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ORIGINAL INVESTIGATION

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SSR181507, a dopamine D_2 receptor antagonist and 5-HT_{1A} receptor agonist, alleviates disturbances of novelty discrimination in a social context in rats, a putative model of selective attention deficit

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Abstract *Rationale:* Selective attention deficit, characterised by the inability to differentiate relevant from irrelevant information, is considered to underlie many cognitive deficits of schizophrenia, and appears to be only marginally responsive to treatment with current antipsychotics. *Objectives:* We compared the activity of the putative atypical antipsychotic SSR181507 (a dopamine D_2 receptor antagonist and $5HT_{1A}$ receptor agonist) with reference compounds, on disturbances of novelty discrimination in a social context in rats, a behavioural paradigm that putatively models selective attention deficit. *Methods:* A first (familiar) juvenile rat was presented to an adult rat for a period (P1) of 30 min. A second (novel) juvenile was then introduced at the end of P1 for a period (P2) of 5 min. The ability of the adult rat to discriminate between the two juveniles, presented at the same time, was evaluated by measuring the ratio of the time spent in interaction with the novel vs the familiar juvenile during P2. *Results:* Adult rats spent more time exploring the novel than the familiar juvenile. This novelty discrimination capacity was disrupted by: (1) parametric modification of the procedure (reduction of time spent in contact with the familiar juvenile during P1); (2) acute injection of psychotomimetics that are known to induce schizophrenia-like symptoms in humans, such as phencyclidine (PCP; 3 mg/kg, i.p.) and *d*-amphetamine (1 mg/kg, i.p.) and (3) neonatal treatment with PCP (three injections of 10 mg/kg, s.c.), a model based on the neurodevelopmental hypothesis of schizophrenia. The potential atypical antipsychotic SSR181507 (0.03–3 mg/kg, i.p.) and the atypical antipsychotics clozapine (0.1–1 mg/kg, i.p.) and amisulpride (1–3 mg/kg, i.p.) attenuated deficits in novelty discrimination produced by parametric manipulation and by acute or neonatal treatment with PCP. The typical antipsychotic haloperidol (up to 0.3 mg/kg, i.p.) attenuated only deficits in novelty discrimination produced by parametric modification. *Conclusion:* Collectively, these results suggest that SSR181507 can alleviate disturbances of novelty discrimination in a social context in rats, and that this paradigm may represent a suitable animal model of selective attention deficits observed in schizophrenia.

Keywords 5-HT_{1A} agonist · Antipsychotic activity · D_2 antagonist · Information processing · Novelty discrimination · Phencyclidine · Schizophrenia · Selective attention · SSR181507

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Introduction

Schizophrenia is mainly characterised by psychotic symptoms such as delusions and hallucinations, but there are many other features associated with this disease, including flattened emotions, cognitive disorders, as well as deficits in attention and information processing. Attention deficit is characterised by the inability to differentiate relevant from irrelevant information (Cohen and Servan-Schreiber 1992; Barch et al. 1999), and has been described as a marker of vulnerability in schizophrenic patients (Addington et al. 1996). It has also been considered to be a predominant characteristic of the disease (Brébion et al. 2000) and to underlie many cognitive deficits, conducive to a lack of coping, poor functioning and difficulties in the reinsertion of these patients (Silverstein 1997; Lewis 2004).

Although current antipsychotics are considered to be reasonably active in alleviating positive symptoms of schizo-

phrenia, they appear less active against negative symptomatology and cognitive deficits such as attention and information processing abnormalities (Meltzer and McGurk 1999; Sharma 1999). Recently, we published a report on SSR181507, a selective dopamine D_2 receptor antagonist and 5-HT_{1A} receptor agonist (Claustre et al. 2003). This compound was found to display an atypical antipsychotic profile, with an absence of catalepsy and with added antidepressant/anxiolytic activities (Depoortere et al. 2003). This lack of catalepsy and these antidepressant/anxiolytic activities were presumed to be related to its agonist activity at 5-HT_{1A} receptors. SSR181507 was also shown to have additional beneficial effects on phencyclidine (PCP)-induced deficits of social interaction in rats (Boulay et al. 2004). The aim of the present study was to develop a preclinical test of selective attention, so as to characterise the activity of SSR181507, in comparison to reference compounds, to reverse deficits of selective attention of various origins.

Attention deficit and information processing abnormalities have been the focus of much interest in both clinical and pre-clinical studies. Schizophrenic patients show impairment in a number of experimental situations that probe information processing mechanisms, including sensory gating models such as the P50 and P300 event-related potentials (see Muller et al. 2001; Freedman et al. 2003 for reviews), prepulse inhibition (PPI) of the startling reflex (Braff et al. 1978; for review, Swerdlow et al. 2000), latent inhibition (Weiner et al. 1996; for review, Moser et al. 2000; Weiner 2003) and discrimination learning (Hofer et al. 2001). Because it is easy to reproduce PPI deficits in laboratory animals, the PPI model is by far the most widely used to study deficits of information processing, and for an extensive pharmacological evaluation in rodents (for review: Geyer et al. 2001). However, one possible weakness of the PPI model is that it relies on a sensory motor response and as such probably involves very early stages (pre-attentive) of information processing. Although deficits at such early levels/stages are likely to participate in the expression of the pathology, the study of abnormalities of attentional processes engaging more integrated levels would benefit this field of research. The latent inhibition model would appear to fulfill the criterion of a higher level of integration, but the complexity of the task (that usually involves multiple sessions of training) renders this test time-consuming and less attractive for screening pharmacological compounds.

