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The corticotropin-releasing factor 1 receptor antagonist, SSR125543, and the vasopressin 1b receptor antagonist, SSR149415, prevent stress-induced cognitive impairment in mice

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ABSTRACT

The vasopressin 1b receptor antagonist, SSR149415, and the corticotropin-releasing factor 1 receptor antagonist, SSR125543, are orally active non-peptidic compounds with anxiolytic- and antidepressant-like activities in animals. In the present study, their effects on stress-induced deficit in cognitive performances as assessed in a modified object recognition test were investigated in mice. The object recognition task measures the ability of a mouse to remember an object it has previously explored in a learning trial. During this acquisition session, the mouse was stressed by the presence of a pair of rats under the grid floor of the apparatus. One hour later, it was placed again in the environment with the known and a novel object, but in the absence of the rats. While non-exposed mice spent more time exploring the new object, mice that had been exposed to the rats during acquisition failed to discriminate between the known and the new object during retrieval. This cognitive impairment in stressed mice was prevented by the administration of SSR149415 (10 mg/kg, ip), SSR125543 (10 mg/kg, ip) and the selective serotonin reuptake inhibitor, fluoxetine (10 mg/kg, ip). Under similar conditions, the cognitive enhancer donepezil (1 mg/kg, ip) failed to reverse object recognition deficit. These results indicate that the effects of SSR149415 and SSR125543 in the modified object recognition test, in stressed mice, involve the ability of mice to cope with stress rather than an effect on cognition *per se*. Together, these data suggest that SSR149415 and SSR125543 may be of interest to reduce the cognitive deficits following exposure to stress-related events, such as acute stress disorder.

1. Introduction

Stress is a potent double-edged modulator of learning and memory processes (McEwen and Sapolsky, 1995; Sandi and Pinelo-Nava, 2007). Stress has been shown to facilitate (Andreano and Cahill, 2006; Lupien et al., 2007; Oitzl and de Kloet, 1992; Roozendaal et al., 2006) or to impair (Diamond et al., 1996; Eysenck et al., 2007; Lupien et al., 2007; Nadel and Payne, 2002) cognitive performances in animals and humans. The beneficial or deleterious effect of stress on learning depends among other aspects, on the intensity, the repetition and the controllability of stress and the memory phase (Sandi and Pinelo-Nava, 2007).

Stress is largely dependent on the activity of the hypothalamic–pituitary–adrenocortical (HPA) axis, which is activated by exposure to emotional and/or physical stressors (Strohle and Holsboer, 2003). The release of corticotropin-releasing factor (CRF) from neurons of the paraventricular hypothalamic nucleus (PVN) into the pituitary portal blood triggers the secretion of adrenocorticotropin (ACTH) from the anterior lobe. Subsequently, corticosterone is secreted from the adrenal cortex into blood and exerts a negative feedback on the HPA axis activity via pituitary, hypothalamic, limbic, and cortical regions (de Kloet, 2000; Sapolsky and McEwen, 1985). Two CRF receptor subtypes, CRF1 and CRF2, with distinct anatomical localization and pharmacology have been identified. In addition to a major projection from the paraventricular nucleus of the hypothalamus to the pituitary corticotropes, CRF-containing neurons and receptors are also found in brain areas involved in stress responses, including the amygdala, lateral septum, locus coeruleus and brainstem raphe. Similar to CRF, the nonapeptide vasopressin (AVP) is also released during the stress response. It acts as a direct ACTH secretagogue and also potentiates the stimulatory effect of CRF in animals and humans (Aguilera and Rabadan-Diehl, 2000). AVP exerts its effects via a dense localization of vasopressin receptors (V1a and V1b receptors) expressed mainly in limbic areas and in the hypothalamus.

Abnormal HPA activity has been implicated in a variety of conditions related to stress, including HPA overactivation in depression and some anxiety disorders. Infusion of CRF, CRF fragments or AVP into the rodent brain, or constitutive transgenic overexpression of CRF in mice, recapitulates some of the behavioural and neuroendocrine consequences of exposure to stress, such as increased anxiety-like behaviour

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and HPA dysfunction. In this context, it was postulated that CRF and AVP receptor antagonists may represent novel agents for the treatment of stress-related disorders. For example, the CRF1 receptor antagonist, SSR125543, has been reported to induce anxiolytic- and antidepressant-like effect in several animal models in rodents (Alonso et al., 2003; Griebel et al., 2002b; Gully et al., 2002; Louis et al., 2006). Likewise, the selective V1b receptor antagonist, SSR149415, was shown to block stress-induced elevation of plasma ACTH, and had anxiolytic and antidepressant-like effect in various animal models (Alonso et al., 2003; Claustre et al., 2006; Griebel et al., 2002a; Iijima and Chaki, 2007; Louis et al., 2006; Overstreet and Griebel, 2004; Overstreet and Griebel, 2005; Serradeil-Le Gal et al., 2002).

