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Antipsychotic-Like *vs* Cataleptogenic Actions in Mice of Novel Antipsychotics Having D_2 Antagonist and 5-HT_{1A} Agonist Properties

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A new generation of proven or potential antipsychotics, including aripiprazole, bifeprunox, SSR181507 and SLV313, exhibit agonist actions at serotonin 5-HT_{1A} receptors, but little comparative data are available on their pharmacological profiles. Here, we compared in mice the in vivo antipsychotic-like *vs* cataleptogenic activities of these compounds with those of drugs that exhibit little interaction at 5-HT_{1A} receptors, such as haloperidol, olanzapine and risperidone. All the drugs dose-dependently reduced apomorphine-induced climbing or sniffing and, with the exception of ziprasidone, produced complete suppression of these responses. In the bar catalepsy test, when administered alone, haloperidol, olanzapine and risperidone produced marked catalepsy, whereas, at doses up to 40 mg/kg, aripiprazole, SLV313, SSR181507, and sarizotan produced little or no catalepsy. The latter compounds, therefore, displayed a large separation between doses with 'antipsychotic-like' and those with cataleptogenic actions. When 5-HT_{1A} receptors were blocked by pretreatment with WAY100635 (2.5 mg/kg, s.c.), cataleptogenic properties of SSR181507 and sarizotan were unmasked, and the catalepsy induced by bifeprunox was enhanced. In the case of aripiprazole and SLV313, although WAY100635 produced upward shifts in their dose–response, the magnitude of catalepsy appeared to reach an asymptotic plateau, suggesting that other mechanisms may be involved in their low cataleptogenic liability. The present data confirm that 5-HT_{1A} receptor activation reduces or even completely prevents the cataleptogenic potential of novel antipsychotic agents. Further, they indicate that the balance of affinity and/or efficacy between D_2 and 5-HT_{1A} receptors profoundly influences their pharmacological activities, and will likely impact their therapeutic profiles. *Neuropsychopharmacology* (2006) **31,** 1869–1879. doi:10.1038/sj.npp.1300940; published online 19 October 2005

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INTRODUCTION

Although conventional neuroleptics control positive symptoms in schizophrenia, they also induce extrapyramidal side effects (EPS) such as dystonia, parkinsonism, akathisia and tardive dyskinesia. These effects are mediated by blockade of dopamine D_2 receptors, but their expression can be modulated by other systems, most notably, serotonin (5-HT) (for review, see: Meltzer *et al*, 2003). Hence, the development of newer generation antipsychotics has been focused on multiple receptorial mechanisms that could lead to improved clinical efficacy and reduced EPS liability. In particular, focus on 5-HT_{2A} and 5-HT_{2C} receptor subtypes led to the development of antipsychotics (eg risperidone and olanzapine) that antagonize these receptors, in addition to D_2 receptors. Recently, particular attention has been given to the 5-HT_{1A} receptor as a promising additional target for antipsychotic therapy (for review, see: Millan, 2000; Bantick *et al*, 2001). In fact, 5-HT_{1A} receptor agonists attenuate antipsychotic-induced EPS in humans (Yoshida *et al*, 1998), non-human primates (Christoffersen and Meltzer, 1998) and rats (Prinssen *et al*, 1999, 2002). In addition, 5-HT_{1A} receptor activation increases dopamine release in a regionally-selective manner in the prefrontal cortex (Ichikawa and Meltzer, 2000), suggesting alleviation of the proposed deficiency in dopaminergic neurotransmission in this brain region of schizophrenics (Honey *et al*, 1999). Indeed, amelioration of this 'hypofrontality' is associated with improvement in negative and cognitive symptoms of schizophrenia (Honey *et al*, 1999). Consistent

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with this idea, clinical studies have reported that buspirone and tandospirone, two partial agonists at 5-HT$_{1A}$ receptors, substantially ameliorate cognitive performance and reduce the incidence of EPS in schizophrenic patients treated with haloperidol (Sumiyoshi *et al*, 2001a, b). The atypical antipsychotic clozapine, which displays improved capacity to treat negative symptoms with minimal EPS liability, exhibits agonist properties at 5-HT$_{1A}$ receptors (Newman-Tancredi *et al*, 1998; Cussac *et al*, 2002) and both its absence of cataleptogenic properties and its elevation of dopamine release in frontal cortex are partially mediated by 5-HT$_{1A}$ receptors (Millan *et al*, 1998; Rollema *et al*, 1997). The ability of clozapine to occupy 5-HT$_{1A}$ receptors in non-human primates at clinically-relevant doses has been demonstrated by PET scans with [^{3}H]WAY100635 (Bantick *et al*, 2000; Chou *et al*, 2003). In addition, the more recent antipsychotic, ziprasidone, which also activates 5-HT$_{1A}$ receptors, has a notably low incidence of EPS in humans (Daniel *et al*, 1999). Lastly, 5-HT$_{1A}$ agonists exert anti-depressant- and anxiolytic-like properties (Blier and Ward, 2003), of particular interest to schizophrenic patients of whom an appreciable proportion suffer from comorbid anxiety and/or depression (Buchanan *et al*, 2002). Thus, combined 5-HT$_{1A}$ agonist and D$_2$ antagonist properties would be expected to have a wider spectrum of activity than currently used antipsychotics, and in particular, exhibit greater efficacy against negative/cognitive symptoms with reduced EPS liability.

In this context, several laboratories have reported the development of a new generation of potential antipsychotic agents with varying levels of agonist/antagonist actions at D$_2$ and 5-HT$_{1A}$ receptors. These compounds, currently in various phases of development, include SLV313 (Glennon *et al*, 2002), SSR181507 (Claustre *et al*, 2003), bifeprunox (DU127090; Wolf, 2003) as well as sarizotan (EMD128130; Bartoszyk *et al*, 2004), that seems, however, to have been lately reoriented towards an antidyskinetic indication. Nonetheless, these compounds display marked diversity in their actions at 5-HT$_{1A}$ receptors *in vitro*, with varying potencies and efficacies for activation of cellular signal transduction (Newman-Tancredi *et al*, 2005), likely to profoundly influence their profile of action. Indeed, the extent to which 5-HT$_{1A}$ agonists are able to reverse neuroleptic-induced catalepsy is dependent on their efficacy: high-efficacy activation seems necessary to completely abolish haloperidol-induced catalepsy (Prinssen *et al*, 1999, 2002). Further, the intrinsic activity of a series of 5-HT$_{1A}$ receptor ligands correlates positively with the magnitude of their antidepressant-like effects in the forced swimming test (Koek *et al*, 2001). The issue, therefore, arises as to what could be the desirable balance of affinity and efficacy between D$_2$ and 5-HT$_{1A}$ receptors that would exhibit antipsychotic activity with reduced EPS liability.

