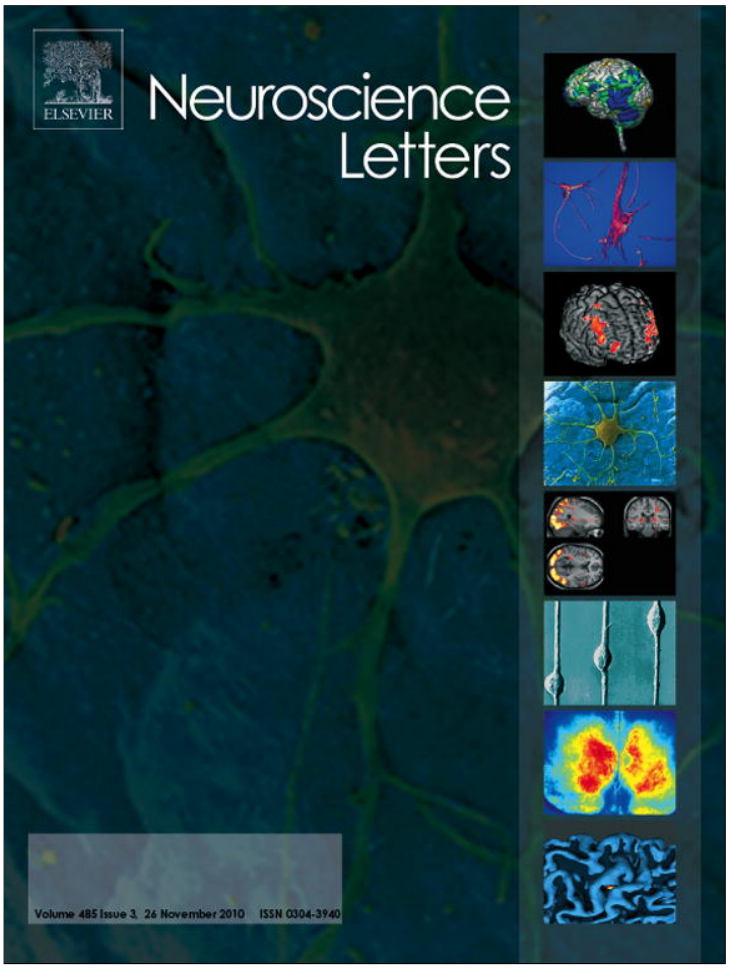

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Effects of intra-hippocampal injections of the NK2 receptor antagonist saredutant on the elevated plus maze, and the mouse defense test battery

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ABSTRACT

Intracerebroventricular (i.c.v.) or intraperitoneal (IP) administration of saredutant (SR48968), an NK2 receptor antagonist, produces anxiolytic-like effects in rodents in a number of animal models of anxiety. NK2 binding sites are present in several limbic structures in rats, including the hippocampus, thalamus, septum and prefrontal cortex, suggesting involvement in the modulation of emotional processes. The current study investigated the behavioral effects of saredutant infused into the ventral hippocampus (VH), a structure associated with cognitive and emotional processes, to clarify the neural substrate underlying the anxiolytic-like effect of the compound. Saredutant (10, 100 or 500 pmol/0.2 μL) was injected bilaterally into the VH of male CD-1 mice tested in the elevated plus-maze and mouse defense test battery (MDTB). Results from the EPM showed that microinjections of 10 pmol/0.2 μL of saredutant increased entries and time spent in the open arms and enhanced end-arm exploration. In the MDTB, saredutant (500 pmol/0.2 μL) decreased vocalizations and increased escape attempts in mice confronted with a rat. Taken together, these results suggest that hippocampal tachykinin mechanisms are involved in the modulation of anxiety and defensive behaviors.

Central tachykinins have been demonstrated to play a role in the modulation of stress-related behaviors. The biological actions of the tachykinins substance P, neurokinin A and neurokinin B are mediated by the activation of three G protein-coupled receptors identified as tachykinin-1 (NK1), tachykinin-2 (NK2) and tachykinin-3 (NK3) [19,22]. Neurochemical and behavioral studies suggest a pivotal role of tachykinin NK2 receptors in the modulation of emotional processes [1,9,18].

