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Research report

Tactile stimulation effects on hippocampal neurogenesis and spatial learning and memory in prenatally stressed rats

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ABSTRACT

Neurogenesis in the dentate gyrus (DG) of the hippocampus is increased by spatial learning and postnatal stimulation. Conversely, prenatal stress (PS) produces a decrease in the proliferation of hippocampal granular cells. This work evaluated the effect of postnatal tactile stimulation (PTS), when applied from birth to adulthood, on cognitive performance and hippocampal neurogenesis (survival and differentiation) in PS female and male rats. The response of the adrenal axis to training in the Morris water maze (MWM) was also analyzed. PS was provided during gestational days 15 through 21. Hippocampal neurogenesis and cognitive performance in the MWM were assessed at an age of three months. Results showed that escape latencies of both female and male PS rats were longer compared to those of their controls (CON). DG cell survival increased in the PS female rats. Corticosterone concentrations were significantly higher in the male and female PS rats after MWM training. PTS improved escape latencies and increased the number of new neurons in the DG of PS animals, and their corticosterone concentrations were similar to those in CON. In CON, PTS diminished DG cell survival but increased differentiation and reduces latency in the MWM. These results show that long-term PTS in PS animals might prevent learning deficits in adults through increase in the number of DG new cells and decrease of the reactivity of the adrenal axis to MWM training.

1. Introduction

Prenatal stress (PS) has been associated with a variety of pathologies and behavioral alterations during postnatal life (Politch and Herrenkohl, 1984; Maccari et al., 1995; Tuchscherer et al., 2002), probably, due to exposure to high corticosterone and catecholamine levels released by the mother as a response before stress, which increases blood concentration of these molecules in the fetus (Ward and Weisz, 1984; Takahashi et al., 1998; Weinstock et al., 1988; Rohde et al., 1983). Several studies have shown the association between PS and diverse alterations such as hyper reactivity of the hypothalamic-pituitary-adrenal (HPA) axis (Koehl et al., 1999; Szuran et al., 2000; Welberg and Seckl 2001), anxiety (Archer and Blackman 1971; Vallée et al., 1997), and learning and memory deficits during the offspring adult life (Hayashi et al., 1998; Vallée et al., 1999; Szuran et al., 2000; Gué et al., 2004) being males more severely altered than females (Lemaire et al., 2000; Zagron and Weinstock, 2006; Yaka et al., 2007; Salomon et al., 2011).

PS, produced either by immobilization for 20–30 min three times a day or by paw electric shocks, results in slow acquisition during spatial learning (Weinstock, 2007). These effects have only been observed in males (Zagron and Weinstock, 2006). However, deterioration in spatial learning due to PS by immobilization has also been reported in females (Gué et al., 2004; Li et al., 2008; Wu et al., 2007). Cognitive deficits due to PS have been associated with changes in neuronal morphology in the hippocampus, a structure highly responsive to stress, with a key role in stress inhibition and playing a role in cognitive and emotional processes (McEwen 2003; Abrous et al., 2005). PS causes reduction in the number of stem cells derived from the sub ependymal lateral ventricle from birth through adult life (Kippin et al., 2004). This reduction has been asso-

Abbreviations: DG, dentate gyrus; LTD, long term depression; MWM, Morris water maze; PS, prenatal stress; PTS, postnatal tactile stimulation.

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ciated to suppression of long-term potentiation (LTP), and increase of long-term depression (LTD) (Ishiwata et al., 2005; Lemaire et al., 2000; Son et al., 2006; Yang et al., 2006). Synaptic density reduction in dendrites of pyramidal neurons of the hippocampal CA3 region has also been reported (Ishiwata et al., 2005; Hosseini-sharifabad and Hadinedoushan, 2007).

Generation of new neurons, neurogenesis, in the dentate gyrus (DG) of the hippocampus occurs during adult life, as well (Abrous et al., 2005), and is related with learning and memory processes (Marín-Burgin and Schinder, 2012). Thus, the number of granular cells and their survival rate increase during spatial learning, which is a hippocampus-dependent task (Gould et al., 1999; Gould and Gross, 2002). This way, neurogenesis plays an important role in cognitive processes. As opposed, PS and glucocorticoid administration during gestation inhibit neuronal proliferation in the hippocampus (Yu et al., 2004), and has been related to deterioration in spatial-learning performance (Abrous et al., 2005; Lemaire et al., 2000; Lemaire et al., 2006).