As no formal comparison between the pharmacological profiles of these new generation ligands is available, we set out to compare the antipsychotic *vs* cataleptogenic activity of drugs varying in 5-HT$_{1A}$ agonist *vs* D$_2$ antagonist properties, along with those of more typical and atypical antipsychotics (see Table 1). First, we used the apomorphine-induced climbing and stereotypies tests (considered predictive of antipsychotic potential) and the catalepsy paradigm (thought to predict EPS liability). Second, drug-interaction studies were conducted using the 5-HT$_{1A}$ antagonist, WAY100635 (Forster *et al*, 1995), with the aim of determining whether activation of 5-HT$_{1A}$ receptors is responsible for 'masking' the induction of catalepsy that would be expected following D$_2$ receptor blockade. Such a pattern of pharmacological interaction has been observed in rats for another antipsychotic exhibiting both D$_2$ antagonist properties and, less potently, 5-HT$_{1A}$ agonist properties, nemonapride (Prinssen *et al*, 1998). This compound induces catalepsy at low doses but, when doses are sufficient to activate 5-HT$_{1A}$ receptors, catalepsy is attenuated, and blockade of 5-HT$_{1A}$ receptors by WAY100635 pretreatment 'unmasks' this 5-HT$_{1A}$ receptor influence (Prinssen *et al*, 1998; Kleven *et al*, 2005).

Table 1 Classification of Tested Compounds Based on an Abbreviated Binding Profile

Family	Compound	Mode of action
Conventional Antipsychotics	Haloperidol Fluphenazine Raclopride Eticlopride	Predominant D$_2$ antagonism
Atypical antipsychotics	Clozapine Risperidone Olanzapine Ziprasidone Nemonapride Aripiprazole*	Multiple actions: predominant D$_2$ and 5-HT$_{2A}$ antagonism
New generation putative antipsychotics	SLV314 SLV313 Sarizotan Bifeprunox SSR181507	Mixed D$_2$ partial agonism or antagonism and 5-HT$_{1A}$ agonism

*Predominant D$_2$ and 5-HT$_{1A}$ partial agonism.

METHODS

Animals

Male NMRI mice (Iffa-Credo, Lyon, France) weighing 20–24 g upon arrival were group-housed for a 5-day quarantine period in polycarbonate Type III cages (internal dimensions 375 × 215 × 149 mm^3, L × l × H; floor surface 806 cm^2) in an environmentally controlled room (ambient temperature, 21 ± 1°C; relative humidity, 55 ± 5%; 12 : 12 light : dark cycle, lights on at 0700). Standard laboratory food (A04; Animal Food and Engineering, Epinay sur Orge, France) and filtered water (0.22 μm pore diameter; in bottles) were freely available. The mice were transferred to the experimental room on the day before experiments and housed individually in polystyrene hanging cages (internal dimensions 220 × 185 × 80 mm^3, L × l × H; floor surface 187 cm^2),

where they were food-restricted but had free access to water. All experiments were performed in a quiet room, between 0900 and 1600, by a single experimenter and in a blind fashion with respect to the treatment administered. Animals were handled and cared for in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health, USA), the European Directive 86/609, and the internal protocoles (No 194 and 240) were carried out in compliance with local ethical committee guidelines for animal research. Mice were used only once and were killed immediately after the experiment.

Apomorphine-Induced Climbing and Sniffing

Each animal was placed into cylindrical wire-mesh cages (diameter, 14 cm; height, 13 cm; mesh size, 3 mm) and allowed to adapt for 60 min. Thereafter, mice were injected twice, first with test compound or saline (i.p. or s.c.), followed 45 min later by s.c. injection of apomorphine (2.5 mg/kg). The observational method used was an adaptation of the method of Fray *et al* (1980), combined with a time-sampling procedure (Waddington, 1986). Behavioral observations were made from 55 to 65 min after the first injection: animals were observed for 10 s every minute for the presence or absence of climbing (ie all fours paws on the cage, above the floor). Sniffing was scored when the animal showed uninterrupted sniffing for at least 3 s during this 10 s sampling period. Thus, the score for climbing or sniffing could vary from 0 to 10 for the entire observation period.

Catalepsy

Each animal was injected with the test compound or saline (i.p. or s.c.) and the catalepsy procedure was measured using the bar test 60 min after the injection: the forelimbs were placed on a cylindrical metal bar (diameter, 0.4; 3.5 cm above the table) and the time during which both forelimbs remained on the bar was recorded up to a maximum of 30 s. The test was repeated three times (inter-trial interval: 1 min). Animals were put back in their home cage after each measurement of catalepsy.

In order to investigate the effects of 5-HT$_{1A}$ receptors on catalepsy induced by some antipsychotics, WAY100635 (2.5 mg/kg) or saline were administered s.c., 15 min before test compounds (s.c. or i.p.) that is, 75 min before recording catalepsy.

Analysis of Data

Drug effects on apomorphine-induced behaviors were expressed as the mean $\pm$ SEM score and the dependent variables used for catalepsy were the mean duration (s) of three trials and the percentage of animals showing a duration of 30 s in one or more trials. Data were analyzed with a one-way ANOVA followed by *post hoc* comparisons using Dunnett's test. Interactions between WAY100635 and antipsychotics were analyzed with a two-way ANOVA, with pretreatment (WAY100635 or saline) and the doses of antipsychotics as the factors, followed by Dunnett's *post hoc* tests. A P-value <0.05 was considered statistically significant. To calculate ED$_{50}$ values, the results were expressed as the percentage of mice showing reduction of apomorphine-induced climbing and sniffing (ie scores <9), and as the percentage of mice presenting at least once a duration of catalepsy of 30 s. The climbing and sniffing criterion for calculation of ED$_{50}$ were based upon the incidence of each particular behavior observed in control animals treated with apomorphine 2.5 mg/kg (Kleven *et al*, 1996). ED$_{50}$ values and their associated confidence limits were calculated with the Litchfield and Wilcoxon probit analysis procedure (Tallarida and Murray, 1987) implemented using a procedure written using the Research Programming Language (RPL) of RS/1 (Bolt, Beranek and Newman, Cambridge, MA), that used all data points between 0 and 100% effects to correct 0 and 100% effects (Litchfield and Wilcoxon, 1949). When less than two intermediate effects were observed, 0 and/or 100% effects were transformed by means of Berkson's adjustment (Hubert, 1984) to permit the use of the Litchfield and Wilcoxon procedure.

