

SSR181507, a putative atypical antipsychotic with dopamine D₂ antagonist and 5-HT_{1A} agonist activities: improvement of social interaction deficits induced by phencyclidine in rats

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Abstract

Social behaviour is frequently impaired in schizophrenic patients, and current antipsychotics appear poorly effective in alleviating this deficit. SSR181507 is a selective dopamine D₂ receptor antagonist and 5-HT_{1A} receptor agonist [Neuropsychopharmacology 28 (2003) 2064] with an atypical antipsychotic profile and additional antidepressant/anxiolytic activities [Neuropsychopharmacology 28 (2003) 1889]. Here, we sought to assess the efficacy of SSR181507, and of reference antipsychotics and antidepressant/anxiolytics, to counteract phencyclidine (PCP)-induced social interaction deficit in rats. Pairs of unfamiliar rats were placed for 10 min each day into a dimly lit arena, during four consecutive days. On the test day (5th day), each pair was placed into the arena 30 min after i.p. treatment with PCP (or vehicle) and a challenge compound or vehicle (same for both rats, i.p. or s.c.). The time spent in social interaction was scored during 10 min. PCP (1 mg/kg) decreased social interaction time by about 35%. This effect was fully antagonized by pre-treatment with SSR181507 (1 mg/kg). In contrast, neither haloperidol (0.05 and 0.1 mg/kg) nor clozapine (0.3 and 1 mg/kg) antagonized this PCP-induced deficit. The selective 5-HT_{1A} receptor agonist 8-OH-DPAT (0.025 and 0.05 mg/kg s.c.), but not the anxiolytic diazepam (0.75 and 1.5 mg/kg), also improved social interaction impairment in PCP-treated rats: this would indicate that the 5-HT_{1A} receptor agonist properties of SSR181507 are responsible for the reversal of PCP-induced social deficit. These data suggest that, in addition to its atypical antipsychotic profile and antidepressant/anxiolytic activities, SSR181507 has a potential therapeutic activity in another key feature of schizophrenia poorly controlled by current antipsychotics, namely deterioration in social functioning.

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1. Introduction

Schizophrenia, a severe mental illness that affects about 1% of the population, is characterised by positive (thought disorder, delusion, hallucination, agitation) and negative symptoms (flattening of affect, poverty of speech, social dysfunction and/or withdrawal) as well as by cognitive deficits (impaired attention, learning and memory problems) (Andreasen et al., 1990). It is increasingly considered that impairment in many

domains of mental functioning, together with anxiety/depressive symptoms that are associated with this disease, lead to a marked deterioration in social behaviour of schizophrenic patients (Dickerson et al., 1996; Escamilla, 2001). However, current antipsychotics, including atypical ones, are considered to be marginally effective in alleviating this social dysfunction (Campbell et al., 1999), and as such may contribute to the low level of reinsertion and normal societal functioning (Aquila et al., 1999). To aggravate the problem, some antipsychotics have been described to have deleterious effects on mood, to worsen anxiety/depressive states and to exacerbate social dysfunction in schizophrenic patients (Barnes and Phillips, 1995).

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Recently, we have reported on a new compound, SSR181507, that combines DA D₂ receptor antagonist and 5-HT_{1A} receptor agonist activities. This compound has been shown to possess an atypical profile, based on biochemical and electrophysiological parameters (Claustre et al., 2003). In behavioural studies, it was found to be active in several tests sensitive to antipsychotic drugs, and with the absence of catalepsy, further strengthening the atypical profile of the compound (Depoortere et al., 2003). This lack of catalepsy was presumed to be related to its agonist activity at 5-HT_{1A} receptors, since co-treatment with the selective 5-HT_{1A} blocker SL88.0338 was shown to induce catalepsy. Furthermore, SSR181507 was active in different tasks predictive of antidepressant/anxiolytic activities: it decreased vocalisation in guinea pig pups separated from their mother, reduced paradoxical sleep in rats and diminished aversion for a saccharin solution induced by treatment with lithium (Depoortere et al., 2003). It also reduced shock-induced ultrasound vocalisation in adult rats and facilitated disinhibitory behaviour in a passive avoidance (“step-down”) procedure (manuscript in preparation). These antidepressant/anxiolytic activities of SSR181507 were shown to be most likely due to stimulation of 5-HT_{1A} receptors, since in most of these tests, the selective 5-HT_{1A} blocker SL88.0338 antagonized these effects. As schizophrenic patients suffer from a high incidence of depression and/or anxiety (Buchanan et al., 2002), the antidepressant/anxiolytic potential of SSR181507 should provide an added benefit.