The aim of the present study was to evaluate the effects of SSR149415 and SSR125543 in a new animal model of acute stress disorder (ASD), which involves the assessment of cognitive performance following stress exposure. This idea is based on the observation that, among the symptoms of ASD, dissociative amnesia, i.e. the inability to recall an important aspect of the trauma, is predominant (DSM-IV-TR, 2000). In the present study, the deficit in recall performance was evaluated using a modified object recognition task (ORT) in mice, which is traditionally used to assess short-term visual episodic memory (Dodart et al., 1997; Ennaceur and Delacour, 1988) and serves as a screening model for compounds with potential promnestic activity. The ORT is based on the natural tendency of rodents to explore a novel object more than a known one and it has the advantage of not involving goal-oriented behaviours (e.g., reward, escape). In a first set of experiments we compared the potential deleterious effects of an exposure to different stimuli (i.e. mice or rats) during the acquisition phase on recall performance. Finally, to validate this procedure pharmacologically as a model of ASD, the effects of the selective 5-HT reuptake inhibitor (SSRI), fluoxetine, and the promnestic agent, donepezil, were evaluated.

2. Material & methods

2.1. Animals

Swiss male mice (Janvier, Le Genest St Isle, France) weighing 30 ± 2 g at the time of testing were used. For the predator stress procedure, male Sprague–Dawley rats (Charles River Laboratory, L'arbresle, France) weighing 300–350 g were used. Animals were fed ad libitum and kept in a controlled environment (12/12 h dark/light cycle, 21 °C, 50% humidity). The experiments made here fully comply with the European treaty on research involving living animals (n° 86/609/EEC) and the protocol was reviewed by Sanofi-Aventis ethical committee before the experiments started.

2.2. Object recognition test

The object recognition test took place in a square open field (side: 52 cm) made of PVC as described before (Pichat et al., 2007); in this experiment, the PVC floor was pierced with small holes in order to let the smell go through. Light intensity was 50 lux and the walls were grey. The objects to be discriminated were a metal triangle and a plastic piece of construction game. The test consisted in 3 sessions. Mice were firstly habituated to the context for 3 min (session 1), 24 h prior to the acquisition. For the acquisition (session 2), mice were placed in the arena, in the presence of 2 identical objects, located 5 cm from the two opposite corners of the back wall. Animals were allowed to investigate the objects until they reached 15 s of exploration (cut-off: 5 min: mice not reaching 10 s after 5 min were removed from the experiment). Exploration of an object was defined as pointing the nose to the object at a distance of less than 2 cm and/or touching it with the nose. The exploration time included only the time when the mouse was really investigating the object and no casually touching it or even "looking" at it. After a forgetting delay, mice were placed again in the enclosure containing one of the previous objects and a new one placed in a counterbalanced manner for 4 min (session 3). With a short (1 h) forgetting delay, mice usually remember the known object and spend more time exploring the new one. This behaviour reflects a significant recall of the previously presented object. With a longer (48 h) forgetting delay, mice usually do not remember the known object and spend the same amount of time exploring both objects. Exposure to predators was done during the acquisition (session 2) only (Fig. 1). The exposure paradigm was inspired by previous work using live rat/mouse exposure (Yang et al., 2004). A pair of male Sprague–Dawley rats was placed under floor, at a distance of 19 cm from it. At this distance, rats were able to touch the floor, but not to lift it up. For the control experiment, the effect of the presence of mice during the session 2 was evaluated using cage-mates of the mouse performing the test. Scoring was done manually online by an experimenter unaware of the treatment conditions.

