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Blockade of drug-induced deficits in prepulse inhibition of acoustic startle by ziprasidone

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Abstract

Ziprasidone, an antipsychotic with efficacy against core symptoms of schizophrenia and schizoaffective disorder, has a low incidence of extrapyramidal syndrome (EPS). Because of its high 5-HT_{2A}/D_2 binding-affinity ratio and low EPS liability, ziprasidone is considered to belong to the newer class of "novel" antipsychotics typified by clozapine. Its unique pharmacological profile, however, distinguishes it from other novel agents. We evaluated ziprasidone in the prepulse inhibition (PPI) model, which is sensitive to clinically active antipsychotics. Male Wistar rats were tested in acoustic startle sessions in which some startle-eliciting stimuli were presented alone, and others were preceded by a weak prepulse. Administration of the dopamine agonist apomorphine (1 mg/kg) or the *N*-methyl-D-aspartate (NMDA) antagonist ketamine (10 mg/kg) significantly disrupted PPI. When coadministered with either of these compounds, clozapine (1–5.6 mg/kg sc) and ziprasidone (5.6–17.8 mg/kg po) significantly attenuated the declines in PPI. Haloperidol (0.03–0.56 mg/kg) also attenuated drug-induced deficits in PPI but to a lesser extent (and at higher doses) with ketamine than with apomorphine. Together, these data confirm that ziprasidone shares common effects in PPI models with other novel antipsychotics. Ziprasidone's affinity for non-D_2 receptors in the central nervous system may partly account for its attenuation of ketamine's effect.

Keywords: Prepulse inhibition; Startle; Ziprasidone; Antipsychotics clozapine; Haloperidol

1. Introduction

Recent efforts to develop new pharmacotherapies for schizophrenia have focused on retaining the proven efficacy of classic antipsychotics while minimizing the deleterious motor side effects (extrapyramidal syndrome, or EPS) common to these medications. Although the therapeutic effect of antipsychotic drugs has been attributed historically to dopamine D_2 receptor antagonism, the unique profile of one medication, clozapine, has inspired an intensive effort to reproduce this compound's proven utility in schizophrenia, along with its low EPS liability and its putatively superior efficacy against negative symptoms (King, 1998; Meltzer, 1992). Clozapine displays affinity for a number of neuronal binding sites, including dopamine D_1, D_2 and D_4, serotonin 5-HT_{2A} and 5-HT_{2C}, and α_1-adrenergic, histamine H_1 and muscarinic receptors (Arnt and Skarsfeldt, 1998). As a result of efforts to reproduce clozapine's efficacy and low EPS liability without the risk of life-threatening blood dyscrasias, a number of clinically effective agents have been developed that offer clozapine-like control of positive and negative symptoms and relative lack of motor side effects. These newer medications are referred to collectively as "novel" antipsychotics (Arnt and Skarsfeldt, 1998).

Ziprasidone (Geodon, Pfizer, New York, NY) is a novel antipsychotic with demonstrated efficacy in schizophrenia and schizoaffective disorder (Daniel et al., 1999; Goff et al., 1998) and a unique neuropharmacologic profile (Fig. 1) (Seeger et al., 1995; Zorn et al., 1999). Like other novel antipsychotics, ziprasidone binds to both D_2 and 5-HT_{2A} receptors with a high 5-HT_{2A}/D_2 binding-affinity ratio (Seeger et al., 1995). This property has been suggested to underlie clozapine's low EPS liability and the relatively robust efficacy of this newer drug class against negative symptoms (Meltzer, 1989). Unlike most novel antipsychotics, however, ziprasidone is also a potent 5-HT_{1A} receptor agonist, a 5-HT_{1D} receptor antagonist and an inhibitor of 5-HT and norepinephrine reuptake, with affinity similar to the tricyclic antidepressants amitriptyline and

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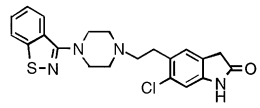

Fig. 1. Chemical structure of ziprasidone.

imipramine; these properties may contribute to its clinical profile (Seeger et al., 1995; Sprouse et al., 1999). Consistent with the properties that define it as a novel antipsychotic, ziprasidone blocks conditioned avoidance behavior and inhibits apomorphine-induced hyperlocomotion and stereotypy in rats, while only weakly inducing catalepsy. In keeping with its 5-HT_{2A} receptor affinity, ziprasidone also potently blocks quipazine-induced head twitches in rats (Seeger et al., 1995).