Drugs

Ziprasidone HCl, risperidone, olanzapine, aripiprazole, bifeprunox mesylate (DU127090; *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), nemonapride and WAY100635 (*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl) cyclohexanecarboxamide dihydrochloride) were synthesized by JL Maurel, Chemistry Department, Centre de Recherche Pierre Fabre (Castres, France). SLV313 (piperazine, 1-(2,3-dihydro-1,4-benzodioxin-5-yl)-4-[[5-(4-fluorophenyl)-3-pyridinyl]methyl) and SLV314 ((2R)-2H-1,4-Benzoxazin-3(4H)-one, 8-[4-[3-(5-fluoro-1H-indol-3-yl)propyl]-1-piperazinyl]-2-methyl) was obtained from Solvay Duphar B.V. (Weesp, The Netherlands). Haloperidol, fluphenazine, eticlopride HCl, raclopride and apomorphine hydrobromide were purchased from Sigma RBI (St Quentin Fallavier, France) and clozapine from Tocris (Illkirch, France).

Raclopride, fluphenazine, eticlopride, WAY100635 and apomorphine were prepared and administered s.c. in distilled water, whereas aripiprazole, bifeprunox, sarizotan, and ziprasidone were prepared as a suspension in aqueous Tween 80 (1% v/v in distilled water) and administered i.p. SSR181507, SLV313, SLV314, nemonapride, haloperidol, clozapine, olanzapine, and risperidone 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 injected s.c. An injection volume of 1 ml/100 g was used throughout and doses refer to the weight of the free base. Taking into consideration that at doses of 40 mg/kg and above several compounds (eg clozapine, olanzapine…) begin to exert major interfering effects (eg ataxia, sedation…) that would greatly complicate interpretation of data, absolute upper limits of 40 mg/kg were retained.

RESULTS

Antagonism of Apomorphine-Induced Climbing and Sniffing

All drugs dose-dependently reduced apomorphine-induced climbing and, with the exception of ziprasidone, produced complete suppression of this response at higher doses (Figure 1, filled circles). Apomorphine-induced sniffing (open circles) was also decreased in a dose-dependent manner over a similar dose-range, except for bifeprunox, SSR181507 and SLV313 that reduced or blocked sniffing only at the higher doses. In contrast, ziprasidone and sarizotan exhibited little effect on apomorphine-induced sniffing, even at the highest dose tested (40 mg/kg).

Table 2 shows a summary of ED_{50} estimates, 95% confidence limits and the maximal effects observed. The majority of compounds were somewhat more potent for antagonism of climbing than sniffing behavior. Nevertheless, the confidence limits of their ED_{50}'s overlapped. Ziprasidone was the only compound that yielded markedly different ED_{50}'s for climbing (2.2 mg/kg) *vs* sniffing (>40 mg/kg). The ability of the antipsychotics to inhibit apomorphine-induced climbing and sniffing correlated positively ($r=0.75$ and 0.78, $P<0.001$, respectively) with their affinity at rat D_2 receptors but not with their affinity at rat 5-HT$_{1A}$ receptors ($r=-0.17$ and -0.28, $P>0.05$, respectively) (based on affinity values published by Newman-Tancredi *et al*, 2005).

Catalepsy

Haloperidol and risperidone dose-dependently induced catalepsy at low doses in the bar test (Figure 2). Although bifeprunox, aripiprazole, clozapine, and SLV313 were substantially less effective or potent than haloperidol and risperidone, they too produced dose-dependent increases in catalepsy. Nemonapride induced catalepsy in a biphasic manner: that is, less catalepsy at higher doses. In contrast, SSR181507 and sarizotan did not induce catalepsy when tested at doses up to 40 mg/kg. As shown in Table 2, the ED_{50} values of drugs that activate 5-HT$_{1A}$ receptors, that is, SSR181507, sarizotan, aripiprazole, clozapine, and SLV313 were greater than 40 mg/kg. In contrast, the ED_{50} values of haloperidol, eticlopride, fluphenazine, and risperidone, none of which interact with 5-HT$_{1A}$ receptors, were 100-fold lower (0.4, 0.4, 0.29, and 0.65 mg/kg, respectively).

The percentage of mice fulfilling the criteria for reduction of apomorphine-induced climbing and presence of catalepsy (for calculations of ED_{50} values) is illustrated in Figure 3. Bifeprunox, aripiprazole, nemonapride, SLV313, sarizotan, and SSR181507 were characterized by potent reversal of apomorphine-induced climbing with a broad separation with respect to cataleptogenic activity. The catalepsy *vs* climbing dose ratio was calculated by dividing ED_{50} values for inhibiting apomorphine-induced climbing with those for eliciting catalepsy: bifeprunox, nemonapride and SLV313 showed wider separation in this dose ratio (173.3–1000) than did haloperidol and risperidone (4.4–5.4: Table 2).

Catalepsy in Combination with WAY100635

When administered in combination with saline, WAY100635 (2.5 mg/kg) did not induce catalepsy (data not shown). Pretreatment with WAY100635 produced a shift to the left of the haloperidol and ziprasidone dose–response curve ($F(1,48)=5.1$ and $F(1,36)=5.3$, $P<0.05$,