2.3. Drug administration

Fluoxetine (Spectrum Chemical Mgf Corp, Gardena, CA) was dissolved in saline; SSR149415, SSR125543 and donepezil synthesized by the CNS Medicinal Chemistry Department of Sanofi-Aventis, were suspended in saline with methylcellulose (0.6%) and Tween80 (0.1%). Drugs were administered intraperitoneally (10 ml/kg of body weight), once, 30 min before session 2 (acquisition) in the short forgetting delay procedure and twice in the long forgetting delay procedure: 30 min before session 2 and 30 min before session 3 (retrieval). The acetylcholinesterase inhibitor, donepezil, was used as a negative control because of its cognitive-enhancing properties and since it represents the mainstay of treatment for the cognitive symptoms of diseases such as mild to moderate Alzheimer. The doses (i.e. 10 mg/kg for fluoxetine, SSR125543 and SSR149415, and 1 mg/kg for donepezil) were selected carefully on the basis on preliminary findings using the current procedure or on previously published findings showing that they are optimal to produce behavioural effects.

2.4. Statistical analysis

The data analysed were: the time to reach 15 s of exploration of the 2 identical objects in the acquisition session, the time of exploration of each object during retrieval session, the total time of exploration of the objects (sum of both objects exploration times), the ratio of the time exploration of the new object over the total time.

For exploration time, data were analysed using a two-way ANOVA with repeated measures with "object" as a fixed factor to analyse the ability of animals to discriminate between known and new object. The effect of "object" factor was then analysed by Winer analysis for each level of "group" factor. For ratios and total exploration time, a one-way ANOVA was performed to analyse the differences between groups, followed by a Dunnett's post-hoc analysis.

3. Results

3.1. Effect of an exposure to mice (no stress condition) or rats (stressful stimulus condition) on short-term memory performance in the object recognition test

The aim of this experiment was to verify whether the deleterious effect induced by the presence of two rats was specific to this species or if the presence of any animal disturbed learning. Performance in the object recognition test was evaluated in 3 conditions: mice were exposed either to mice (cage-mates, no-stress) or to a pair of rats (stress) or were left undisturbed (control). No physical contact was possible with the animals (mice or rats) located below the grid and the mouse performing the test.

During the acquisition session (session 2), the time needed to reach 15 s of exploration of the objects was not different between

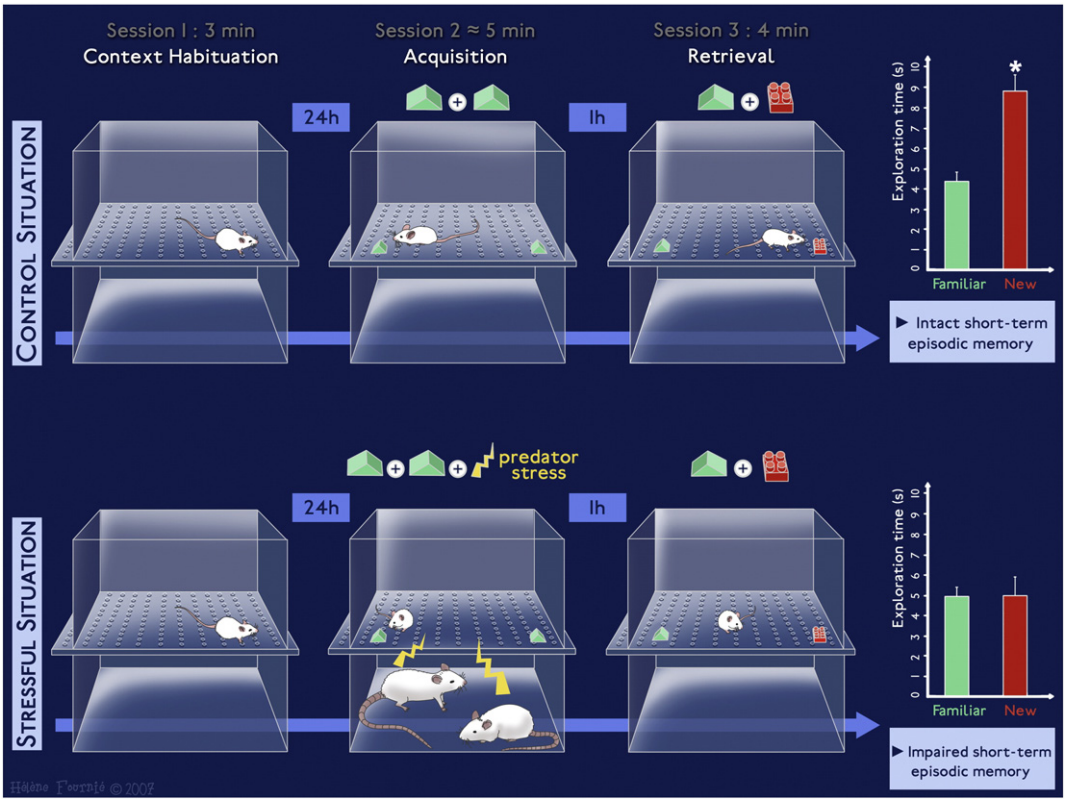

Fig. 1. Procedure of the object recognition task under stressful conditions.

groups ($F_{(2;21)}=1.747$; $p=0.2$; Table 1), showing that the presence of mice or rats beneath the mouse performing the test did not affect its interest for the objects.

