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Research report

Histamine acting on the basolateral amygdala reverts the impairment of aversive memory of rats submitted to neonatal maternal deprivation

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HIGHLIGHTS

- Histaminergic compounds in basolateral amygdala have effects in drug study on inhibitory avoidance memory.
- Maternal deprivation has permanent effects in impairment in aversive memory.
- Histamine improves aversive memory and reverse cognitive deficits in rats with maternal deprivation during neonatal period.
- Histaminergic antagonist type 3 impair aversive memory in basolateral amygdala (BLA).

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ABSTRACT

Recent findings suggest a role of brain histamine in the regulation of memory consolidation, particularly in one-trial inhibitory avoidance (IA) learning and that disruption in the mother infant relationship i.e. maternal deprivation induces cognitive deficits. We investigate whether histamine itself, and histaminergic compounds given into the basolateral amygdala (BLA) immediately post-training can affect retention (24 h after training) of one-trial (IA) in rats submitted to early postnatal maternal deprivation. In all cases, deprived (Dep) animals had lower retention scores than non-deprived controls (N-dep). Histamine induced memory enhancement on its own in N-dep animals and was able to overcome the deleterious effect of Dep. The effects by SKF-91488 is similar to histamine. The H3 agonist, imetit mimetized the enhancing effects of histamine; neither agonist H1 pyridylethylamine nor the H2 dimaprit had any effect. Ranitidine and thioperamide (50 nmol) co-infused with histamine (10 nmol) fully blocked the restorative effect of histamine on retention in Dep animals. Thioperamide, in addition, blocked the enhancing effect of histamine on memory of the N-dep animals as well. None of the drugs used given into BLA had any effect on open-field or elevated plus-maze behavior in N-dep or Dep rats. Our results are limited to experimental design in rats. Extrapolation i.e. in humans requires further experimentations. The present results suggest that the memory deficit induced by early postnatal maternal deprivation in rats may at least in part be due to an impairment of histamine H3 receptor-mediated mediated mechanisms in the BLA.

1. Introduction

Some experiences in early life can leave enduring effects on brain structure and function [1]. During early postnatal life the quality of the surrounding environment and experiences [1,2] in particular the parent–child relationship, is associated with emotional and cognitive development later in life [2–5]. Partial or total

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deprivation of maternal care in early life leaves animals with an increased vulnerability to diverse psychopathologies [6], including changes in the synthesis, storage or release of neurotransmitters [3,6–10]. In addition, prolonged maternal separation decreases granule cell number in the dentate gyrus in male rats [11], alters glutamate receptor expression [12], and reduces the expression of BDNF and NMDA receptor subunits in the hippocampus [13].

Modulation of the consolidation of aversive memory depends on a variety of neurotransmitters acting on the basolateral amygdala (BLA) and the hippocampus [14,15]. The former is believed to modulate the latter [14]. Recent data suggest a role of brain histaminergic systems in this modulation, both in the dorsal hippocampus and in the BLA [16–20]. The consolidation of extinction of fear-motivated behavior is modulated by histamine in these two structures and, in addition, in the ventromedial prefrontal cortex [21].

Maternal deprivation in early life leaves animals with a cognitive deficit measurable in several tasks particularly in one-trial inhibitory avoidance learning [18,22,23] and other aversive [24] and non-aversive tasks [3,5,7,13]. We recently reported that anticholinesterase inhibitors [24] and histamine or histamine enhancing drugs infused into the rat hippocampus [16,18] can reverse this effect, and that an H2, but not an H1 or an H3 histamine receptor antagonist can block it [16,17,19,20].

Abundant evidence documents the modulation of memory formation by histamine [18–20,27–31,34,36]. It has been studied by the localized infusion of histamine or its mimetics and antagonists into brain areas known to regulate memory consolidation and by enhancing the action of endogenous histamine, and has been observed in various forms of learning, including fear extinction [21].

Here we study the influence of histamine, histaminergic drugs and histamine receptor antagonists given into BLA on consolidation of one-trial inhibitory avoidance learning in rats submitted to neonatal maternal deprivation.