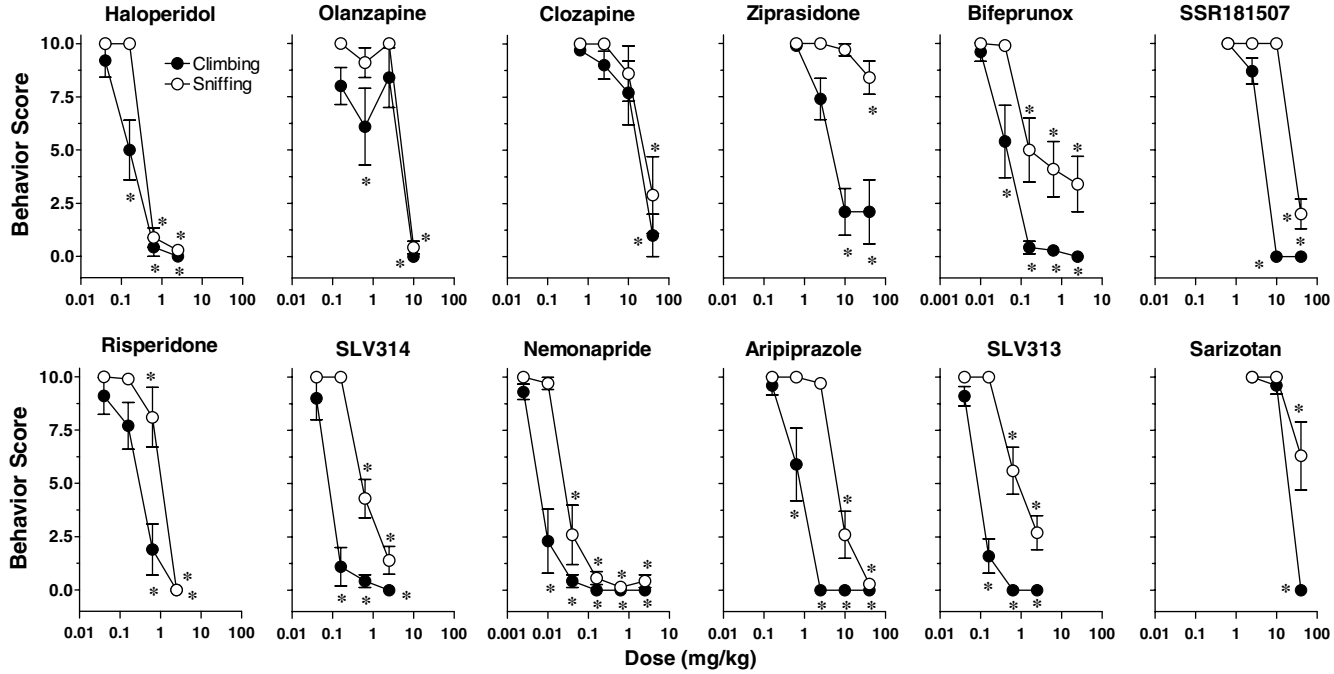

Figure 1 Effects of antipsychotics on apomorphine-induced climbing (filled circles) and sniffing (open circles) in mice. Values represent the mean ± SEM behavioral score of seven animals during observation periods (10 s every min, from 55 to 65 min after drug administration). Apomorphine (2.5 mg/kg, s.c.) was administered 45 min after different doses of antipsychotics. *$P<0.05$ compared with apomorphine control groups using Dunnett's test, following significant ANOVA. Note the different *x*-axis scale for nemonapride and bifeprunox. $N=7$/dose.

Table 2 Antagonism of Apomorphine-Induced Climbing and Sniffing Compared with Induction of Catalepsy in Mice

			Apomorphine-induced climbing			Apomorphine-induced sniffing			Catalepsy			
Drug	**Route**	**Dose range (mg/kg)**	**ED_{50}**	**95% CL**	**Maximum effects**[a]	**ED_{50}**	**95% CL**	**Maximum effects**[a]	**ED_{50}**	**95% CL**	**Maximum effects**[a]	**Dose-Ratio**[b]
Haloperidol	s.c.	0.04–10	0.09	0.05–0.17	0±0 (2.5)	0.32	0.19–0.53	0.3±0.2 (2.5)	0.4	0.07–2.2	21.5±3.2 (10)	4.4
Risperidone	s.c.	0.04–40	0.12	0.04–0.35	0±0 (2.5)	0.79	0.26–2.4	0±0 (2.5)	0.65	0.15–2.7	27.4±2.4 (40)	5.4
Fluphenazine	s.c.	0.01–2.5	0.05	0.02–0.13	0±0 (0.16)	0.08	0.04–0.18	0±0 (0.63)	0.29	0.13–0.64	28.2±1.1 (2.5)	5.8
Olanzapine	i.p.	0.16–40	1.5	0.18–12	0±0 (10)	4.3	1.2–16	0.43±0.3 (10)	13	4.6–38	22.2±3.9 (40)	8.7
Raclopride	s.c.	0.63–40	1.2	0.55–2.5	0±0 (2.5)	1.9	0.91–4.2	0.7±0.1 (10)	11	2.8–42	21.5±4.2 (40)	9.2
SLV314	s.c.	0.04–2.5	0.06	0.03–0.14	0±0 (2.5)	0.34	0.16–0.72	1.4±0.6 (2.5)	0.5	0.19–1.3	17±3.3 (2.5)	8.3
Clozapine	i.p.	0.63–40	8.7	3.1–25	1±1 (40)	24	9.1–65	2.9±1.8 (40)	>40	—	11.8±5.1 (40)	>4.6
Eticlopride	s.c.	0.0025–40	0.02	0.008–0.05	0±0 (0.04)	0.03	0.01–0.07	0.3±0.2 (0.16)	0.4	0.004–39	19.6±3.5 (40)	20
Nemona pride	s.c.	0.0025–40	0.001	0.0002–0.006	0±0 (0.16)	0.03	0.01–0.06	0.1±0.1 (0.63)	0.76	0.27–2.1	17.1±4(0.63)	760
Ziprasidone	i.p.	0.63–40	2.2	0.76–6.2	2.1±1.5 (40)	>40	—	8.4±0.8 (40)	36	13–96	17.8±4.4 (40)	16.4
Aripiprazole	i.p.	0.16–40	2.2	0.39–12	0±0 (2.5)	4.1	2.1–8.1	0.3±0.2 (40)	>40	—	8.7±3.6 (2.5)	>18.2
Bifeprunox	i.p.	0.01–40	0.03	0.01–0.07	0±0 (10)	0.11	0.038–0.35	3.4±1.3 (2.5)	5.2	1.5–18	23.8±1.8 (40)	173.3
SLV313	s.c.	0.04–40	0.04	0.01–0.16	0±0 (2.5)	0.34	0.16–0.72	2.7±0.8 (2.5)	>40	—	8.8±3.7 (40)	>1000
SSR181507	s.c.	0.63–40	3.6	1.5–8.7	0±0 (10)	20	9.4–41	2±0.7 (40)	>40	—	2.5±2.4 (40)	>11.1
Sarizotan	i.p.	2.5–40	14	5.2–37	0±0 (40)	>40	—	6.3±1.6 (40)	>40	—	2±0.9 (40)	>2.9

[a]The maximal scores that could be obtained for climbing/sniffing and catalepsy were 10 and 30, respectively. Between parentheses: dose at which the maximal effect was observed.
[b]Dose-ratio was calculated by dividing the ED_{50} values for inhibition of apomorphine-induced climbing with that for induction of catalepsy.