Presently, we investigated a behavioural paradigm, based on novelty discrimination in a social context in rats, in an attempt to model selective attention. The novelty discrimination procedure analysed here uses the ability of an adult rat to discriminate between a familiar and a novel juvenile rat (Engelmann et al. 1995) and presents the advantage of involving highly integrated social behaviours, and since it relies on spontaneous behaviour, it requires no previous training. Briefly, it consists in exposing a first (familiar) juvenile to an adult rat for an initial presentation period (P1) of 30 min, and then introducing a second (novel) juvenile at the end of P1 for a second period (P2) of 5 min. Under these conditions, the adult rat preferentially investigates—i.e. spends more time exploring—this novel juvenile during P2. If one posits that the novel juvenile represents the pertinent or relevant stimulus in this context of social exploratory behaviour, then, one step further, one might assume that this experimental situation represents a model of selective attention. Note that the present protocol varies from the one used in so-called "social recognition" paradigms (Perio et al. 1989), in which one juvenile is presented twice to the adult rat.

In a first step, we investigated how to produce impairments of novelty discrimination—i.e. to decrease the ratio of the time spent by the adult rat investigating the novel vs the familiar juvenile during P2—in an attempt to reproduce deficits of selective attention (see above). This was done: (1) by administering to the adult rat acute challenges with psychotomimetics, such as PCP (a non-competitive NMDA receptor antagonist) and *d*-amphetamine (an indirect dopamine receptor agonist), both known to induce schizophrenia-like symptoms in humans; (2) by parametric modification of the protocol (shortening of the duration of P1); and (3) by a neonatal treatment with PCP, with the aim of using a neurodevelopmental approach.

In a second step, we examined the ability of SSR181507 and of atypical (clozapine, amisulpride; Perrault et al. 1997) or typical (haloperidol) antipsychotics to reverse some of these various impairments of selective attention. In addition, the effects of the acetylcholinesterase inhibitor tacrine, a compound known to improve memory performances (Wang and Tang 1998; Stemmelin et al. 1999), and of the antidepressant imipramine, were also tested. This was done to verify that deficits of novelty discrimination were not the consequence of interference with mnesic processes, and to assess the pharmacological selectivity of these deficits.

Material and methods

The procedures described below were approved by the Animal Ethics Committee of Sanofi-Synthélabo Recherche and are in compliance with current French legislation on animal experimentation.

Animals

All animals (adults, juveniles, mothers and pups) were purchased from Charles River (Saint-Aubin-les-Elbeuf, France). They were kept on a reversed light–dark cycle (lights on from 7.00 P.M. to 7.00 A.M.) and under constant room temperature (21±2°C) and humidity (50%). Food and water were freely available. Adult (160–200 g on arrival) and juvenile (3 weeks old, 45–50 g on arrival) male Wistar Han rats were housed individually, or five per cage, respectively, in 30×40×18 cm high cages. Juvenile rats were left five per cage for 1 week, and were then used for 1 week in experiments (presentation to adult rats). They were used only once a day, and were chosen at random as first or second juvenile for presentation to the adult.

For neonatal PCP treatment experiments, female Wistar Han rats with ten male pups on postnatal day 3 (PN3) were used. Pups were treated on days PN7, PN9 and PN11 with 10 mg/kg of PCP (s.c. administration, 1 ml/100 g body weight) or vehicle (saline). Pups from the same litter received identical treatment. The mother and pups were housed together until weaning at PN21, at which stage pups were housed five per cage until 2 weeks before the start of behavioural experiments, when they were housed individually. Pups were not used until they reached the adult stage, when they were used for behavioral experiments (performed from PN56).

Procedures

Experiment 1: novelty discrimination using a protocol that favors exploration of the novel juvenile

Experiments were performed during the dark phase, under infrared illumination (15 lx). Juvenile rats were isolated 30 min before being placed into the home cage of an adult rat. One cage was placed underneath a video camera, the mesh top removed and replaced by a Plexiglas cover. A first juvenile (A, familiar) was placed inside the home cage containing one adult rat for a first presentation period (P1) of 30 min. The second juvenile (B, novel) was then introduced at the end of P1 for a period of 5 min (P2). Duration of investigative behaviour (nosing, sniffing, grooming, "close following" of the juvenile rat) between the adult rat and the juvenile A during P1, and between the adult and each of the two juveniles during P2, were recorded manually by a well-trained observer located in an adjacent room via a video link.

Experiment 2: effects of acute challenge with psychotomimetics on novelty discrimination using a protocol that favors exploration of the novel juvenile

Phencyclidine (3 mg/kg), *d*-amphetamine (1 mg/kg) or vehicle were administered i.p. to the adult rat 15 min (PCP) or 30 min (*d*-amphetamine) before exposure to juvenile A using a protocol similar to that described for Experiment 1. Treatments were administered in a pseudo-randomised order, with a 1- or 2-day interval between each treatment. The doses of PCP and amphetamine chosen were found in pilot studies not to significantly increase spontaneous motility under our experimental conditions.

Experiment 3: impairment of novelty discrimination produced by a shortening of the duration of the first presentation and a lengthening of the inter-period interval

The procedure was slightly different from that described for Experiment 1, in the sense that the two presentation periods (P1 and P2) were 5 min, and were separated by a 30-min inter-period interval, during which the familiar juvenile was returned to its home cage. This parametric manipulation was implemented to produce an impairment of novelty discrimination by the adult rat during P2.

In a control experiment, identical to that described just above, each juvenile was prevented from freely moving in the environment during P2 by being restrained into small mesh cages (5×7.5×16 cm high). This control experiment aimed at assessing if the deficit produced by parametric manipulation could be counteracted by facilitating the interaction with each of the two juveniles.