2. Materials and methods

2.1. Animals

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

2.2. Maternal deprivation procedure

The day of delivery was considered as post-natal day 0. On postnatal day 1 (PND 1) litters were culled to as close as possible to 10 pups (5 males and 5 females) per dam. The pups were deprived from their mother for 3 h a day every day from PND 1 through PND 10. Maternal deprivation (Dep) was by removing the mother from the home cage. The pups were maintained in that cage where the maternal odor persisted in the "nest", and the cages were transferred to another room at 32 ± 1 °C to compensate for the mother's body heat [23,32]. Maternal deprivation was carried out between 8:00 a.m. and 2:00 p.m. N-dep animals simply stayed in the home cages with their mothers in the same room at 21 ± 2 °C. The first bedding was changed only on PND 11 for both Dep and N-dep animals. During maternal deprivation, the experimenter never touched directly deprived pups in order to avoid introducing the odor of human hands or gloves in the nest [23]. All experiments were performed in the males after they reached 130 days of age. The females were donated to other research groups. We adapted this maternal deprivation protocol by Renard and co-workers 2005 mainly because we focused study memory mechanisms in male rats in which this model produce male without anxiety changes. For more details about of maternal deprivation please see [20,23,32,40] papers.

2.3. Surgery

On PND 130–140, 27-gauge stainless steel cannulae were implanted in the Basolateral amygdala (BLA) region of the rats, under 75 mg/kg ketamine plus 10 mg/kg xylazine anesthesia with bilateral 22-g guide cannulae aimed 1.0 mm above the BLA. The coordinates were AP: −2.8, L: ± 4.7 mm, and *V*: −0.31 mm in accordance from the atlas by Paxinos et al. [33]. Infusions were 0.5 μl/side over 30 s using an infusion pump. Cannula placements were verified post-mortem: 3–4 h after the last behavioral test, 0.5 μl of 4% methylene blue were infused as described above and the animals were sacrificed 30 min later by an overdose of the anesthetics; the brains were withdrawn and stored in formalin, and the diffusion of the dye was measured in histological sections and taken as estimates of the drug infusions (see below). Placements were considered correct if they were within 1 mm^3 of the intended infusion site [18,20]. This occurred in 97% of the animals. Only behavioral data from these animals were analyzed.

2.4. Post-operative handling and inhibitory avoidance learning

After recovery from surgery each animal was handled by the experimenters. This consisted of gently touching and holding the rats with both hands using gloves during about 5 min for 3 consecutive days. Rats were transferred to an isolated room at 21 ± 1 °C 1 h prior to one-trial step-down avoidance training. The apparatus was a 50 cm × 25 cm × 25 cm Plexiglass box with a 5 cm-high, 8 cm-wide, 25-cm long Formica platform on the left end of a grid of 1 mm-caliber bronze bars. The rats were gently placed on the platform facing the left rear corner. When they stepped down placing their four paws on the grid, they received a 2-s 0.4 mA scrambled footshock and then were immediately withdrawn from the training box. Immediately after training, as has become customary for consolidation studies in the past 60 years, they received specific drug or saline infusions (see below). Test sessions were carried out 24 h after the training sessions. The procedure was the same except that the footshock was omitted. Latency to step down was measured using an automated stopwatch.

2.5. Drug infusions and treatments

Rats were infused intra-BLA bilaterally, first on the right side and 30 s later on the left side, through a 5 μl Hamilton syringe coupled to a pump (EICOM, Japan) at a flow rate of 0.5 μl/min; infusion cannule were left in place 30 s after each infusion so as to minimize backflow. The doses were chosen from those described in the literature as being effective, based on pilot experiments [19,20]

Drugs were purchased from Sigma–Aldrich (USA), Promega (USA) or Tocris Cookson (UK). They were dissolved in saline with 2% DMSO and stored at −20 °C. Aliquots diluted to working concentrations with saline at pH 7.3 were prepared and infused at room temperature. The drugs used were histamine HCl, the histamine N-methyl-transferase inhibitor (and histamine enhancer) SKF 91488; the H1, H2 and H3 receptor agonists pyridylethylamine, dimaprit and imetit respectively, and antagonists of these 3 specific histaminergic receptors, pyrilamine, ranitidine and thioperamide respectively. The doses chosen were based on pilot experiments as