Saredutant (SR48968), an NK2 receptor antagonist, has been evaluated in a number of animal models of anxiety, showing anxiolytic-like effects with systemic or intracerebroventricular (i.c.v.) administration in the mouse defense test battery (MDTB), elevated plus maze (EPM) [12,13,28], light/dark [27,30] and social interaction tests [16,25]. Saredutant restored acquisition of passive avoidance in olfactory bulbectomized rats and decreased ultrasonic distress cries in rat pups separated from their mothers [16]. This compound also produced antidepressant-like effects in the forced swim test [8] and, with chronic administration, attenuated stress-induced physical degradation in a chronic mild stress paradigm in mice [16]. Altogether, these results clearly show that saredutant given systemically or i.c.v. to rodents is effective in improving behavioral performance in tests widely used to screen anxiolytic or antidepressant drugs under basal and stress-related conditions.

An additional question relates to the effects of this NK2 antagonist in specific brain structures. In the adult rat brain, the autoradiographic distribution of tachykinin NK2 binding sites includes the dorsal and ventral hippocampus, septum, thalamus and prefrontal cortex [24]. It has been proposed that NK2 receptor antagonists may produce in vivo effects by interaction with other neuropeptides such as corticotrophin releasing factor (CRF) [26]. The abundance of NK2 receptors, as well as substance P and CRF receptors in hippocampus suggest this structure as a site for such neuropeptide interactions [11,26,29]. In addition, a considerable body of evidence indicates involvement of the hippocampus in fear conditioning and defensive behaviors [10,14,17,21].

The present study evaluated the effects of direct infusion of saredutant into the hippocampus on the EPM, and on an ethological test of anxiety in mice, the MDTB. Because a previous study indicated that ventral, but not dorsal, hippocampal lesions strikingly reduced a variety of defensive responses of rats exposed to a cat, cat odor

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or shock, and to situations associated with these threats [4,21], the ventral hippocampus (VH) was selected as the site of the saredutant infusions.

Male CD-1 mice, obtained from Charles River Laboratories (Wilmington, MA) were singly housed under controlled temperature (23 °C) and illumination (12-h light:12-h dark cycle, with lights on at 06:00 h) with free access to food and water. The mice were acclimatized for 2 weeks until they reached a weight range of 35–45 g at the time of surgery. Male Long–Evans rats, weighing 500–600 g at time of testing, were used as threat stimulus in the mouse defense test battery. They were deeply anesthetized with sodium pentobarbital (80 mg/kg, i.p.) 10 min before the test session began in order to minimize their discomfort. A total of two rats were used for this experiment. EPM testing was conducted during the light cycle between 9 a.m. and 12 p.m.; MDTB testing was conducted between 12 p.m. and 5 p.m. All procedures were conducted in accordance with protocols approved by the University of Hawaii Institutional Animal Care and Use Committee.

Prior to surgery, subjects were deeply anesthetized with an injection of sodium pentobarbital (0.9 mg/kg, i.p.; Sigma, USA) and were mounted in a stereotaxic apparatus (David Kopf Instruments). 26-Gauge stainless steel guide cannulas, 0.80 cm in length, were bilaterally implanted into the ventral hippocampus using the following coordinate: AP −2.70 mm from bregma, ML ±3.30 mm, DV −3.00 mm [20]. The guide cannulas were fixed in place with dental cement and two screws. At the end of the surgery, each guide-cannula was sealed with a stainless steel wire to prevent obstruction. Five days after surgery, each mouse was transported to the experimental room and left undisturbed for 60 min prior to testing. In the microinjection procedure a 32-gauge injector was introduced through the guide-cannula until its lower end was 1 mm below the tip of the cannula. This injector was linked to a 10 μL Hamilton syringe and a microinfusion apparatus (Harvard, USA) by polyethylene-10 tubing (Plastic One, VA). A constant volume of 0.2 μL was injected during 30 s and the cannula was left in the place for an additional 30 s to allow complete drug diffusion. Saredutant, obtained from Sanofi-Aventis, was diluted in 0.2% Tween-80 and saline (0.9% NaCl). Mice were randomly assigned to one of the four groups: saline and Tween-80 solution (0.2 μL) used as the vehicle ($n = 11$), saredutant 10 pmol ($n = 11$), 100 pmol ($n = 11$) and 500 pmol ($n = 11$). The dose selections were based on previous studies [3,28]. Subjects were tested in the EPM and, five days later, in the MDTB. Thus, each animal received two 0.2 μL injections separated by 5 days.