Another animal model used in recent years to characterize antipsychotics is the prepulse inhibition (PPI) procedure. PPI is a model of sensorimotor gating in which a weak acoustic stimulus (the prepulse) decreases the reflexive flinching response (startle) produced by a second, more intense, stimulus (the pulse). PPI is a cross-species phenomenon that is notable by its relative absence in schizophrenics (Braff et al., 1978). PPI has been called a model of sensorimotor gating that may reflect the ability of organisms to filter out irrelevant stimulation — a characteristic thought to contribute to certain manifestations of schizophrenia (McGhie and Chapman, 1961). Supporting the concept of PPI as a reflection of sensorimotor filtering are studies detailing sensory gating deficits, measured electrophysiologically, in schizophrenics or in animals administered dopamine agonists (Adler et al., 1986; Freedman et al., 1991).

Antipsychotics have been frequently reported in animal studies to block disruptions in PPI induced by the dopamine agonist apomorphine, and their potencies in these models correlate well with their clinical potencies in schizophrenia (Swerdlow et al., 1994). Although dopaminergic stimulation is often used to recreate aspects of schizophrenic pathophysiology, it has also been reported that the *N*-methyl-D-aspartate (NMDA) receptor blockade produced by phencyclidine and related drugs both disrupts PPI and reproduces schizophrenia-like psychotic behaviors (Luby et al., 1959; Mansbach and Geyer, 1989). Typical antipsychotics are usually effective in preventing apomorphine- but not NMDA antagonist-induced losses in PPI, whereas novel antipsychotics have been reported to block the effects of both drugs (Bakshi and Geyer, 1995; Bakshi et al., 1994; Swerdlow and Geyer, 1993; Swerdlow et al., 1996). It has been suggested that this property may differentiate the two classes of antipsychotics and potentially explain some of their clinical differences. Recent data, however, have called this suggestion into question (Swerdlow et al., 1998).

The present study evaluated the effects of ziprasidone on both apomorphine- and ketamine-induced disruption of PPI. Ketamine is a phencyclidine-like, open channel-blocking NMDA antagonist known to produce schizophrenia-like reactions in human beings (Krystal et al., 1994) and to disrupt PPI (Mansbach and Geyer, 1991; Swerdlow et al., 1998). The effects of ziprasidone were compared with those of clozapine and the typical antipsychotic haloperidol, a drug with high D_2 receptor-binding affinity, high EPS liability, and a low 5-HT_{2A}/D_2 receptor-binding ratio (Arnt and Skarsfeldt, 1998). Blockade of the effects of both apomorphine and ketamine by ziprasidone would support suggestions that attenuation of behavioral deficits induced by NMDA antagonists is a common property of novel antipsychotic agents.

2. Method

2.1. Subjects and apparatus

Adult male Wistar rats (Charles River) were individually housed with continuous access to water and lab chow. Studies were conducted using San Diego Instruments (San Diego, CA) startle chambers and associated interface equipment. An IBM-compatible personal computer delivered stimuli and collected data, which were stored on magnetic media. Acoustic stimuli were delivered by a Radio Shack Supertweeter located in the chamber's ceiling. A sealed accelerometer was used to detect responses. Data were collected as one hundred 1-ms voltage readings that began immediately after the onset of startle-eliciting stimuli. Responses were rectified, digitized and stored on microcomputer. The average of the 100 readings was selected as the dependent measure.