Experiment 4: activity of antipsychotics on the deleterious effects of an acute challenge with phencyclidine on novelty discrimination

Rats were first injected intraperitoneally (see Results section for doses used) with SSR181507, clozapine, amisulpride, haloperidol or vehicle, 15 min before an i.p. injection of 3 mg/kg of PCP (injection 15 min before P1). Rats were exposed to juveniles using the protocol of Experiment 1. For a given antipsychotic, doses were administered in a pseudo-randomised order, with a 1- or 2-day interval between two successive drug treatments.

Experiment 5: effects of antipsychotics on the impairment of novelty discrimination produced by a shortening of the duration of the first presentation and a lengthening of the inter-period interval

Rats were injected intraperitoneally (see Results section for dose used) with SSR181507, clozapine, amisulpride, haloperidol or vehicle, 30 min before being exposed to juveniles, with the protocol of Experiment 4 (juveniles freely moving during P2). For a given antipsychotic, doses were administered in a pseudo-randomised order, with a 1- or 2-day interval between two successive drug treatments. Tacrine and imipramine were also tested as reference compounds.

Experiment 6: effects of phencyclidine treatment at the neonatal stage on novelty discrimination in adult rats

Experiments were performed in adult rats between days PN51 and PN91, following treatment with PCP at the neonatal stage (at PN7, PN9 and PN11; see the section "Animals" for details). The protocol used in this study was identical to that described for Experiment 1. This experiment was undertaken to verify that a deficit was observable during an extended period of time, a sine qua non condition for being able to conduct further in-depth pharmacological tests.

Experiment 7: effects of antipsychotics on the impairment of novelty discrimination produced in adult rats by phencyclidine treatment at the neonatal stage

Acute drug treatment were performed in adult rats (treated with PCP at the neonatal stage) between days PN113 and PN119 for SSR181507, between PN64 and PN100 for clozapine, between PN92 and PN100 for amisulpride, between PN105 and PN112 for haloperidol, and between PN52 and PN57 and between PN105 and PN106 for tacrine and imipramine, respectively. Variations in the range of PN dates for experiments between the four antipsychotics were due to calendar constraints. The protocol used in this experiment was identical to that described for Experiment 3.

Drugs

Amisulpride and SSR181507 were synthesised by the CNS Medicinal Chemistry Department of Sanofi-Synthélabo Recherche (Bagneux, France). Clozapine, haloperidol, imipramine, PCP, *d*-amphetamine and tacrine were purchased from Sigma (St Louis, MO, USA). All drugs were suspended in physiological saline with Tween 80 (two drops for 20 ml), except for *d*-amphetamine and PCP, which were dissolved in saline, and haloperidol, which was dissolved in tartaric acid (0.1%). Injection volume for adult rats was 5 ml/kg body weight, i.p. route.

Data analysis

Data are expressed as the mean and SEM of individual interaction duration (IID, in s) during P1 (recorded during the first 5 min) and P2 (recorded during the entire 5 min), and/or as a novelty discrimination index (NDI), which was calculated as the ratio of the IID for juvenile B divided by that for juvenile A, during P2. IIDs and NDIs were first log-transformed because of the limited number of subjects and the lack of homogeneity of variances between groups. For Experiments 1, 2 and 3, IIDs were submitted to one-way ANOVAs, followed by Dunnett's post-hoc tests. For

