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SSR181507, a dopamine D_2 receptor and 5-HT_{1A} receptor ligand: Evidence for mixed anxiolytic- and antidepressant-like activities☆

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ABSTRACT

SSR181507, a dopamine D_2 receptor antagonist/partial agonist and 5-HT_{1A} receptor agonist, is active in animal models of schizophrenia. Furthermore, it shows activity in several anxiety and/or depression models (Depoortere et al. 2003). Presently, we sought to further characterize the latter two activities in rats, using a step-down passive avoidance procedure, a shock-induced ultrasonic vocalization (UV) test in adult subjects and a social interaction test.

SSR181507 (0.3 & 1 mg/kg ip), but not the atypical antipsychotics clozapine and olanzapine, decreased the latency time to step-down from a "safety" platform. Effects of SSR181507 were reversed by the selective 5-HT_{1A} receptor antagonist SL88.0338. SSR181507 also reduced UV (0.3 & 1 mg/kg ip), an effect not reversed by SL88.0338, and observed with olanzapine, haloperidol, fluoxetine and the 5-HT_{1A} receptor agonists 8-OH-DPAT and buspirone, but not diazepam. Furthermore, SSR181507 remained active following 3 weeks of administration (1 mg/kg ip, once daily) in the UV test. Lastly, SSR181507 (3 mg/kg ip) potentiated social interaction, an effect shared by diazepam and buspirone, but not by olanzapine, clozapine, haloperidol and 8-OH-DPAT.

These data further strengthen previous findings that the putative atypical antipsychotic SSR181507 has mixed antidepressant and anxiolytic activities.

1. Introduction

Schizophrenia is a disease characterized by a multitude of facets, most notably psychosis, negative symptoms and cognitive deficits. Furthermore, two co-morbid states, namely depression and anxiety, are prevalent in a substantial proportion of schizophrenic patients (Barnes et al., 1989; Buchanan et al., 2002) and add to the psychological distress endured by patients (Buckley et al., 2009). Although there are some indications that a few antipsychotics might be endowed with anxiolytic or antidepressant activities (Kennedy and Lam, 2003; McIntyre and Katzman, 2003), it is a common clinical practice to make use of adjunctive therapy (classical anxiolytics or antidepressants) in order to combat these co-morbid states (Clark et al., 2002). There are also hints that depression might be a core feature of the prodromal phase, and that its presence is associated with poorer outcome once the disease has declared (An der Heiden and Hafner, 2000). Interestingly, amisulpride, an antipsychotic with potent dopamine (DA) $D_{2/3}$ receptor antagonist profile (Scatton et al., 1997), demonstrated antidepressant properties in schizophrenia (Kim et al., 2007), an effect possibly attributed to its antagonist activity at 5-HT_7 receptors (Abbas et al., 2009). As no other DA $D_{2/3}$ receptor antagonist appears to be highly effective as antidepressant in animal models or in humans (Abbas et al., 2009), this observation suggests that DA antagonism does not exert antidepressant-like effects on its own, and that combination with other targets, such as serotonin receptors, might be required to exert anxiolytic and antidepressant activities. Thus, it would appear that an antipsychotic with in-built antidepressant and anxiolytic effects might offer clear advantages over currently used therapeutics.

Several authors have claimed that second generation antipsychotic drugs such as aripiprazole, olanzapine and clozapine may be used as adjunctive therapy in major depression refractory to treatment with classical antidepressants (Nelson et al., 2009; Bobo and Shelton, 2009; Weizman et al., 2001). Interestingly, all three antipsychotics have varying degrees of agonistic activity at 5-HT_{1A} receptors (Newman-Tancredi et al., 1996; Claustre et al., 2003; Bruins Slot et al., 2006). Indeed, 5-HT_{1A} receptor agonists exert antidepressant- and anxiolytic-like properties (Blier and Ward, 2003; Celada et al., 2004), and the 5-HT_{1A} receptor partial agonists buspirone and tandospirone are marketed as anxiolytics,

☆ All experiments were approved by the in-house Ethics Committee and were performed in accordance with current French and European legislation on animal experimentation and with the "Guide for the Care and Use of Laboratory Animals" adopted and promulgated by the NIH.

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worldwide for the former, and in Japan for the latter (Tajima, 2001). Gepirone, another 5-HT_{1A} receptor partial agonist, has also demonstrated antidepressant and anxiolytic efficacy in preclinical and clinical studies (Wilcox et al., 1996; Alpert et al., 2004). Consequently, a molecule combining both DA D_2 receptor antagonist and 5-HT_{1A} receptor agonist activities should prove to be quite innovative and constitute an interesting alternative to current antipsychotic armamentarium (Millan, 2000).

