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Actions of Novel Antipsychotic Agents on Apomorphine-Induced PPI Disruption: Influence of Combined Serotonin 5-HT_{1A} Receptor Activation and Dopamine D_2 Receptor Blockade

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The dopamine D1/D2 agonist apomorphine (0.63 mg/kg) disrupted prepulse inhibition (PPI) of acoustic startle in rats, a model of sensorimotor gating deficits observed in schizophrenia. All current antipsychotics, which antagonize D_2 receptors, prevent this apomorphine-induced deficit. A novel class of antipsychotics possesses, in addition to D_2 antagonist property, various levels of 5-HT_{1A} agonist activity. Considering that the latter itself produces PPI deficits, it appeared necessary to assess the potential of this novel class of antipsychotics to reverse apomorphine-PPI deficits. Potent D_2 antagonists, like haloperidol (0.63–2.5 mg/kg), risperidone (0.63–10 mg/kg), and olanzapine (0.63–40 mg/kg) prevented apomorphine PPI disruption. The atypical antipsychotics, clozapine (40 mg/kg), nemonapride (0.01–2.5 mg/kg), ziprasidone (10 mg/kg), and aripiprazole (0.01 and 10 mg/kg), which all exhibit 5-HT_{1A} agonist properties, reversed PPI deficits at some doses only, whereas the anti-dyskinetic agent sarizotan (0.16–10 mg/kg), an efficacious 5-HT_{1A} agonist, did not. New generation antipsychotics with marked 5-HT_{1A} agonist properties, such as SLV313 and SSR181507 (0.0025–10 mg/kg and 0.16–10 mg/kg, respectively) did not reverse these deficits whereas bifeprunox (0.04–2.5 mg/kg) did. To reveal the contribution of 5-HT_{1A} agonist properties in the lack of effects of SLV313 and SSR181507, we pretreated rats with the 5-HT_{1A} antagonist WAY100635 (0.63 mg/kg). Under these conditions, significant reversal of PPI deficit was observed, indicating that D_2 antagonist properties of SLV313 and SSR181507 are now sufficient to overcome the disruptive effects of apomorphine. To summarize, antipsychotics possessing agonist efficacy at 5-HT_{1A} receptors exhibit diverse profiles against apomorphine-induced PPI deficits, depending on the balance between D_2 and 5-HT_{1A} activities, suggesting that they may display distinct activity on some aspects of gating deficits in schizophrenic patients.
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INTRODUCTION

Several neuropsychiatric disorders, such as schizophrenia, are associated with deficits in sensorimotor gating, and the prepulse inhibition (PPI) model of the acoustic startle reflex was developed in rodents to mimic these deficits (Geyer and Braff, 1987; Braff and Geyer, 1990, 2001). PPI is defined as the attenuation of the response to a startling stimulus (pulse), when such a stimulus is briefly preceded by a stimulus of subthreshold intensity (prepulse). PPI can be disrupted by acting on developmental and environmental factors such as isolation rearing of rats (Geyer *et al*, 1993; Varty *et al*, 1999), early maternal or nutritional deprivation (Ellenbroek *et al*, 1998), and neonatal lesions of neuronal circuitry linking the limbic structures and basal ganglia (Lipska *et al*, 1995). However, the pharmacological disruption approach, for reasons of ease of implementation, is more commonly used. Among the three main pharmacological models of disruption of PPI in rats, that is, those induced by dopamine (DA) receptor agonists, 5-HT_{2A} receptor agonists, and NMDA/glutamate receptor antagonists, the DA receptor agonist-induced PPI deficit model appears to be the best-validated for the identification of antipsychotics with DA D_2 receptor blocking properties. Indeed, PPI can be disrupted by either direct DA receptor agonists, such as apomorphine, or indirect DA agonists that facilitate dopaminergic transmission, such as d-amphetamine,

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and these effects can be prevented by DA D_2 (and/or D_1) receptor antagonists (Swerdlow *et al*, 1986, 1994; Mansbach *et al*, 1988). Hence, antipsychotics that have appreciable affinity for DA D_2 receptors such as haloperidol, reliably prevent apomorphine-induced deficits in rats (Mansbach *et al*, 1988; Geyer *et al*, 2001; Ralph and Caine, 2005).

All current antipsychotics have more or less marked DA D_2 receptor antagonists properties, thought to be responsible for their efficacy, at least against positive symptoms (Kapur and Remington, 2001; Wadenberg *et al*, 2000b). Another major monoaminergic system, the serotonergic system, has also been implicated in various aspects of the neurobiology of schizophrenia. Two subtypes of serotonin receptors, the 5-HT_2 and the 5-HT_{1A}, have been the objects of great interest. As a matter of fact, most atypical antipsychotics are DA D_2 and 5-HT_2 receptors blockers, and it has been proposed that antagonist activity at 5-HT_2 receptors prevents the deleterious effects of DA D_2 receptor blockade, that is, extrapyramidal signs (EPS) (Kapur, 1996; Remington and Kapur, 1999). Besides, there is ample preclinical evidence that activation of 5-HT_{1A} receptors should also prove beneficial in schizophrenia (Millan, 2000; Bantick *et al*, 2001; Ichikawa *et al*, 2001). Hence, it has been repeatedly shown that 5-HT_{1A} receptor agonists prevent catalepsy (an animal model of EPS) produced by blockade of DA D_2 receptors (Wadenberg and Ahlenius, 1991; Wadenberg *et al*, 1994; Neal-Beliveau *et al*, 1993; Prinssen *et al*, 1998, 1999; Depoortere *et al*, 2003; Kleven *et al*, 2005). Consistent with this idea, clinical studies have reported that buspirone and tandospirone, two partial agonists at 5-HT_{1A} receptors, reduce the incidence of EPS in schizophrenic patients treated with haloperidol (Sumiyoshi *et al*, 2001a, b). Furthermore, these studies have also shown that buspirone and tandospirone substantially ameliorate cognitive performance of patients. At the pre-clinical level, microdialysis experiments have shown that 5-HT_{1A} receptor activation increases DA release in prefrontal cortex (Rollema *et al*, 1997, 2000; Millan *et al*, 1998; Sprouse *et al*, 1999; Ichikawa and Meltzer, 2000). In the light of the proposed deficiency in dopaminergic neurotransmission in this brain area in schizophrenic patients, this 5-HT_{1A} receptor-mediated augmentation of cortical DA tone should help in alleviating negative and cognitive deficits of schizophrenia. In addition, 5-HT_{1A} receptor expression is increased in the dorsolateral prefrontal, temporal, and orbital frontal cortices of autopsied brains from chronic schizophrenics (Hashimoto *et al*, 1991; Simpson *et al*, 1996; Burnet *et al*, 1997). Further, PET studies have revealed an increase in cortical 5-HT_{1A} receptor binding in schizophrenia (Kasper *et al*, 2002).