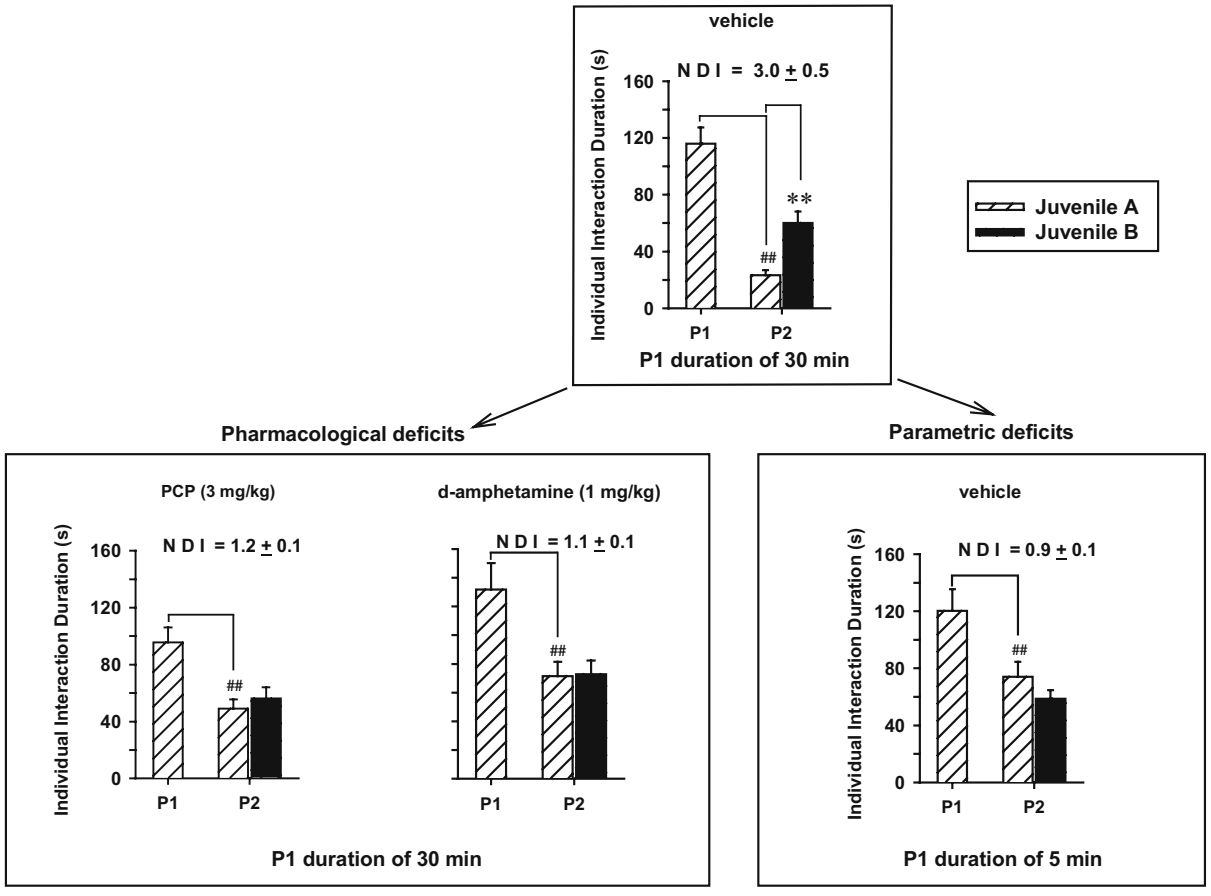

Fig. 1 Impairment of novelty discrimination by acute treatment with psychotomimetic drugs and by parametric manipulation. The protocol for the control condition (*top panel*) and the acute pharmacological challenges (*bottom left panel*) was as follows: P1=30 min, inter-presentation interval=0 min, P2=5 min. For the parametric manipulation, the protocol was as follows: P1=5 min, inter-presentation interval=30 min, P2=5 min). Each *bar* represents the mean±SEM individual interaction duration. *IID* Time spent by the adult rat to interact either with the familiar or the novel juvenile (s). The novelty discrimination index (*NDI*) was calculated by dividing the IID for the juvenile B by the IID for the juvenile A during P2. $^{**}P<0.01$, vs juvenile A at P2, $^{\#\#}P<0.01$, vs juvenile A during P1, Dunnett's post-hoc tests following one-way ANOVAs. *N*=10 rats per group

Experiments 4 and 5, NDIs were subjected to one-way ANOVAs for repeated measures, followed by Dunnett's post-hoc tests. For Experiments 6 and 7, NDIs were submitted to two-way ANOVAs, with treatment at the neonatal stage as the between-subjects factor, and postnatal day of testing (Experiment 6) or acute treatment at the adult stage (Experiment 7) as the within-subjects factor, followed by appropriate post-hoc tests. All statistical analyses were performed using the SAS software (SAS Institute Inc., Cary, NC, USA).

Results

Experiments 1, 2 and 3: novelty discrimination in adult rats: deficits induced by psychotomimetic drugs and by parametric manipulation

Under the protocol where the confrontation between an adult rat and the first juvenile (A, familiar) lasted 30 min (P1), with no inter-period interval, the adult rat spent significantly more time investigating the other (B, novel) juvenile during the second period of investigation (P2, 5 min), when the two juveniles were present in the cage (Fig. 1, top panel). This was confirmed by statistical analysis, showing that the individual interaction durations (IIDs) for juvenile A between P1 and P2, and those between the two juveniles during P2 were significantly different Dunnett's post-hoc tests, following a significant one-way ANOVA analysis: $F_{2,18}$=70.75, P<0.01). The Novelty Discrimination Index (NDI) was 3.0±0.5 (i.e. greater than unity), indicating that the adult rat spent thrice more time investigating juvenile B than juvenile A during P2.

Administration of PCP and *d*-amphetamine, at doses that did not significantly increase spontaneous motility under our experimental conditions (data not shown), prevented adult rats from discriminating between juvenile A and B (Fig. 1, left bottom panel): there was a lack of significant difference of IIDs between the two juveniles at P2 (Dunnett's post-hoc tests, following significant one-way ANOVAs: $F_{2,18}$=24.87, P<0.01 and $F_{2,18}$=23.04, P< 0.01, for PCP and *d*-amphetamine, respectively). This absence of preferential investigation of juvenile B during P2 translated into NDIs close to unity: 1.2±0.1 for PCP and 1.1±0.1 for amphetamine.

A shortening of the duration of P1 and a lengthening of the inter-period interval induced a reduction in the time spent by the adult rat interacting preferentially with juvenile B during P2 (Fig. 1, right bottom panel). This was inferred from a lack of significant difference for IIDs between the two juveniles during P2 (Dunnett's post-hoc test following significant one-way ANOVA $F_{2,18}$=10.89, P<0.01). This absence of preferential investigation for the second juvenile during P2 translated into an NDI close to unity (0.9±0.1).

However, restraining juveniles into small mesh cages during P2 restored novelty discrimination (NDI=3.6±0.8). This was further confirmed by statistical analysis on IIDs for juvenile A between P1 and P2 (104.5±9.6 vs 41.0±7.7 s), and those between the two juveniles during P2 (41.0±7.7 vs 106.7±8.4 s) (Dunnett's post-hoc tests, following a significant one-way ANOVA analysis: $F_{2,18}$=25.85, P< 0.01).

Experiment 4: impairment of novelty discrimination induced by an acute injection of PCP in adult rats: effects of antipsychotics

PCP administration induced an impairment of novelty discrimination (compare the first and second lines for each antipsychotic in Table 1). This was confirmed by significant decreases in the NDI for PCP-treated vs control groups (Dunnett's post-hoc tests following one-way ANOVAs: $F_{4,45}$=6.68, P<0.001, $F_{4,45}$=6.69, P<0.001, $F_{5,50}$= 2.99, P<0.05 and $F_{6,58}$=5.94, P<0.001, for SSR181507, clozapine, amisulpride and haloperidol, respectively).