As mentioned earlier, social dysfunction is a major item of the cluster of negative symptoms of schizophrenia. Hence, a compound that would be endowed with efficacy against social disability would be of greater benefit to patients. Administration of phencyclidine (PCP) or of PCP-like compounds (such as ketamine) is considered as the most appropriate pharmacological intervention to mimic not only positive and negative symptoms, but also cognitive impairment of schizophrenia in human volunteers (Javitt and Zukin, 1991; Krystal et al., 1994). These compounds have also been reported to precipitate psychotic episodes in otherwise stabilized patients (Itil et al., 1967; Lahti et al., 1995). PCP-like compounds are known to interfere with the *N*-methyl-D-aspartate (NMDA) receptor subtype of glutamatergic neurotransmission (Thomson et al., 1985), and this mechanism of action, together with the effects of these compounds in humans (see above), have laid the foundations for the hypoglutamatergic hypothesis of schizophrenia (Javitt, 1987; Krystal et al., 1994).

PCP-like compounds have been documented to induce a state of social withdrawal, not only in humans (Javitt, 1987), but also in primates (Schlemmer and Davis, 1983) and in rats (Sams-Dodd, 1995; Steinpreis et al., 1994). The latter authors have shown, using a

model adapted from the social interaction task initially described by File and Hyde (1978), that some antipsychotics are able to reverse the deleterious effect of PCP on social behaviour in rats.

In the present study, we sought to assess the efficacy of SSR181507 to counteract PCP-induced social interaction deficit in rats, in a model derived from the one described by Sams-Dodd (1995). For comparison purposes, we examined the effects of the classical antipsychotic haloperidol, the atypical antipsychotic clozapine, the prototypical anxiolytic diazepam, and the 5-HT_{1A} receptor agonist 8-OH-DPAT (based on the marked affinity of SSR181507 for this type of receptor).

2. Methods

2.1. Subjects

Male Sprague–Dawley rats (Janvier, France) weighing 150–175 g at the beginning of the experiments were housed in groups of four per cage for four consecutive days before starting the experiment. Food and water were available ad libitum. Animals were kept in conditions of constant temperature (21 ± 1 °C), humidity (50%) and light–dark cycle (light on from 7:00 am to 7:00 pm). All experiments were performed in accordance with current French legislation on animal experimentation and were approved by the in-house Ethical Committee.

2.2. Apparatus and behavioural procedures

The social interaction test arena consisted of a grey Plexiglas box (75 × 75 × 42 cm high) with a red light (5 lux) located above and on the side of the arena. The floor of the arena was divided into 25 quadrants of equal surface (by tape material affixed to the Plexiglas to materialize lines), for measurement of global locomotor activity (number of line crossings). A camera fixed above the arena was connected to a video monitor and to a videotape recorder placed in an adjacent room, for visioning and recording of animal behaviour. Following an i.p. injection of saline and 30 min of isolation (one rat per cage), pairs of unfamiliar rats (from two different home cages) were placed into the arena for exploration and interaction during 10 min, for four consecutive days. This daily exposure to the arena and to the presence of an unfamiliar rat (different every day for a given rat, and chosen at random, to avoid the establishment of dominance phenomena and territorial behaviour, that lead to aggressive/defensive displays) was introduced to optimise social interaction. On the 5th day, both rats from a newly formed dyad were treated i.p. with the same treatment (vehicle or one dose of a challenge compound, immediately followed by injection of vehicle or 1 mg/kg of PCP). They were

isolated one rat per cage, and 30 min later the pair was placed into the arena during 10 min for observation. The time spent in social interaction (physical contacts, sniffing, following or grooming the partner, social play, kicking, boxing, biting) was scored manually during 10 min with a computer keyboard, which allowed to record the duration of each period of social interaction. At the end of the session, rats were removed from the arena and replaced into their respective home cage. Rats were not used over the next 2 days. On the 8th day, pairs were exposed to the arena (exposure protocol similar to the one used on days 1–4). Finally, on the 9th and last day, rats were subjected to a second drug-challenge session in all points similar to the one of the 5th day, but with a new treatment (newly formed pairs of rats were used on days 8 and 9).