These considerations have led to the development of compounds with preferential DA D_2 receptor antagonist or partial agonist, and 5-HT_{1A} agonist activities, such as bifeprunox (Feenstra *et al*, 2001; Wolf, 2003), SSR181507 (Claustre *et al*, 2003; Depoortere *et al*, 2003; Boulay *et al*, 2004), SLV313 (Feenstra *et al*, 2002; McCreary *et al*, 2002), and sarizotan (that has been re-oriented towards an antidyskinetic indication: Bibbiani *et al*, 2001; Rabiner *et al*, 2002; Bartoszyk *et al*, 2004).

However, it has been reported that activation of 5-HT_{1A} receptors by agonists such as 8-OH-DPAT and buspirone, disrupts PPI of the acoustic startle response in rodents (Nanry and Tilson, 1989; Rigdon and Weatherspoon, 1992; Sipes and Geyer, 1994, 1995a; Sipos *et al*, 2000). Notwithstanding the numerous reports of deleterious effects of 5-HT_{1A} receptor agonists on PPI, activity of mixed DA D_2 receptor antagonist/partial agonist and 5-HT_{1A} agonist on models of sensorimotor gating deficits have not been characterized. We therefore examined the ability of such drugs to prevent apomorphine-induced PPI deficits, since the influence of their 5-HT_{1A} agonist properties on sensorimotor gating is unknown. The present study had two objectives: *First*, to compare the effects of these new compounds with those of older antipsychotic agents (haloperidol, clozapine, ziprasidone, risperidone, olanzapine, aripiprazole, and nemonapride) acting by a variety of mechanisms in addition to/instead of 5-HT_{1A} receptor activation. For the purpose of internal validation, we included the selective 5-HT_{1A} receptor agonist, F13714 (Koek *et al*, 2001) to verify, under our experimental conditions, the disruptive influence of 5-HT_{1A} receptor activation. *Second*, to verify that effects of compounds with preferential 5-HT_{1A} receptor agonist properties were specifically mediated through this receptor; to that end, interaction studies with the specific 5-HT_{1A} receptor antagonist WAY100635 were undertaken whenever appropriate.

MATERIALS AND METHODS

Animals

Male Sprague–Dawley rats (ICO: OFA SD, Iffa Credo, Les Oncins, France), weighing 180 ± 20 g upon arrival were group-housed ($n = 5$/cage) in an environmentally controlled room (temperature $21 \pm 1^{\circ}$C and relative humidity $55 \pm 5\%$) on a 12 h : 12 h light : dark cycle (lights on at 0700), in stainless steel cages with grid flooring (internal dimensions: $26 \times 42 \times 18$ cm; W × L × H). Animals were held in quarantine for 4–8 days, with free access to standard laboratory food (A04, Scientific Animal Food and Engineering, Epinay sur Orge, France) and filtered water (0.22 μm pores; in bottles). A 5-day acclimatization period was allowed before animals were used in experiments. Twenty-four hours before testing, the animals were individually housed in an environmentally controlled test room in plastic hanging cages with a grid floor (internal dimensions: $11 \times 31 \times 18$ cm; W × L × H), where they had free access to water, but not food. Animals were handled and cared for in accordance with the 'Guide and Care and Use of Laboratory Animals (National Institutes of Health) and the European Directive 86/609, and was carried out in compliance with French regulations and the local ethical committee guidelines for animal research.

Apparatus

Startle chambers (SR LAB, San Diego Instruments, San Diego, CA) were used. Each chamber consisted of a transparent acrylic cylinder (inside diameter: 8.8 cm; inside length: 18.4 cm), resting on a Plexiglas base in a sound-attenuated ventilated enclosure illuminated by a 15 W lamp. Pulses and pre-pulses (white noise bursts) were presented

via a loudspeaker mounted 28 cm above the animal. Startle reflexes within the cylinder were detected by a piezoelectric accelerometer attached to the base. Response sensitivities were calibrated using a standard calibrator tube (San Diego Instruments), and were adjusted to 150 units. Sound levels were calibrated (± 1 dB) using the A scale of a sound level meter (Radio Shack, Tandy Corp., Fort Worth, TX). All events were controlled and recorded on a PC using the San Diego Instruments Startle software.