The tropanemethanamine benzodioxane SSR181507 ((3-exo)-8-benzoyl-*N*-[[(2 *S*)7-chloro-2,3-dihydro-1,4-benzodioxin-1-yl]methyl]-8-azabicyclo[3.2.1]octane-3-methanamine, monohydrochloride) is a compound that fulfils this criterion of mixed affinity: it has been shown to behave as an antagonist at the human DA D_2 long form (hD_2L), and as an agonist at the h5-HT_{1A} receptor, when expressed in CHO cells (Claustre et al., 2003). However, a partial agonist activity has been reported by (Cosi et al., 2006) in Sf9 insect cells transfected with hD_2L receptors. SSR181507 has no appreciable affinity for a variety of other receptors, in particular serotonergic 5-HT_{2A}, 5-HT_{2C}, adrenergic α_1 and α_2, histaminergic H_1 and muscarinic M_1, some of which associated with troublesome side-effects. SSR181507 was found to be active in several rodent models of schizophrenia addressing both positive and negative symptoms (Depoortere et al., 2003; Claustre et al., 2003; Boulay et al., 2004; Bruins Slot et al., 2005). In addition, there is preliminary evidence for an anxiolytic and antidepressant potential of SSR181507 (Depoortere et al., 2003), at doses encompassing those efficacious in tests predictive of antipsychotic activity: 1) it decreased the amount of time guinea pig pups spent vocalizing following a period of separation from the mother; 2) it reduced paradoxical sleep in rats, through an increase in the latency to enter this stage of sleep (an effect shared by antidepressants such as fluoxetine and imipramine: (Slater et al., 1978; Kleinlogel, 1982) and 3) it diminished aversion to a saccharin solution induced by treatment with lithium, as do 5-HT_{1A} receptor agonists and benzodiazepines. Furthermore, SSR181507 has been described to be devoid – even at high doses – of cataleptogenic potential in rats (Kleven et al., 2005), presumably owing to its partial agonist activity at 5-HT_{1A} receptors, since co-treatment with the selective 5-HT_{1A} blocker SL88.0338 (Cohen et al., 1998) induced catalepsy (Depoortere et al., 2003). This absence of cataleptogenic potential has been confirmed in non-human primates (Auclair et al., 2009). However, the low cataleptogenic potential of SSR181507 might also partially result from its partial agonist activity at DA D_2 receptors (Kleven et al., 2005), as reported by Cosi et al. (2006) in in vitro measures performed in Sf9 insect cells expressing hD2L receptors. All these data suggest that SSR181507 should control the positive and negative symptoms of schizophrenia, in the absence of extra-pyramidal signs, with the additional benefit of antidepressant and anxiolytic activities.

Here, we sought to further confirm the putative antidepressant- and anxiolytic-like potential of acute or chronic i.p. treatment with SSR181507, using three additional rat models: 1) a "step-down" passive avoidance task, 2) emission of ultrasonic vocalization (UV) induced by delivery of mild electric shocks to paws of adult rats and 3) a social interaction test. The step-down procedure seems to detect preferentially anxiolytics of the buspirone family, i.e. 5-HT_{1A} receptor agonists (Sanger and Joly, 1989; Sanger et al., 1989). The UV procedure is sensitive to anxiolytics such as diazepam and buspirone, and to antidepressants such as fluoxetine and clomipramine (see (Sanchez, 2003) for review). The social interaction model with non-pharmacologically-induced low basal levels of interaction (produced by high illumination of the arena and no habituation to the experimental environment), originally developed by File and Hyde (1978), is sensitive to anxiolytics such as chlordiazepoxide and buspirone (see review by File and Seth (2003)). The role of 5-HT_{1A} receptors in the effects of SSR181507 in these three models was assessed by co-treatments with either SL88.0338, an antagonist with high affinity (Ki = 2.6 nM) and selectivity (>100 fold) for the 5-HT_{1A} receptor (Cohen et al., 1998), or with the prototypical 5-HT_{1A} receptor antagonist WAY100,635 (Mensonides-Harsema et al., 2000). Reference compounds (antidepressants or anxiolytics: fluoxetine, diazepam; antipsychotics: haloperidol, clozapine, olanzapine and 5-HT_{1A} receptor agonists: 8-OH-DPAT and buspirone) were also tested for comparison purposes.

2. Methods

2.1. Animals

Male Wistar rats (175–220 g) were used in the passive avoidance task. Male Sprague-Dawley rats were used in the ultrasonic vocalization (180–200 g at the start of the experiment) and social interaction (200–220 g) tests. Preliminary strain comparison experiments have shown that Wistar rats are more suitable for the step-down test than Sprague-Dawley rats as they display more stable baseline performance after repetitive shock exposure. Animals were supplied by Iffa-Credo, Les Oncins, France or Janvier, Le Genest Saint Isles, France. They were kept in temperature- and humidity-controlled rooms (22 °C, 50%) with light on from 7am to 7pm, with water and food available ad libitum. All experiments were approved by the in-house Ethics Committee and were performed in accordance with current French legislation on animal experimentation and with the "Guide for the Care and Use of Laboratory Animals" adopted and promulgated by the NIH.

2.2. Effects of treatment with SSR181507, alone or in association with the 5-HT_{1A} receptor antagonist SL88.0338, on the latency time to step-down from a platform in a passive avoidance task

On day 1, each rat was placed for 1 min in a box (30 × 30 × 28 cm high) fitted with a grid floor (3 mm diameter bars spaced 1.8 cm apart, center to center) connected to a scrambled shocks generator (model E13-08, Coulbourn Instruments, Allentown, PA, USA). It was then gently picked up and placed on a platform (12 × 12 cm) located 5 cm above the floor in one of the corners of the cage. When the animal stepped down from the platform, it received an electric shock (bipolar square pulses, 20 ms, 50 Hz, 0.4 mA, 1 s duration), and was put back into its home cage for 1 min. It was then replaced on the platform for a further cycle. Rats were subjected to a maximum of 5 cycles until they remained at least 120 s on the platform. Rats that did not stay for a minimum of 120 s on the platform during at least one cycle were not retained for the second day of the experiment (about 1 to 2 out of 8 rats in each group).

On day 2, rats were injected **i.p.** with vehicle, SSR181507 or a reference compound, 30 min before being placed on the platform: the latency time to step-down was recorded with a cut-off of 300 s. Rats were injected once only.

The role of 5-HT_{1A} receptors in the effects of SSR181507 was assessed in a separate experiment by co-treating rats 30 min pre-session with vehicle or SL88.0338, immediately followed by vehicle or SSR181507.

Data (latency time to **step-down** from the platform, in s) were analyzed by means of one-way ANOVA's, followed by Dunnett's post-hoc tests for comparison with the vehicle-injected groups. All statistical analyses were performed using the SAS software (SAS Institute Inc., Cary, NC, USA).