2.3. Drugs

Phencyclidine, 8-OH-DPAT and SSR181507 ((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) were synthesized by the CNS Medicinal Chemistry Department of Sanofi-Synthélabo Recherche. Haloperidol and clozapine were purchased from Sigma Aldrich (St Quentin Fallavier, France). Diazepam was obtained from Roche (Basel). PCP, SSR181507, clozapine, diazepam and 8-OH-DPAT were dissolved/suspended in sterile saline with a few drops of Tween 80. Haloperidol was dissolved in sterile water to which 10% w/w of ascorbic acid was added (final pH: 4–5). Drug doses refer to the weights of the free base. Injections were given *i.p.* (except for 8-OH-DPAT, *s.c.*), 30 min pre-test, in a volume of 5 ml/kg body weight.

2.4. Data analysis

Data are expressed as the mean duration of global social interaction (sum of the times spent for each social interaction event) measured for each dyad of rats. In pilot studies, it was observed that PCP reduced social interaction by decreasing the duration, but not the frequency, of contact events. This observation justified the use of the duration of interaction for subsequent data analysis. Global locomotor activity was assessed by counting the number of line crossings during a post-session reading of the videotapes. For practical reasons, locomotor activity was measured for only one rat of each pair, chosen at random. Data were analysed by one-way ANOVA's with drug treatment as the between-groups factor, and followed when appropriate by post-hoc Newman–Keuls tests. All statistical analyses were performed using the SAS software (SAS Institute Inc., Cary, NC, USA).

3. Results

Dyads of unfamiliar rats placed in a novel environment (day 1) displayed a relatively low level of social interaction. However, repeated daily habituation to the arena and exposure to a new congener steadily decreased exploratory behaviour of the environment and consequently increased the time spent in social interaction between the two unfamiliar rats (data not shown). Owing to this habituation procedure, pairs of animals reached an average level of social interaction time of about 270 s, that is 45% of the session time (see Veh/Veh groups in Figs. 1 and 2). Social interaction consisted of physical contacts, sniffing, grooming and social play, with no overt aggressive behaviours such as offensive/defensive postures, biting, kicking and boxing (which were also not observed after treatment with PCP or combinations of compounds/PCP).

In all five sets of experiments, PCP at 1 mg/kg (see Veh/PCP groups in Figs. 1 and 2) was found to significantly (all p 's < 0.02) decrease social interaction time (post-hoc Newman–Keuls tests applied between Veh/Veh and Veh/PCP groups, following significant treatment effects with one-way ANOVA's).

3.1. Effects of SSR181507 on PCP-induced social interaction deficit in rats

SSR181507, at 1 mg/kg (Fig. 1a), significantly reversed the deleterious effect of PCP in this paradigm (p < 0.01, post-hoc Newman–Keuls test applied between the Veh/PCP group and the SSR(1)/PCP group, following significant treatment effects with a one-way ANOVA: $F(4, 43) = 8.6$, p < 0.01). The low dose of SSR181507 (0.3 mg/kg) produced a partial but non-significant ($p = 0.082$) normalisation of social interaction behaviour in PCP treated rats. SSR181507 at 1 mg/kg did not significantly affect the time spent in social interaction when given on its own (SSR(1)/Veh group on the far right of Fig. 1a).

3.2. Effects of haloperidol and clozapine on PCP-induced social interaction deficit in rats

In contrast to SSR181507, haloperidol (0.05 and 0.1 mg/kg, Fig. 1b) and clozapine (0.3 and 1 mg/kg, Fig. 1c) did not counteract the decreasing effect of PCP on the time spent in social interaction (p 's > 0.05, post-hoc analyses, following significant treatment effects with one-way ANOVA's: $F(4, 43) = 8.1$, p < 0.01, and $F(4, 43) = 3.8$, p < 0.05, for haloperidol and clozapine, respectively). Similarly to SSR181507, the highest doses of haloperidol (0.1 mg/kg) and clozapine (1 mg/kg) did not significantly affect the time spent in social interaction, when administered alone.

