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Histamine reverses a memory deficit induced in rats by early postnatal maternal deprivation

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ABSTRACT

Early partial maternal deprivation causes long-lasting neurochemical, behavioral and brain structural effects. In rats, it causes a deficit in memory consolidation visible in adult life. Some of these deficits can be reversed by donepezil and galantamine, which suggests that they may result from an impairment of brain cholinergic transmission. One such deficit, representative of all others, is an impairment of memory consolidation, clearly observable in a one-trial inhibitory avoidance task. Recent data suggest a role of brain histaminergic systems in the regulation of behavior, particularly inhibitory avoidance learning. Here we investigate whether histamine itself, its analog SKF-91844, or various receptor-selective histamine agonists and antagonists given into the CA1 region of the hippocampus immediately post-training can affect retention of one-trial inhibitory avoidance in rats submitted to early postnatal maternal deprivation. We found that histamine, SKF-91844 and the H2 receptor agonist, dimaprit enhance consolidation on their own and reverse the consolidation deficit induced by maternal deprivation. The enhancing effect of histamine was blocked by the H2 receptor antagonist, ranitidine, but not by the H1 receptor antagonist pyrilamine or by the H3 antagonist thioperamide given into CA1 at doses known to have other behavioral actions, without altering locomotor and exploratory activity or the anxiety state of the animals. The present results suggest that the memory deficit induced by early postnatal maternal deprivation in rats may in part be due to an impairment of histamine mediated mechanisms in the CA1 region of the rat hippocampus.

1. Introduction

Postnatal maternal deprivation is one the most potent natural stressors. It can causes a developmental delay and a variety of neuroendocrine and memory impairments in several species, including rats and humans. Early partial maternal deprivation induces a number of behavioral alterations visible later in adult life, not only in rats but also in humans. An impairment of memory function is among those alterations. It has been studied in rats (Ardiel & Rankin, 2010; Benetti et al., 2009; Huang et al., 2002; Llorente et al., 2011; Mello, Benetti, Cammarota, & Izquierdo, 2008; Renard, Suarez, Levin, & Rivarola, 2005) and also in several other species, including humans (Hennessy, Deak, & Schiml-Webb, 2010; Voorhees & Scarpa, 2004). We have recently reported that physical exercise (Mello et al., 2008) or the pro-cholinergic agents, galantamine and donepezil (Benetti et al., 2009) reverse those deficits. The latter effect suggests a role of a cholinergic deficit in the memory impairment brought about by maternal deprivation (Benetti et al., 2009).

Recent (Baldi et al., 2005; Bonini et al., 2011; Da Silva, Bonini, Bevilaqua, Izquierdo, & Cammarota, 2006; Zarrindast, Ahmadi, Oryan, Parivar, & Haeri-Rohani, 2002) and not-so-recent findings (Almeida & Izquierdo, 1986) suggest a role for brain histamine in learning and memory in rats, including both the acquisition (Da Silva et al., 2006) and the extinction of inhibitory avoidance behavior (Bonini et al., 2011). The last two effects seem to be mediated by H2 receptors (Bonini et al., 2011; Da Silva et al., 2006). Indeed, histamine activates hippocampal pyramidal cells in slices by actions mediated by H2 receptors (Haas & Greene, 1986).

Histamine is synthesized by a small number of neurons in the tuberomammillary nucleus of hypothalamus and released from the varicosities of axons that ramify profusely throughout the brain (Wada, Inagaki, Itowi, & Yamatodani, 1991). Histamine exerts its effects in the brain through three types of receptors, H1, H2 and

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H3. The first two are in general excitatory and H3 is an auto receptor that modulates the release of both histamine and other transmitters (McCormick & Williamson, 1991).

Here we investigate the effect of histamine, of its enhancer SKF-91844, and of various histamine receptor antagonists and agonists on the post-trial consolidation of one-trial inhibitory avoidance task (Benetti et al., 2009; Da Silva et al., 2006) in adult rats submitted or not submitted to early postnatal maternal deprivation during the first 10 days of life, in which that process is seemingly impaired (Mello et al., 2008). All the antagonists were given at doses shown to be supramaximal in previous experiments (Da Silva et al., 2006). As will be seen, the findings suggest a key involvement of histamine H2 receptors in the recovery from that impairment, and therefore a role of a deficit of histaminergic transmission in hippocampal CA1 in its pathogenesis. There are, to be sure, other papers suggesting a role of H3 receptors in memory processes (Baldi et al., 2005; Cangioli et al., 2002). Whether this role is additional to that of H2 receptors remains to be studied.