2.3. Effects of acute treatment with SSR181507, alone or in association with the 5-HT_{1A} receptor antagonist SL88.0338, on shock-induced ultrasonic vocalization

Rats were placed in a cage (25 × 32 × 25 cm high) fitted with a grid floor (5 mm diameter bars spaced 1.6 cm apart, center to center) connected to a scrambled shocks generator (model ENV-410 A, Med

Associates, East Fairfield, VT, USA). The cage was enclosed in a sound-attenuating cubicle. The Ultravox system (Noldus, Wageningen, The Netherlands) was used to record UV (in the 18–22 kHz range). First, a modified ultrasound detector (Mini-3 bat model) connected to an electret microphone (positioned behind a 8×8 cm area of one of the walls of the cage, area that was drilled with 1 mm diameter holes to facilitate sound diffusion) was used to transform ultrasonic sound into audible sound. The signal was then filtered (user-defined frequency range and amplitude threshold) and sent to a PC, where the UltraVox software recorded each bout of UV and calculated the total duration of UV emission. Each session lasted 7.5 min, during which 14 scrambled foot-shocks (sinusoidal, 0.6 mA, 3 s duration, 30 s apart) were delivered by the shocker.

Rats were first subjected to 2–3 screening sessions, and only those emitting UV for more than 100 s during these sessions were retained for further testing (about 1 to 2 rats out of 5 were excluded in each group). They were then split into three or four groups with comparable average amounts of time spent vocalizing (to homogenize the groups for acute challenges with drugs). During the test session, rats were injected **i.p.** with vehicle or SSR181507 or reference compounds, 30 min before being placed into the chamber for UV recording. Rats were challenged with 2 or 3 treatments, with a screening session (used to re-homogenize groups) in between two consecutive test sessions.

Implication of 5-HT_{1A} receptors in the effects of SSR181507 was assessed in a separate experiment by co-treating rats 45 min pre-session with vehicle or SL88.0338, followed 15 min later by vehicle or SSR181507.

Data (time spent emitting UV, in s) were analyzed by means of one-way ANOVA's, followed by Dunnett's post-hoc tests to compare drug-injected groups to their respective vehicle-injected groups.

2.4. Effects of chronic treatment with SSR181507 on shock-induced ultrasonic vocalization

Note: This test was retained for chronic administration for two reasons: 1) it has been reported that UV responding is stable for extended periods of time, allowing rats to be repeatedly tested (Schreiber et al., 1998), and 2) chronic administration for weeks requires adult animals, thus precluding the use of vocalization in guinea pig pups as a suitable test (Depoortere et al., 2003).

Rats were first screened as described above, and were split into three groups with comparable average basal levels of time spent vocalizing. The experiment was then started: on day 0 (pre-chronic), rats were acutely treated ip, 30 min before a test session, with vehicle (first group) or 1 mg/kg of SSR181507 (second and third groups). During the following 21 days, rats were injected daily with vehicle (first and second groups) or 1 mg/kg of SSR181507 (third group) and were returned to their home cage. On days 7, 14 and 21 of the chronic treatment, they were tested in the UV cages 30 min after injection of vehicle (first group) or 1 mg/kg of SSR181507 (second and third groups). Test sessions during the chronic regimen were in all respects similar to sessions used during screening or assessment of acute treatment effects.

Data (time spent emitting UV, in s) were analyzed by means of a two-way ANOVA for repeated measures, with the test session (pre-chronic test, tests during the chronic regimen on days 7, 14 and 21) as the within factor, and the treatment (chronic SSR181507 or chronic vehicle) as the between factor.

2.5. Effects of treatment with SSR181507, alone or in association with the 5-HT_{1A} receptor antagonist WAY100,635, on social interaction

The social interaction arena consisted of a grey Plexiglas box (75×75×42 cm high) with four white lights located above and on the side of the arena (delivering 235 lux at the level of the floor of the arena). A camera fixed above the arena was connected to a computer that controlled the Ethovision® Pro 2.3 software (Noldus, Wageningen, The Netherlands), and was used to track each animal of the dyad. To that end, the system recorded the xy coordinates of the isobaric center of each rat. The system considered that a social interaction episode was taking place between the two rats whenever the distance between the two isobaric centers was less than 14 cm (user-defined distance, corresponding to the length between the head and the basis of the tail for rats weighing 180–200 g). We had previously checked that automated recording by the Ethovision® system corroborated the manual scoring method (computer keyboard chronometer) used in our preceding study (Boulay et al., 2004).

Pairs of unfamiliar rats (from two different home cages) were first treated i.p. (same treatment for both rats: vehicle or one dose of the challenge compound) and individually isolated for 30 min. The pair was then placed into the arena during 10 min for recording. Rats were used only once.

Implication of 5-HT_{1A} receptors in the effects of SSR181507 was assessed in a separate experiment by co-treating rats 30 min pre-session with vehicle or WAY100,635, immediately followed by vehicle or SSR181507.

Data (time spent in social interaction measured for each dyad of rats, in s) were analyzed by one-way ANOVA's, followed by post-hoc Dunnett's tests for comparison with the vehicle-injected groups.

2.6. Drugs

SSR181507 ((3-exo)-8-benzoyl-*N*-[[(2 *S*)7-chloro-2,3-dihydro-1,4-benzodioxin-1-yl]methyl]-8-azabicyclo[3.2.1]octane-3-methanamine, monohydrochloride), SL88.0338 (fumarate salt of (4-((3,4-dihydro-5,8-dimethoxy-2(1 H)-iso-quinolinyl)methyl)-1-(3-ethoxybenzoyl)-piperidine), 8-OH-DPAT, WAY100,635 and fluoxetine) were synthetized by the Medicinal Chemistry Department of Sanofi-Synthelabo Recherche. Haloperidol and clozapine were purchased from Sigma Aldrich (St Quentin Fallavier, France). Olanzapine, diazepam and buspirone were obtained from Eli Lilly (Indianapolis, USA), Roche (Basel, Switzerland) and Bristol Myers Squibb (New York, USA), respectively. Due to a limited supply at time of testing, WAY100,635 was only used in the social interaction test. All drugs were dissolved/suspended in saline with a few drops of Tween 80, with the exception of haloperidol (water + a few drops of 10% w/w of ascorbic acid, final pH: 4–5). All drug doses refer to the weight of the base. All drug solutions were prepared fresh daily and injected i.p. (5 ml/kg) except 8-OH-DPAT and buspirone (sc route, 5 ml/kg).