The elevated plus-maze used in the present study was a modified version of the previously described apparatus [15]. The two opposing closed arm runways were 30 cm × 5 cm, enclosed by 15 cm high walls on each side and ends. The two opposing open arms were also 30 cm × 5 cm with a 0.25-cm high Plexiglas edge on either side and at the end of each runway. The center platform was 5 cm × 5 cm. The enclosed arm walls were constructed with urethane-coated wood and lined with Plexiglas. The floor of the maze was covered with a thin layer of vulcanized black rubber to facilitate inter-trial cleaning. The apparatus was positioned 40 cm from the floor on a wooden stand hidden from view and the floor under the stand was covered with black cloth to minimize possible height cues. Mice were placed individually in the center of the maze facing a closed arm and allowed 5-min free exploration. Behaviors were recorded by a video camera (Everfocus, USA) positioned above the maze with the signal relayed to a monitor in another room via a closed-circuit TV camera. Luminosity at the open arms level was 12 lx. Videotapes were subsequently scored by a trained observer blind to the drug condition using ethological analysis software (Observer) developed by Noldus (Amsterdam, The Netherlands). The performance of each animal in the maze was analyzed using standard measures, including the frequency of open and closed arm entries (an arm entry defined as all four paws into an arm); total arm entries and the amount of time spent by the animals in each section of the maze. In addition, the frequency of the head-dipping, end-arm exploration, stretched-attend postures, flat-back approach and head out were also analyzed, utilizing definitions consonant with previous analyses [2,7,23].

The mouse defense test battery was run in an oval runway, 0.40 m wide, 0.30 m high and 4.4 m in total length, consisting of two 2-m straight segments joined by two 0.4-m curved segments and separated by a median wall (2.0 m × 0.30 m × 0.06 m). The apparatus was elevated 0.8 m from the floor to enable the experimenter to hold the rat and move with ease, while minimizing the subjects' ability to view the experimenter. All parts of the apparatus were constructed from black Plexiglas. The floor of the apparatus was marked every 20 cm with white lines to facilitate measurement of locomotion distances. Two ceiling-mounted video cameras were used to record the test and the room was illuminated with one 100-W red light. MDTB measures [5] were scored both live and from videotape using the same ethological analysis software as was used with the EPM. The MDTB involves a number of subtests:

Three-minute pre/posttest. Line crossings, wall rears and wall climbs during the pre-predator (familiarization) period provided baseline activity data following treatment. The same measures, during the post-predator period were compared to the pretest period to provide an index of enhanced contextual defense following predator exposure

Predator avoidance test. Avoidance and escape distance are measured when a predator stimulus (a hand-held rat) is brought up to the subject at a speed of approximately 0.5 m/s. Approach is terminated when contact with the subject is made or the subject runs away from the approaching rat. This is repeated five times

Chase/flight test. The hand-held anesthetized rat is brought up to the subject at a speed of approximately 2 m/s. The time required to chase the subject: 2 complete laps of the runway or 2 min are recorded. Stops and reversals of orientation of the fleeing mouse serve as measures of risk assessment