2.2. Procedure

One week after arrival, rats were tested in a brief startle response session consisting of 10 presentations of a 120-dB[A] noise, 40 ms in duration. The session began with a 5-min period of 67-dB[A] background noise. Startle trials were separated by 15-s periods of background noise. The mean score for each animal was used for group assignment, so that all groups would have approximately equal mean scores. PPI sessions, which occurred 24–48 h later, consisted of a single startle stimulus alone (120 dB[A]) followed by three blocks of 12 trials. Within each block, there were four presentations of the 120-dB[A] stimulus alone; four presentations of this stimulus preceded by 100 ms with a 20-ms, 72-dB[A] prepulse; two presentations of the prepulse alone; and two trials involving no changes in stimulus conditions but a recording of stabilimeter samples (no-stimulus trials). The initial 120-dB trial was not used in the data analysis.

Startle results were analyzed for effects on PPI and on startle amplitude. Trials were separated by a variable intertrial interval averaging 15 s and ranging from 10 to 20 s. PPI was defined as amplitude of startle in trials preceded by a prepulse, expressed as a percentage of startle magnitudes in trials where a prepulse was not presented. Prior to PPI sessions, rats were injected with vehicle or antagonist,

which was followed by an injection of 1.0 mg/kg apomorphine, 10 mg/kg ketamine or the respective vehicles. The challenge doses of apomorphine and ketamine were selected from preliminary data as being those that were reliable in disrupting PPI (data not shown).

2.3. Data analysis

To evaluate the effects of ziprasidone and other drugs on PPI, analysis of variance (ANOVA) was conducted on the percentage PPI scores with the challenge drug or its vehicle. Dunnett's tests with vehicle or challenge drug alone as a reference followed any significant results from these one-way ANOVAs. In addition, weighted orthogonal contrasts (Winer, 1971) were conducted in agonist-challenged groups to assess whether drug treatment, considered collectively, differed from vehicle control. Finally, analyses were conducted on absolute startle amplitude measures. These data were analyzed by two-way ANOVA, with the challenge drug and antagonist as factors. To gain an understanding of the intrinsic effects of antipsychotics on startle independently of their effects on PPI, one-way ANOVA was performed on pulse-alone startle amplitudes. Significant results were followed by Dunnett's t comparisons to vehicle-treated groups. Only trial types containing startle-eliciting stimuli were included in this analysis. For all analyses, the significance level was set to $P < .05$.

2.4. Drugs

Ziprasidone free base was dissolved in a 1:1:18 ratio of emulphor, ethanol and saline, and administered orally 3 h prior to testing (first startle stimulus). Clozapine free base (Clozaril, Novartis Pharmaceuticals, East Hanover, NJ) was dissolved in 0.1% acetic acid and administered subcutaneously 30 min prior to testing. Haloperidol free base (Sigma, St. Louis, MO) was dissolved in 0.1% tartaric acid and administered subcutaneously 30 min prior to testing. (+)-Apomorphine HCl (Sigma) was dissolved in 0.9% saline and administered subcutaneously 5 min prior to testing. Ketamine HCl (Ketaject, Phoenix Pharmaceutical, St. Joseph, MO) was diluted from its commercial vehicle with 0.9% saline and administered subcutaneously 15 min prior to testing.