3. Results

3.1. Reduction by SSR181507 of the latency time to step-down from a platform in a passive avoidance task in rats

Compared to control animals injected with vehicle, which spent 274 ± 12 s on the platform, treatment with SSR181507 dose-dependently [$F(3,52) = 13.37$, $p<0.001$] diminished the time rats remained on the platform (Fig. 1). The effect was significant from the dose of 0.3 mg/kg, i.p. (45 and 84% decreases with respect to controls, for 0.3 and 1 mg/kg, respectively).

3.2. Reversal by the 5-HT_{1A} receptor antagonist SL88.0338 of the effects of SSR181507 on the latency time to step-down from a platform in a passive avoidance task in rats

SSR181507 at 1 mg/kg, i.p. reduced the latency time to **step-down** from the platform (Fig. 2) to an extent (76%) equivalent to that found in the preceding experiment (84%) at this dose. Co-treatment of SSR181507 with 3 mg/kg SL88.0338 (which had minimal effects of its own: circa 17% reduction) fully reversed the decrease of latency time seen with SSR181507 alone. This was supported by statistical analysis, with post-hoc Dunnett's tests following a one-way ANOVA [F

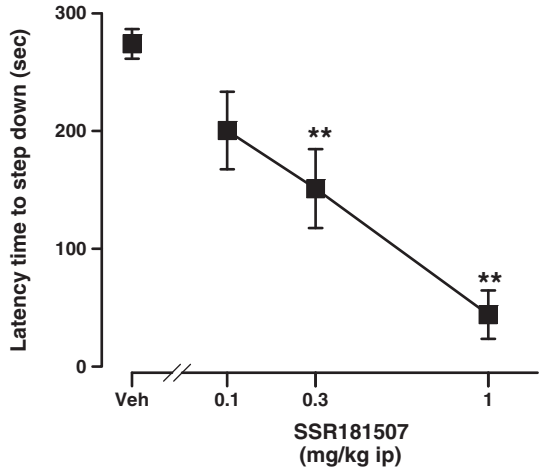

Fig. 1. Decrease by SSR181507 of the latency time to step-down from a platform in a passive avoidance task. Each symbol represents the mean (± SEM). **p<0.01 compared to vehicle (Dunnett's post-hoc test following significant one-way ANOVA). N = 14 rats per group.

(3,24) = 5.32, p<0.01] showing that the group treated with SSR181507 alone was the only group that differed significantly from the group treated with vehicle/vehicle.

Under similar experimental conditions, neither olanzapine nor clozapine, two atypical antipsychotics, significantly affected the latency time to step-down [F(4,51) = 1.09, p>0.05, F(5,50) = 1.59, p>0.05, respectively] (Table 1).

3.3. Reduction by acute treatment with SSR181507 of the time spent in ultrasonic vocalization

There was a dose-dependent relationship [F(3,48) = 9.18, p<0.001] between the amount of time rats spent vocalizing and the dose of SSR181507 administered (Fig. 3). Under control conditions, rats spent on average 233.3 ± 21.3 s emitting UV, and this time was

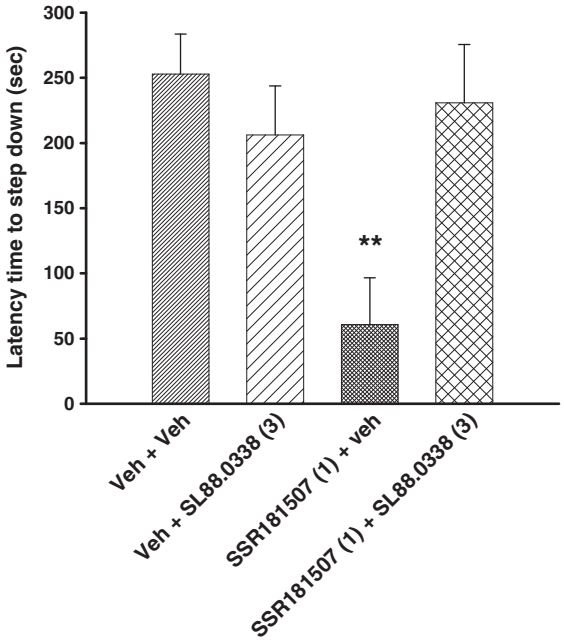

Fig. 2. Reversal by the 5-HT_{1A} receptor antagonist SL88.0338 of the decreasing effects of SSR181507 on the latency time to step-down from a platform in a passive avoidance task. Each bar represents the mean (+ SEM). Doses (numbers in parentheses) are in mg/kg ip. **p<0.01 compared to vehicle (Dunnett's post-hoc test following significant one-way ANOVA). N = 7 rats per group.

Table 1
Effects of reference antipsychotics on the latency time to step-down in the passive avoidance procedure. N: number of rats.

Drug	Doses (mg/kg, ip)	Mean latency time to step-down (s)	SEM	N
Olanzapine	0	268	20	14
	0.1	176	47	7
	0.3	213	31	14
	1.0	202	32	14
	3.0	204	43	7
Clozapine	0	254	26	14
	0.125	168	42	7
	0.25	271	19	7
	0.50	196	31	14
	1.0	277	14	7
	2.0	228	47	7

significantly reduced to 131.0 ± 26.1 and 67.3 ± 21.3 s following administration of 0.3 and 1 mg/kg ip, respectively.

