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Histone deacetylase inhibition abolishes stress-induced spatial memory impairment

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ABSTRACT

Acute stress induced before spatial training impairs memory consolidation. Although non-epigenetic underpinning of such effect has been described, the epigenetic mechanisms involved have not yet been studied. Since spatial training and intense stress have opposite effects on histone acetylation balance, it is conceivable that disruption of such balance may underlie acute stress-induced spatial memory consolidation impairment and that inhibiting histone deacetylases prevents such effect. Trichostatin-A (TSA, a histone deacetylase inhibitor) was used to test its effectiveness in preventing stress' deleterious effect on memory. Male Wistar rats were trained in a spatial task in the Barnes maze; 1-h movement restraint was applied to half of them before training. Immediately after training, stressed and non-stressed animals were randomly assigned to receive either TSA (1 mg/kg) or vehicle intraperitoneal injection. Twenty-four hours after training, long-term spatial memory was tested; plasma and brain tissue were collected immediately after the memory test to evaluate corticosterone levels and histone H3 acetylation in several brain areas. Stressed animals receiving vehicle displayed memory impairment, increased plasma corticosterone levels and markedly reduced histone H3 acetylation in prelimbic cortex and hippocampus. Such effects did not occur in stressed animals treated with TSA. The aforementioned results support the hypothesis that acute stress induced-memory impairment is related to histone deacetylation.

1. Introduction

Although it is usually an adaptive response, depending on its intensity or reiteration stress can enhance or impair hippocampus-dependent memory (Sandi & Pinelo-Nava, 2007). It has been described that intense or chronic stress impairs spatial memory (Kim & Diamond, 2002). In this sense, acute stress induced before spatial training has a deleterious effect on spatial memory consolidation without affecting spatial acquisition (Almaguer-Melian et al., 2012; Diamond et al., 2006; Kim, Koo, Lee, & Han, 2005; Kim, Lee, Han, & Packard, 2001; Park, Zoladz, Conrad, Fleshner, & Diamond, 2008; Sandi et al., 2005); such stress-induced consolidation impairment in spatial as well as in non-spatial tasks has been associated to cellular and molecular alterations, including significant reduction of total and phosphorylated Ca^{2+}/calmodulin-dependent protein kinase II (pCAMK-II), phosphorylated cAMP response element-binding (pCREB), transcription factor c-fos expression, brain-derived neurotrophic factor (BDNF), neural cell adhesion molecule (NCAM), activity-regulated cytoskeleton-associated protein (Arc), and dendritic spine density in the hippocampus (Almaguer-Melian et al., 2012; Diamond et al., 2006; Sandi et al., 2005; Sardari, Rezayof, & Khodagholi, 2015; Vanelzakker et al., 2011; Zoladz et al., 2012). By contrast, epigenetic mechanisms involved in acute stress-induced memory impairment have not been reported.

Due to the emerging interest in the epigenetic mechanisms involved in learning and memory, it has been found that training in several hippocampus-dependent learning tasks promotes histone acetylation in rodents' hippocampus and prelimbic cortex several hours after training (Bousiges et al., 2010; Dagnas, Micheau, Decorte, Beracochea, & Mons, 2015; Dagnas & Mons, 2013; Gräff, Woldemichael, Berchtold, Dewarrat, & Mansuy, 2012; Levenson et al., 2004). On the other hand, it has been reported that persistent or high intensity stress reduces histone acetylation (Benoit, Rakic, & Frick, 2015; Miller et al., 2011; Rei et al., 2015; Sailaja, Cohen-Carmon, Zimmerman, Soreq, &

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Meshorer, 2012; Tran, Schulkin, Ligon, & Greenwood-Van Meerveld, 2014). Similarly, adult animals receiving prenatal stress display spatial memory impairment and reduced histone H3 lysine 14 acetylation (acH3K14) (Benoit et al., 2015). Furthermore, chronic stress impairs recognition memory through up-regulation of glucocorticoid receptor activity and histone deacetylase 2 (HDAC2) expression and down-regulation of memory related genes in the hippocampus (Rei et al., 2015). Taking this evidence together, it is plausible that acute stress-induced memory impairment could be mediated by enhanced histone deacetylase activity.

In fact, pharmacological inhibition of histone deacetylases prevents acute- and chronic-stress induced anxiety (Miyagawa, Tsuji, & Takeda, 2012; Tran et al., 2014), chronic stress-induced visceral pain and somatic hypersensitivity (Tran, Chaloner, Sawalha, & Greenwood Van-Meerveld, 2013), and cognitive deficits observed in neurodegenerative diseases (Didonna & Opal, 2015; Rumbaugh et al., 2015); however, its effectiveness in preventing stress-induced memory impairment has not been studied. The potential of TSA (an effective inhibitor of zinc-dependent histone deacetylases; Sanderson et al., 2004) to impede acute stress-induced memory impairment was tested in order to determine the role of histone deacetylation in such deleterious effect.