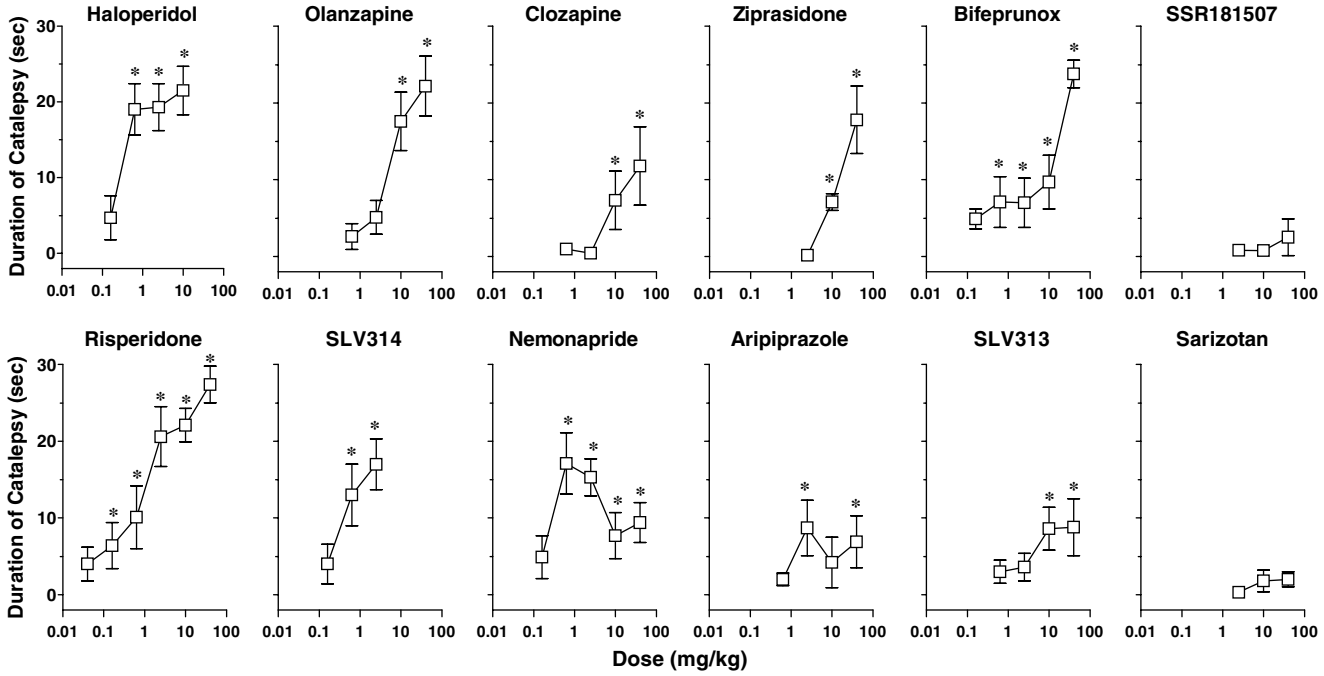

Figure 2 Effects of antipsychotics in the catalepsy bar test in mice. Values represent the duration of catalepsy in s and are expressed as mean ± SEM, $N = 7$/dose. The antipsychotics were administered s.c. or i.p. at 60 min before testing. *$P < 0.05$ compared with saline control using Dunnett's test, following significant ANOVA.

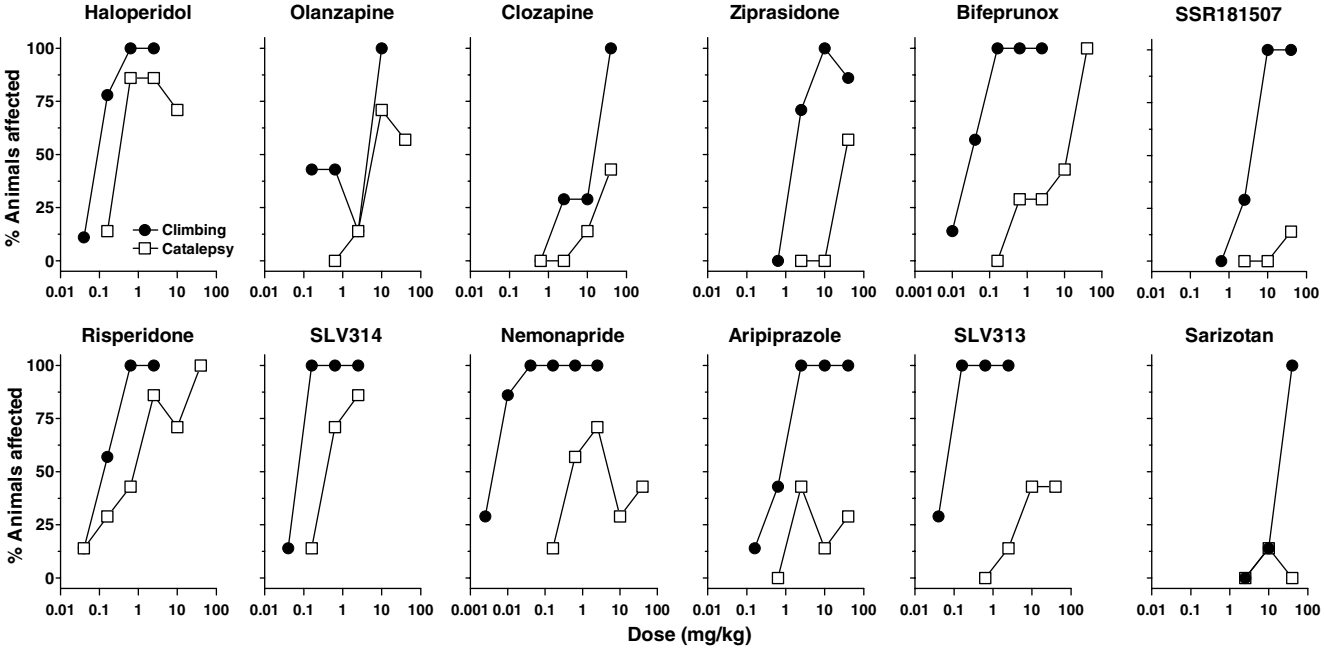

Figure 3 Effects of antipsychotics on apomorphine-induced climbing (filled circles) and in the catalepsy bar test (open squares) in mice. Values represent the percentage of animals showing climbing scores <9 and one or more catalepsy duration of 30s (see Materials and Methods section for details). Drugs on the left-hand side of the graph have little or no interaction at 5-HT$_{1A}$ receptors whereas drugs on the right-hand side of the graph have 5-HT$_{1A}$ agonist properties. This order was retained based on the data of affinity at 5-HT$_{1A}$ receptors for these compounds (Newman-Tancredi *et al*, 2005). Note the different *x*-axis scale for nemonapride and bifeprunox. $N = 7$/dose.