Pretreatment with 1 mg/kg of SL88.0338 failed to reverse the reduction of duration of UV produced by 1 mg/kg of SSR181507: in fact, the duration of UV in the SL88.0338/SSR181507 group (38.0 ± 11.5 s) was notably lower than that of the Veh/SSR181507 group (81.2 ± 30.1). This might be explained by the fact that SL88.0338 on its own reduced (140.7 ± 26.1 s) the duration with respect to controls (Veh/Veh: 244.2 ± 33.8 s). Statistical analysis with post-hoc Dunnett's tests following a one-way ANOVA [F(3,18) = 11.70, p<0.01] confirmed that all 3 treated groups were significantly different from the control group.

The atypical and typical antipsychotics olanzapine and haloperidol significantly [F(3,20) = 7.70, p<0.01 and F(2,18) = 7.29, p<0.001, respectively] decreased the time spent vocalizing (Table 2). Shortage of clozapine at time of testing explains the lack of data concerning this compound. The same effect was observed with the 5-HT_{1A} receptor agonists buspirone and 8-OH-DPAT [F(3,35) = 12.41, p<0.001, and F(3,20) = 7.81, p<0.01, respectively] and the antidepressant fluoxetine [F(3,35) = 7.18, p<0.001]. By contrast, the prototypical benzodiazepine anxiolytic diazepam, although showing a robust trend towards a reduction at the highest dose tested, did not significantly affect ultrasonic vocalization [F(3,24) = 1.51, p>0.05].

3.4. Reduction by SSR181507 of the time spent in ultrasonic vocalization is preserved following chronic administration

A two-way ANOVA showed that there was a significant treatment effect [F(2,18) = 11.81, p<0.001], but a non-significant test session

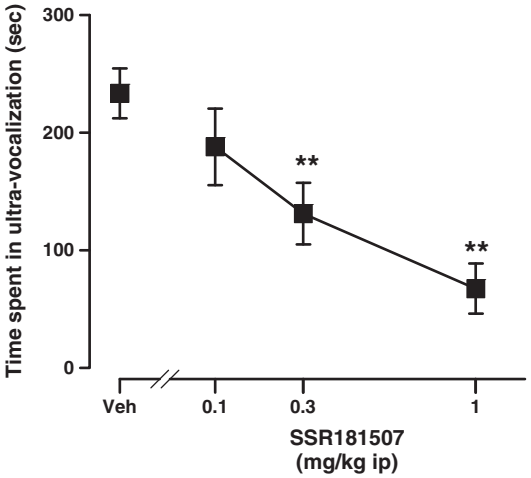

Fig. 3. Reduction by acute treatment with SSR181507 of shock-induced ultrasonic vocalization. Each symbol represents the mean (± SEM). **p<0.01 compared to vehicle (Dunnett's post-hoc test following significant one-way ANOVA). N = 11–17 rats per group.

Table 2
Effects of reference compounds on the time spent emitting ultrasonic vocalization. *p<0.05, **p<0.01, (*)p=0.06, versus vehicle condition, Dunnett's post-hoc test following significant one-way ANOVA. N: number of rats.

Drug	Doses (mg/kg)	Mean time spent vocalizing (s)	SEM	N
Olanzapine (ip)	0	220	30	6
	0.3	21	43	6
	1.0	176	40	6
	3.0	**21	9	6
Haloperidol (ip)	0	232	22	7
	0.1	233	23	7
	0.3	**93	41	7
Buspirone (sc)	0	202	19	13
	0.1	230	28	7
	0.3	*126	22	13
	1.0	**26	10	6
8-OH-DPAT (sc)	0	198	35	6
	0.025	255	38	6
	0.050	106	31	6
	0.10	*66	11	6
Fluoxetine (ip)	0	237	16	12
	3.0	232	30	5
	10.0	(*)185	20	14
	30.0	**109	17	8
Diazepam (ip)	0	241	32	7
	1.0	207	27	7
	2.5	182	46	7
	5.0	129	44	7

[F(3,54)=2.50, p>0.05] and treatment X test session interaction [F(6,54)=0.89, p>0.05] effects. This suggests that there was no difference in the efficacy of an acute challenge with SSR181507 to decrease the amount of time spent to vocalize, whether rats were chronically treated with SSR181507 or vehicle (Fig. 4). In other words, there was no tachyphylaxis (tolerance) to the effects of SSR181507 in this paradigm following a 3-week regimen of chronic administration. Indeed, post-hoc analyses [one-way ANOVA's comparing the control (chronic vehicle/acute vehicle) group to the chronic vehicle and chronic SSR181507 groups at each test session] revealed that both chronic groups were significantly different from the control group at all time points.

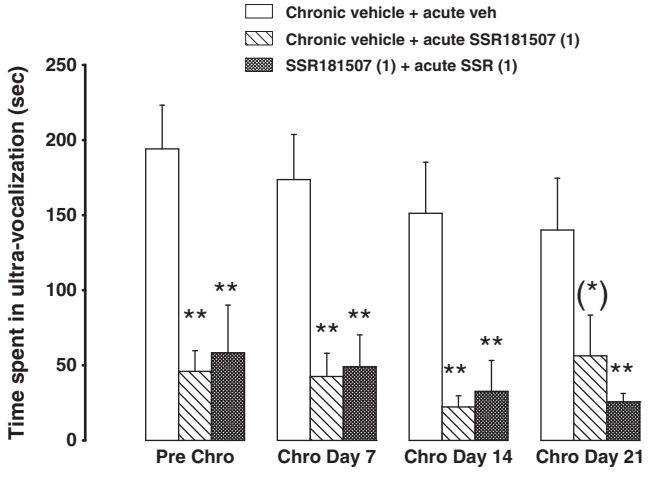

Fig. 4. Maintenance upon chronic administration of the effects of SSR181507 on shock-induced ultrasonic vocalization. Rats were subjected to a session (Pre Chro) 30 min following an acute i.p. challenge with vehicle or SSR181507 (1 mg/kg), before starting the chronic regimen consisting of one i.p. injection per day of vehicle (Chro Veh) or SSR181507 at 1 mg/kg (Chro SSR). Rats were then tested on days 7, 14 and 21 of the chronic regimen (Chro Day x), 30 min after the chronic injection. Each bar represents the mean (+SEM). Doses (numbers in parentheses) are in mg/kg ip. (*) p=0.06, **p<0.01 compared to vehicle, for the considered period (Dunnett's post-hoc tests, following significant one-way ANOVA's for each period). N=7 rats per group.