During the retrieval session (session 3), control mice spent more time exploring the novel object than the known ($F_{(1;21)}=20.812$; $p<0.001$; Fig. 2A) with a discrimination ratio of 68.3% (Fig. 2B). Mice previously exposed to cage-mates during the session 2 also spent more time exploring the novel object than the known ($F_{(1;21)}=8.036$; $p<0.01$; Fig. 2A) with a ratio of 66.4% (Fig. 2B). Mice previously exposed to the pair of rats failed to discriminate between both objects: they spent the same amount of time exploration of the two objects ($F_{(1;21)}=0.00309$; $p=0.95$; Fig. 2A) with a ratio of 50,1%, close to the chance level (Fig. 2B). The rat-exposed group was thus significantly different from the other groups ($F_{(2;21)}=6.662$; $p<0.05$; Fig. 2B). Total time of exploration of both objects during retrieval was affected by the previous presence of animals beneath the grid. This decrease in total time of exploration was almost significant ($F_{(2;21)}=4.017$; $p=0.0688$; Fig. 2C) in the group exposed to cage mates, while it was significant ($F_{(2;21)}=4.017$; $p<0.05$; Fig. 2C) in the group exposed to the rats.

3.2. Reversal of the stress effect by drugs

As with the previous experiment, the presence of rats during the acquisition session did not affect the time to reach 15 s of exploration of both objects (Table 2). However, the treatment with fluoxetine had a significant effect in non-stressed mice: they needed more time (275.5 s ± 11.9 vs 219.7 s ± 16.4; $p<0.05$, Table 2) to reach 15 s of exploration. There was no effect of fluoxetine in stressed mice.

While non-stressed animals discriminated well ($F_{(1;44)}=69.35$; $p<0.001$; Fig. 3), animals exposed to rats during session 2 spent an equal amount of time exploration of both the new and the known object during session 3 ($F_{(1;44)}=0.057$; $p=0.81$; Fig. 3). Fluoxetine, did not affect discrimination in non-stressed animals ($F_{(1;44)}=42.92$; $p<0.001$; Fig. 3) and it reversed the effect of rat exposure : fluoxetine-treated rat-exposed mice spent more time exploration of the new object ($F_{(1;44)}=18.01$; $p<0.001$; Fig. 3). The total time of exploration during session 3 was unaffected by either stress or treatment ($F_{(3;44)}=1.52$; $p=0.22$; not shown).

Expressed as a ratio, the relative time of exploration of the novel object was significantly higher in fluoxetine-treated stressed animals compared to vehicle-treated stressed animals ($F_{(3;44)}=10.72$; $p<0.01$).

SSR149415 (10 mg/kg, ip) reversed stress-induced deficit of object recognition (Fig. 4). Vehicle-treated stressed animals failed to discriminate ($F_{(1;43)}=0.008$; $p=0.93$; Fig. 4), while stressed mice treated with SSR149415 were able to discriminate the novel from the known object ($F_{(1;43)}=19.38$; $p<0.001$; Fig. 4). When expressed as a ratio, the SSR149415-treated stressed group significantly differed from the vehicle-treated group ($F_{(3,43)}=8.01$, $p<0.001$). SSR149415 was devoid of effect on non-stressed animals (Fig. 4). Total time of exploration of both objects during session 3 was significantly affected by stress in this experiment ($F_{(3;43)}=4.83$; $p<0.01$; not show) without effect of the treatment on this variable. Time to reach 15 s of exploration during session 2 remained unaffected by stress or treatment ($F_{(3;43)}=2.06$; $p=0.12$; Table 2).

Administration of SSR125543 (10 mg/kg, ip) also reversed stress-induced deficit of object recognition (Fig. 5). Vehicle-treated stressed animals failed to discriminate ($F_{(1;41)}=0.36$; $p=0.55$; Fig. 5), while SSR125543-treated stressed mice spent more time exploration of the novel object ($F_{(1;41)}=19.8$; $p<0.001$; Fig. 5). The compound was devoid of effect in non-stressed animals (Fig. 5). In terms of ratio, the vehicle-

Table 1
Time to reach 15 s of exploration during acquisition session.