respectively; Figure 4). After pretreatment with WAY100635, significant levels of catalepsy were observed for aripiprazole ($F(1,72) = 12.4$, $P < 0.001$), SLV313 ($F(1,60) = 25.6$, $P < 0.001$), bifeprunox ($F(1,96) = 33.6$, $P < 0.001$) and nemonapride ($F(1,60) = 14.1$, $P < 0.001$). In the case of nemonapride, pretreatment with WAY100635 enhanced significantly the effects of low doses and prevented the decrease in catalepsy at higher doses. For aripiprazole and SLV313, the magnitude of catalepsy appeared to reach an asymptotic plateau (Figure 4). In contrast, pretreatment with WAY100635

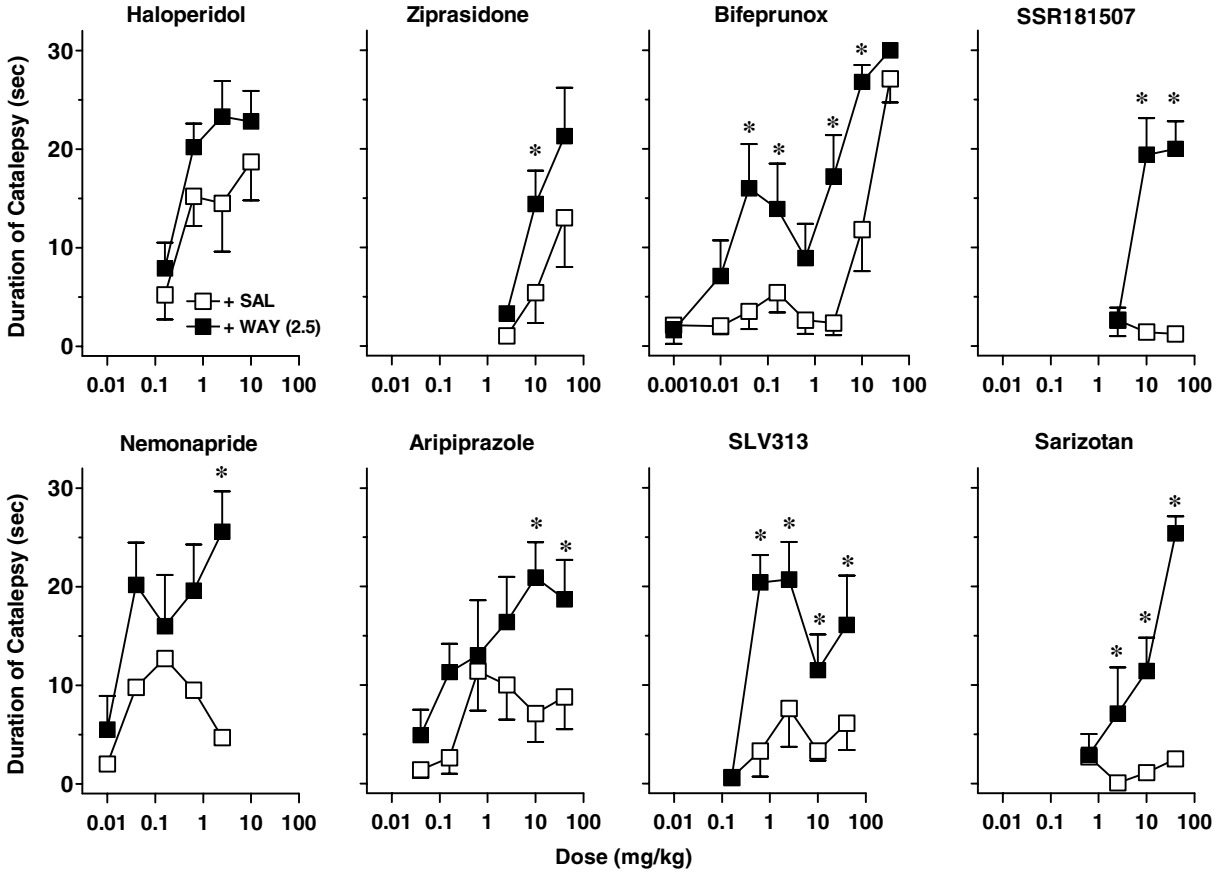

Figure 4 Effects of haloperidol, nemonapride, ziprasidone, aripiprazole, bifeprunox, SSR181507, SLV313 or sarizotan alone or in combination with WAY100635 in the catalepsy bar test. Values are means ± SEM of the duration of catalepsy in s, $N = 7$/group. WAY100635 (2.5 mg/kg, s.c.; filled squares) or saline (open squares) was administered 15 min before antipsychotics, which were administered 60 min before testing. *$P < 0.05$ compared with animals treated with saline using Dunnett's test, following significant ANOVA.

produced a marked incidence of catalepsy in SSR181507- and sarizotan- treated rats ($F(1,36) = 51.2$, $P < 0.001$ and $F(1,48) = 31.8$, $P < 0.001$, respectively).

DISCUSSION

Several laboratories have reported the development of a new generation of potential antipsychotic agents with varying levels of agonist/antagonist actions at D_2 and agonist activity at 5-HT$_{1A}$ receptors. These compounds, currently undergoing various stages of clinical development, include SLV313, SSR181507, and bifeprunox, along with another compound with potent 5-HT$_{1A}$ agonist properties, sarizotan, originally developed as an antipsychotic but more recently redirected towards an antidyskinetic indication. However, these compounds display marked diversity in their actions at 5-HT$_{1A}$ receptors *in vitro*, with varying potencies and efficacies for activation of cellular signal transduction (Newman-Tancredi *et al*, 2005). The present data confirm that 5-HT$_{1A}$ receptor activation reduces the cataleptogenic potential of novel antipsychotic agents but show also that their profile of action is highly diverse and is likely to be related to their affinity/efficacy at both D_2 and 5-HT$_{1A}$ receptors.