3.5. Increase by SSR181507 of the time spent in social interaction

Compared to control values (212±10 s), SSR181507 dose-dependently increased the time rats spent in social interaction [F(2,21)=5.08, p<0.05], with the 3 mg/kg, i.p. dose producing a two-third augmentation (Fig. 5).

Pretreatment with 0.3 or 0.6 mg/kg, i.p. of WAY100,635 did not attenuate or reverse the increase of social interaction seen with 3 mg/kg of SSR181507. Indeed, all three treatment combinations increased social interaction (Veh/Veh: 198.4±13.3 s; Veh/SSR181507: 335.1±47.1 s; WAY100,635 (0.3)/SSR181507: 310.4±29.4 s and WAY100,635 (0.6)/Veh: 323.0±44.4 s). Statistical analysis with post-hoc Dunnett's tests following significant one-way ANOVA [F(3,20)=3.03, $p=0.05$] confirmed that all 3 treatment combination groups were significantly different from the control (veh/veh) group.

Diazepam and buspirone were the only reference compounds tested that, like SSR181507, significantly potentiated social interaction [F(2,21)=7.55; p<0.01 and F(2,21)=6.75, p<0.001, for diazepam and buspirone, respectively: Table 3]. None of the other antipsychotics tested was found to increase social interaction: as a matter of fact, clozapine, at the highest dose tested (1 mg/kg), significantly decreased social behavior [F(2,21)=3.24, p<0.05]. The 5-HT_{1A} receptor full agonist 8-OH-DPAT was also inactive in this test [F(3,20)=1.3, p>0.05].

4. Discussion

The present results further strengthen previous findings (Depoortere et al., 2003) that SSR181507 has potential mixed anxiolytic and antidepressant-like activity, as shown here by positive effects in a "step-down" passive avoidance test, a shock-induced UV procedure, and a social interaction test.

The "step-down" passive avoidance test has been shown to be very sensitive to – and quite selective for – full (8-OH-DPAT: (Sanger and Joly, 1989)) and partial (buspirone, gepirone, ipsapirone: (Sanger et al., 1989) 5-HT_{1A} receptor agonists). SSR181507 was active in this test and co-treatment with the 5-HT_{1A} receptor antagonist, SL88.0338, nearly fully reversed its effect, highlighting the pivotal role of the 5-HT_{1A} receptor agonist activity of SSR181507 in this model. Haloperidol (up to 0.2 mg/kg ip) was found inactive when tested under similar experimental conditions (Sanger et al., 1989): since this latter compound has high affinity for DA $D_{2/3}$ receptors, it is unlikely that the activity of SSR181507 in this test is mediated by blockade of these DA receptors, and reinforces the assumption of an implication of 5-HT_{1A} receptors in the beneficial activity of SSR181507. Furthermore, neither clozapine nor olanzapine, two atypical antipsychotics with

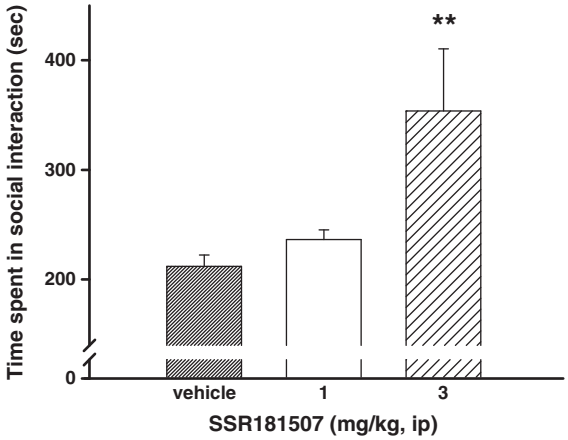

Fig. 5. Increase by SSR181507 of the time spent in social interaction. Each symbol represents the mean (±SEM). **p<0.01 compared to vehicle (Dunnett's post-hoc test following significant one-way ANOVA). N=8 rats per group.

Table 3
Effects of reference compounds on social interaction in rats. *p<0.05, **p<0.01, versus vehicle condition, Dunnett's post-hoc test following significant one-way ANOVA. N: number of dyads of rats.

Drug	Doses (mg/kg)	Mean time spent interacting (s)	SEM	N
Diazepam (ip)	0	208	14	8
	0.5	231	20	8
	1.0	**307	21	8
Buspirone (sc)	0	219	18	8
	0.3	235	13	8
	1.0	**339	38	8
Olanzapine (ip)	0	204	15	8
	0.3	165	8	8
	1.0	180	11	8
Haloperidol (ip)	0	191	13	8
	0.1	212	9	8
	0.2	212	19	8
Clozapine (ip)	0	215	10	8
	0.5	172	10	8
	1.0	*168	20	8
8-OH-DPAT (sc)	0	189	16	6
	0.25	235	58	6
	0.5	164	23	6
	1	147	20	6

moderate in vitro affinity for, and efficacy at 5-HT_{1A} receptors (respectively: 391 and 1000 nM (Claustre et al., 2003) and 33.4 and 0% Emax efficacy versus 5-HT : (Bruins Slot et al., 2006)), against 4.5 nM and 73.3% Emax efficacy versus 5-HT for SSR181507 (Claustre et al., 2003; Bruins Slot et al., 2006) were found to have an effect. This provides a basis for the argument that clozapine and olanzapine, at doses active in behavioral tests, do not appear to have marked in vivo activity at 5-HT_{1A} receptors mediating anxiolytic activity in this type of test.