3. Results

3.1. Drug effects on apomorphine-disrupted PPI

3.1.1. PPI effects

As reported previously, clozapine blocked apomorphine-induced losses in PPI (Fig. 2A). Statistical analysis revealed a significant effect, $F(2,42) = 36.4$, $P = .001$, of clozapine in apomorphine-treated groups but not in vehicle-treated groups. Also in agreement with published studies, haloperidol attenuated apomorphine-induced losses in PPI (Fig. 2B). In apomorphine-treated groups, there was a significant overall effect on PPI, $F(3,44) = 4.1$, $P = .01$, and a significant effect of the 0.1-mg/kg dose from the vehicle control, as confirmed by post hoc Dunnett's t comparisons ($P < .05$). Orthogonal contrast analysis confirmed that the drug groups differed significantly ($P = .003$) from control. Because the blockade was not complete and the effects of 0.17 mg/kg

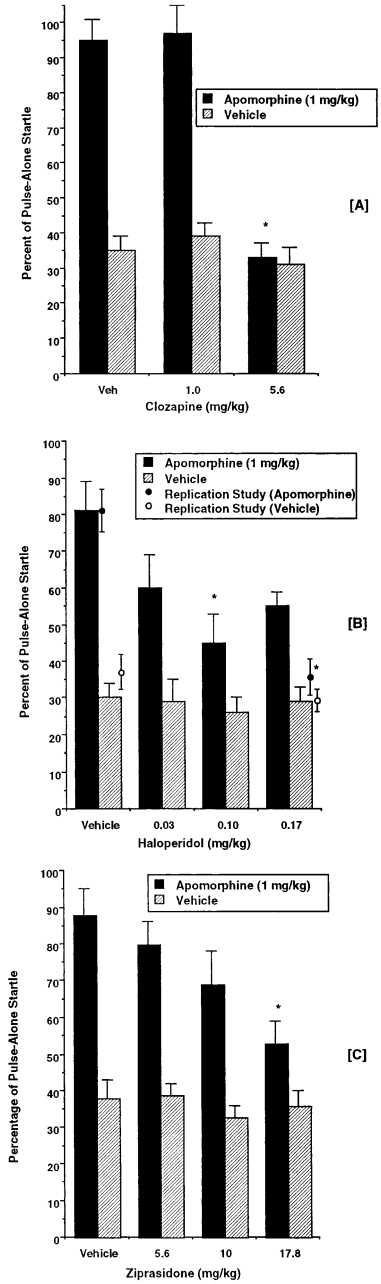

Fig. 2. Drug effects on apomorphine-disrupted PPI. Prepulse-inhibited startle amplitudes are expressed as a percentage (+S.E.M.) of the amplitude observed in startle trials not containing prepulses ("pulse-alone" startle). Gray bars illustrate the effects of clozapine, haloperidol or ziprasidone given alone on PPI. Asterisks indicate significant restoration of PPI as compared to apomorphine-alone control group. Circles appearing in panel B represent the effects of haloperidol in a replication study of the 0.17-mg/kg dose ($n = 11–12$). S.E.M. = standard error of mean.

were not significant, a replication study of this dose was conducted. In this study, 0.17 mg/kg haloperidol produced near-complete blockade of apomorphine-disrupted PPI, $F(1,22) = 31.7$, $P < .001$ (Fig. 2B).

Ziprasidone was also effective in preventing apomorphine-disrupted PPI (Fig. 2C). In apomorphine-treated groups, a significant main effect, $F(3,41) = 4.6$, $P = .007$, was followed by post hoc comparisons demonstrating a significant difference between the 17-mg/kg dose and the control. Collectively, apomorphine-treated groups pretreated with ziprasidone displayed significantly greater PPI than those injected with the ziprasidone vehicle ($P = .01$). In groups dosed with apomorphine vehicle, there was no effect of ziprasidone on PPI.

3.1.2. Amplitude effects

For the clozapine study, analysis of startle amplitudes confirmed significant main effects of apomorphine, $F(1,84) = 42.4$, $P < .001$ (reflecting increases), and clozapine, $F(2,84) = 10.1$, $P < .001$ (reflecting decreases) ($P < .001$), but no significant interaction. At the dose combination that protected PPI, startle amplitudes resembled values observed when the vehicles for both drugs were administered (Table 1). No-stimulus and prepulse-alone trials resulted in very low amplitudes and were not systematically affected by drugs in this or subsequent experiments (data not shown).