2. Material and methods

2.1. Animals

Pregnant Wistar rats were obtained from the Animal House center, Federal University of Rio Grande do Sul, Porto Alegre, Brazil on gestation days 16–18, and individually housed in a temperature (21 ± 2 °C) and humidity (55 ± 5%) controlled room on a 12-h light/dark cycle (lights on at 7:00 a.m.) with food and water ad libitum. All experimental procedures followed the guidelines of the USA National Institutes of Health Guide for the Care and Use of Laboratory Animals (DHEW Publications, NIH 80–23) and were approved by the Animal Care and Use Committees of the Pontifical Catholic University of Rio Grande do Sul.

2.2. Maternal deprivation procedure

The day of delivery was designated as post-natal day (PND) 0. As described by Benetti et al. (2009) and Mello et al. (2008), on postnatal day 1 (PND 1), litters were culled to 10 pups (five males and five females when possible) per dam. The rat pups were daily deprived of their mother for 3 h during the first 10 days of life. Deprivation consisted of removing the mother from the home cage. The pups were maintained in the original home-cage (grouped in the nest in presence of maternal odor), which was transferred to a different room kept at 32 ± 1 °C to compensate for the mother's body heat (Renard et al., 2005). Deprivation was carried out between 08:00 a.m. and 1:30 p.m. Non-deprived rats remained undisturbed in the home cage with their mothers. The first bedding was changed only on PND 11 for both the groups (non-deprived and deprived rats) studied. Rats were weaned on PND 21 and only males were chosen for the present work. The females were donated to other research groups. All subsequent experiments were performed when the animals were adult (100–120 days of age).

2.3. Surgery

On PND 130-140, the rats were bilaterally implanted with 27-gauge stainless-steel cannulae in the CA1 region of the dorsal hippocampus under ketamine/xylazine anesthesia. Stereotaxic coordinates were 4.0 mm posterior to bregma, 3.0 mm lateral to the midline, and 1.8 mm ventral to the skull surface (Paxinos & Watson, 1986). Infusions (1 μl/side) were carried out using an infusion pump. Placement of the cannula was verified post-mortem: 2–4 h after the last behavioral test, 1 μl of 4% methylene blue solution was infused as described above and the extension of the dye 30 min thereafter taken as an indication of the diffusion of the drug previously injected (Bonini et al., 2011).

2.4. Handling and habituation to experimenter

After the recovery of surgery and before the behavioral experiments began each animal was handled by the experimenters. This consisted of gently touching and holding the rat with two hands using gloves during approximately 5 min for 3 consecutive days. One hour before training in the avoidance task, all cages were transferred in an isolated room at 21 ± 2 °C.

2.5. Inhibitory avoidance task

Rats were trained in a one-trial step-down inhibitory avoidance between PND 140 and 150, as described in Da Silva et al. (2006) or Bonini et al. (2011). The training apparatus was a 50 × 25 × 25 cm Plexiglas box with a 5-cm high, 8-cm wide and 25-cm long platform on the left end of a grid of bronze bars. During training, animals were gently placed on the platform facing the left rear corner of the training box. When they stepped down and placed their four paws on the grid, received a 0.4 mA scrambled footshock during 2 s and were immediately withdraw from the training box. Immediately after training session, each rat was submitted to a specific drug infusion, for more detail see below. Inhibitory avoidance retention was evaluated in a non-reinforced test session carried out 24 h later. At test, trained animals were put back on the training box platform until they eventually stepped down to the grid. The time in the platform was expressed in latency to step-down during the test session and taken as an indicator of memory retention (Da Silva et al., 2006).

2.6. Drugs

Drugs were purchased from Sigma–Aldrich (USA), Tocris Cookson Ltd. (UK) or Promega (USA). Drugs were dissolved in saline or DMSO and stored at −20 °C. Before use aliquots were diluted to working concentration and were infused at room temperature with pH 7.2. The doses used were based on pilot experiments (Da Silva et al., 2006) and on studies showing their effect on behavioral and physiological variables (Almeida & Izquierdo, 1986; Alvarez & Ruarte, 2002, 2004; Baldi et al., 2005; Blandina, Efoudebe, Cenni, Mannaioni, & Passani, 2004; Bonini et al., 2011; Da Silva et al., 2006; Passani & Blandina, 2011).