Antipsychotic Activity of the New Generation of Antipsychotics: Influence of 5-HT$_{1A}$ Receptor Agonist Properties

In accordance with previous studies, conventional (haloperidol, fluphenazine), atypical (olanzapine, clozapine, risperidone, and ziprasidone) as well as new generation potential antipsychotic agents (eg SSR181507, bifeprunox, SLV313) dose-dependently antagonized apomorphine-induced climbing in mice. Apomorphine-induced sniffing was also blocked in a dose-dependent manner over a similar dose range by all these drugs, with the exception of ziprasidone and sarizotan, which did not block sniffing at the highest dose tested, 40 mg/kg. Activity in this model is predictive of efficacy against the positive symptoms of psychosis (Protais *et al*, 1976) and demonstrates *in vivo* antagonist activity at dopamine D_2 receptors of these compounds. A correlation analysis based on affinities at rat striatal D_2 sites (Newman-Tancredi *et al*, 2005) shows that the ability of antipsychotics to inhibit apomorphine-induced climbing and sniffing correlated positively with their affinity at rat D_2 receptors. Indeed, reflecting its potent blockade of D_2 receptors in limbic/striatal structures, haloperidol was highly active in this model ($ED_{50} = 0.09$ mg/kg) whereas clozapine was active only at higher doses

($ED_{50} = 8.7$ mg/kg), which corresponds to its lower affinity at D_2 receptors (Brunello *et al*, 1995). The activity of haloperidol and clozapine in this preclinical test is consistent with their clinical potency requiring low- and high-dose ranges, respectively, to control the positive symptoms of schizophrenia (Meltzer, 1995). Nemonapride potently blocked apomorphine-induced stereotyped behavior: this compound interacts with both D_2 and 5-HT$_{1A}$ receptors but D_2 receptor antagonism is seen at doses approximately 16–64 times lower than those having 5-HT$_{1A}$ agonist properties (Assié *et al*, 1997). In clinical studies, nemonapride was reported to have therapeutic efficacy in schizophrenia and to produce relatively mild EPS (Kudo *et al*, 1989). SLV313, SSR181507 and bifeprunox, compounds that have balanced affinity at D_2 and 5-HT$_{1A}$ receptors, dose-dependently and potently reduced climbing and stereotyped behaviors produced by apomorphine. In contrast, ziprasidone and sarizotan have little effect at the highest doses tested in this model. It might have been the case that antagonist effects could have been observed at higher doses (or alternatively at other postinjection observation times). However, as mentioned in the Methods section, the use of doses above 40 mg/kg was precluded because of interfering side-effects that could be observed with some compounds at this ceiling dose. Ziprasidone has similar affinity at 5-HT$_{1A}$ and D_2 receptors but also multiple interactions at numerous other receptor subtypes (Seeger *et al*, 1995; Newman-Tancredi *et al*, 2005) whereas sarizotan has high efficacy at 5-HT$_{1A}$ receptors and partial agonist properties at D_2 receptors (Kuzhikandathil *et al*, 2004; Bartoszyk *et al*, 2004, Newman-Tancredi *et al*, 2005). The results with sarizotan are in agreement with earlier studies showing its weak antagonism of methylphenidate-induced behaviors in rats, another measure predictive of antipsychotic activity (Kleven *et al*, 2004). Taken together, these data indicate that 5-HT$_{1A}$ activation does not alter the antipsychotic-like effects of D_2 antagonists in this model of positive symptoms of schizophrenia. Accordingly, for active avoidance behavior in mice, another animal model of antipsychotic potential, the coadministration of the 5-HT$_{1A}$ antagonist SL88.0338 did not modify the activity of SSR181507 (Depoortere *et al*, 2003). In addition, data obtained in rats suggest that the potency of D_2 antagonists (such as raclopride) in the same test is even enhanced by addition of a compound with 5-HT$_{1A}$ agonist properties (such as 8-OH-DPAT: Prinssen *et al*, 1996).

In clinical studies, buspirone and tandospirone, two partial agonists at 5-HT$_{1A}$ receptors, substantially improved negative symptoms scores and reduced the incidence of EPS in schizophrenic patients treated with haloperidol (Sumiyoshi *et al*, 2001a, b). In a single case study, Pantelis and Barnes (1993) have found that, when given together with neuroleptics, low doses of buspirone had beneficial effects on anxiety and psychosis whereas higher doses exacerbated psychosis. Thus, whereas preclinical studies generally find that 5-HT$_{1A}$ agonists attenuate neuroleptic-induced EPS (see Introduction), the therapeutic effects of combined 5-HT$_{1A}$ agonist/D_2-like antagonist compounds remain largely uncharacterized and await further clinical studies. Indeed, sarizotan, which exhibits very high efficacy at 5-HT$_{1A}$ receptors and partial agonist properties at D_2 receptors (Bartoszyk *et al*, 2004; Newman-Tancredi *et al*, 2005) is now in development as an antidyskinetic agent in L-DOPA-treated Parkinson's disease patients (Bartoszyk *et al*, 2004) likely because of insufficient antipsychotic activity (present data and Kleven *et al*, 2004). In contrast, interestingly, an older neuroleptic, tiospirone, with very low efficacy at 5-HT$_{1A}$ receptors (Newman-Tancredi *et al*, 1998, 2005), exhibited antipsychotic properties in humans comparable with those of haloperidol, but with a lower incidence of EPS (Moore *et al*, 1987).

Non-Catalepogenic Properties of the New Generation of Antipsychotics: Role of 5-HT$_{1A}$ Receptors