Acquisition session	Control	Exposure to cage-mates	Exposure to rats
Time to reach 15 s of exploration	212 ± 21.0	259 ± 11.5	254 ± 22.8

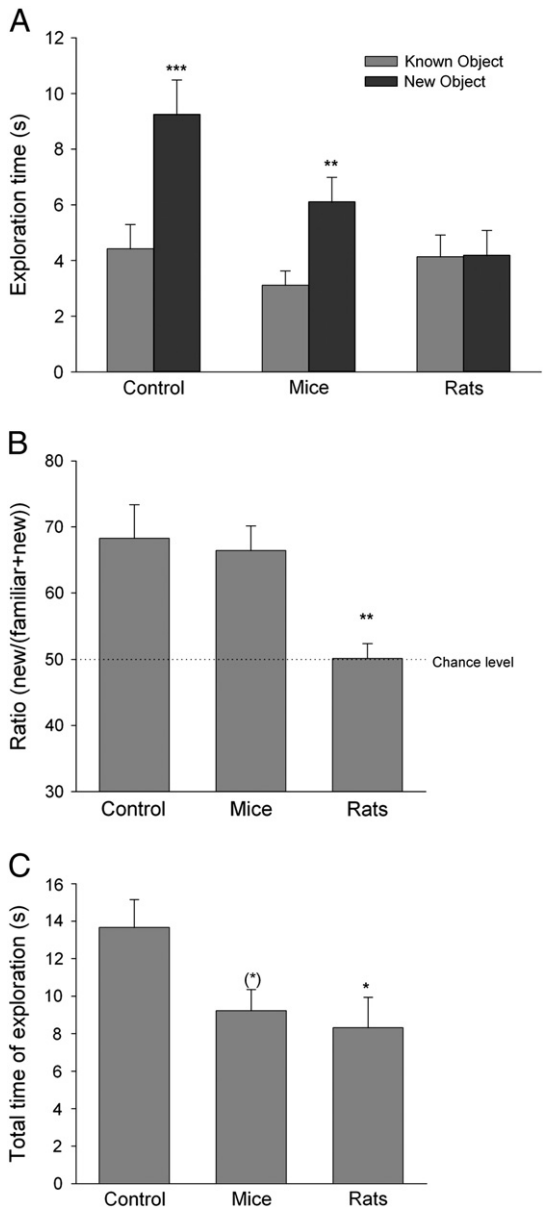

Fig. 2. Effect of an exposure to mice (no stress) or rats (stress) on short-term memory performance in the object recognition test. Animals performing the test were exposed during acquisition session (session 2). A: bars represent means of the time of exploration + s.e.m. of each object during the retrieval session (session 3). n = 12 mice per group. *** $p<0.001$ and * $p<0.05$ vs known object. B: bars represent mean + s.e.m. of the ratio of the time of exploration of the new object over the total time of exploration (known + new). ** $p<0.01$ vs control group. C: bars represent the total exploration time (new + known). (*) $p<0.07$ and * $p<0.05$ vs control group.

treated stressed group differed significantly from the control group ($F_{(3;41)}=4.25$; $p<0.01$) and the SSR125543-treated stressed group had a higher discrimination ratio than the vehicle group ($F_{(3;41)}=4.25$; $p<0.05$). In this experiment, neither stress nor treatment affected the total time of exploration ($F_{(3;41)}=0.675$; $p=0.57$; not shown). Time to reach 15 s of exploration during session 2 was also independent from stress or treatment ($F_{(3;44)}=0.22$; $p=0.88$; Table 2).

The cognitive enhancer donepezil (1 mg/kg, ip) failed to reverse the stress-induced deficit (Fig. 6). As in the other experiments, mice exposed to rats during session 2 did not discriminate between the novel and the known object ($F_{(1;41)}=0.26$; $p=0.61$; Fig. 6). Donepezil in non-stressed animals did not affect discrimination ($F_{(1;41)}=34.81$; $p<0.001$; Fig. 6). However, donepezil-treated stressed animals spent a similar amount of time exploring both objects ($F_{(1;41)}=0.93$; $p=0.34$; Fig. 6).

Table 2
Time to reach 15 s exploration during the acquisition session. (*) $F_{(3,44)}=4.25$; $p<0.05$ vs non exposed vehicle group.