In haloperidol experiments, startle amplitudes were generally decreased in all drug groups with respect to vehicle controls; however, there was no significant main effect of apomorphine and no Apomorphine × Haloperidol interaction. There was also no significant effect, $F(3,44) = 2.0$, $P = .13$, of haloperidol alone on pulse-alone startle. For the haloperidol replication study, pulse-alone startle amplitudes were decreased in the haloperidol-alone condition, $F(1,44) = 5.5$, $P = .02$, but were unaffected in the apomorphine group (Table 1).

There was an overall main effect (decrease) of ziprasidone on startle amplitude, $F(3,81) = 2.7$, $P = .048$, but this effect was not dose dependent. There was no significant effect of ziprasidone alone on pulse-alone startle, and there was no main effect of apomorphine on amplitude and no Apomorphine × Ziprasidone interaction.

Table 1
Mean startle amplitudes: apomorphine studies

		Apomorphine vehicle		Apomorphine 1 mg/kg	
Compound	Dose	Startle stimulus alone	+Prepulse	Startle stimulus alone	+Prepulse
Clozapine	Veh	131.1	41.0	204.4	202.7
	1.0	78.3[a]	31.4	182.2	165.1
	5.6	42.0[a]	14.2	140.6	46.6
Haloperidol	Veh	271.1	72.1	166.5	125.6
	0.03	195.4	62.6	178.6	116.0
	0.1	159.0	47.6	149.0	60.9
	0.17	153.3	48.3	155.8	87.5
Haloperidol (replication)	Veh	247.9	91.9	188.3	155.0
	0.17	136.0[a]	41.6	209.6	65.5
Ziprasidone	Veh	216.6	97.0	180.7	162.9
	5.6	145.9	56.5	182.7	134.1
	10.0	135.4	44.5	108.2	78.0
	17.8	158.3	56.8	156.8	67.8

Veh = vehicle.

[a] Significant decrease in pulse-alone startle versus control (Dunnett's t following significant ANOVA).

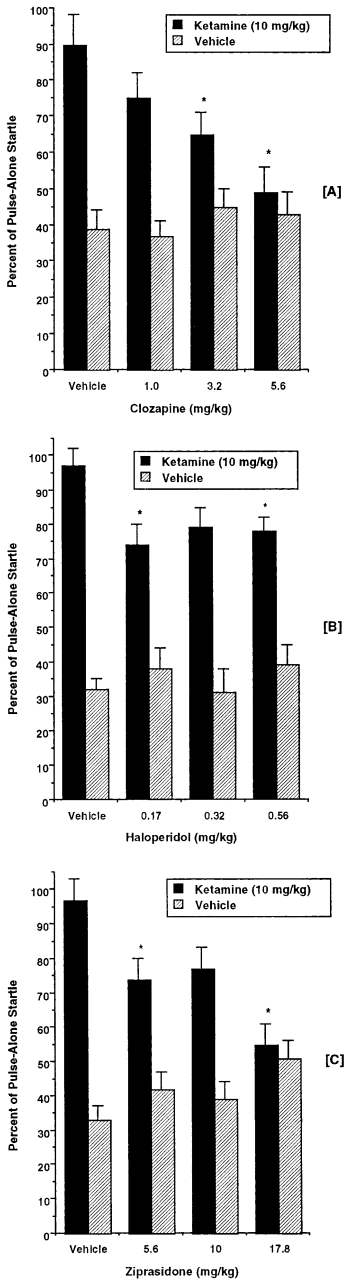

Fig. 3. Drug effects on ketamine-disrupted PPI. Other details as in Fig. 2 ($n = 11–12$).

