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

Fernando Benetti [a,b], Clarice Kras Borges da Silveira [c], Weber Cláudio da Silva [d], Martín Cammarota [a,b], Iván Izquierdo [a,b,*]

[a] Centro de Memória, Instituto do Cérebro, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Avenida Ipiranga 6690, 2° andar, Porto Alegre, RS 90610-000, Brazil
[b] Instituto Nacional de Neurociência Translacional, Conselho Nacional de Desenvolvimento Científico e Tecnológico, Avenida Ipiranga 6690, 2° andar, Porto Alegre, RS 90610-000, Brazil
[c] Universidade Federal de Ciências da Saúde de Porto Alegre, Brazil
[d] Departamento de Farmácia, Universidade Estadual do Centro-Oeste, Simeão Camargo de Sá 03, Guarapuava, PR 85040-080, Brazil

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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

* Corresponding author at: Centro de Memória, Instituto do Cérebro, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Avenida Ipiranga 6690, 2° andar, Porto Alegre, RS 90610-000, Brazil. Fax: +55 51 3320 3312.
E-mail address: izquier@terra.com.br (I. Izquierdo).

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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