Acquisition session	No rat exposure (control)		Rat exposure	
	Vehicle	Fluoxetine	Vehicle	Fluoxetine
Time to reach 15 s exploration	219.7 ± 16.4	275.5 s ± 11.9 (*)	255.5 ± 15.6	282.7 ± 9.7
	Vehicle	SSR149415	Vehicle	SSR149415
Time to reach 15 s exploration	263.8 ± 15.4	240 ± 15.3	286 ± 6.1	247 ± 15.8
	Vehicle	SSR125543	Vehicle	SSR125543
Time to reach 15 s exploration	232 ± 15.3	218 ± 16.4	221 ± 21.6	211 ± 21.5
	Vehicle	Donepezil	Vehicle	Donepezil
Time to reach 15 s exploration	242 ± 17.5	251 ± 15.5	252 ± 14.3	277 ± 14.6

The total time of exploration was unaffected by stress or treatment ($F_{(3;41)}=2.01$; $p=0.13$; Fig. 6). The time to reach 15 s exploration of the objects during session 2 was not different between groups ($F_{(3;42)}=1.09$; $p=0.36$; Table 2).

3.3. Control experiment

When the forgetting delay was long enough (48 h) between session 2 and session 3, control mice failed to discriminate between the previously explored object and the new one. In this experiment, the cognitive enhancer donepezil improved performance as shown by a higher discrimination rate between the new object and the one presented 48 hours before ($F_{(1;61)}=39.75$; $p<0.001$; Fig. 7). In this procedure, fluoxetine, SSR149415 and SSR125543 failed to increase discrimination ($F_{(1;61)}=39.75$; $p>0.05$; Fig. 7).

4. Discussion

In the present study, we report the activity of the V1b receptor antagonist, SSR149415, and the CRF1 receptor antagonist, SSR125543, in a new animal model of ASD in mice, which is based on the assessment of cognitive performance following stressful exposure.

The behavioural findings show that when mice are exposed to a pair of adult rats during the acquisition phase in the object recognition test, their cognitive performances were subsequently altered during the recall session. It is important to note that rat exposure did not affect the global behaviour of mice performing the task as they did not

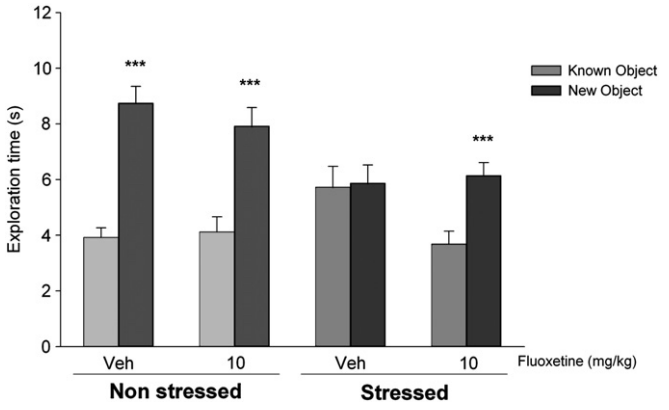

Fig. 3. Effect of fluoxetine in the object recognition test in stressed and non-stressed mice. Bars represent means of the time of exploration + s.e.m. of each object. n = 12 mice per group. *** $p<0.001$ vs known object.

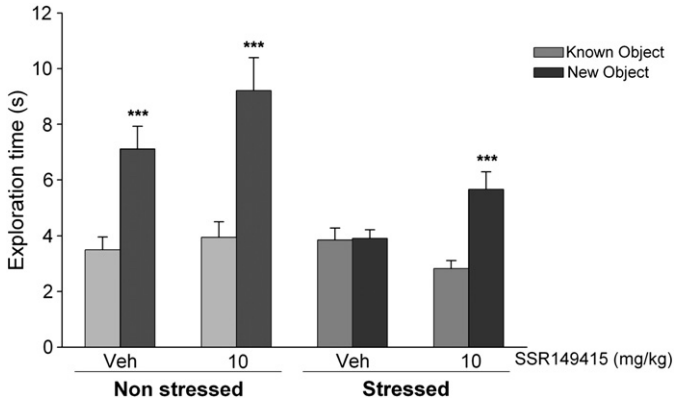

Fig. 4. Effect of SSR149415 in the object recognition test in stressed and non-stressed mice. Bars represent means of the time of exploration + s.e.m. of each object. n = 12 mice per group. *** $p<0.001$ vs known object.