Benzodiazepine ligands (chlordiazepoxide, diazepam and CL 278,872) and the antidepressant imipramine are without effects on this type of passive avoidance (Sanger et al., 1989), so that, as already discussed by Sanger and collaborators, the nature of the effects ("disinhibitory", "anti-fear", "anxiolytic") revealed by this test is at present still not resolved. It cannot be totally excluded that SSR181507 impaired rats' performance in this task by interfering with memory processes or by attenuating the emotional impact of the shock through an anxiolytic action. Nonetheless, considering that several buspirone-like compounds (i.e. partial 5-HT_{1A} receptor agonists) have shown clinical activity against anxiety (see review by Blier and Ward (2003)), the positive effects of SSR181507 in this test might be considered as indicative of anxiolytic-like activity.

We have previously reported that SSR181507 dose-dependently reduced the time guinea pig pups spent vocalizing (in the audible frequency range) following maternal separation, and that this effect was mediated by 5-HT_{1A} receptors (Depoortere et al., 2003). The present findings extend these observations, as SSR181507 showed activity in a test using shock-induced UV in adult rats. This test is sensitive to the antidepressant fluoxetine, and to a lesser extent (non-significant but circa 50% decrease at the highest dose) to the anxiolytic diazepam. However, in opposition to what was observed in the guinea pig pups test, direct and unambiguous experimental proof for the preferential or exclusive implication of 5-HT_{1A} receptors in the activity of SSR181507 in this UV test is not as straightforward. This is underlain by the lack of efficacy of the 5-HT_{1A} receptor antagonist SL88.0338 to reverse the activity of SSR181507. This was unlikely to be consecutive to the use of too low a dose of SL88.0338, as similar results (data not reported) were obtained with 10 mg/kg, i.p. of SL88.0338 (which by itself had even more marked effect than at 1 mg/kg). However, one should emphasize that the difficulty to reverse the effects of SSR181507 could possibly result from the fact that SL88.0338 had a certain effect on its own. It might seem contradictory that both partial agonists and antagonists can have similar effects in a test, but it has already been observed with the 5-HT_{1A} system. This has been putatively explained by the fact that by binding to presynaptic receptors (i.e. by activating inhibitory somatodendritic autoreceptors that lower 5-HT neuronal firing, 5-HT outflow and consequently reduce 5-HT binding to post-synaptic 5-HT_{1A} receptors), partial agonists can mimic the effects of antagonists, and vice versa (Griebel, 1999). In addition, activity at 5-HT_{1A} receptors alone is sufficient to reveal an effect in this test, as buspirone and 8-OH-DPAT, selective 5-HT_{1A} receptor agonists, were found positive. It would thus become reasonable to assume that the 5-HT_{1A} receptor agonist property most likely participates to the activity of SSR181507 in this test.

Another possibility is that SSR181507 is active through blockade of DA $D_{2/3}$ receptors. Such an assumption is partially supported by the finding that haloperidol and olanzapine (two antipsychotics with substantial antagonist activity at DA $D_{2/3}$ receptors and low (olanzapine) or no (haloperidol) affinity for 5-HT_{1A} receptors) were also active. However, activity of these two compounds might result from non-specific (sedative or motoric) effects, considering that the active doses were rather high (3 and 0.3 mg/kg, i.p. for olanzapine and haloperidol, respectively). In such a case, the hypothesis for a putative involvement of DA D_2/D_3 receptors in their effects is somehow weakened. Alternatively, activity of both compounds might reflect some sort of a mixed anxiolytic- or antidepressant-like activity: this might not be so incongruous for olanzapine, considering that it is now being used to treat resistant depression (Masan, 2004). However, activity of haloperidol is rather unexpected, since this compound is not renowned for having "classical" antidepressant- or anxiolytic-like activity, either in the clinic or in animal models. Effects of haloperidol in UV in adult rats vary greatly depending on the authors: doses up to 1 mg/kg sc (Bartoszyk, 1998) or 10 mg/kg po (De Vry et al., 1993) were ineffective. For others, doses as low as 0.26 mg/kg sc (Millan et al., 1999) or higher: 1.5 mg/kg, i.p. (Sanchez et al., 1995) or 3 mg/kg, i.p. (Molewijk et al., 1995) significantly reduced UV. However, in the clinic, there are some indications that haloperidol can be useful in the management of anxiety states (Stevenson et al., 1976; Budden, 1979). Furthermore, one should note that haloperidol, and especially its congener droperidol, have been used, alone or in combination with a benzodiazepine, for their "tranquilizing" effects. They are part of the therapeutic armamentarium present in psychiatry and emergency wards to control extreme agitation and anxiety, or available to anaesthetists for their sedative/anti-anxiety properties as pre-operative medication (Pilowsky et al., 1992); (Richards et al., 1998; McAllister-Williams and Ferrier, 2002). To sum up, we are confronted with a lack of unambiguous proof for the preferential or exclusive implication of the 5-HT_{1A} receptor agonist property of SSR181507 for activity in this UV test. Hence, the exact extent of the respective implications of the 5-HT_{1A} receptor agonist and of the DA $D_{2/3}$ receptors antagonist components of SSR181507 in this test remains a matter for debate.