Table 2
Mean startle amplitudes: ketamine studies

		Ketamine vehicle		Ketamine 10 mg/kg	
Compound	Dose	Startle stimulus alone	+Prepulse	Startle stimulus alone	+Prepulse
Clozapine	Veh	143.1	51.7	79.9	69.3
	1.0	93.5	35.2	68.5	48.9
	3.2	90.5	40.3	56.2	38.0
	5.6	77.7	35.7	98.2	54.7
Haloperidol	Veh	188.7	58.2	107.1	102.8
	0.17	95.4[a]	35.2	133.6	101.3
	0.32	92.2[a]	28.2	133.6	108.3
	0.56	107.0[a]	46.5	114.9	88.8
Ziprasidone	Veh	222.3	69.7	106.9	105.1
	5.6	139.6	57.3	129.2	97.1
	10.0	203.5	81.2	149.7	119.4
	17.8	156.1	76.1	150.7	84.6

Veh = vehicle.
[a] Significant decrease in pulse-alone startle versus control (Dunnett's *t* following significant ANOVA).

3.2. Drug effects on ketamine-disrupted PPI

3.2.1. PPI effects

In rats pretreated with clozapine, the disruptive effect of 10 mg/kg ketamine on PPI was diminished in a dose-dependent manner, $F(3,42) = 5.9$, $P = .002$, with significance versus control in the 3.2 mg/kg and 5.6 mg/kg groups (Fig. 3A). The orthogonal contrast analysis confirmed significant effects of drug treatment versus control ($P = .002$). PPI was not affected by clozapine in groups administered the ketamine vehicle.

Ketamine-disrupted PPI was partially blocked by haloperidol pretreatment (Fig. 3B). Although there was no clear evidence for dose responsiveness, ANOVA on ketamine-treated groups revealed a main effect, $F(3,44) = 3.5$, $P = .02$, and significant post hoc differences between control and the 0.17- and 0.56-mg/kg groups. Collectively, the responses of the haloperidol-pretreated groups were significantly different from those of rats receiving vehicle ($P < .01$). There was no significant effect of haloperidol on PPI in groups injected with the ketamine vehicle.

Ziprasidone also blocked ketamine-disrupted PPI (Fig. 3C). In ketamine-treated groups, a main effect of ziprasidone emerged, $F(3,41) = 7.9$, $P < .001$, with significant differences between vehicle and the 5.6- and 17.8-mg/kg doses. The orthogonal contrast analysis also confirmed that the drug groups, considered collectively, differed significantly from control ($P < .001$).

3.2.2. Amplitude effects

In the clozapine experiment, there was no main effect of ketamine on startle amplitude but a trend toward a main effect of decreased startle induced by clozapine was noted, $F(3,86) = 2.4$, $P = .07$. Analysis of pulse-alone amplitudes in clozapine-alone groups also yielded a strong decreasing trend, $F(3,44) = 2.6$, $P = .06$. There was no Ketamine × Clozapine interaction on the startle amplitude measure (Table 2).

There was no main effect of haloperidol on startle amplitude but a significant main effect of ketamine was observed, $F(1,86) = 9.5$, $P < .01$ (attributable to increases in prepulse-inhibited startle), as well as a Haloperidol × Ket-Ketamine interaction, $F(3,86) = 3.4$, $P = .02$. Examination of pulse-alone startle in haloperidol-alone conditions revealed a significant decrease, $F(3,42) = 4.5$, $P < .01$, with all three doses significantly different from vehicle.

In the ziprasidone study, there were no significant main effects or interaction revealed by the analysis of absolute startle amplitudes. Ziprasidone had no effect on pulse-alone amplitudes.

4. Discussion

Ziprasidone was tested in rats administered a dose of apomorphine sufficient to disrupt PPI. As would be expected from a high-affinity dopamine D_2 receptor antagonist, ziprasidone blocked apomorphine-induced PPI deficits in a dose-dependent manner. Consistent with most published reports, both haloperidol and clozapine also attenuated the effect of apomorphine (Mansbach et al., 1988; Swerdlow and Geyer, 1993).