2.7. Open field and plus maze

To analyze their exploratory activities, animals were placed in a 50 × 50 × 39 cm open-field arena with the floor divided into 12 equal rectangles by black lines. Line crossings and rearings were measured over a 5-min period and their number over that period was taken, as is usual, as indicators of the locomotor and exploratory activity of the animals (Benetti et al., 2009; Mello et al., 2008).

To evaluate their anxiety state, rats were exposed to an elevated plus-maze as described by Pellow, Chopin, File, and Briley (1985). The total number of entries into the four arms and the number of entries and time spent in the open arms were recorded over a 5-min session. As is usual, the findings were taken as indicators of their anxiety state: the larger the number of entries into the open arms and the longer their permanence there, the lower the anxiety level the animals would have.

The animals used for inhibitory avoidance training were not reutilized in open field and plus maze experiments. Twenty-four hours before exposure to the open field or the plus maze, the animals received bilateral 1 μl/side infusions into the CA1 region of

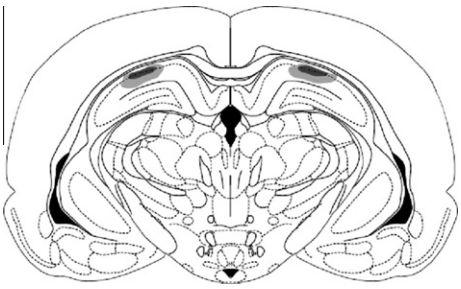

Fig. 1. Schematic drawing taken from the atlas of Paxinos and Watson (1986) showing the location of the sites reached by the microinfusions aimed at the CA1 region of the hippocampus.

the dorsal hippocampus. This interval was the same used in the posttraining avoidance experiment between the injections and the test sessions.

2.8. Statistical analysis

Data are presented as medians ± interquartile ranges and were analyzed using the Mann–Whitney U test or by Dunn's post hoc multiple comparison as appropriate, after a Kruskal–Wallis one-way analysis of variance.

3. Results

Fig. 1 shows the minimum (dark hatching) and the maximum (light hatching) extension of micro-infusions of 2% methylene blue given at the end of behavioral testing in the animals used in these experiments. Data on animals in which the infusions were outside the boundaries in this figure (3 animals in all) were discarded.

The influence of maternal deprivation on one-trial, step down inhibitory avoidance task, and the effect of the several drugs tested thereupon was examined by giving the drugs immediately post training and measuring their retention test latency 24 h later, comparing the data with those obtained in saline controls.

3.1. Effect of histamine and ranitidine given into CA1 on explorator activity in an open field or anxiety levels in a plus maze

Neither histamine (10 nmoles/side), nor ranitidine (50 nmoles/side) affected the number of crossings of the lines on the floor and the number of rearings in then open field and did not change the total number of entries into the four arms or the number of entries and the time spent into the open arms of the elevated plus maze when given into CA1 24 h before the respective behavioral session (Table 1).

3.2. Effect of post-training bilateral infusion of histamine and of the N-methyltransferase inhibitor SKF-91844 into the CA1 region of rat hippocampus on retention of inhibitory avoidance

Maternal deprivation during the first 10 days of postnatal life was followed by a deficit of one-trial inhibitory avoidance behavior of male rats at the age of 120–150 days. This deficit could be overcome by the post-training bilateral infusion of 10 nmoles/side of histamine (Fig. 2A), an effect that was dose-dependent at a $p < 0.001$ level in a Kruskal–Wallis analysis followed by Dunn tests. The effect of histamine was irrespective of the ceiling imposed on the test session latency, and was shared the inhibitor of histamine N-methyltransferase SKF-91844 (50 nmoles/side). This drug is an enhancer of histamine effect by blocking its catabolism (Da Silva et al., 2006).

3.3. Effect of the histamine receptor agonists pyridylethylamine (H1), dimaprit (H2) and imetit (H3) given bilaterally posttraining into the CA1 region of rat hippocampus on retention of inhibitory avoidance

Fig. 3 shows that of the three histamine receptor agonists tested, only the H2 agonist dimaprit (Fig. 3B) was found to mimick both the enhancing effect of histamine or SKF91844 on retention on their own, and their reversal of the retention deficit seen in maternally-deprived animals. It may be noted here that the three receptor types are present in the hippocampus (see Baldi et al., 2005; Blandina et al., 2004; Da Silva et al., 2006).