Straight alley test. The runway is then converted to a straight alley, 80 cm long, by the closing of a door at one end. The rat is placed at one end while the mouse begins the test at the other. Measures are taken for 30 s and include immobility time (freezing) and closest distance between the subject and the rat, as well as the number of approaches/withdrawals (measures of risk assessment)

Forced contact test. The rat is brought up to contact the subject five times. For each such contact, bites, vocalizations, upright postures and jump attacks by the subjects are recorded and used as measures of defensive threat and attack

Upon completion of the experiments, the animals were sacrificed with an overdose of sodium pentobarbital and decapitated. Brains were removed and kept in a 20% sucrose–formalin solution. Serial 50 μm brain coronal sections were cut using a cryostat and mounted on gelatin-coated slides and stained with cresyl violet (5%) (Sigma–Aldrich) in order to localize the positions of the microinjection sites according to the atlas of [20]. The microinjection sites were evaluated by microscopic examination. The great majority of the sites of injections were concentrated between −2.70 and −3.08 mm in relation to bregma at field CA3 of ventral hippocampus (Fig. 1). Seven mice were deemed to have inappropriate placements of one or both cannulas.

One-way analysis of variance (ANOVA) was used to analyze data. *Post hoc* Newman–Keuls tests were conducted for significant treatment effects relative to control means. A p value <0.05 was considered significant.

Results for the EPM are shown in Table 1. One-way ANOVA indicated a significant effect of saredutant injections into the VH on the frequency of open arm entries [$F_{(3,40)} = 25.75$; $p < 0.01$] and time spent [$F_{(3,40)} = 4.22$; $p < 0.01$] on the open arms of the maze (Fig. 2).

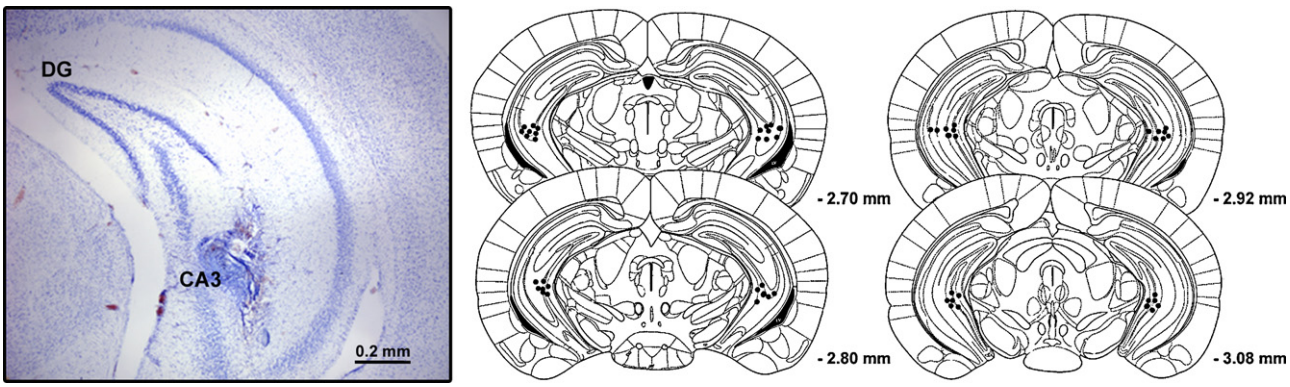

Fig. 1. Representative photomicrograph of microinjections into the ventral hippocampus (VH). DG: dentate gyrus; CA3: field CA3 of hippocampus. Schematic representation taken from the atlas of Paxinos and Franklin's atlas [20] illustrating the location of injections sites into the VH. Due to some overlapping, the number of points in the figure is less than the total number of mice used.

Table 1
Effect of saredutant infusions in the ventral hippocampus on behavioral responses of mice exposed to elevated plus-maze test.