Both SSR181507 and clozapine, at the two highest doses tested, significantly reversed the decrease in NDI

Table 1 Effects of antipsychotics on impairment of novelty discrimination induced by an acute injection of PCP

Doses of drug (mg/kg)	Dose of PCP (mg/kg)	NDI (mean±SEM)	Number
SSR181507			
0	0	9.7±1.9	10
0	3	3.0±0.4**	10
0.01	3	2.9±0.6	10
0.1	3	7.5±2.1$^{\#}$	10
1	3	8.1±1.7$^{\#\#}$	10
Clozapine			
0	0	3.0±0.5	10
0	3	1.1±0.1**	10
0.03	3	1.3±0.2	10
0.1	3	2.4±0.4$^{\#\#}$	10
1	3	2.0±0.2$^{\#}$	10
Amisulpride			
0	0	6.4±1.0	12
0	3	2.9±0.7**	12
0.1	3	3.9±0.4	8
0.3	3	4.1±1.5	8
1	3	4.2±0.3	8
3	3	5.3±0.9$^{\#}$	8
Haloperidol			
0	0	5.4±2.0	10
0	3	1.3±0.2**	10
0.05	3	1.3±0.1	10
0.1	3	1.3±0.1	10
0.125	3	1.1±0.1	5
0.15	3	1.7±0.3	10
0.3	3	1.4±0.4	10

Results are expressed as the novelty discrimination index (NDI) at P2

**P<0.01 vs controls (0/0 group), $^{\#}P$<0.05, $^{\#\#}P$<0.01 vs 0/PCP(3) group, Dunnett's post-hoc tests following one-way ANOVAs. N= 8–12 rats per group

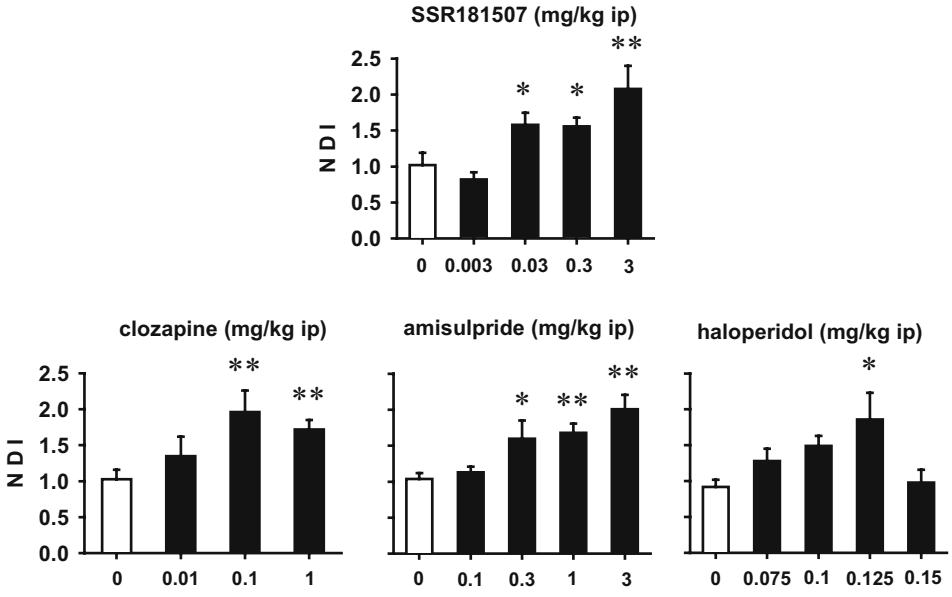

Fig. 2 Reversal by antipsychotics of impairment of novelty discrimination produced by a parametric manipulation. The protocol was as follows: P1=5 min, inter-presentation interval=30 min, P2=5 min). Each *bar* represents the mean±SEM novelty discrimination index (*NDI*) at P2. **P*<0.05, ***P*<0.01 vs the vehicle (0) group, Dunnett's post-hoc tests following one-way ANOVAs. *N*=10 rats per group

induced by PCP; amisulpride was significantly active at the highest dose only, while haloperidol was clearly inactive (Dunnett's post-hoc tests comparing the vehicle/PCP group to drug/PCP groups for each antipsychotic).

Experiment 5: impairment of novelty discrimination produced in adult rats by a parametric manipulation: effects of antipsychotics

All four antipsychotics (Fig. 2) reversed decreases of NDI produced by a parametric modification of the protocol [Dunnett's post-hoc tests between the vehicle (0) and drug groups, following significant one-way ANOVAs: ($F_{4,36}$= 8.83, P<0.01, $F_{3,37}$=5.24, P<0.01, $F_{4,36}$=7.85, P<0.01 and $F_{4,36}$=3.37, P<0.05 for SSR181507, clozapine, amisulpride and haloperidol, respectively].

Note that with haloperidol, at the highest dose tested, the NDI value returned towards control value, due to a marked reduction of motor activity (visual observation) without significant modification of the time spent by the adult in juvenile interactions (sum of interactions towards the two juveniles during P2: 132.3±8.9 vs 113.5±11.9, for vehicle and haloperidol 0.15 mg/kg, respectively; NS).

Experiments 6 and 7: impairment of novelty discrimination in adult rats produced by administration of phencyclidine at the neonatal stage: effects of antipsychotics

A first cohort of rats was utilised to assess the robustness of the effects of a neonatal PCP treatment on novelty discrimination at the adult stage. Statistical analysis showed that NDIs were significantly decreased (Fig. 3, hatched bars) in neonatal PCP-treated rats in comparison with saline-treated neonate rats (white bars) at each postnatal time point investigated (post-hoc tests following a significant neonatal treatment effect, two-way ANOVA: $F_{1,8}$=63.32, P<0.0001).