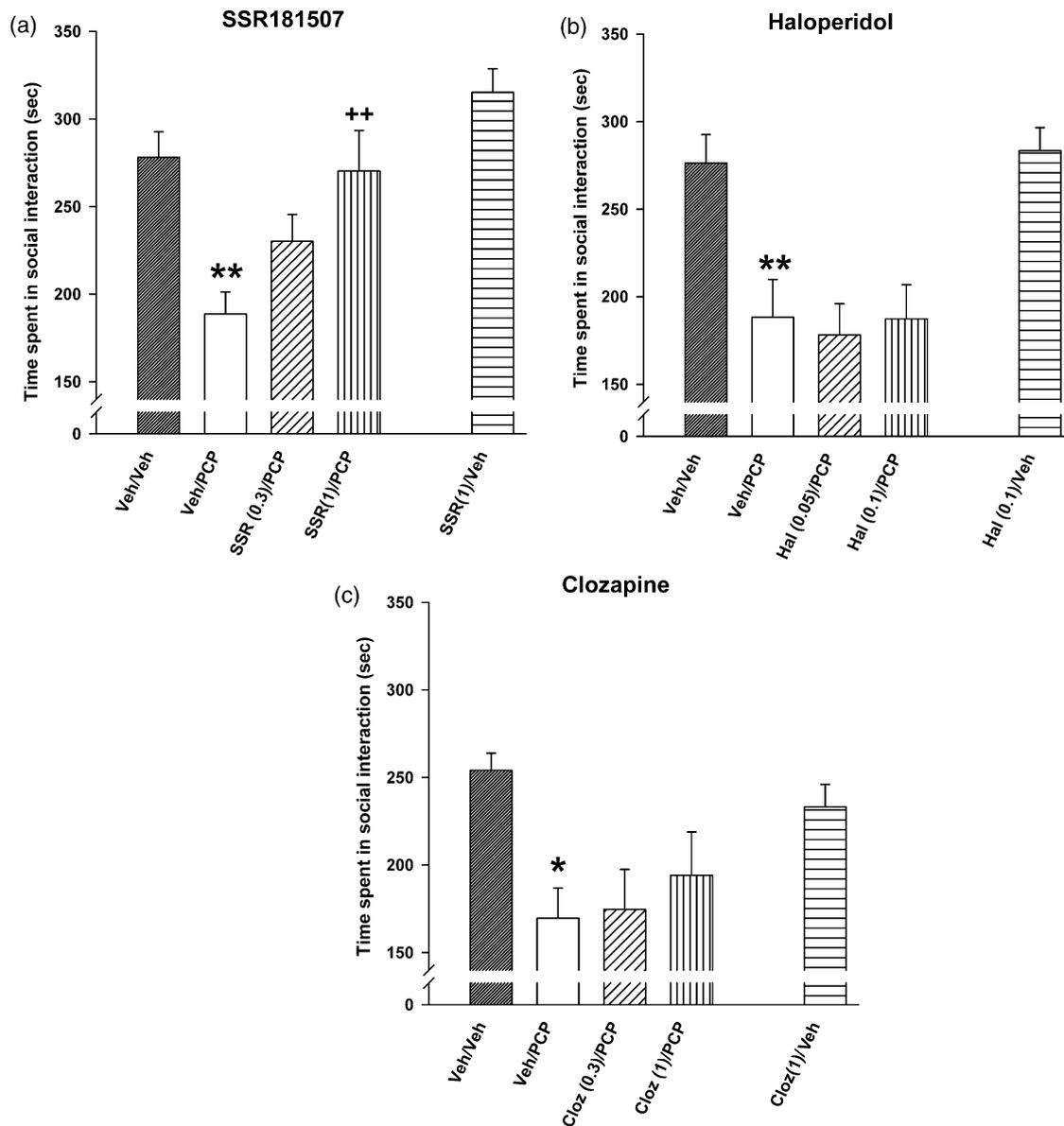


Fig. 1. Effects of SSR181507 (a), haloperidol (b) and clozapine (c) on PCP-induced social interaction deficits in dyads of rats. Drugs in combination with PCP (1 mg/kg) were administered i.p. 30 min before placing the pair of rats in the observation arena. Each bar represents the mean (+ SEM) of the time spent in social interaction during a session of 10 min. * $p < 0.05$, ** $p < 0.01$, Newman–Keuls post-hoc tests versus the Veh/Veh group. ++ $p < 0.01$, Newman–Keuls post-hoc tests versus the Veh/PCP group. $N = 9$ –10 dyads of rats per group.