Otherwise, experiences acquired during the newborn stage might modify behavior, neuroendocrine function and brain structure (Champagne et al., 2009; Daskalakis et al., 2009). These experiences could redirect the development of the immature brain, which is highly plastic, and permanently alter the cognitive and behavioral development of the organism (Greenough 1987; Raineki et al., 2013). Animals with maternal separation during the early postnatal stage show long-term improvement in spatial learning and memory (Kosten et al., 2012). In addition, corticosterone secretion during stress response is decreased in these animals (Levine, 1962; Meaney et al., 1988; Ogawa et al., 1994; Vallée et al., 1997). Adult animals exposed to an enriched environment for a month show increased length and complexity of dendritic arborization and increased density of dendritic spines in prefrontal cortex and hippocampus (Kozorovitskiy et al., 2005). Moreover, decreased neurogenesis in the hippocampal DG due to PS in male rats may be reverted by postnatal stimulation through maternal separation during the first three weeks of postnatal life (Lemaire et al., 2006). Currently there are no reports which examine simultaneously the effect of postnatal stimulation on cognitive processes, neurogenesis as well as the activity of the HPA axis in PS offspring, females and males. Hence, the objective of this work was to test if long-term tactile stimulation in PS female and male rats improves cognitive performance as well as cellular survival and differentiation in the DG of the hippocampus and reduces the reactivity of the adrenal axis. Corticosterone serum levels in the gestating rats were also measured.

2. Materials and methods

Animal management and experiments were carried out in accordance with Mexican official norms (NOM-062-ZOO-1999), and the domestic and laboratory animal regulation published in the Ethical conduction guidelines for research, teaching and dissemination of the Division de Ciencias Biologicas y de la Salud (2010).

2.1. Animals

Three-month-old, pregnant Wistar female rats (n = 33) from the *vivarium* of the Universidad Autónoma Metropolitana Iztapalapa housed in transparent plexiglas individual cages were used. Animals were maintained in optimal conditions of constant room temperature (22 ± 2 °C), reverse light-dark cycle (12-h: 12-h, lights of at 1000) and continuous *ad libitum* access to food and water.

2.2. Prenatal stress

During the last gestational week (days 15 through 21), pregnant females of the PS group (n = 18), went through two stress sessions by immersion in cold water at 1000 and 1500 h (Lemaire et al., 2000). Rats were individually set in a Plexiglas cage filled with water at 15 °C and a height of 15 cm for 15 min per stress session. The cage was covered with a grill to prevent rats to escape. Females of the control group (n = 15) were kept in their cages and were only exposed to routine cage cleaning. After delivery, number of offspring in litters were homogenized within their respective group. Pups remained with their mother until weaning (day 21 of postnatal life). Pups were distributed into groups as follows: females, CON (n = 55) and PS (n = 50); males, CON (n = 54) and PS (n = 53).

2.3. Postnatal tactile stimulation

Pups undergoing postnatal tactile stimulation (PTS) from PS and CON groups were distributed as follows: CON females with PTS (female PTS group), n = 26; PS females with PTS (female PS + PTS group), n = 25; CON males with PTS (male PTS group), n = 25; PS males with PTS (male PS + PTS group), n = 25. PTS involved the researcher to slide her fingers on the back of every rat (using index, middle, ring and little fingers) in a cephalo-caudal direction during 60 s (Imanaka et al., 2008). The procedure was carried out daily between 1000 and 1100 h, from birth to the age of three months.

2.4. Spatial navigation task

Spatial learning and memory were evaluated using the Morris water maze (MWM) task. MWM consisted of a cylindrical pool (170 cm of diameter and 50 cm of height) surrounded by white walls. The pool was filled with water to a height of 30 cm and water was kept at a temperature of 21 ± 2 °C.

The pool was divided into four imaginary quadrants tagged according to the cardinal points (NE, north-east; north-west, NW; SE, south-east; SW, south-west) and considering the starting quadrant as the reference. Three colorful images were set on the walls of the room as special visual cues. An acrylic transparent platform (19 cm × 22 cm) was set 2 cm under the water surface in the NE quadrant, equidistantly to the wall and the center of the maze.

When the animals reached three months of age, they underwent learning sessions consisting of four trials per session during four consecutive days (days 1–4). At day 6 (48 h later), a single-trial memory session with the platform was carried out and the latencies were registered. Also, a memory session was carried out 24 h after the single trial session (day 7) consisting of a single trial without the platform, and letting the rat to swim for 60 s. All the trials were recorded. Thirteen days after the first learning session, a single-trial session with the platform inside the maze was carried out. Trials started when the rat was set on the water with the snout pointing at the pool wall. The starting quadrant changed from trial to trial. For the first trial, if a rat did not find the platform within a period of 60 s, the experimenter guided the rat to the platform and left it on the platform for 30 s (Kapoor et al., 2009). When rats found the platform within the 60 s period, they were left there for 30 s.

The behavioral measurements analyzed were: latency to reach the platform for the learning sessions, and time spent in the platform quadrant and number of platform-site crossovers for the memory sessions.

2.5. Administration of the DNA-synthesis marker 5-bromo-2′-deoxyuridine (BrdU)

Female (n = 4) and male (n = 4) rats of every group were daily i.p. injected with BrdU (Sigma, USA, 50 mg/kg) dissolved in 0.9% NaCl