Procedure

Pre-test and test sessions. Animals, which were used only once, were pre-tested in startle chambers 1 h 45 min before the pharmacological challenge (test) session. This pre-test session that lasted 13 min, was used to habituate rats to the procedure. Three different trial types were presented against a continuous 70 dB background noise: no pulse (NP), 118 dB pulse (pulse alone; PA), and 78 dB prepulse (pp) followed by a 118 dB pulse (prepulse-pulse; ppP). The PA and P duration was 40 ms, the pp duration 20 ms, and the interval between the end of the pp and the onset of the PA or P 80 ms. Sessions started with a 5-min adaptation period after which the animals were exposed to 10 PA (included to induce habituation to startle, such that habituation during the following PPI assessment would be minimized: these trials were not used for data analysis). These 10 PA trials were followed by 10 PA, 10 ppP, and 3 NP trials presented in a pseudo-random order. The interval between trials was variable but with a median of 15 s. The startle response was defined as the average amplitude measured during 100 consecutive samples of 1 ms, which were recorded from the onset of the pulse by means of a 12-bit AD acquisition card (range: 0–4095 arbitrary units). Rats were returned to their home cages at the end of the pre-test session.

Test sessions were in all respects similar to the pre-test sessions (vide supra). Rats that showed any one of these four criteria at least once during either the pre-test or test session were not retained for data analysis: (i) an amplitude of the startle reflex following presentation of the PA less than 10 arbitrary units, or (ii) more than four amplitudes for PA equal to 4095 (ceiling value of the 12-bits AD acquisition card) for the PA condition or for the ppP condition, or (iii) a (PA-NP) amplitude/PA amplitude $<80\%$ or (iv) a pp amplitude $>$ PA amplitude (this last elimination criterion was used only for the pre-test session).

Pharmacological treatments. At the end of the pre-test session, animals were treated as follows: for the dose-effect study of apomorphine and F13714, animals were injected s.c. 60 min before the beginning of the test session with vehicle, and 45 min later with apomorphine or F13714. For the reversion of the apomorphine-induced PPI deficits with antipsychotics, animals were injected 60 min before with the test compound or its vehicle, and 45 min later with apomorphine. For the interaction of the 5-HT_{1A} antagonist and SLV313 or SSR181507, WAY100635 or its vehicle was injected s.c. 75 min before the beginning of the test session, followed by the injection protocol described right above. The dose of apomorphine used in double and triple treatments was 0.63 mg/kg. After each injection, the animals were put back in their home cages. Following is a schematic of the injection protocol:

Data Analysis

For each test session, the median of the amplitude of the startle responses for the last 10 PA trials and for the 10 ppP was calculated. The percentage PPI was calculated as follows:

$$\frac{(\text{median PA amplitude} - \text{median ppP amplitude}) \times 100}{(\text{median PA amplitude})}$$

Data (percentage PPI) were analyzed with an one-way ANOVA with the treatment as the between-subjects factor, followed by a Dunnett's *post hoc* test for comparison with the saline/saline group (for the apomorphine and F13714 dose–response study) or the saline/apomorphine group (for the apomorphine/antipsychotics interaction experiments). For the experiments on the interaction between WAY100635 and SLV313 or SSR181507, a non-parametric (Kruskal–Wallis) test was used (due to heterogeneity of variance) to compare the saline/test compound/apomorphine groups to the WAY100635/test compound/apomorphine groups. It was followed by a Dunn's *post hoc* test for comparing pretreatment with saline or WAY100635 for selected doses of test compounds.

Drugs

Haloperidol, clozapine, and apomorphine HCl were obtained commercially (Sigma RBI, St Quentin Fallavier, France). Ziprasidone HCl, aripiprazole, bifeprunox mesylate (DU-127090; *N*-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(morpholin-4-yl)propoxy]quinazolin-6-yl]prop-2-enamide mesylate), SSR181507 HCl ((3-exo)-8-benzoyl-*N*-[[(2S)7-chloro-2,3-dihydro-1,4-benzodioxin-1-yl]methyl]-8-azabicyclo[3.2.1]octane-3-methanamine monohydrochloride), sarizotan HCl (EMD-128130; (-)-3-[[[(*R*)-2-chromanylmethyl]amino]methyl]-5-(*p*-fluorophenyl)pyridine monohydrochloride), risperidone, olanzapine, nemonapride, F13714 (3-chloro-4-fluorophenyl-(4-fluoro-4-{[(5-methyl-6-methylamino-pyridin-2-ylmethyl)-amino]-methyl}-piperidin-1-yl-methanone fumaric acid salt) and WAY100635 (*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]-*N*-(2-pyridinyl) cyclohexanecarboxamide) were synthesized by J-L Maurel at the Centre de Recherche Pierre Fabre (Castres, France). SLV313 HCl (piperazine, 1-(2,3-dihydro-1,4-benzodioxin-5-yl)-4-[[5-(4-fluorophenyl)-3-pyridinyl]methyl) was generously donated by Solvay Pharmaceuticals (Weesp, The Netherlands). SSR181507 (0.16–10 mg/kg), F13714 (0.0025–10 mg/kg), apomorphine (0.04–2.5 mg/kg), and WAY100635 (0.63 mg/kg) were prepared in distilled water and administered s.c., whereas aripiprazole (0.01–10 mg/kg), bifeprunox (0.01–40 mg/kg), sarizotan (0.16–10 mg/kg), and ziprasidone (0.04–10 mg/kg) were prepared as a suspension in aqueous Tween 80 (two drops/10 ml distilled water) and administered i.p. SLV313 (0.0025–10 mg/kg), nemonapride

(0.00063–2.5 mg/kg), olanzapine (0.16–40 mg/kg), risperidone (0.04–10 mg/kg), clozapine (2.5–40 mg/kg), and haloperidol (0.01–2.5 mg/kg) were prepared in distilled water with a drop of lactic acid, after which the pH was adjusted to 5–7 with a 1 N solution of sodium hydroxide, and were injected s.c. (except clozapine: i.p.). An injection volume of 10 ml/kg was used throughout and doses refer to the weight of the free base. For each compound, doses were administered in an unsystematic order.