Behavior	$F_{(3,40)}$	Control	SR 10 pmol	SR 100 pmol	SR 500 pmol
Head dip	2.74	30.36 ± 3.90	40.10 ± 5.00	24.10 ± 3.70	23.25 ± 5.23
End arm exploration	5.14	7.64 ± 1.82	14.00 ± 2.18*	2.64 ± 1.07	6.25 ± 5.55
Stretch posture	0.08	1.72 ± 0.82	1.30 ± 0.43	1.45 ± 1.07	1.25 ± 0.48
Flat back	0.76	12.55 ± 2.89	8.10 ± 1.40	12.73 ± 2.32	9.83 ± 2.84
Head out	0.58	1.27 ± 0.51	0.60 ± 0.32	0.55 ± 0.16	0.92 ± 0.57

* $p < 0.05$ compared to control group (Newman–Keuls test).

Newman–Keuls *post hoc* analysis ($p < 0.05$) showed that the dose of 10 pmol/0.2 μL increased these parameters. ANOVA showed no significant treatment effects on closed arm entry or times [$F_{(3,40)} = 0.20$ and 2.84, respectively; $p > 0.05$]. For the novel ethological measures, ANOVA indicated a significant drug effect on end-arm exploration [$F_{(3,40)} = 5.13$; $p < 0.01$] and an effect on head-dipping [$F_{(3,40)} = 2.75$; $p = 0.055$] that approached, but failed to reach, an acceptable level of statistical significance. Newman–Keuls *post hoc* analyses ($p < 0.05$) indicated that both of these effects reflected increases with the lower dose level of saredutant. The remaining behaviors were not affected by saredutant.

Scores for measures of the MDTB are shown in Table 2. ANOVA indicated a significant effect of saredutant injections into the VH on two measures, vocalization and jump escapes in the forced contact test [$F_{(3,41)} = 3.89$ and 3.88, respectively; $p < 0.05$]. Newman–Keuls *post hoc* analyses ($p < 0.05$) indicated that the 500 pmol/0.2 μL dose decreased vocalizations in the forced contact test, while increasing jump escapes. There was also a trend toward reductions in defensive uprights in the forced contact test that did not reach an acceptable level of statistical significance [$F_{(3,41)} = 2.49$; $p = 0.073$].

In this study we evaluated behavioral effects of intra-hippocampal saredutant on various defensive behaviors in CD-1

Table 2
Effect of saredutant infusions into the ventral hippocampus on behavioral responses of mice confronted with a rat in the mouse defense test battery.

Behaviors	$F_{(3,41)}$	Control	SR 10 pmol	SR 100 pmol	SR 500 pmol
Pretest activity					
Line crossing	2.02	159.45 ± 15.46	159.64 ± 12.47	129.27 ± 9.72	127.33 ± 12.44
Rears	0.22	25.91 ± 5.62	20.73 ± 3.73	32.82 ± 10.18	14.67 ± 3.65
Predator avoidance test					
Avoidance distance (cm)	0.78	23.64 ± 8.77	38.18 ± 24.04	5.45 ± 3.12	28.33 ± 16.46
Avoidance frequency	0.85	1.00 ± 0.23	1.09 ± 0.39	0.45 ± 0.25	0.92 ± 0.31
Escape distance (cm)	2.18	235.45 ± 62.57	350.00 ± 47.60	172.73 ± 44.70	223.33 ± 44.61
Escape frequency	1.99	2.82 ± 0.58	4.27 ± 0.30	2.64 ± 0.58	3.42 ± 0.54
Chase/flight test					
Flight speed (m/s)	0.64	23.16 ± 2.04	26.32 ± 4.01	24.86 ± 4.14	29.08 ± 3.29
Stops	1.52	13.09 ± 1.82	9.09 ± 1.23	12.64 ± 1.67	12.42 ± 1.11
Reversals	0.36	0.82 ± 0.46	0.45 ± 0.21	0.55 ± 0.28	0.83 ± 0.27
Closed alley test					
Approaches/withdrawals	0.02	2.36 ± 0.34	2.36 ± 0.73	2.45 ± 0.47	2.50 ± 0.58
Contacts	0.90	0.55 ± 0.31	1.82 ± 0.72	1.45 ± 0.53	1.58 ± 0.66
Freezing (s)	0.52	3.91 ± 1.65	1.45 ± 0.98	4.00 ± 2.33	2.58 ± 1.43
Jump escapes	0.71	0.18 ± 0.12	0.73 ± 0.49	0.27 ± 0.19	0.33 ± 0.19
Forced contact test					
Vocalization	3.89	13.36 ± 0.82	10.73 ± 1.03	11.18 ± 1.28	7.75 ± 1.46*
Uprights	2.49	10.45 ± 1.47	7.18 ± 1.18	5.91 ± 1.16	5.75 ± 1.59
Jump escapes	3.88	1.27 ± 0.38	3.18 ± 0.62	2.64 ± 0.62	4.33 ± 0.85*
Jump attack	0.91	0.91 ± 0.46	1.82 ± 0.71	0.73 ± 0.38	0.92 ± 0.43
Bites	0.34	2.55 ± 1.03	3.18 ± 1.30	3.00 ± 1.36	1.75 ± 0.60
Posttest					
Line crossing	1.02	149.45 ± 14.91	143.00 ± 16.12	119.82 ± 10.22	124.42 ± 14.35
Rears	0.81	40.36 ± 5.33	36.00 ± 3.53	37.45 ± 3.57	30.33 ± 5.81