Neonatal PCP treatment induced a significant impairment of novelty discrimination [compare the first pair of bars in each panel of Fig. 4, post-hoc tests for the vehicle (0) condition]. SSR181507, amisulpride and clozapine, but not haloperidol, significantly normalised this impairment (Fig. 4, black bars), without modifying novelty discrimination in saline neonatal-treated rats (Fig. 4, white bars). For reasons of clarity, the main points of the two-way ANOVAs are given in Table 2: all antipsychotics,

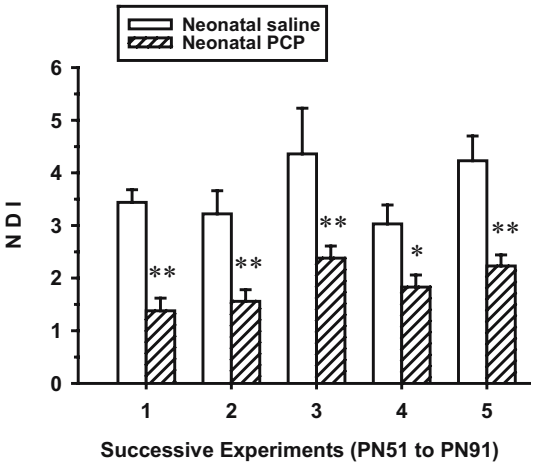

Fig. 3 Persistent impairment of novelty discrimination in adult rats treated with phencyclidine at the neonatal stage. In this experiment, the protocol was as follows: P1=30 min, inter-presentation interval=0 min, P2=5 min. Each *bar* represents the mean±SEM novelty discrimination index (*NDI*) at P2. **P*<0.05, ***P*<0.01 vs the group treated with saline at the neonatal stage, for each successive experiment [from postnatal (*PN*) period 51 to PN91], post-hoc tests following two-way ANOVAs. *N*=5 rats per group

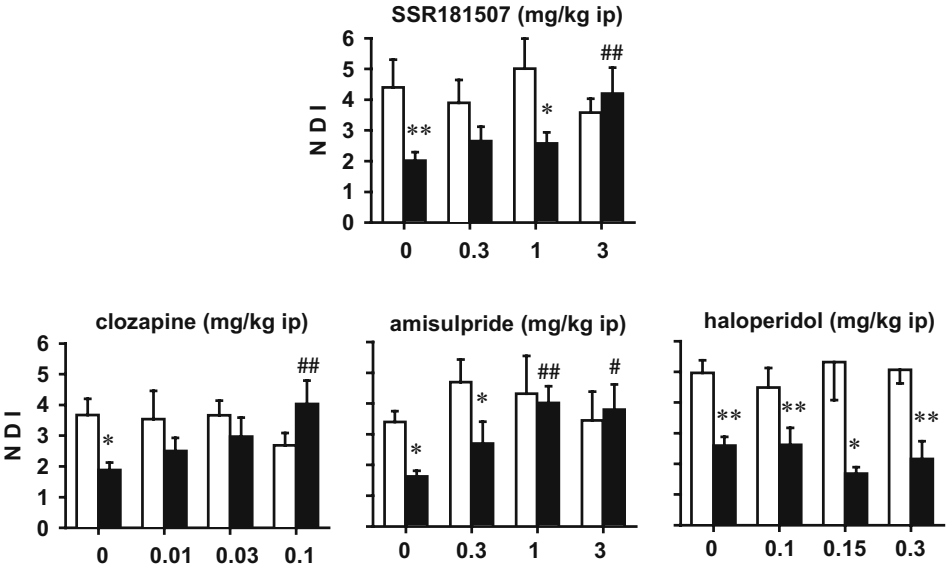

Fig. 4 Reversal by acute treatment with antipsychotics of impairment of novelty discrimination in adult rats treated with phencyclidine at the neonatal stage. In this experiment, the protocol was as follows: P1=30 min, inter-presentation interval=0 min, P2=5 min. Each *bar* represents the mean±SEM novelty discrimination index (*NDI*) at P2. **P*<0.05, ***P*<0.01, vs the group treated with saline at the neonatal stage, at the considered dose; $^{\#}P$<0.05, $^{\#\#}P$<0.01, vs the vehicle-injected group, for neonatal PCP treatment, post-hoc tests following two-way ANOVAs. *N*=5 rats per group

except haloperidol, showed significant interaction effects, and significant effects of acute drug treatment for the neonatal PCP condition only (post-hoc Winer analyses). By contrast, in the haloperidol group, there was only a significant neonatal treatment effect.

Experiment 8: effects of tacrine and imipramine on impairment of novelty discrimination in adult rats produced by parametric manipulation and by neonatal phencyclidine treatment

At doses that are known to improve memory performances, tacrine (1 mg/kg, i.p.) did not significantly modify disruption of NDI induced either by a parametric manipulation or by neonatal PCP treatment (Table 3). Similarly, the antidepressant imipramine (16 mg/kg, i.p.) was devoid of activity in both types of deficits. Details of statistical analyses for the neonatal PCP experiment are given at the bottom of Table 2.

Discussion

Novelty discrimination in a social context as a model of selective attention

When presented to two juveniles, a familiar (juvenile A), to which it has recently been exposed for 30 min, and a novel one (juvenile B), to which it has not been exposed recently, an adult rat will naturally preferentially investigate the novel one. This reflects an innate ability to distinguish between the two juveniles, i.e. to discriminate novelty (Engelmann et al. 1995). It can be assumed that the novel juvenile represents the "pertinent" or "relevant" stimulus that preferentially captures the attention of the rat. As such, the ratio of the time spent investigating the novel vs the familiar juvenile (what we call the novelty discrimination index) might possibly represent a surrogate marker of the selective attention capacity of the adult.