RESULTS

Disruptive Effects on PPI of a Direct DA Receptor Agonist and a 5-HT$_{1A}$ Receptor Agonist

Apomorphine (Figure 1a) significantly disrupted PPI at doses of 0.63 and 2.5 mg/kg in comparison with saline ($F(4,143) = 25.76$, $p < 0.0001$, Dunnett's *post hoc* test: $p < 0.01$ for both doses). Similarly, F13714 (Figure 1b) disrupted PPI in comparison with saline ($F(6,66) = 25.89$, $p < 0.0001$, Dunnett's *post hoc* test: $< p < 0.01$ at doses from 0.04 to 2.5 mg/kg).

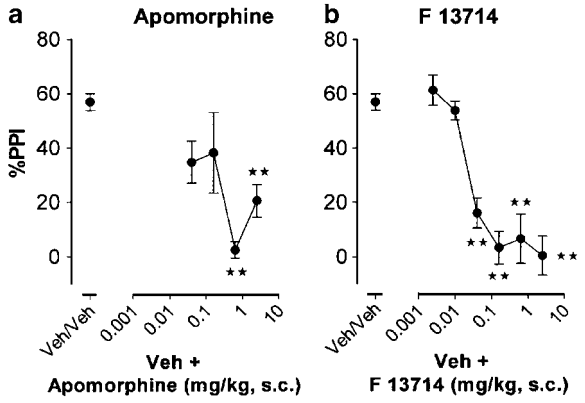

Figure 1 Dose–response curves of the disruption of PPI induced by apomorphine (panel a) or by F13714 (panel b). Rats were injected 60 min before testing with vehicle, followed 45 min after by apomorphine or F13714 or vehicle. The percentage PPI was calculated as: [(median PA amplitude − median ppP amplitude) × 100]/(median PA amplitude). Symbols are means ± SEM. Data were analyzed using one-way ANOVA's followed by Dunnett's *post hoc* tests. $^{**}p < 0.01$, compared with the vehicle/vehicle control group. $N = 7$–9 rats per dose.

Reversal of Apomorphine-Induced PPI Deficits by Antipsychotics with Marked D$_2$ Antagonist Properties and Devoid of 5-HT$_{1A}$ Agonist Activity

Haloperidol (0.63 and 2.5 mg/kg) significantly reversed the disruption of PPI induced by apomorphine (0.63 mg/kg, s.c.) ($F(5,198) = 8.19$, $p < 0.0001$, Dunnett's *post hoc* test: $p < 0.01$: Figure 2a). Similar significant effects were obtained for olanzapine (Figure 2b) at 0.63, 10, and 40 mg/kg ($F(5,197) = 7.68$, $p < 0.0001$, Dunnett's *post hoc* test: $p < 0.05$, $p < 0.01$, and $p < 0.01$, respectively) and for risperidone (Figure 2c) at 0.63, 2.5, and 10 mg/kg ($F(5,197) = 10.36$, $p < 0.0001$, Dunnett's *post hoc* test: $p < 0.01$, $p < 0.05$, and $p < 0.01$, respectively).

Effects on Apomorphine-Induced PPI Deficits of Multireceptorial Antipsychotics Possessing Some 5-HT$_{1A}$ Agonist Properties

Clozapine (40 mg/kg) ($F(3,181) = 6.44$, $p < 0.001$, Dunnett's *post hoc* test $p < 0.01$), ziprasidone (10 mg/kg) ($F(5,196) = 3.387$, $p < 0.01$, Dunnett's *post hoc* test $p < 0.05$), and aripiprazole (0.04 and 10 mg/kg) ($F(6,202) = 2.620$, $p < 0.05$, Dunnett's *post hoc* test $p < 0.05$) significantly reversed the deficits of PPI (Figure 3a–c). Over a wider range of doses, nemonapride (0.01–2.5 mg/kg: Figure 3d) significantly prevented the disruption of PPI ($F(7,213) = 5.37$, $p < 0.0001$, Dunnett's *post hoc* test for 0.01 mg/kg: $p < 0.05$, for 0.04 mg/kg: $p < 0.05$, for 0.16 mg/kg: $p < 0.05$, for 0.63 mg/kg: $p < 0.01$, for 2.5 mg/kg: $p < 0.05$).

Effects on Apomorphine-Induced PPI Deficits of Novel Putative Antipsychotics Selectively Targeting D$_2$ and 5-HT$_{1A}$ Receptors

Deficits induced by apomorphine were not significantly reversed by SSR181507 ($F(4,189) = 1.64$, $p = 0.16$) or sarizotan ($F(4,189) = 0.43$, $p = 0.79$) (Figure 4a and b).