3.4. Effect of the histamine receptor antagonists pyrilamine (H1), ranitidine (H2) and thioperamide (H3) and of the NMDAr polyamine binding site, ifenprodyl (IFEN) given bilaterally posttraining into the CA1 region of rat hippocampus on retention of inhibitory avoidance

Of the four antihistaminic compounds tested, neither the H1 antagonist pyrilamine nor the H2 antagonist ranitidine, nor the H3 antagonist thioperamide or the antagonist at the polyamine-binding site of the NMDA receptor ifenprodil affected memory retention in non-deprived rats (Fig. 4). In the deprived rats, only the H2 blocker, ranitidine (Fig. 4B) was able to impede the reversal by histamine of the avoidance deficit seen in those animals.

4. Discussion

The present findings are quite straightforward. They corroborate previous data on the enhancement of consolidation of the inhibitory avoidance task obtained with intracerebroventricular (Almeida & Izquierdo, 1986) and with intra-CA1 administration of histamine (Da Silva et al., 2006), show that the histamine N-methyl transferase inhibitor, SKF-91844 and the H2 receptor agonist, dimaprit share this effect but H1 or H2 agonists do not, and that the H2 antagonist, ranitidine blocks the action of histamine. These data suggest an involvement of endogenous histamine in

Table 1
Infusion of histamine or ranitidine into the CA1 region of the dorsal hippocampus has no effect on locomotors in the anxiety state or exploratory activities at the same infusion/test interval used for retention testing in the experiments of Figs. 1–3.

	Saline		Histamine		Ranitidine	
	Non-deprived	Deprived	Non-deprived	Deprived	Non-deprived	Deprived
Time in open arms (s)	80.5 ± 12.1	106.7 ± 20.5	87 ± 14.9	104.0 ± 18.0	85.0 ± 13.2	94.1 ± 19.1
Entries in open arms	4.0 ± 0.76	3.6 ± 0.7	5.2 ± 1.4	4.2 ± 0.8	7.2 ± 1.8	6.8 ± 0.8
Rearings	24.2 ± 2.3	22.2 ± 2.7	21.0 ± 1.7	23.8 ± 3.1	19.0 ± 1.8	24.5 ± 4.1
Crossings	48.6 ± 4.8	51.1 ± 6.2	51.4 ± 4.4	50.2 ± 2.8	52.1 ± 4.5	50.1 ± 2.9

Saline, Histamine (HIS; 10 nmoles/side) or Ranitidine (50 nmoles/side) were infused into the CA1 region of the dorsal hippocampus 24 h before submitting rats to open field or plus maze sessions. Data are expressed as mean (±SEM) seconds spent in the open arms or number of entries into the open arms of the plus maze, or of the number of crossings and rearings in the open field.