3.3. Effects of 8-OH-DPAT on PCP-induced social interaction deficit in rats

As shown in Fig. 2 (a), the 5-HT_{1A} receptor agonist 8-OH-DPAT, at 0.025 mg/kg, totally reversed the deleterious effect of PCP in this paradigm ($p < 0.01$, post-hoc Newman–Keuls tests applied between the Veh/PCP group and the 8-OH(0.025)/PCP group, following significant treatment effects with a one-way ANOVA: $F(4, 43) = 6.9$, $p < 0.01$), whereas 0.05 mg/kg of 8-OH-DPAT produced a partial but just significant ($p = 0.052$) normalisation of social interaction time. The highest dose (0.05 mg/kg) did not significantly

affect the time spent in social interaction when given on its own.

3.4. Effects of diazepam on PCP-induced social interaction deficit in rats

Diazepam (0.75 and 1.5 mg/kg, Fig. 2b) did not counteract the decreasing effect of PCP on the time spent in social interaction, and had no effect when administered alone (p is >0.05 , post-hoc Newman–Keuls tests, following significant treatment effects with a one-way ANOVA: $F(4, 43) = 4.8$, $p < 0.01$).

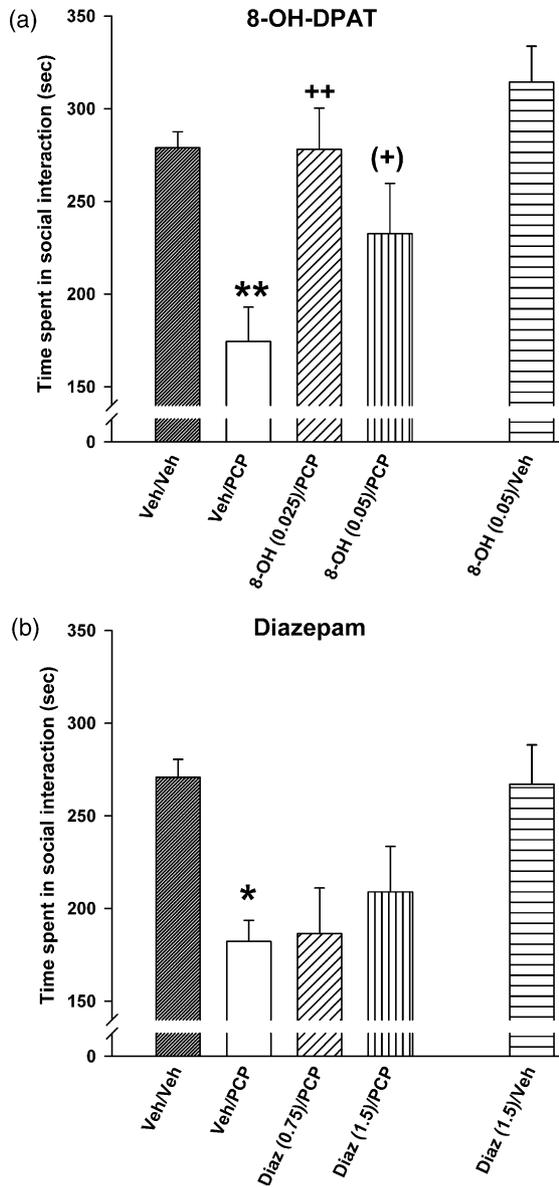


Fig. 2. Effects of 8-OH-DPAT (a) and diazepam (b) on PCP-induced social interaction deficits in dyads of rats. See Fig. 1 for details. * $p < 0.05$, ** $p < 0.01$, Newman–Keuls post-hoc tests versus the Veh/Veh group. (+) $p = 0.05$, ++ $p < 0.01$, Newman–Keuls post-hoc tests versus the Veh/PCP group. $N = 9$ –10 dyads of rats per group.

3.5. Effects of pharmacological treatments on global locomotor activity

Acute administration of PCP (1 mg/kg) significantly decreased social interaction time (see above) without significantly modifying locomotor activity (compare the first and second columns of Table 1, for all five sets of experiments). At this dose, PCP did not produce ataxia (visual observation, data not shown).

It can be seen that the ability of a compound to reverse these PCP-induced social interaction deficits was independent of its effect on locomotor activity. For example,

reversal could be obtained in the absence (for 8-OH-DPAT) or presence (for SSR181507) of an effect on locomotor activity (column 4). It should also be noted that because of the marked effects of haloperidol, clozapine and diazepam on locomotor activity, whether in association with PCP (columns 3 and 4) or alone (column 5), higher doses of these compounds could not be tested.