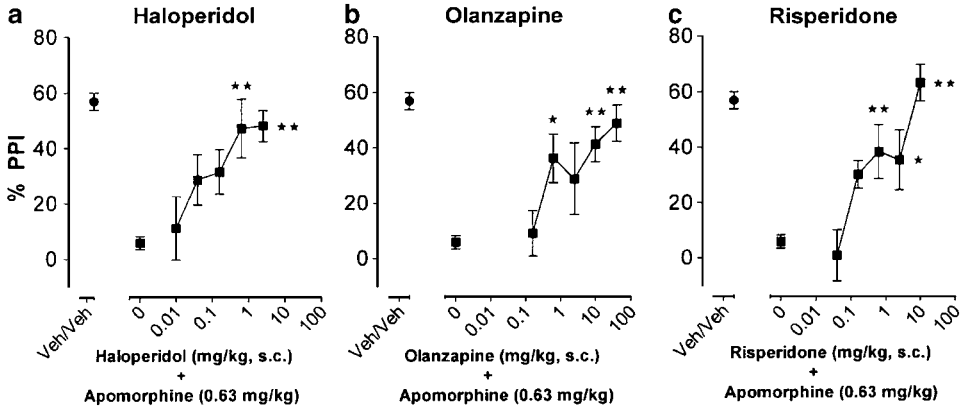

Figure 2 Effects of haloperidol (panel a), olanzapine (panel b) and risperidone (panel c) on the disruption of PPI induced by apomorphine. Rats were injected with vehicle or test compounds 60 min before testing, followed 45 min later by apomorphine (0.63 mg/kg, s.c.). See legend of Figure 1 for details. $^{*}p < 0.05$ and $^{**}p < 0.01$, compared with the vehicle/apomorphine control group, following significant one-way ANOVA. $N = 9$ rats per dose.

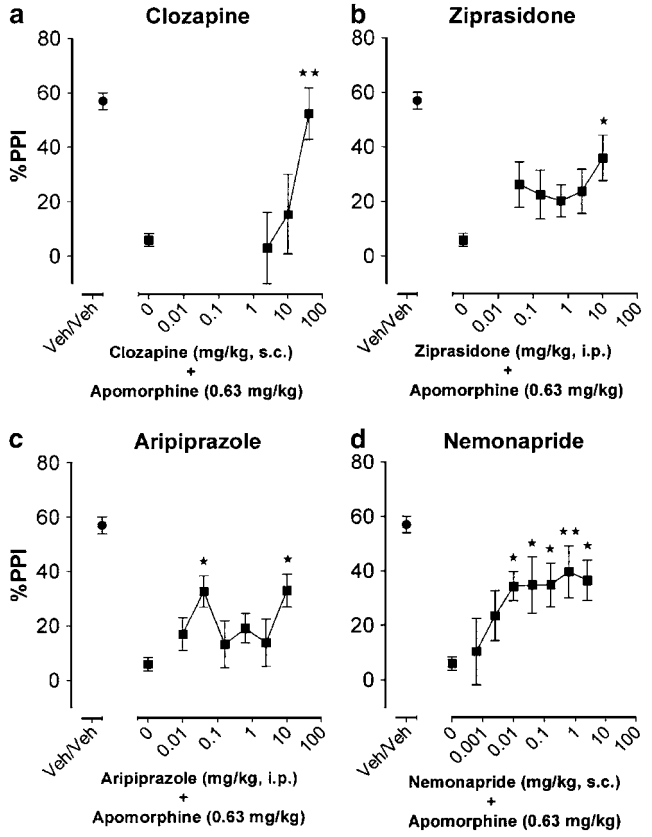

Figure 3 Effects of clozapine (panel a), ziprasidone (panel b), aripiprazole (panel c) and nemonapride (panel d) on the disruption of PPI induced by apomorphine. Rats were injected with vehicle or test compounds 60 min before testing, followed 45 min later by apomorphine (0.63 mg/kg, s.c.). See legend of Figure 1 for details, and legend of Figure 2 for statistical analysis. $N = 9$ rats per dose.

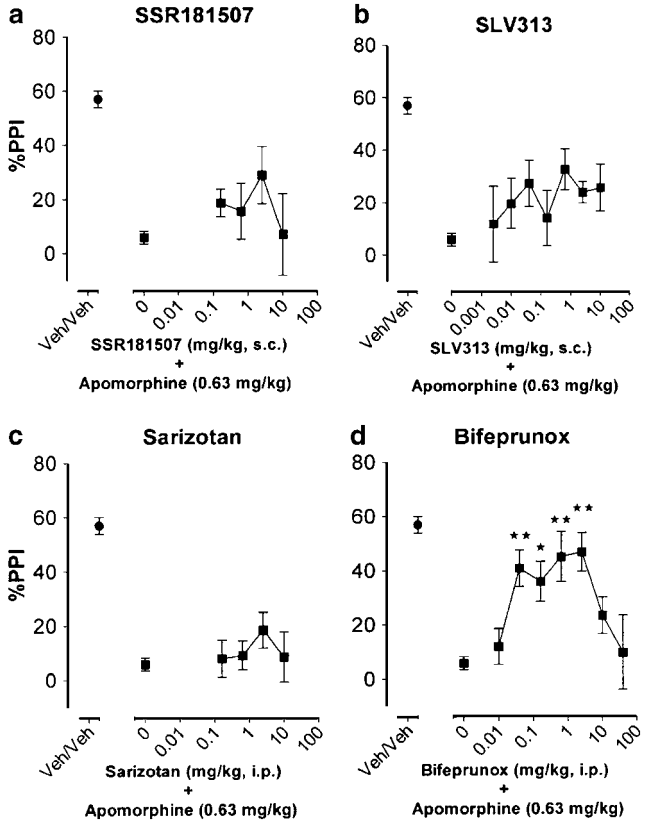

Figure 4 Effects of SSR181507 (panel a), SLV313 (panel b), sarizotan (panel c) and bifeprunox (panel d) on the disruption of PPI induced by apomorphine. Rats were injected with vehicle or test compounds 60 min before testing, followed 45 min later by apomorphine (0.63 mg/kg, s.c.). See legend of Figure 1 for details, and legend of Figure 2 for statistical analysis. $N = 9$ rats per dose.