Although the disruption of PPI induced by apomorphine and other stimulants is consistent with the classical dopaminergic hypothesis of schizophrenia, there is considerable evidence that dysregulation of glutaminergic neurotransmission may also play a role in the disease (Duncan et al., 1999). Phencyclidine and other antagonists of the NMDA class of glutamate receptors have been reported to reproduce several aspects of psychosis, including behaviors similar to the positive and negative symptoms of schizophrenia (Krystal et al., 1994). Although disruptions in PPI produced by NMDA receptor antagonists were previously found to be insensitive to haloperidol (Keith et al., 1991), Bakshi et al. (1994) reported that clozapine was effective in preventing the effects of phencyclidine. It was suggested that one or more of clozapine's pharmacologic effects beyond D_2 antagonism might play a role in this response. Subsequently, other novel antipsychotics with high affinities for multiple receptors in the central nervous system were found to block the effects of NMDA antagonists, including olanzapine, quetiapine and risperidone (Bakshi and Geyer, 1995; Swerdlow et al., 1996; Yamada et al., 1999).

One line of evidence implicates the serotonin system in PPI and its modification by novel antipsychotic drugs. Ziprasidone displays particularly high affinity for 5-HT_{2A} (0.4 nM) and 5-HT_{1A} (3.4 nM) sites (Seeger et al., 1995; Zorn et al., 1999), and these activities have been suggested to contribute to its clinical spectrum of activity (Tandon et al., 1997). Because novel antipsychotics in general are also

potent 5-HT_{2A} receptor antagonists, Yamada et al. (1999) hypothesized that this receptor was responsible for the observed blockade of NMDA antagonist-induced behaviors. Their data suggest a significant correlation between 5-HT_{2A}, but not D_2 or α_1-adrenergic, receptor affinity and the potency of various drugs in opposing phencyclidine-disrupted PPI. In support of a role of the 5-HT_{2A} receptor, Varty et al. (1999) reported that MDL 100907 selectively prevented MK-801-disrupted PPI. Thus, ziprasidone's efficacy in the ketamine model may have been due, at least in part, to its potent 5-HT_{2A} receptor activity.

Bakshi and Geyer (1997, 1999) hypothesized that α_1 receptors are partly responsible for the effects of novel agents in PPI, basing this conjecture on the observation that most antipsychotics known to block NMDA antagonist-induced losses in PPI also possess high affinity for α_1-adrenergic receptors and that NMDA antagonists influence noradrenergic systems. Their work demonstrated that prazosin, a selective α_1- receptor antagonist, opposed the effects of clozapine. Subsequent experiments (Carasso et al., 1998) revealed that α_1-receptor stimulation produced a disruption of PPI that was blocked by quetiapine. Further support for the α_1 hypothesis appeared in a study by Swerdlow et al. (1998), which reported that chlorpromazine, a "typical" antipsychotic with high affinity for α_1 receptors, but not haloperidol, blocked ketamine-induced PPI deficits. At odds with the α_1 hypothesis were the results of a study by Johansson et al. (1994), who reported that remoxipride, an antipsychotic with no detectable affinity for α_1 receptors (Arnt and Skarsfeldt, 1998; Moore et al., 1993), blocked phencyclidine-disrupted PPI. This study was unusual, however, in that clozapine also failed to attenuate the deficit.

Ziprasidone is a modest antagonist at α_1 receptors, possessing lower affinity at this site than at D_2 and 5-HT_{2A} receptors; unlike the α_1 antagonists clozapine and olanzapine, its effects in depressing raphe cell firing are not reversed by the norepinephrine reuptake inhibitor desipramine (Sprouse et al., 1999). There is also little indication of α_1-receptor antagonism by ziprasidone at therapeutic doses in human beings, as reflected by the low incidence of postural hypotension associated with this agent (Tandon et al., 1997). Thus, the role of α_1 receptors in the behavioral effects of ziprasidone, including PPI, remains unclear.