* $p < 0.05$ compared to control group (Newman–Keuls test).

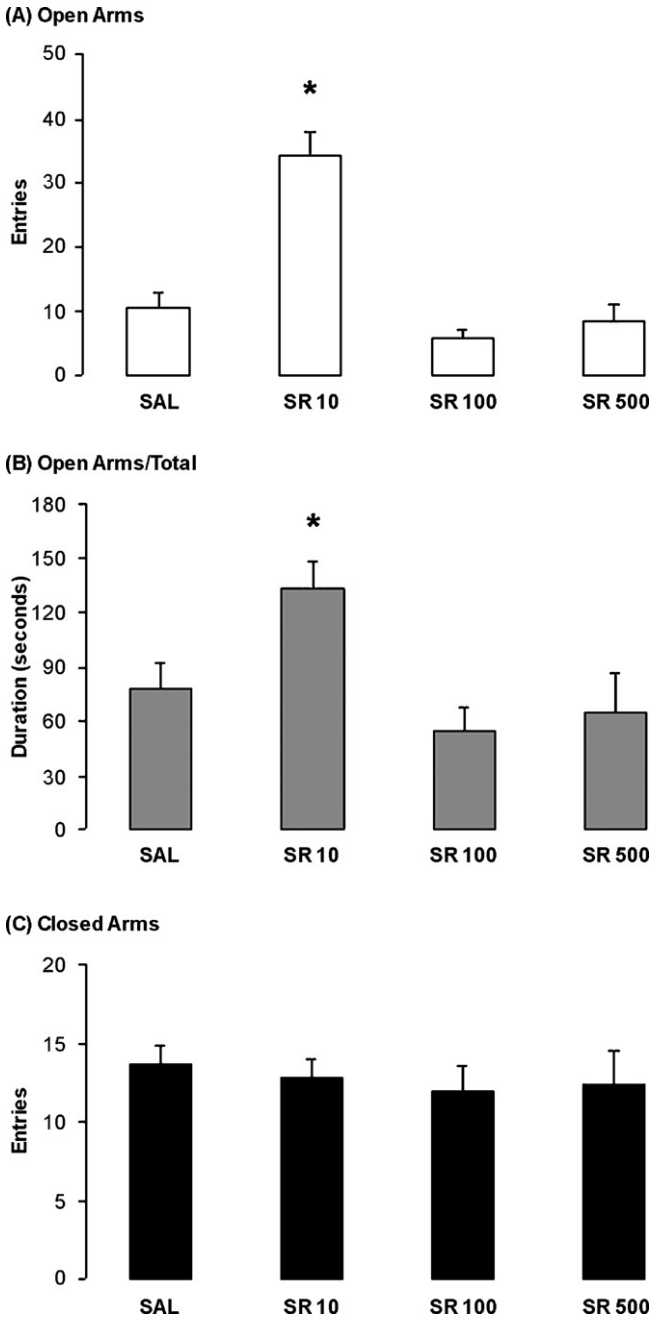

Fig. 2. Effects of saredutant (SR) intra-ventral hippocampus on the exploratory behavior of mice submitted to the elevated plus-maze. Each animal was injected 5 min before test either with vehicle saline + 0.2% Tween-80 (SAL; $n = 11$) or SR 10 ($n = 10$), SR 100 and SR 500 pmol/0.2 μL ($n = 11$). (A) Number of entries in the open arms of the maze; (B) time spent in the open arms; (C) number of entries in the closed arms of the maze. The values are mean ± SEM. *$p < 0.05$, compared to control group, Newman–Keuls *post hoc* test.

mice. Results indicated that infusion of this compound into the ventral hippocampus produces a pattern similar to that obtained with systemic administration of saredutant, with increased open arm times and a higher number of head dips [13]. These behavioral measures, plus open arm entries and end arm exploration, both significantly higher following saredutant infusions into the VH, are associated with direct exploration, indicating an increased tendency to actively explore the potentially dangerous areas. This exploration appears to be specific to the potentially dangerous open arms, in that closed arm entries and time were not affected. The anxiolytic-like effects were limited to the 10 pmol group suggesting that the effective action of the compound was in the VH.

In the MDTB, saredutant effects were limited to behavioral measures associated with forced contact with the threatening (rat) stimulus: vocalization was significantly reduced and jump escapes were increased at the 500 pmol dose level. An additional measure that approached, but failed to reach, an acceptable level of significance was defensive uprights, suggesting a switch from defensive uprights to escape in response to forced contact with the discrete threat source, a switch that might also have influenced the number of vocalizations: defensive vocalizations respond precisely to threat-subject distance [6] such that escape may reduce the instances of proximity that trigger them. The dose–response patterning of these changes was very different than that obtained with the EPM, in that *post hoc* analyses found differences from controls only in the highest dose groups, rather than