For SLV313, although there was a significant global effect of the ANOVA ($F(7,213) = 2.38$, $p = 0.02$: Figure 4c), *post hoc* Dunnett's test did not detect any dose that differed significantly from control. In contrast, bifeprunox (0.04–2.5 mg/kg: Figure 4d) prevented PPI deficits ($F(7,213) = 6.83$, $p < 0.0001$, Dunnett's *post hoc* test: for 0.04 mg/kg: $p < 0.01$, for 0.16 mg/kg: $p < 0.05$, for 0.63 mg/kg: $p < 0.01$, for 2.5 mg/kg: $p < 0.01$). For the higher doses of 10 and 40 mg/kg, bifeprunox did not significantly reverse the effects of apomorphine ($p > 0.05$).

Masking by Pretreatment with WAY100635 of the 5-HT$_{1A}$ Agonist Properties of SLV313 and SSR181507: Effects on Apomorphine-Induced PPI Deficits

By blocking the 5-HT$_{1A}$ agonist properties of SLV313 (Figure 5a) and SSR181507 (Figure 5b), WAY100635 (0.63 mg/kg) permitted the reversal of PPI deficits induced by apomorphine. PPI deficits were opposed by 0.01, 2.5, and 10 mg/kg of SLV313 (Kruskal–Wallis test: $H = 43.44$, $p < 0.0001$, Dunn's *post hoc* test: $p < 0.05$ for all three doses) and by 10 mg/kg of SSR181507 (Kruskal–Wallis test: $H = 21.74$, $p < 0.01$, Dunn's *post hoc* test: $p < 0.01$).

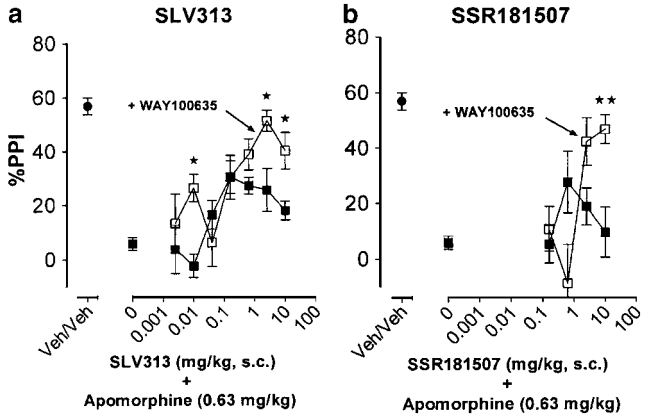

Figure 5 Pretreatment with the 5-HT$_{1A}$ receptor antagonist WAY100635 reveals the ability of SLV313 (panel a) or SSR181507 (panel b) to reverse the disruption of PPI induced by apomorphine. Rats were injected with vehicle or WAY100635 (0.63 mg/kg, s.c.), vehicle or test compound, followed by apomorphine (0.63 mg/kg, s.c.), 75 min, 60 min and 15 min, respectively, before testing. Data were analyzed using non-parametric Kruskal–Wallis tests followed by a Dunn's post-hoc tests. $^{*}p < 0.05$ and $^{**}p < 0.01$, comparing the WAY100635 pretreated with the saline-pretreated group, at the considered dose of the test compound. See legend of Figure 1 for details. $N = 9$ rats per dose.

Table 1 Effects of Treatments on Pulse Alone (PA) Amplitude and % PPI

Control group	Treatment group	PA amplitude (dB)	% PPI
Vehicle/Vehicle	Vehicle/Apomorphine (0.63)	116±14 *vs* 182±16[a]	56.9±3.1 *vs* 2.4±3.0[a]
Vehicle/Apomorphine (0.63)	Aripiprazole (10)/Apomorphine (0.63)	133±22[b] *vs* 125±39	0.5±9.0[b] *vs* 32.7±5.9
Vehicle/Apomorphine (0.63)	Haloperidol (2.5)/Apomorphine (0.63)	182±16 *vs* 30±5	2.4±3.0 *vs* 48.0±5.6
Vehicle/Apomorphine (0.63)	Aripiprazole (0.01)/Apomorphine (0.63)	133±22 *vs* 105±15	0.5±9.0 *vs* 2.3±15.5
Vehicle/Apomorphine (0.63)	Bifeprunox (2.5)/Apomorphine (0.63)	133±22 *vs* 213±41	0.5±9.0 *vs* 46.8±7.1

Doses in mg/kg are given in parenthesis.
[a]Vehicle administered s.c.
[b]Vehicle administered i.p.

Note: effects of compounds on PPI and on pulse alone (PA) amplitude did not appear to be correlated. Table 1 contains a non-exhaustive list of a series of drug treatments, with their effects on PA amplitude and on %PPI. It can be seen that some treatments increased the PA amplitude but decreased the %PPI (first line), while others did not modify the PA amplitude but increased the %PPI (second line), diminished the PA amplitude but augmented (third line) or left intact (fourth line) the %PPI, and finally increased both the PA amplitude and the %PPI (fifth line).