The atypical antipsychotics, clozapine, ziprazidone as well as the new generation of potential antipsychotic agents (eg SSR181507, aripiprazole, SLV313) induced little or no catalepsy compared with the typical antipsychotics, haloperidol, or fluphenazine in the bar test. ED_{50} values for SSR181507, sarizotan, aripiprazole, clozapine, and SLV313 were greater than 40 mg/kg, which is 100-fold higher than for haloperidol. However, we cannot exclude that pharmacokinetic peculiarities of some of these drugs (such as slow brain penetration or else: see below) may explain the fact that little or no catalepsy was observed under our experimental conditions (ie observation 1 h after drug administration). In fact, it has been reported that the maximum catalepsy response to aripiprazole occurred at 8 h post-administration (Hirose *et al*, 2004). This is an interesting observation, considering that in both rats and humans, a major metabolite of aripiprazole is a pure dopamine D_2 antagonist (Lawler *et al*, 1999), which may mitigate the D_2 receptor partial agonist properties of aripiprazole. Nevertheless, these results are generally consistent with previous literature for these ligands concerning their low cataleptogenic liability in rats (Glennon *et al*, 2002; Depoortere *et al*, 2003; Wolf, 2003; Bartoszyk *et al*, 2004; Kleven *et al*, 2005). Additionally, pretreatment with the 5-HT$_{1A}$ receptor antagonist, WAY100635, enhanced or reinstated catalepsy induced by antipsychotics, consistent with results reported by Kleven *et al* (2005). For example, WAY100635 pretreatment induced near maximal catalepsy in the bar test for SSR181507 and sarizotan, which alone, even at doses up to 40 mg/kg, induced no catalepsy. Depoortere *et al* (2003) have also reported that in coadministration with SL88.0338, another 5-HT$_{1A}$ antagonist, SSR181507 produced catalepsy in rats. Nemonapride induced catalepsy in a biphasic manner: that is, catalepsy at low but not at high doses, and pretreatment with WAY100635 reinstated nemonapride-induced catalepsy at higher doses. These findings extend previous data reported by Prinssen *et al* (1998), indicating that the 5-HT$_{1A}$ receptor agonist properties of nemonapride at high doses are responsible for its lowered propensity to produce catalepsy in rats. These observations demonstrate that activation of 5-HT$_{1A}$ receptors plays an important role in the relatively low or noncataleptogenic liability seen with compounds reported to have dual D_2/5-HT$_{1A}$ actions (for review, see: Millan, 2000; Bantick *et al*, 2001). Another important finding of the present study was that pretreatment with WAY100635 enhanced catalepsy induced by the dopamine D_2-like receptor antagonist haloperidol in mice. This confirms previous data reported by Prinssen *et al* (1998), showing that cotreatment with

WAY100635 slightly, but significantly, enhanced haloperidol-induced catalepsy in rats. While having no effect on catalepsy itself, WAY100635 likely increases neuroleptic-induced catalepsy by blockade of 5-HT$_{1A}$ auto-receptors controlling tonic 5-HT release. Thus depletion of 5-HT by repeated treatment with the 5-HT synthesis inhibitor *p*-chlorophenylalanine methyl ester, abolished the enhancement by WAY100635 of catalepsy induced by raclopride (Prinssen *et al*, 2000). In addition, tonic 5-HT$_{1A}$ receptor activity has been demonstrated in animals during periods of active arousal (for review, see Routledge, 1996) and antipsychotic-induced catalepsy is very sensitive to 5-HT$_{1A}$ receptor stimulation (for review, see Wadenberg, 1996).

In the case of aripiprazole and SLV313, although WAY100635 produced upward shifts in their dose–response curves, the magnitude of catalepsy appeared to reach an asymptotic plateau, suggesting that other mechanisms may be involved in their low cataleptogenic liability. Indeed, although a partial agonist at 5-HT$_{1A}$ receptors, aripiprazole exhibits efficacy lower than that of other antipsychotics in assays of G-protein activation and adenylyl cyclase activity in cloned human and native rat hippocampal membranes (Newman-Tancredi *et al*, 2005). Moreover, as well as activating 5-HT$_{1A}$ receptors, aripiprazole is also a D$_2$ receptor partial agonist (Bartoszyk *et al*, 2004) and has interactions at numerous other receptor subtypes (Shapiro *et al*, 2003) including 5-HT$_{2A}$ and 5-HT$_{2C}$, targets that are known to profoundly influence antipsychotic drug action (Meltzer *et al*, 2003). In this context, it is likely that aripiprazole's partial D$_2$ agonist properties or multi-receptor profile contribute to both its weak cataleptogenic profile and the limited catalepsy obtained in the presence of WAY100635. It has been recently suggested that aripiprazole is capable of directing D$_2$ receptor signalling to specific intracellular responses (Urban *et al*, 2004) and it may be speculated that such signalling pathways are specifically involved in motor control, for example in brain regions such as striatum that display high densities of D$_2$ receptor expression. In contrast, SLV313 exhibits balanced 5-HT$_{1A}$/D$_2$ affinity and intermediate efficacy at 5-HT$_{1A}$ receptors, but little interaction with D$_1$, 5-HT$_{2A}$ or $\alpha_{1/2}$ adrenergic receptors (Newman-Tancredi *et al*, 2005; Assié MB, unpublished observations). SLV313 blocks psychostimulant-induced behaviors in rodents in the absence of catalepsy; of the compounds tested here SLV313 had the highest antipsychotic-like *vs* catalepsy separation (present data; Glennon *et al*, 2002; Kleven *et al*, 2005) suggesting that its balance of 5-HT$_{1A}$/D$_2$ properties produces a favorable antipsychotic profile. In contrast, SLV314, another 'selectively nonselective' 5-HT$_{1A}$ agonist/D$_2$ antagonist (Roth *et al*, 2004), exhibits affinity at 5-HT$_{1A}$ receptors that is two orders of magnitude lower than that of D$_2$ receptors and its cataleptogenic liability is higher than that of SLV313 (ED$_{50}$ = 0.5 *vs* >40 mg/kg). In addition to exerting classical antipsychotic-like effects, SLV314 has also been reported to induce antidepressant and anxiolytic-like effects (McCreary *et al*, 2002) probably due to its potent serotonin reuptake inhibition properties rather than to its direct 5-HT$_{1A}$ activation (Tuinstra *et al*, 2002). Taken together, these data suggest that the lack of catalepsy of these novel antipsychotics (eg SSR181507, aripiprazole, SLV313) depend on both the affinity and efficacy of these ligands at 5-HT$_{1A}$ and D$_2$ receptors.

Conclusions

A new generation of potential antipsychotics is being developed, including bifeprunox, SSR181507 and SLV313, which selectively targets 5-HT$_{1A}$ receptors as well as dopamine D$_2$ receptors. The present data confirm that antipsychotics that activate 5-HT$_{1A}$ receptors exhibit low EPS liability and support the concept that combined D$_2$ receptor blockade and 5-HT$_{1A}$ activation is a promising strategy to reduce the EPS liability of antipsychotics, while retaining desired antipsychotic properties (Bantick *et al*, 2001; Millan 2000). Nevertheless, the present data indicate also that the balance of affinity and efficacy at both D$_2$ and 5-HT$_{1A}$ receptors profoundly influences the pharmacological profile of these new generation antipsychotics, and will likely impact their therapeutic profiles.

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