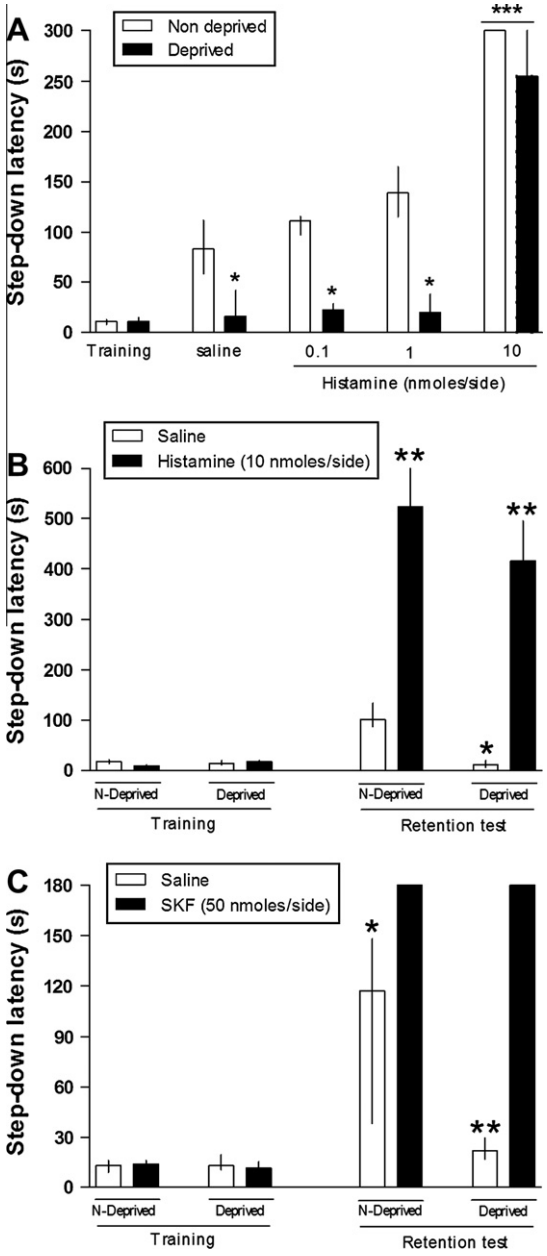

Fig. 2. Infusion of histamine into the CA1 region of the hippocampus can improve aversive memory in non-deprived rats and at least at the dose of 10 nmoles/side can reverse the cognitive deficit in deprived rats. (A) Histamine effects at the doses of 0.1, 1 or 10 nmoles/side given immediately post training into the CA1 region of dorsal hippocampus. In this and following figures, bars represent median (±interquartile range) step-down latencies during a memory retention test carried out 24 h after training. In this and all other figures, $N = 8–10$ per group; significant differences were at $^{*}p < 0.05$ and at $^{***}p < 0.001$ level between non-deprived vs. deprived rats and/or between the latter and saline controls in Dunn's comparison after Kruskal–Wallis test. (B) Effect of 10 ng/side of histamine on retention tested with a higher test session cut-off latency (300 instead of 180 s). In all other figures, the test session cut-off latency was 180 s. (C) N-methyltransferase inhibitor SKF-91844 (50 nmoles/side) also reverses the cognitive deficit in deprived rats and enhances consolidation of inhibitory avoidance memory.

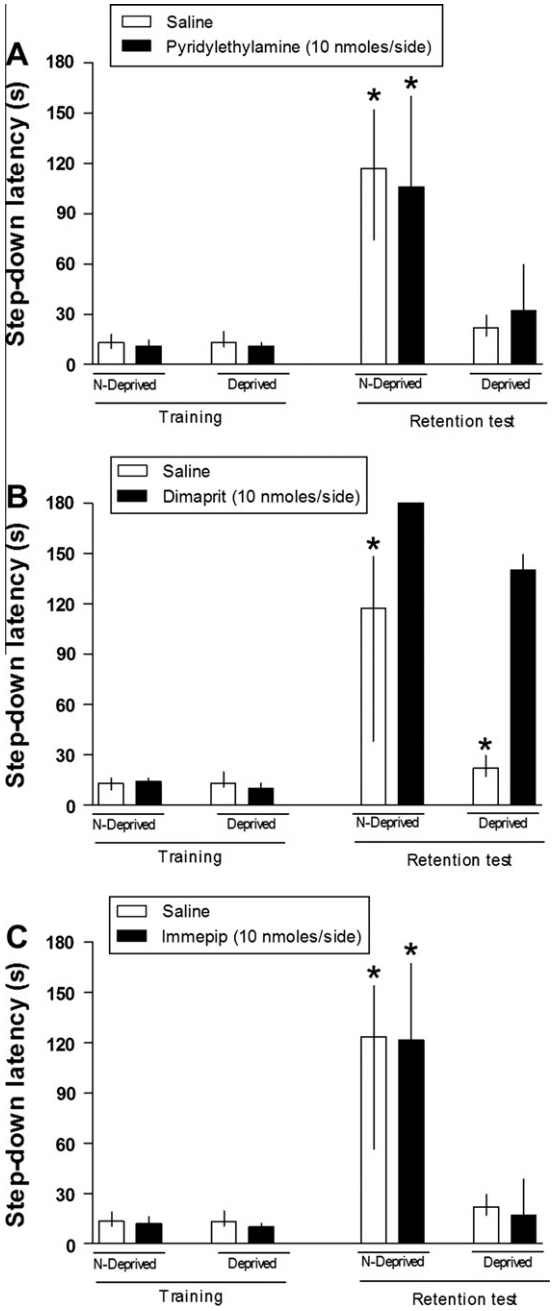

Fig. 3. Animals trained in inhibitory avoidance task received 1.0 μl bilateral infusions into CA1 of saline (SALINE), or the H1 agonist, pyridylethylamine, the H2 agonist, dimaprit or the H3 agonist H3, Immepip; all treatments were given at the dose of 10 nmoles/side immediately posttraining. (A) The H1 and H3 agonists have no effects in memory consolidation in deprived rats. (B) Dimaprit enhanced consolidation in non-deprived rats and reversed the cognitive deficits in deprived rats.

the recovery from the memory deficit induced by maternal deprivation and point to a lack of involvement of H1, H3 and NMDAr polyamine receptors in these effects of histamine.