DISCUSSION

The PPI paradigm employed in the present study is widely used for characterizing antipsychotic drugs, and has been claimed to possess face validity, since apomorphine-induced startle gating deficits in rats mimic the abnormalities of gating that are thought to underlie sensory flooding and cognitive fragmentation present in schizophrenic patients (McGhie and Chapman, 1961; Braff *et al*, 2001). These deficits can be reversed by 'typical' high-potency DA D_2 receptor antagonists and 'atypical' antipsychotics with low activity at 5-HT_{1A} receptors (Swerdlow *et al*, 1986, 1994; Mansbach *et al*, 1988; Geyer *et al*, 2001). However, activation of 5-HT receptor subtypes, such as 5-HT_{2A} and 5-HT_{1A} interferes with sensorimotor gating (Mansbach *et al*, 1988; Nanry and Tilson, 1989; Rigdon and Weatherspoon, 1992; Sipes and Geyer, 1994, 1995a, b, 1997; Sipos *et al*, 2000; Wadenberg *et al*, 2000a; Roth *et al*, 2004). As such, the exploration of activity of drugs acting preferentially at DA D_2 and 5-HT_{1A} receptors (currently under development as antipsychotics) in the apomorphine-PPI model was warranted. The present data show that a wide diversity of responses is observed among these novel compounds (including SSR181507, bifeprunox, SLV313, and sarizotan), which distinguishes them from existing classes of conventional and 'atypical' antipsychotics.

Antipsychotics with Marked DA D_2 Antagonist But Devoid of 5-HT_{1A} Agonism Properties

Over a broad range of doses (0.63–10 mg/kg or 40 mg/kg), haloperidol, risperidone, and olanzapine prevented the PPI disruptive effects of apomorphine, confirming previous data (Mansbach *et al*, 1988; Geyer *et al*, 1990; Schwarzkopf *et al*, 1993; Rasmussen *et al*, 1997). These antipsychotics behave as DA D_2 receptor antagonists, with low or no affinity at 5-HT_{1A} receptors (Newman-Tancredi *et al*, 1998; Leysen, 2005). Indeed, the ratios of Ki (rKi) at 5-HT_{1A} *vs* DA D_2 receptors were 275, 468, and 1738, for olanzapine, risperidone, and haloperidol, respectively (Newman-Tancredi *et al*, 2005). Considering that disruption of PPI by the DA receptor agonist apomorphine has been demonstrated to result primarily by activation of DA D_2 receptors in rats (Swerdlow *et al*, 1986; Mansbach *et al*, 1988; Geyer *et al*, 2001), the reversion observed with these three compounds is consistent with their receptorial profile.

'Atypical' Antipsychotics Possessing, Among Other Properties, 5-HT_{1A} Agonist Activities

Clozapine at the highest dose tested (40 mg/kg) reversed the reduction of PPI induced by apomorphine, confirming previous results for this 'atypical' antipsychotic (Swerdlow *et al*, 1991, 1998; Mansbach *et al*, 1998). This reversing effect can be explained based on a low efficacy at 5-HT_{1A} receptors (12% that of (+)8-OH-DPAT in an assay of [^{35}S]GTPγS stimulation in rat hippocampal membrane: Newman-Tancredi *et al*, 2005) combined with a rather low pKi (3.3). The low potency of clozapine is consistent with its very moderate affinity for the DA D_2 receptor (pKi: 6.31: Newman-Tancredi *et al*, 2005). In contrast, nemonapride almost completely prevented PPI deficits over a dose-range of 0.01–2.5 mg/kg. Here again, the rKi was high (37), indicating that over this dose-range, DA D_2 receptor blockade largely predominates over the agonist activity at 5-HT_{1A} receptors. Its rather potent efficacy to activate 5-HT_{1A} receptors (39% that of (+)8-OH-DPAT in an assay of [^{35}S]GTPγS stimulation in rat hippocampal membrane: Newman-Tancredi *et al*, 2005) might explain why the reversing effect is not full at higher doses. Indeed, in a catalepsy test, it was observed that nemonapride produced catalepsy at lower doses (0.04–0.63 mg/kg s.c.) but not at higher doses (from 2.5 to 40 mg/kg s.c.), indicating that the 5-HT_{1A} agonist properties of nemonapride appear at doses approximately 16–64 fold higher than those blocking DA D_2 receptors (Prinssen *et al*, 1998).

The 5-HT_{1A} receptor partial agonist/DA D_2 receptor antagonist ziprasidone, and the DA D_2 receptor and 5-HT_{1A} receptor partial agonist aripiprazole, reversed apomorphine-induced PPI deficits at some doses only (10 mg/kg,

and 0.16 and 10 mg/kg, respectively). Similar results (partial reversal) were obtained by Mansbach *et al* (2001) with 17 mg/kg (p.o.) of ziprasidone in Wistar rats. As concerns aripiprazole, we believe we are the first group to provide data concerning its actions in this model of sensorimotor gating deficit. The partial reversal seen with ziprazidone might be tentatively explained by a rKi lower than unity (0.4), and a somewhat potent efficacy at 5-HT_{1A} receptors (31 % that of (+)8-OH-DPAT). A similar explanation would be less applicable to aripiprazole: the compound has a rKi of 15, and an efficacy at 5-HT_{1A} receptors of 22%. However, it behaves as a DA D_2 receptor partial agonist (efficacy: 26% that of apomorphine in an assay of [^{35}S]GTPγS stimulation in membrane from Sf9 cells expressing the human D_{2L} receptor: (Cosi *et al*, in press). As a consequence, the partial agonist activity at DA D_2 receptors at low doses is relayed by the 5-HT_{1A} receptor partial agonist properties at higher doses, resulting in a lack of clear-cut reversing effect. In addition, in both rats and humans, a major metabolite of aripiprazole is a pure DA D_2 receptor antagonist (Lawler *et al*, 1999), which adds a further dimension to the complexity of pharmacological interaction between apomorphine and aripiprazole in this test.