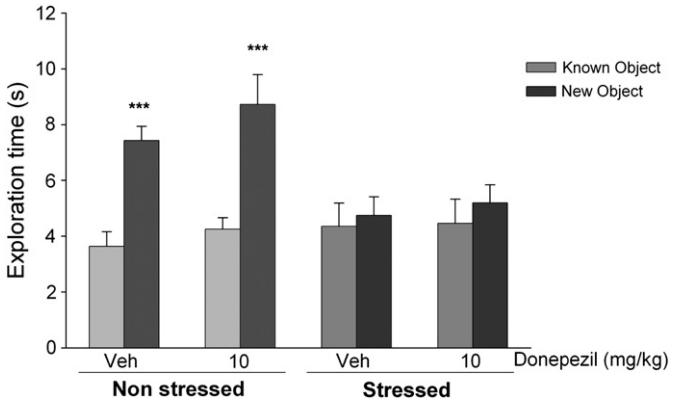

Fig. 6. Effect of donepezil in the object recognition test in stressed and non-stressed mice. Bars represent means of the time of exploration + s.e.m. of each object. n = 12 mice per group. *** $p<0.001$ vs known object.

display any freezing, they explored normally their environment and spent the same time as unexposed mice to reach the acquisition criteria, i.e. 15 seconds of exploration of the two identical objects. In contrast, non-exposed/stressed mice or those exposed to cage-mates were able to recall the previously explored object and, as a consequence, spent more time exploring the new one, indicating normal episodic memory performance (Poucet, 1989). It is not clear based on current findings whether stress exposure affected acquisition, consolidation and/or retrieval as mice were exposed to the rats only during the acquisition phase. It is possible that, during the recall session, the environment was associated with the presence of the rats during the previous session, suggesting a deficit in retrieval as well. Additional experiments, such as exposure to rats during the recall session would be necessary to determine more precisely which phase of the object recognition test was impacted by stress exposure. In any case, we propose that the deficit observed in this situation is indicative of a cognitive impairment elicited by the inability to cope with a stressful stimulus. It is noteworthy also that during the recall session, the total time of exploration of both objects was lower in rat- and cage-mate-exposed mice than in non-exposed animals, indicating that the presence of a live animal during the acquisition session has decreased the interest for both objects during the recall session. Whether this effect is specific to a moving stimulus and/or to rodents remains to be determined.

Other studies have reported cognitive impairment following unavoidable stressful exposure, in particular to predator (El Hage W. et al., 2004). More recently, Cohen et al. (2009) developed the differential contextual odour conditioning (DCOC) paradigm, which revealed that stressed animals are unable to discriminate a cue acquired in a "safe" or a "dangerous" contex when encountered in a novel neutral environment. Along with the current findings these results are consistent with the idea that, when it is uncontrollable, stress produces a deleterious effect on cognition (El Hage W. et al., 2004; Park et al., 2008; Sandi et al., 2005). The stress-induced deficit in episodic memory observed in the modified object recognition test may be reminiscent of some aspects of the cognitive impairment observed in human following exposure to traumatic stressor. For example, patients suffering from ASD experience difficulty concentrating and dissociative amnesia (i.e. they have difficulty recalling specific details of the traumatic event). Ehlers and Clarks (2000) suggested that deficient contextualisation of the traumatic event is determinant for the development of traumatic stress related disorders.

The drug experiments showed that fluoxetine, a selective 5-HT reuptake inhibitor (SSRI), given 30 minutes before the learning session, prevented the effects of rat exposure. SSRIs are widely used in the treatment of ASD or PTSD, including the cognitive symptoms of these conditions (Bremner and Vermetten, 2004; Meltzer-Brody et al., 2000; Stein et al., 2009). The current data are in line with those reported previously showing that fluoxetine prevented episodic memory deficit in the object recognition test 2 days following unavoidable cat exposure (El Hage W. et al., 2004). Both the CRF1 receptor antagonist, SSR125543, and the V1b receptor antagonist, SSR149415, were able to prevent the deleterious effects of rat exposure on episodic memory as assessed in the object recognition