However, SSR181507 has been described to be inactive against marble burying behavior in mice (Bruins Slot et al., 2008), a putative preclinical test for anxiety disorders as sensitive as the UV model to selective serotonin reuptake inhibitors, benzodiazepines, typical and atypical antipsychotics and 5-HT_{1A} receptor agonist, (+)-8-OH-DPAT (Bruins Slot et al., 2008). This difference of sensitivity for SSR181507 in these two distinct experimental models of anxiety suggests that partial agonist activity at DA D_2 receptor play a particular role in the UV model.

Although there is no robust indication in the preclinical or clinical literature that tolerance develops to the effects of 5-HT_{1A} receptors agonist in the domain of anxiety or depression, tolerance to some agonists-induced effects (i.e. 8-OH-DPAT-induced hypothermia, flat body posture and forepaw treading) has been reported (Murthy and Pranzatelli, 1992). This was in our opinion sufficient to justify assessing if the effects of SSR181507 were retained following chronic (three weeks) administration. The results clearly show that over such a period,

the efficacy of SSR181507 to decrease UV in rats remained unaltered (the reader is referred to the Methods section for justification of the use of this test for chronic administration). In other words, there appears to be no tachyphylaxis (tolerance) to the activity of the compound in this test, under the present experimental conditions.

SSR181507 was found to increase the amount of time spent in social interaction in a variant of the test that produce non-pharmacologically-induced low basal levels of interaction (high illumination, no habituation), and classically used for the screening of anxiolytics. Similar effects were obtained with the prototypical anxiolytic diazepam and the 5-HT_{1A} receptor partial agonist buspirone. Furthermore, neither atypical (olanzapine, clozapine) nor classical (haloperidol) antipsychotics were found to have an effect in this model. These findings further support the assumption that these compounds have negligible or no in vivo activity at 5-HT_{1A} receptors implicated in this type of social behavior. However, the 5-HT_{1A} receptor full agonist 8-OH-DPAT was ineffective in potentiating this type of social interaction. Reasons for this difference between full and partial 5-HT_{1A} receptor agonists are obscure at present, but not so surprising given that similar discrepancies have been described in social interaction as well as in other anxiety paradigms (Griebel, 1995). It is noteworthy that the minimal effective dose (MED) in the passive avoidance and ultrasonic vocalization tests (i.e. 0.3 mg/kg, i.p.) is 10 times lower than the MED in the social interaction procedure. This difference is unclear, but the observation that 5-HT_{1A} receptor agonists such as 8-OH-DPAT and buspirone display similar differences in MED in the ultrasonic vocalization and social interaction tests (see Tables 2 and 3) tends to suggest that the social interaction procedure is globally less sensitive to 5-HT_{1A} receptor stimulation than the ultrasonic vocalization test. For one thing, these social interaction data provide a supplementary experimental argument that SSR181507 is a 5-HT_{1A} receptor partial agonist in vivo (see Claustre et al., 2003 and Depoortere et al., 2003). To the extent that this social interaction test is classically considered to detect anxiolytic-like activity, these data also strengthen the assumption on the potential of SSR181507 to alleviate co-morbid anxiety associated with schizophrenia. It is important to emphasize that the co-morbid anxiety symptoms displayed by schizophrenic patients probably differ from those of non-schizophrenic patients suffering from anxiety disorders. Therefore, to assess in a more satisfactory manner the anxiolytic-like potential of SSR181507 in preclinical studies, models combining aspects of schizophrenic- and anxiety-like behaviors should be used.

The present results also provide additional arguments for the potential beneficial effects of SSR181507 on social functioning, also known to be perturbed in schizophrenic patients (Grant et al., 2001). They also strengthen previous observations on the advantageous activity of SSR181507 on social behavior. Hence, we (Boulay et al., 2004) and others (Bruins Slot et al., 2005) have previously observed that SSR181507, contrary to diazepam and other anxiolytics, reversed a low level of social interaction in dyads of rats pretreated with phencyclidine (PCP), under conditions that facilitated social interaction (low illumination and habituation to the apparatus). Similar beneficial effects of F15063, a DA D_2 receptor antagonist and 5-HT_{1A} receptor agonist, were observed against this type of social interaction impairment in rats (Depoortere et al., 2007). This beneficial effect of F15063 was nearly fully blocked in the presence of the 5-HT_{1A} receptor antagonist WAY100,635. It thus looks as if antipsychotics combining antagonist/partial agonist activity at DA D_2 receptors and agonist activity at 5-HT_{1A} receptors share the ability to ameliorate social interaction deficits produced by PCP, and possibly by other means, as shown presently with SSR181507.

5. Conclusion

To summarize, the present data consolidate previous ones suggesting that SSR181507 has anxiolytic- and antidepressant-like activities, at doses overlapping with those at which we observed activity in tests predictive of antipsychotic-like activity (Depoortere et al., 2003). Additionally, these effects appear to be preserved following long-term administration (based on the three week chronic study in the UV test). Anxiety and depressive states are two co-morbid elements that are fairly commonly observed in schizophrenic patients, and against which current antipsychotics are considered to be marginally active, necessitating the use of antidepressants or anxiolytics for augmentation therapy (Barnes et al., 1989; Buchanan et al., 2002; Clark et al., 2002). Furthermore, depression is more and more considered as a key element not only of the prodromal, but also of the interictal phase of the pathology (Green et al., 1990; Siris and Bench, 2003), so that aggressive management of this co-morbid condition might minimize the phenomenon of relapse, by delaying the onset and/or attenuating the severity of acute psychotic episodes. An antidepressant activity would also hopefully reduce the rate of suicide in schizophrenic patients, a population that is very much exposed to this tragic risk (Caldwell and Gottesman, 1990). It is anticipated that SSR181507, owing to its combined atypical antipsychotic, antidepressant and anxiolytic profile, and to its potential activity against a major item of schizophrenia, poor social functioning (present study and (Boulay et al., 2004)), will have a wider therapeutic spectrum than that of antipsychotics currently in use.

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