4. Discussion

In this model adapted from the social interaction task initially described by File and Hyde (1978), the main findings were: (a) acute injection of PCP decreased social interaction in dyads of unfamiliar rats; (b) the potential atypical antipsychotic SSR181507, in contrast to haloperidol and clozapine, significantly reversed this PCP-induced deficit of social interaction; (c) similarly, the selective 5-HT_{1A} receptor agonist 8-OH-DPAT, but not the anxiolytic diazepam, was shown to reverse this deficit.

4.1. PCP-induced social interaction deficit

Under conditions with reduced levels of aversion/anxiety, that favour social interaction, the non-competitive NMDA receptor antagonists PCP (Steinpreis et al., 1994; Corbett et al., 1995; Sams-Dodd, 1995) and ketamine (Silvestre et al., 1997) decrease social interaction. This effect mediated by PCP-like compounds is reminiscent of the social withdrawal presented by a substantial proportion of schizophrenic patients, and as such this social interaction deficit procedure has been proposed as an animal model of negative symptoms (Sams-Dodd, 1995). Consistent with this literature, under our experimental conditions, a single injection of 1 mg/kg of PCP (a relatively low dose that does not produce locomotor effects, ataxia or stereotypies) decreased social interaction by about a third. In agreement with data published by Steinpreis et al., (1994), higher doses of PCP (2 or 3 mg/kg, data not shown) also decreased social interaction, but concomitantly increased motor activity and produced ataxia in our model. Contaminating effects seen with high acute doses of PCP render more difficult the interpretation of reversal effects of challenge compounds. This confound led Sams-Dodd (1995, 1997, 1998a) to administer PCP (2 mg/kg) for 3–5 days to get a tolerance to the motor activating and ataxic effects of PCP (cf. Sams-Dodd, 1998b).

4.2. Reversal by SSR181507, but not by clozapine and haloperidol, of PCP-induced social interaction deficit

Acute administration of the DA D₂ receptor antagonist and 5-HT_{1A} receptor agonist SSR181507, dose-dependently prevented the PCP-induced social

Table 1
Effects of pharmacological treatments on global locomotor activity

| | Veh/Veh | Veh/PCP | Low dose/PCP | High dose/PCP | High dose/Veh |
|--|----------|----------|-------------------------|-------------------------|-------------------------|
| SSR181507 $F(4, 43) = 3.6, p < 0.05$ | 299 ± 18 | 327 ± 42 | 226 ± 27 | 208 ± 20 ^c | 236 ± 18 |
| Haloperidol $F(4, 43) = 11.6, p < 0.01$ | 366 ± 22 | 359 ± 28 | 307 ± 24 | 220 ± 13 ^{b,d} | 214 ± 13 ^{b,d} |
| Clozapine $F(4, 43) = 4.9, p < 0.01$ | 368 ± 20 | 332 ± 24 | 262 ± 30 ^a | 230 ± 31 ^{b,c} | 260 ± 18 ^a |
| 8-OH-DPAT $F(4, 43) = 0.5, p > 0.05$ | 327 ± 19 | 278 ± 27 | 322 ± 45 | 333 ± 53 | 347 ± 30 |
| Diazepam $F(4, 43) = 14.6, p < 0.01$ | 397 ± 25 | 403 ± 35 | 256 ± 30 ^{b,d} | 193 ± 26 ^{b,d} | 180 ± 23 ^{b,d} |

Refer to Figs. 1 and 2 for the value of the low and the high dose for each particular compound. Each number represents the mean (± SEM) number of line crossings. For a given treatment, the F and p values of the one-way ANOVA are given in the first column; ^a $p < 0.05$, ^b $p < 0.01$, Newman–Keuls post-hoc tests versus the Veh/Veh group. ^c $p < 0.05$, ^d $p < 0.01$, Newman–Keuls post-hoc tests versus the Veh/PCP group. $N = 9–10$ rats per group.

interaction deficit. As DA D₂ antagonism does not appear to be sufficient to reverse this social interaction deficit (lack of effects of haloperidol, see below), and as the selective 5-HT_{1A} receptor agonist 8-OH-DPAT attenuated or blocked this deficit, it is likely that the 5-HT_{1A} receptor agonist property of SSR181507, independently of its DA D₂ receptor antagonist activity, accounts for its reversal effects. Further confirmation for this was provided by the observation that the 5-HT_{1A} receptor antagonist WAY 100635, at 3 mg/kg i.p., reversed the effects of 1 mg/kg of SSR181507. We decided not to include these data in the Results section, since they were collected under conditions (recent automation of data acquisition with a software) that differ slightly from those used for all other compounds reported here (previous manual recording with a computerized chronometer).

