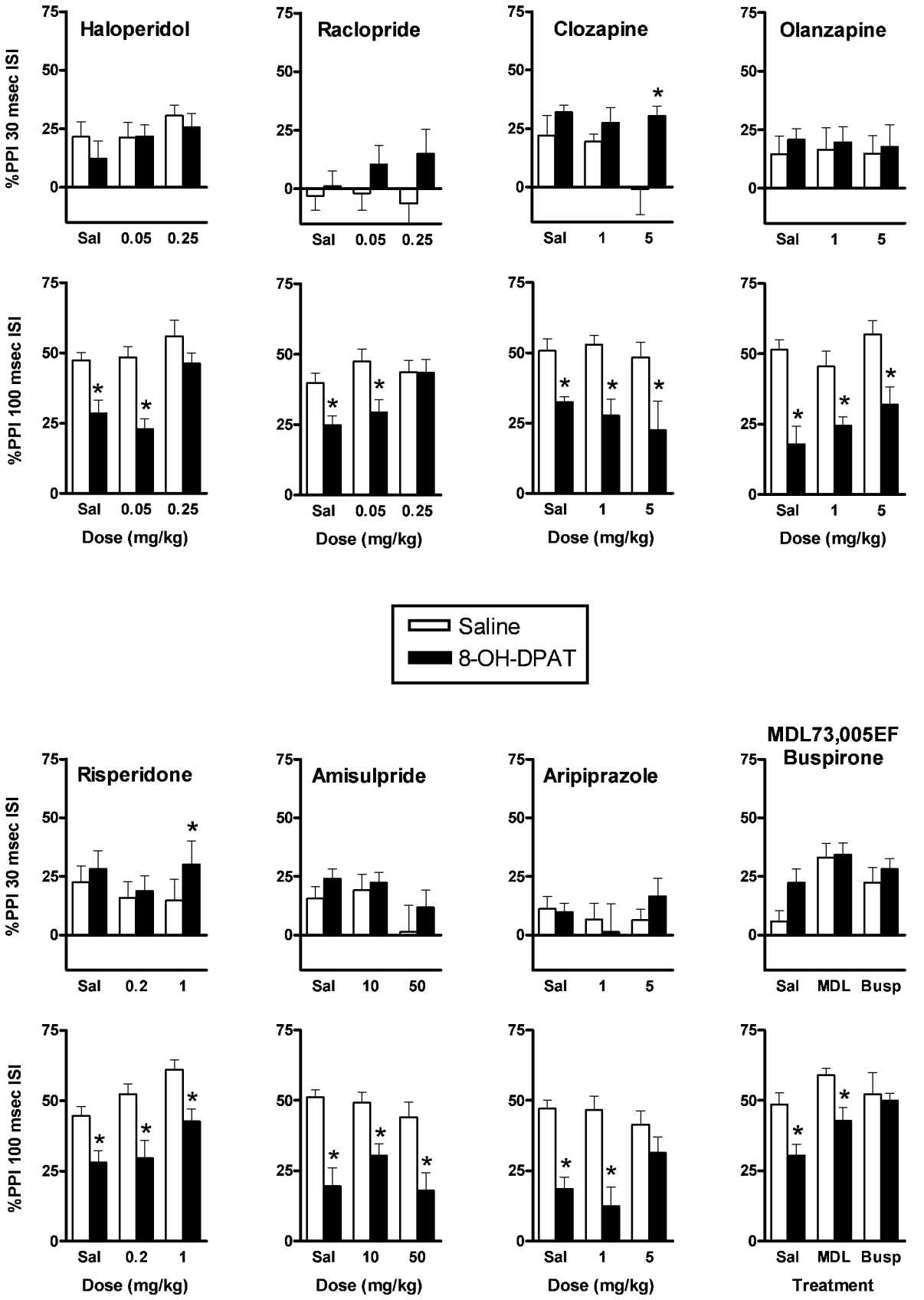

PP2
PP4
PP8
PP16
%PPI 30 msec ISI
%PPI 100 msec ISI
100
50
0
-50
75
25
Sal
MDL
Busp
*
+
Saline 30 ms
8-OH-DPAT
Saline 100 ms
8-OH-DPAT
Pretreatment

Figure 9


Haloperidol
Raclopride
Clozapine
Olanzapine
%PPI 30 msec ISI
%PPI 100 msec ISI
75
50
25
0
Sal
0.05
0.25
1
5
*
Dose (mg/kg)
Saline
8-OH-DPAT
Risperidone
Amisulpride
Aripiprazole
MDL73,005EF
Buspirone
0.2
10
50
MDL
Busp
Treatment