Further, and importantly, the present findings suggest that an impairment of histaminergic H2 receptor-mediated mechanisms in CA1 can explain at least part of the memory deficit induced by early postnatal maternal deprivation in the rat, which is manifested in the present experiment by an impairment of histaminergic transmission.

So far, there had been evidence only for a possible cholinergic impairment in this condition (Benetti et al., 2009). Clearly, then, the memory impairment that follows early maternal deprivation may be quite more complex than hitherto thought, and involve both a cholinergic and a histaminergic failure. This opens an entirely new possibility for eventual therapeutic approaches to this problem (Passani & Blandina, 2011), which in humans may be quite devastating (see Hennessy et al., 2010; Voorhees & Scarpa, 2004). Interactions between both neurotransmitter systems in

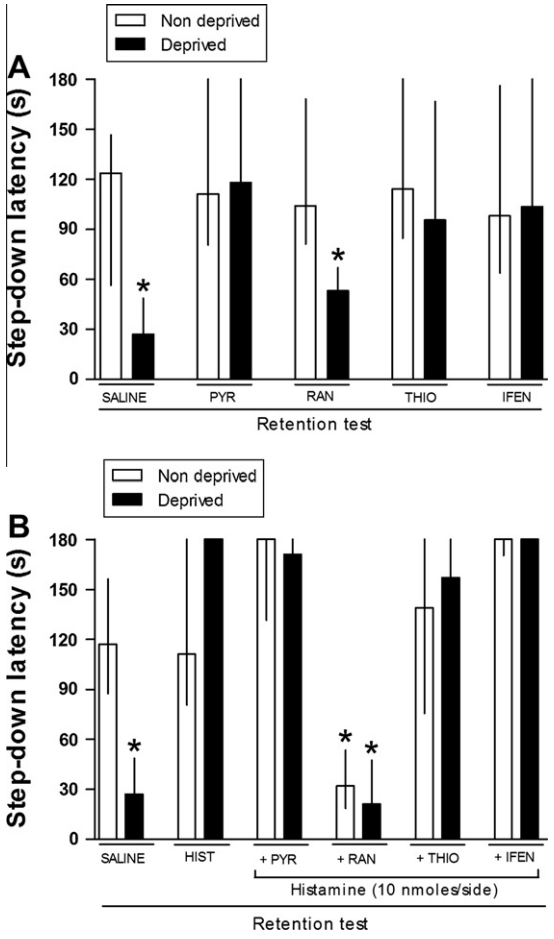

Fig. 4. Antagonists of H1, H2 or H3 receptors or of the NMDAr-polyamine-binding site have no effect on inhibitory avoidance memory consolidation in non-deprived rats and did not affect the cognitive deficit seen in maternally deprived rats. In (A) the H1 antagonist pyrilamine (PYR), the H2 antagonist ranitidine (RAN), and the H3 antagonist thioperamide (THI) or the antagonist at the polyamine-binding site of the NMDAr ifenprodil (IFEN) were bilaterally infused (1.0 μl) into the CA1 region of the dorsal hippocampus immediately after inhibitory avoidance training and, if this was the case, right after the histamine infusion) at the dose 50 nmoles/ side. (B) Both the memory enhancement caused by histamine (10 nmoles/side) in non-deprived rats and the reversion of the cognitive deficit induced by the same dose of histamine in deprived rats are blocked by H2, but not H1, H3 or NMDAr site antagonists. In this experiment, animals trained in inhibitory avoidance task received bilateral infusions intra- CA1 (1.0 μl) of saline (SALINE), histamine (HIS, 10 nmoles/side) or histamine (10 nmoles/side) plus another specific antagonist (50 nmoles/side) of H1 receptors pyrilamine (+PYR); or ranitidine (+RAN); or thioperamide (+THIO) or ifenprodil (+IFEN) immediately after training.

aversive memory (Blandina et al., 2004) have been described in rats using systemic treatments (Eidi, Zarrindast, Eidi, Oryan, & Parivar, 2003) and drug infusions into the basolateral amygdala (Cangioli et al., 2002).

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