Table 2 Summary of statistical analyses (two-way ANOVAs) for acute treatment with antipsychotics tacrine and imipramine on impairment of novelty discrimination in adult rats treated with phencyclidine at the neonatal stage

	Neonatal treatment effect	Acute treatment effect	Interaction effect	Winer analyses	
				Neonatal saline	Neonatal PCP
SSR181507	$F_{1,8}$=6.10, P<0.05	$F_{3,24}$=1.33, NS	$F_{3,24}$=3.15, P<0.05	$F_{3,24}$=0.72, NS	$F_{3,24}$=3.76, P<0.05
Clozapine	$F_{1,8}$=0.91, NS	$F_{3,24}$=0.95, NS	$F_{3,24}$=4.74, P<0.01	$F_{3,24}$=1.24, NS	$F_{3,24}$=4.44, P=0.01
Amisulpride	$F_{1,8}$=3.05, NS	$F_{3,24}$=2.75, NS	$F_{3,24}$=3.31, P<0.05	$F_{3,24}$=1.02, NS	$F_{3,24}$=5.02, P<0.01
Haloperidol	$F_{1,8}$=29.86, P<0.001	$F_{3,24}$=0.82, NS	$F_{3,24}$=1.39, NS	$F_{3,24}$=0.23, NS	$F_{3,24}$=1.98, NS
Tacrine	$F_{1,8}$=27.23, P<0.001	$F_{1,8}$=0.02, NS	$F_{1,8}$=0.28, NS	$F_{1,8}$=0.23, NS	$F_{1,8}$=0.08, NS
Imipramine	$F_{1,8}$=16.54, P<0.01	$F_{1,8}$=0.16, NS	$F_{1,8}$=0.37, NS	$F_{1,8}$=0.51, NS	$F_{1,8}$=0.02, NS

The Winer analyses correspond to post-hoc one-way ANOVAs for each of the two neonatal treatment groups

Table 3 Effects of tacrine and imipramine on impairment of novelty discrimination induced by parametric modifications and phencyclidine neonatal injections of PCP

Parametric deficits (mg/kg, i.p.)	PCP neonate deficits (mg/kg, i.p.)	NDI (mean±SEM)	Number
Tacrine			
0		1.24±0.37	5
1		0.97±0.08	15
	0 (saline group)	3.22±0.44	5
	0 (PCP group)	1.56±0.22**	5
	1 (saline group)	3.62±0.57	5
	1 (PCP group)	1.45±0.16**	5
Imipramine			
0		1.02±0.07	5
16		1.09±0.31	5
	0 (saline group)	4.19±0.66	5
	0 (PCP group)	2.07±0.34**	5
	16 (saline group)	4.58±0.52	5
	16 (PCP group)	2.04±0.35**	5

Results are expressed as the novelty discrimination index (NDI) at P2

**$P<0.01$ vs corresponding saline neonate treated group [0(saline) group], Dunnett's post-hoc tests following one-way ANOVAs

Deficits in this model of selective attention can be obtained by various means

We observed that deficits in novelty discrimination could be induced using several approaches: acute administration of psychotomimetic drugs such as PCP or *d*-amphetamine, neonatal administration of PCP, and increased difficulty of the task (parametric manipulation) by shortening the time of the first presentation of juvenile A and lengthening the interval between P1 and P2.

The hypoglutamatergic hypothesis of schizophrenia has provided a cogent rationale for the exploration of PCP and its analogues in various animal models. Such compounds have been shown to have numerous deleterious effects, in particular in pre-attentive (i.e. reflexive) processes such as the PPI of the startle reflex (Mansbach and Geyer 1989), or attentional processes that call upon more integrated behaviours, such as the multi-choice serial reaction time task (Jin et al. 1997) and the latent inhibition model (Turgeon et al. 1998). The present demonstration that acute injection of PCP induces deficits in novelty discrimination is congruent with findings in the above-mentioned paradigms, and its pertinence is further strengthened by the observations that PCP or ketamine affected selective attention in human volunteers (Bakker and Amini 1961; Oranje et al. 2000).

It has traditionally been assumed that *d*-amphetamine has a facilitatory effect on tasks involving selective attention components in humans (Servan-Schreiber et al. 1998) and in laboratory animals (Robbins 2002). However, this seems to hold true for low doses only, as higher doses in animals (or chronic use in humans (McKetin and Solowij 1999; Salo et al. 2002 for methamphetamine) have been shown to have the opposite (i.e. deleterious) effect on attentional tasks such as the PPI of the startle reflex or latent inhibition (Moser et al. 2000; Geyer et al. 2001; Russig et al. 2003). In light of these latter results, the disturbance of selective attention processes seen here with *d*-amphetamine is not at all incongruous.

Based on the neurodevelopmental concept of schizophrenia (Lieberman et al. 1997), there is increasing interest in animal models of schizophrenia that rely on the development of behavioural deficits in adulthood after neonatal brain lesions. For example, postpubertal alteration in PPI, and hyper-responsiveness to stress, novelty, dopamine agonists and glutamate antagonists have been well documented following neonatal lesions of the ventral hippocampus (Lipska et al. 1993, 1995; Black et al. 1998; Al-Amin et al. 2000; Lipska and Weinberger 2000). More recently, Wang et al. (2001, 2003) showed that administration of high doses of PCP to rat pups produced long-term behavioural changes associated with neuronal alterations at the adolescent or adult stage. Hence, treatment with PCP at the neonatal stage retarded the acquisition of a delayed spatial alternation task, produced a spontaneous deficit in PPI, and potentiated the hyperlocomotor effects of an acute challenge with PCP. Interestingly, some of these deficits were reversed by pretreatment with the atypical antipsychotic olanzapine (Wang et al. 2001). The present results complement those of Wang and colleagues, showing that PCP at the neonatal stage has a major negative impact on the selective attention capacities of adult rats, and that atypical antipsychotics can reverse these deleterious effects (see below).