Influence of 5-HT_{1A} Receptor Agonism on the Ability of Novel Antipsychotics Selectively Targeting DA D_2 and 5-HT_{1A} Receptors to Reverse Apomorphine-Induced PPI Deficits

Neither SSR181507, SLV313 nor sarizotan reversed apomorphine-induced PPI deficits. All three compounds are characterized by their strong affinity for and fairly high efficacy at 5-HT_{1A} receptors (Newman-Tancredi *et al*, 2005). These data are consistent with the disruptive influence of the selective 5-HT_{1A} agonist, F13714 (Figure 1b), and of the prototypic 5-HT_{1A} agonist, 8-OH-DPAT, as well as the partial 5-HT_{1A} agonists, buspirone, gepirone, and ipsapirone (Rigdon and Weatherspoon, 1992; Sipes and Geyer, 1995a; Sipos *et al*, 2000). Among a whole series of compounds tested (Newman-Tancredi *et al*, 2005), sarizotan exhibited the highest efficacy at 5-HT_{1A} receptors (100% that of (+)8-OH-DPAT), and possessed a low rKi (0.3). Furthermore, sarizotan behaved as a partial DA D2 receptor agonist (Bartoszyk *et al*, 2004; Kuzhikandathil *et al*, 2004). These observations indicate that the 5HT_{1A} receptor agonist properties of sarizotan are predominant: this most likely explains the lack of activity of this compound against apomorphine-induced PPI disruption, and might also be the reason why it was originally developed as an antipsychotic, but has been more recently re-oriented towards an anti-dyskinetic indication (Bibbiani *et al*, 2001). SSR181507 exhibited a moderate efficacy at 5-HT_{1A} receptors (39% that of (+)8-OH-DPAT) with a rKi of 0.8, and also behaved as a partial DA D_2 receptor agonist (18% that of apomorphine, Cosi *et al*, in press). Here again, it can be considered that the compound preferentially activates 5-HT_{1A} receptors, hence its lack of activity against apomorphine-induced PPI impairment. The case for SLV313 is slightly different: despite the fact that it had even more moderate efficacy at 5-HT_{1A} receptors (28% that of (+)8-OH-DPAT), its rKi was also close to unity (0.9: Newman-Tancredi *et al*, 2005) but it behaved as a DA D_2 receptor antagonist (Feenstra *et al*, 2002; McCreary *et al*, 2002; Cosi *et al*, in press). Nonetheless, it seems that overall, its 5-HT_{1A} receptor agonist activity predominates. It should be noted, however, that in the only other study (in an abstract form) published on SLV313, it was reported that the compound could attenuate effect of PPI disruption at doses less than 0.1 mg/kg (McCreary *et al*, 2002). The reasons for this discrepancy between this study and ours are not clear at the moment. Administration of the 5-HT_{1A} receptor antagonist WAY-100635 revealed the ability of SSR181507 and SLV313 to prevent apomorphine-induced PPI deficits. This provides a cogent demonstration implicating the 5-HT_{1A} receptor agonist activity of these compounds in their lack of efficacy for reversal of this type of disruption.

Surprisingly, bifeprunox potently prevented apomorphine-induced gating deficits at doses from 0.04 to 2.5 mg/kg, with a loss of activity at 10 and 40 mg/kg. One possible explanation is that bifeprunox, although having a quite substantial efficacy at 5-HT_{1A} receptors (54% that of (+)8-OH-DPAT), has higher affinity for D_2 than for 5-HT_{1A} receptors (rKi of 44). It thus appears that the partial agonist activity at DA D_2 receptors (27% that of apomorphine, Cosi *et al*, in press) predominates over this dose-range, and reverses the deficit produced by the full D_2 receptor agonist apomorphine whereas at higher doses (10 and 40 mg/kg), the 5-HT_{1A} agonist activity exerts its deleterious effects on PPI.

SUMMARY AND CONCLUSIONS

Although several novel antipsychotics share the capacity to interact at both 5-HT_{1A} and DA D_2 receptors, their ability to reverse apomorphine-induced PPI deficits is highly diverse. In fact, this variety of profiles could be related to their diverging affinities and efficacies at 5-HT_{1A} and DA D_2 receptors, as has been characterized in detail in cellular models of receptor interaction (Newman-Tancredi *et al*, 2005, Cosi *et al*, in press). Thus, the present data suggest that in this apomorphine-induced gating deficits model, a narrow window of efficacy exists between DA D_2 receptor blockade and serotonin 5-HT_{1A} receptor activation. While the latter property is considered to be desirable for attenuating negative, cognitive, and affective symptoms of schizophrenia, as well as neuroleptic-induced EPS (Millan, 2000; Bantick *et al*, 2001; Kleven *et al*, 2005), it appears that too pronounced an activation of 5-HT_{1A} receptors impairs the ability of compounds, such as SLV313 and SSR181507 to reverse apomorphine-induced PPI deficits. Taken together, these data indicate that 5-HT_{1A} activation can alter the antipsychotic-like effects of DA D_2 receptor antagonists in this model of positive symptoms of schizophrenia. However, this does not hold true for at least one other model predictive of antipsychotic activity, such as the active (two-way) avoidance task: in mice, the coadministration of the 5-HT_{1A} antagonist SL88.0338 did not modify the activity of SSR181507 in this test (Depoortere *et al*, 2003). In addition, data obtained in the same test but in rats, suggest that the potency of DA D_2 receptor antagonists (such as raclopride and haloperidol)

is even enhanced by addition of a compound with 5-HT_{1A} agonist properties such as 8-OH-DPAT (Prinssen *et al*, 1996).

Taken together, these considerations indicate complex interactions in the balance of DA D_2 and 5-HT_{1A} activities that could profoundly influence the pharmacological and therapeutic profiles of new generation ligands targeting these receptors.

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