It should also be stressed that the reversals by SSR181507 and 8-OH-DPAT were obtained in the absence of effects in control (vehicle-treated) rats. This point is important, as it argues in favour of a specific effect of these two compounds on the decrease of social interaction produced by PCP.

Acute administration of the typical antipsychotic haloperidol (a relatively selective DA D₂-like receptor antagonist) did not antagonize the deleterious effects of PCP on social interaction. These data are consistent with those reported in the literature: typical antipsychotics, such as haloperidol and chlorpromazine, failed to reverse such deficits (Corbett et al., 1995; Sams-Dodd, 1997). This result is also in agreement with the clinical observation that whereas typical antipsychotics are fairly successful in treating the positive symptoms in schizophrenic patients, they are only marginally effective against negative symptoms, and notably against poor social functioning (McLaren et al., 1992; Meltzer et al., 1990; Meltzer, 1992).

Likewise, acute injection of clozapine (0.3–1 mg/kg) did not reverse this PCP-induced social interaction

deficit. We also found an absence of effects of olanzapine (0.3 and 1 mg/kg i.p.: results not shown for the reasons exposed above for the WAY 100635/SSR181507 experiment). Clozapine and olanzapine have been reported to have only moderate in vitro affinity for rat 5-HT_{1A} receptors, as compared to that of SSR181507 (in the order of 400–1000 nM, versus 4.5 nM: Claustre et al., 2003). This reinforces the notion that activation of 5-HT_{1A} receptors plays a central role in the reversion of PCP-induced social interaction deficit. Consistent with our data, Steinpreis et al. (1994) showed that acute administration of clozapine (2 mg/kg) was unable to reverse a social interaction deficit induced by a higher dose of PCP (4 mg/kg) in rats. However, chronic treatments (3 or 21 days) with clozapine and remoxipride partially reversed the social interaction deficit induced by three daily injection of PCP (2 mg/kg/day), whereas haloperidol, risperidone and olanzapine were without effects (Sams-Dodd, 1997). In mice, social behaviour deficit induced by chronic treatment with PCP (10 mg/kg/day, for 14 days), was attenuated by chronic administration for 7 days with clozapine (10 mg/kg), but not haloperidol (Qiao et al., 2001). In accord with these preclinical data using repeated administrations of clozapine, in humans, limited effects on negative symptoms (including social withdrawal) are seen only after sub-chronic administration of atypical antipsychotics (Meltzer et al., 1990). Hence, the potential reversing effect of chronically administered clozapine and olanzapine in our model would warrant further investigation.

4.3. Hypotheses for the mechanism underlying the reversal by SSR181507 of PCP-induced social interaction deficit

An aversive/anxiogenic state produced by PCP could explain the decrease of social explorative behaviour in rats. Thus, the beneficial effects of SSR181507 and of

8-OH-DPAT in these PCP-treated rats could result from their potential anxiolytic effects exerted via stimulation of 5-HT_{1A} receptor (Depoortere et al., 2003; Koek et al., 1998). However, this hypothesis is weakened by the following observations: (1) NMDA receptor antagonists have been found to display anxiolytic rather than anxiogenic properties in classical models of anxiety (Porter et al., 1989; Kehne et al., 1991; Xie and Commissaris, 1992) and (2) the prototypical anxiolytic diazepam did not antagonize this PCP-induced social interaction deficit. Similarly, three daily injections of diazepam were reported to be ineffective against PCP-induced social deficit in rats (Sams-Dodd, 1998a).