in the low dose group, as in the EPM. The differential findings of low dose reactivity in the EPM and high dose reactivity in the MDTB suggest separate mechanisms of drug action in the two tests; possibly accounted for by neurochemical interactions and location of responding cells, assuming a more localized effect at lower doses. The current study provides a foundation for subsequent work aimed at determining more specific effects of this compound.

Systemic administration of saredutant produced a more expansive pattern of defense-related changes in the MDTB, with decreased flight and risk assessment behaviors in the chase test, defensive biting in the forced contact and escape attempts during the posttest [12]. This pattern indicates a widespread reduction in defensiveness with saredutant, whereas the present results suggest a more limited array of defense changes associated with infusion of this compound into the VH.

The differences between the present EPM and MDTB results are also interesting. The threat source in the EPM is a novel, raised, exposed space, the open arms, whereas the MDTB brings the subject into confrontation with a discrete, animate, intense, threat stimulus, the chasing and contacting predator [5]. In the EPM, a low dose of saredutant reduced avoidance of the threat stimulus, whereas in the MDTB, only the highest dose was effective in changing behavior, and its effects were apparently limited to switching from an upright immobile behavior to flight, with an accompanying drop in vocalization. This difference is compatible with previous findings that manipulations involving the VH may be sensitive to the intensity of threat stimuli [21]. Moreover, the specific behavior patterns altered in the two situations are compatible with an interpretation that the VH is associated with behavioral inhibition [10,17], and that saredutant in this area reduces these inhibitory defenses.

In summary, our present findings corroborate and extend the idea of the involvement of the hippocampal tachykinergic mechanisms in the modulation of aversive responses suggesting that the NK2 receptor may represent an interesting neurochemical target for new and selective drugs designed to control pathological anxiety states.

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