Taken together, the available data provide some basis for suggestions that non-D_2 receptors may mediate, through indirect means, the efficacy of novel antipsychotics in opposing PPI deficits induced by NMDA antagonists. However, as suggested by Swerdlow et al. (1998), this property may not necessarily signal clinical superiority in terms of EPS liability or superior efficacy in otherwise treatment-resistant settings.

One unexpected result of the present study was the attenuation of ketamine's effect on PPI by haloperidol. Although only partial, the statistically significant blockade is inconsistent with most reports using open channel-blocking NMDA antagonists. One important difference from earlier reports is our use of relatively high doses of haloperidol. In the studies by Keith et al. (1991) and Swerdlow et al. (1998), the highest haloperidol dose used was 0.1 mg/kg, and no blockade was reported. In a study by Hoffman et al. (1993), a somewhat higher haloperidol dose of 0.5 mg/kg partially, though not significantly, attenuated the effects of MK-801. As suggested by the work of Swerdlow et al., α_1-adrenergic receptor blockade may have played a role in the weak effect of higher haloperidol doses in the present study. 5-HT_{2A} receptor effects cannot be completely ruled out, however, as haloperidol displays moderate affinity for this site (Seeger et al., 1995). Interestingly, two recent reports (Feifel and Priebe, 1999; Pietraszek and Ossowska, 1998) suggested that haloperidol is effective in attenuating NMDA antagonist-disrupted PPI when given chronically, mirroring the typically delayed efficacy of antipsychotics (Keck et al., 1989).

None of the antipsychotics tested in the present study affected PPI when given alone. One limitation of the PPI model is that it generally requires a pharmacologic challenge for evaluation of potential antipsychotics. Work by Bakshi et al. (1998) demonstrates that PPI deficits induced by isolation rearing are attenuated by antipsychotics. In addition, a few studies have reported significant increases in PPI under baseline conditions in rats (Geyer et al., 1999; Hoffman et al., 1993; Swerdlow and Geyer, 1993). However, these findings are far from consistent within and between laboratories, and more work will be necessary to understand whether strain, methodology or some other factor is responsible for the differences.

More recent findings have revealed large variability in PPI across a number of mouse strains, and some work has suggested that antipsychotics may increase PPI in mouse strains with inherently poor gating (McCaughran et al., 1997). Such an approach may eventually yield a promising method for antipsychotic screening. Of particular relevance to the pharmacology of ziprasidone is the recent finding that 5-HT_{1A} receptor agonists significantly increase PPI in wild-type, but not 5-HT_{1A} receptor-knockout, mice (Dulawa et al., 2000). These findings contrast with earlier findings in rats given 5-HT_{1A} agonists (Sipes and Geyer, 1995). Unlike clozapine and olanzapine, ziprasidone is a potent agonist at this site, decreasing dorsal raphe-cell firing and increasing dopamine release in the prefrontal cortex by a 5-HT_{1A} receptor-mediated mechanism (Rollema et al., 2000; Sprouse et al., 1999). Although we did not note increases in PPI when ziprasidone was administered alone, it is possible that this activity could play a role in the observed blockade of ketamine's effect.

In conclusion, the novel antipsychotic ziprasidone was effective in preventing PPI deficits induced both by apomorphine and by ketamine in this experimental model. As is the case with most novel agents, ziprasidone binds with high affinity to both D_2 and 5-HT_{2A} receptor sites, induces dopamine and norepinephrine release in the prefrontal cortex, and has low liability for EPS (Tandon et

al., 1997; Westerink et al., 1998). The previously proposed classification of antipsychotics on the basis of blockade of NMDA antagonist-induced deficits in PPI may be clouded by published data with drugs not considered to be novel antipsychotics. However, the present data confirm an additional similarity between ziprasidone and other novel medications with known efficacy in schizophrenia and superiority to typical agents in terms of motor side effects.

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