2. Materials and methods

2.1. Animals

Forty-three, naïve, male Wistar rats weighing 300 ± 15 g (mean ± standard error of the mean), supplied by the Instituto Nacional de Salud (Bogotá, Colombia), were used as subjects. Animals were housed in a sound-attenuated room in polycarbonate cages (32 × 38 × 18 cm) in groups of four, had free access to water and food during the whole experiment and were kept in controlled environmental conditions: 12-h light/dark cycle (lights on from 07:00 to 19:00), 20 ± 1 °C room temperature, and 50 ± 10% relative humidity. Animals were kept in the laboratory for one week before any experimental procedure to allow them to become acclimatized to their new housing conditions. Behavioral procedures were conducted between 08:00 and 13:00 to avoid circadian corticosterone peak. All experimental procedures were performed according to local and international guidelines (NIH Guide for the Use and Care of Laboratory Animals) and were approved by the local Ethics Committee (School of Medicine, Universidad Nacional de Colombia).

2.2. Experimental design

After acclimatization, animals underwent a habituation session (Fig. 1, Day 1). The next day they were randomly assigned either to be subjected to stress (Stress) or to stay in their cages without manipulation (No-Stress) before being trained in the spatial task. At the end of training, animals from each group were randomly assigned to be injected either with TSA or vehicle (VEH), thereby forming four groups (Fig. 1, Day 2): (a) No-Stress/VEH (n = 9), (b) No-Stress/TSA (n = 9), (c) Stress/VEH (n = 9), and (d) Stress/TSA (n = 9). Experimental design had two factors: pharmacological treatment (Vehicle or TSA) and stress (No-Stress or Stress).

2.3. Acute stress induction

Animals randomly assigned to be submitted to stress were gently placed in polycarbonate cylinders (20 cm long, 6.5 cm in diameter) for 1 h to restraint major movements (Buynitsky & Mostofsky, 2009; Ortega et al., 2013; Pacák & Palkovits, 2001), and then allowed to get out of the restrainers 30 min before acquisition trials and to move freely around their home cages to avoid non-specific motor effects. Animals assigned to the no-stress condition stayed in their home cage before acquisition trials.

2.4. Drugs

Trichostatin A (TSA – Sigma, St Louis, MO, USA) was dissolved in dimethyl-sulfoxide (DMSO) and diluted in saline solution to reach 18% DMSO concentration and 1 mg/ml TSA final concentration. This solution was injected intraperitoneally (i.p., 1 ml/kg) into animals designated to receive TSA. Dosing was chosen on the basis of reports demonstrating that it increases histone acetylation in hippocampal neurons (Sng, Taniura, & Yoneda, 2005) and enhances memory consolidation (Fontán-Lozano et al., 2008). 18% DMSO in saline was injected i.p. (1 ml/kg) into animals designated to receive vehicle (VEH). TSA and VEH were administered immediately after the acquisition trials.

2.5. Abbreviated spatial training

As formerly described (Vargas-López, Lamprea, & Múnera, 2011), rats were trained on a 122 cm diameter, black acrylic circular platform placed 80 cm above the floor with 18 evenly-spaced peripheral holes. A randomly chosen hole (escape hole) allowed the animal to get into the escape box. At the beginning of any trial, the animal was placed in the platform's center inside a start box. The labyrinth was placed at the center of a square room having white walls and floor. High-contrast signals were fixed in the walls of the experimental room giving the subject extra-maze visual cues. A 90-dB white-noise generator and two white-light 150-W bulbs placed above provided motivation for escaping from the platform. Whenever the white-light bulbs were switched off, a 20-W red light was switched on to permit subject's removal and olfactory clue elimination using 10% ethylic alcohol solution.

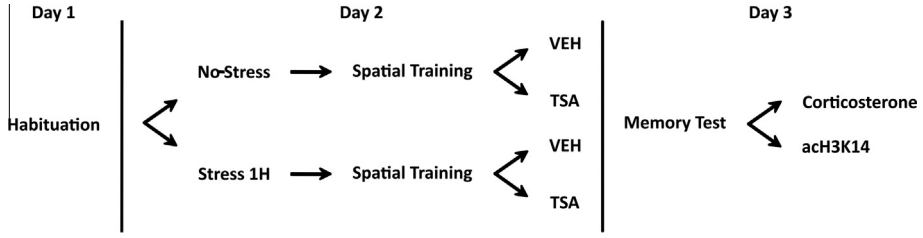

Fig. 1. Experimental design. Animals were habituated to the experimental room and Barnes maze during day 1. At the beginning of day 2, animals were randomly assigned to either No-Stress or Stress groups. Animals assigned to undergo stress were subjected to movement restriction during 1 h and the remaining animals (No-Stress) were manipulated and returned to their home-cage. Both groups' animals were trained in a spatial task in the Barnes maze. Immediately after training, animals from each group were randomly assigned to receive an intraperitoneal injection of either vehicle (18% dimethylsulfoxide in saline solution, VEH) or 1 mg/kg of trichostatin A (TSA). Twenty-four hours later (Day 3), all animals underwent a single memory test trial (without escape box) to evaluate stress and TSA effects on long-term spatial memory. Blood samples and brain tissue were collected immediately after memory test to perform either plasma corticosterone measurement or histone acetylation immunohistochemistry.