The PCP-induced social interaction deficit could result from a “depressive-like” state. Noda et al. (1997) have shown that chronic treatment with PCP increased immobility time in mice submitted to the forced swimming test, which was interpreted as resulting from a “depressive-like” state. Therefore, the beneficial effects of SSR181507 and of 8-OH-DPAT on this PCP-induced social interaction deficit could stem from their antidepressant-like effects exerted via 5-HT_{1A} receptor stimulation (Kennett et al., 1987; Depoortere et al., 2003). However, under our experimental conditions, the prototypical antidepressant drug citalopram (3 and 10 mg/kg i.p.), active after a single injection in some depression models in rats (Sanchez and Meier, 1997; Plaznik et al., 1989), failed to antagonize PCP-induced social interaction deficit (data not shown for reasons similar to those exposed previously). This result is consistent with that of Sams-Dodd (1998a), who reported that citalopram given in combination with PCP (2 mg/kg) for 3 days, could not reverse a PCP-induced social interaction deficit.

The beneficial effects of SSR181507 and 8-OH-DPAT on PCP-induced social interaction deficit may therefore involve a genuine effect of these two compounds on neurochemical processes that are responsible for a decreased interaction consecutive to administration of PCP. Prefrontal cortex abnormalities have been directly related to negative symptoms (Wible et al., 2001), and particularly to abnormal social functioning in schizophrenia (Chemerinski et al., 2002). The beneficial effects of SSR181507 and of 8-OH-DPAT on PCP-mediated social behaviour deficit could result from neurochemical changes taking place in prefrontal cortical areas, resulting from activation of 5-HT_{1A} receptors. SSR181507 has been shown to increase DA synthesis and release in the prefrontal cortex, and to reduce 5-HT synthesis in cortical regions (Claustre et al., 2003). A similar neurochemical profile has been reported for 8-OH-DPAT (Larsson et al., 1998; Ichikawa and Meltzer, 1999). Both clozapine and olanzapine have also been shown to increase DA release in the prefrontal cortex (Volonté et al., 1997), and this increase has been shown to involve (indirectly)

activation of 5-HT_{1A} receptors (Ichikawa et al., 2001). However, contrary to SSR181507 and 8-OH-DPAT, olanzapine did not reduce 5-HT release and/or its metabolism in cortical regions (Li et al., 1998). Instead, both olanzapine and clozapine might even increase 5-HT release (Ichikawa et al., 1998). Considering that these latter two compounds were inactive, in our hands, in reversing a PCP-induced social deficit, increased DA availability in the prefrontal cortex alone does not appear to be responsible for the reversing effects of SSR181507 and 8-OH-DPAT. The ability common to both SSR181507 and 8-OH-DPAT to concomitantly increase DA utilization and decrease 5-HT turnover in cortical areas might possibly form the basis for their efficacy in counteracting a reduced social interaction produced by administration of PCP. Another possibility would be that a decrease of 5-HT release and/or synthesis in cortical regions, in the absence of an augmented DA tone, might be sufficient to oppose deleterious effects of PCP on social behaviours, but testing of this hypothesis would be out of the scope of the present study.

Finally, it should be emphasized that under conditions that favour a low level of social interaction in rodents (i.e. high illumination conditions, withdrawal from diazepam or from chronic forced ethanol exposure), various 5-HT_{1A} receptor agonists such as buspirone, 8-OH-DPAT and ipsapirone (and SSR181507, manuscript in preparation) have been shown to enhance interaction (File and Andrews, 1991; File and Seth, 2003; Overstreet et al., 2003). Overall, these various preclinical data strengthen the notion that targeting the 5-HT_{1A} receptors system should result in beneficial effects on dysfunctional social behaviour, possibly not only in schizophrenic patients, but also in populations suffering from social withdrawals of various etiologies.

5. Conclusions

Acute administration of the DA D₂ receptor antagonist and 5-HT_{1A} receptor agonist SSR181507 prevented a PCP-induced social interaction deficit in rats. This reversal would appear to recruit properties that are distinct from anxiolytic and/or antidepressant properties. It might result from a genuine effect of this compound on this type of social interaction deficit, effect apparently not shared by other atypical antipsychotic such as clozapine and olanzapine. The role of 5-HT_{1A} receptors stimulation in this effect is suggested by the similar effects obtained with 8-OH-DPAT, a rather selective 5-HT_{1A} receptor agonist. These data support the hypothesis that in addition to its atypical antipsychotic profile and anxiolytic/antidepressant activity (Claustre et al., 2003; Depoortere et al., 2003), SSR181507 could

possess a potential therapeutic activity on another key feature of schizophrenia, namely poor social functioning. This should confer on SSR181507 a wider spectrum of activity than that of currently marketed antipsychotics, and facilitate reinsertion of patients.

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