Deficits in this model might reflect altered selective attention capacities

These deficits might be explained by an impairment in selective attention capacities: the fact that both juveniles move freely and quickly as well as play with each other induces perpetual changes in spatial location of the two stimuli. This renders more difficult a preferential interaction with the relevant stimulus (juvenile B) when the attentional system of the adult rat is prevented from working under optimal conditions by parametric manipulation or pharmacological treatment.

Alternative explanations for the origin of these deficits could be envisaged. The first one, based on a modification of memory function, seems unlikely, however: when disturbances of novelty discrimination are induced by parametric manipulation or by neonatal PCP treatment, tacrine, a promnesic compound (Jackson and Soliman 1996), did not restore novelty discrimination (present data). Furthermore, under experimental conditions that putatively recruit more selectively mnesic processes (a social memory test using only one juvenile presented twice, described by Perio et al. 1989), acute PCP did not induce deficits (data not shown). Secondly, novelty discrimination deficits induced by acute PCP were observed in the absence of major effects on locomotor activity (data not shown), ruling out

an unspecific motor effect. Thirdly, an implication of disturbances in the sensorial capacities of the adult, or by a non-specific lack of interest for the environment, also seems improbable. Individual interaction durations (that supposedly reflect the level of interest of the adult rat) with juvenile A during P1, and with either of the two juveniles during P2, were not affected either by pharmacological treatments or by parametric manipulations (data not shown).

Additionally, shortening of P1 from 30 min down to 5 min did not result in a deficit of novelty discrimination when each juvenile was prevented from freely moving in the environment during P2 (by being restrained into a small mesh cage). This shows that when the adult rat is not disturbed by the moving around of the two juveniles, there is preservation of the capacity for novelty discrimination. In addition, it provides a supplementary argument in favour of a lack of implication of a mnesic deficit, of altered sensorial capacities or level of interest for the environment, in the deficits seen with parametric manipulation—and possibly with pharmacological treatments—under standard conditions (i.e. when both juveniles are freely moving). Finally, the absence of effects of imipramine on deficits produced by neonatal PCP and parametric manipulation militates against a "depressive-like" state (reduction of the motivation) that could be at the origin of these deficits.

Effects of antipsychotics on deficits of novelty discrimination

SSR181507, clozapine and, to a lesser extent, amisulpride restored deficits induced either by acute PCP, neonatal-PCP treatment or parametric manipulation. In sharp contrast, haloperidol was only marginally (i.e. at a single dose) effective against deficits induced by parametric manipulation. These results are in accord with those showing that haloperidol has no effect against PCP-induced PPI deficits (i.e. Geyer et al. 1990) or social interaction deficits (Boulay et al. 2004). Unfortunately, scrutiny of the receptor binding profiles of these four compounds does not seem to allow one to extrapolate on the particular mechanisms putatively responsible for beneficial effects against these various deficits. SSR181507 is a DA D_2 receptor antagonist and $5HT_{1A}$ receptor agonist (Claustre et al. 2003); amisulpride is a selective D_2 receptor antagonist (Schoemaker et al. 1997); haloperidol is a mixed D_2 and to a lesser extent5-HT_2 and α_1 adrenergic receptor antagonist; and clozapine binds with more or less affinity to a myriad of receptors, in particular, α_1, histaminergic H_1, muscarinic M_1 and5-HT_{2A} receptors, to cite the most pertinent ones (Coward et al. 1989). It is clear that no particular receptor or receptorial combination stands out as being responsible for activity in this test. On the other hand, one possible common point between SSR181507, clozapine and amisulpride might be their ability to elevate cortical levels of dopamine (Schoemaker et al. 1997; Kuroki et al. 1999; Claustre et al. 2003). Hypofrontality, possibly resulting from suboptimal dopaminergic local tone, has been proposed to be responsible for various cognitive problems encountered by schizophrenic patients, including attentional disturbances (Craft et al. 1992; Pinelli et al. 2000). It might be that elevation of cortical DA tone is responsible for the beneficial effects of these three compounds. In essence, whatever the mechanism(s) responsible for a pharmacological effect in this model of selective attention, the results confirm that SSR181507 conforms to the profile of antipsychotics (clozapine and amisulpride) with an atypical profile.

The reversal by SSR181507 of the acute PCP-induced deficits of novelty discrimination complements and extends the beneficial reversing effects found by Boulay et al. (2004) in social behaviour deficits induced by PCP. The conjunction of these results emphasises that SSR181507 shows a consistent activity in reversing deficits in models that rely on a highly integrated social behaviour. This strengthens the assumption that the compound should possess a therapeutic potential against social dysfunctioning in schizophrenia, which is considered to be a major obstacle to the normal functioning and social reinsertion of patients affected by this pathology (Mueser and McGurk 2004).

Summary of findings

The discriminative capacities of adult rats using juvenile rats as stimuli may be a useful approach for exploring selective attention deficits in animals. Putative or established atypical antipsychotics such as SSR181507, clozapine and amisulpride were more effective than the typical antipsychotic haloperidol in improving pharmacologically or parametrically induced deficits in this model. One must, however, exert caution at attempting to transpose what is observed in rats with this model to the deficits of selective attention seen in patients with schizophrenia. It should be emphasised that the transposition is not as straightforward as that for the PPI and LI models, for which deficits have been documented both in laboratory animals and patients. Nonetheless, the reversal of these attentional deficits can tentatively be suggested to be predictive of a clinical activity against the information-processing deficit aspects of schizophrenia.

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