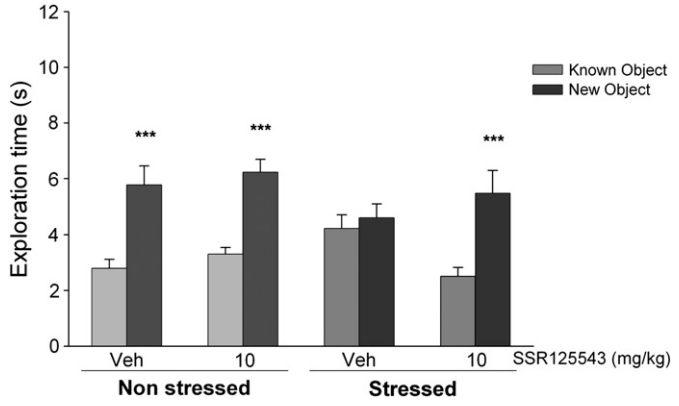

Fig. 5. Effect of SSR125543 in the object recognition test in stressed and non-stressed mice. Bars represent means of the time of exploration + s.e.m. of each object. n = 12 mice per group. *** $p<0.001$ vs known object.

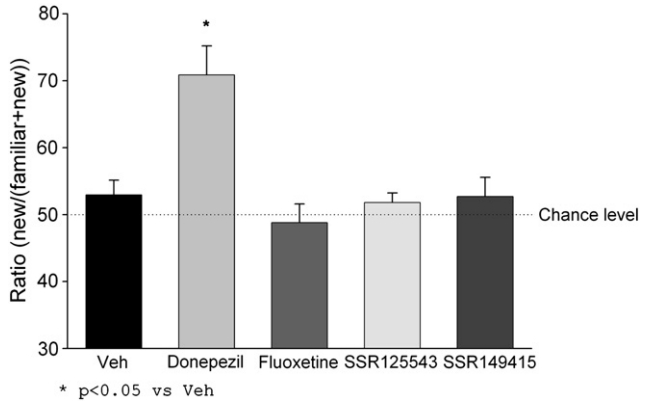

Fig. 7. Effect of donepezil, fluoxetine, SSR125543 and SSR149415 in the object recognition task (long forgetting delay version). Bars represent mean + s.e.m. of the ratio of the time of exploration of the new object over the total time of exploration (known + new). * $p<0.05$ vs control group.

test. Importantly, SSR149415, SSR125543 and fluoxetine did not improve the cognitive performance of mice when using a long-term forgetting delay procedure, in which a cognitive enhancer such as donepezil was able to improve episodic memory. The present data with SSR149415 confirm that the drug is devoid of deleterious effect on cognition as shown previously in another test, i.e. the Morris water maze in rats (Griebel et al., 2002a). It should be emphasised that the cognitive enhancer donepezil did not improve performance in stressed mice. However, since only the 1 mg/kg dose of donepezil was tested, it cannot be totally ruled out that the use of lower or higher doses may have produced effects. The present findings that SSR125543 and SSR149415 are able to prevent the deleterious effects of stress exposure are in line with previous experiments showing that these compounds produce anxiolytic-like effects in a variety of animal models, in particular those relating to aspects of acute or post-traumatic stress disorder (Griebel et al., 2002a; 2002b). Taken as a whole these findings suggest that the current effects of SSR149415, SSR125543 and fluoxetine were related to an increased ability to cope with the stressor, and not to cognitive effects *per se*.

It has been suggested that a good strategy for short-circuiting the deleterious effects of acute stress would be to prevent CRF, ACTH and glucocorticoids from exerting their actions (Holmes et al., 2003; Holsboer and Ising, 2008). Both SSR125543 and SSR149415 have been shown to prevent restraint stress-induced elevation of ACTH levels in rats (Gully et al., 2002; Ramos et al., 2006; Serradeil-Le Gal et al., 2002). It can therefore be hypothesised that the beneficial effects of SSR149415 and SSR125543 in this modified object recognition test may be explained by their regulatory action on the HPA axis. However, their action might, alternatively or in addition, involve extra-HPA axis sites since both CRF1 and V1b receptors are found in brain structures associated with the integration and transduction of stressful stimuli, such as the amygdala, the lateral septum, and the hippocampus, and in case of SSR149415 have been shown to play a role in some of the behavioural effects of the drug (Chalmers et al., 1996; Hernando et al., 2001; Stemmelin et al., 2005).

In conclusion, this modified version of the object recognition test may represent a valid animal model of acute stress disorder addressing the cognitive abnormalities of this condition, i.e. the inability to recall an important aspect of the trauma. The finding that SSR149415 and SSR125543, the non-peptidic antagonists at V1b and CRF1 receptors respectively, prevented the cognitive impairment following stress in this model suggest further that the blockade of these two receptors may provide an alternative strategy to SSRIs for stress disorders following traumatic events.

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