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Depressive behavior induced by unpredictable chronic mild stress increases dentin hypersensitivity in rats

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ABSTRACT

Objective: The present study evaluated the nociceptive response induced by dentin hypersensitivity after dental erosion in rats that were exhibited to unpredictable chronic mild stress (UCMS)-induced depressive-like behavior.

Design: Adult male rats were subjected to UCMS (depression [D] group) or not (no depression [ND] group) for 30 days and received either acidic solution to induce dental erosion (E) or water (W), thus forming the WND, END, WD, and ED groups. After the end of treatment, depressive-like parameters (i.e., sucrose preference and immobility in the forced swim test) and dentin hypersensitivity were evaluated. Plasma tumor necrosis factor α (TNF-α) and corticosterone levels were measured, and astrocytic glial fibrillary acidic protein (GFAP) expression was evaluated in the prefrontal cortex, hippocampus, amygdala, and hypothalamus.

Results: Administration of the acidic solution potentiated dentin hypersensitivity and increased corticosterone levels in the ED group compared with the WD group. TNF-α levels only increased in the WD group. The ED group exhibited an increase in astrocytic GFAP expression in the hypothalamus and prefrontal cortex but decreases in the hippocampus.

Conclusions: These results suggest that UCMS exacerbated the nociceptive response associated with dentin hypersensitivity, concomitant with an increase in plasma corticosterone levels. Hypothalamic and prefrontal cortex astrogliosis in the ED group may be attributable to the increase in corticosterone associated to UCMS procedure. The reduction of astrocytic GFAP expression in the hippocampus in the ED group supports the association between dentin hypersensitivity and depression.

1. Introduction

Depression is characterized by alterations in mood and cognitive function and recurrent thoughts of death or suicide, with a lifetime incidence of 15–25% (Paykel, 2006). Depression directly affects not only the patients themselves but also their families and job performance, accounting for a high cost to society (Ustün, Ayuso-Mateos, Chatterji, Mathers, & Murray, 2004). Mood disorders are one of the most common types of mental disorders, approximately 75% of which are depressive disorders, making them a leading cause of disability worldwide (Ferrari et al., 2013; Stovner, Hoff, Svalheim, & Gilhus, 2014).

Although depression and pain are common comorbidities, their interaction is not fully understood (Shi, Wang, & Luo, 2010). Depression is often associated with a higher incidence of clinical pain complaints. Thus, comorbid pain and depression have been suggested to be a common phenomenon (Bair, Robinson, Katon, & Kroenke, 2003). Animal studies have shown either reduced or enhanced responses in nociceptive tests, depending on the animal model and experimental procedures. Exposure to unpredictable chronic stress has been reported to increase nociceptive thresholds in response to thermal and mechanical stimuli (Pinto-Ribeiro, Almeida, Pêgo, Cerqueira, & Sousa, 2004; Shi, Wang et al., 2010), causes hyperalgesia in response to persistent inflammatory pain (Forbes, Stewart, Matthews, & Reid, 1996), and reduces mechanical allodynia following nerve injury (Shi, Qi, Gao, Wang, & Luo, 2010).

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Dentin hypersensitivity is defined as a response to the stimulation of vital dentin that is exposed to thermal, volatile, tactile, osmotic, or chemical stimuli in the oral environment, causing extreme discomfort to the patient. It is characterized by short-term, acute pain of variable intensity (West, Seong, & Davies, 2014). The etiology of dentin hypersensitivity is multifactorial, but the importance of enamel erosion has become more evident (Walters, 2005). Pain may be localized or generalized, affecting the surface of one tooth or many teeth simultaneously, and generally ceases immediately after removal of the stimulus (West et al., 2014). The most widely accepted theory to explain pain that results from dentin hypersensitivity is Hydrodynamic Theory (Brännström, 1963). This theory is based on the movement of dentinal fluid that, in turn, excites mechanoreceptors in the periphery of the pulp. The prevalence, distribution, and presentation of dentin hypersensitivity have been reported in many studies. Differences in these characteristics have been attributed to different patient populations, habits, and diets. Davari et al. (Davari, Ataei, & Assarzadeh, 2013) reported a prevalence of 5–85% in adult populations with non-carious cervical lesions, including erosion lesions, which are among the most common clinical complaints of dental patients.

Although some treatments have been suggested in the literature, they are not always sufficient or successful. We sought to investigate possible physical or psychological influences on nociceptive perception. Dentin hypersensitivity can affect the patient's quality of life and consequently negatively influence dietary and oral health (Davari et al., 2013).

We previously showed that treatment with an acidic solution for 30 days caused dentin hypersensitivity after erosive challenge, and severe dentin hypersensitivity was observed after acidic solution treatment for 45 days (Bergamini et al., 2014). Nociceptive behavioral response that was induced by cold stimuli was consistent with the grade of erosion. Additionally, chronic stress plays an important role in dentin hypersensitivity, reflected by an increase in corticosterone levels, a decrease in body weight, and behavioral data (Bergamini et al., 2016).

The present study evaluated the nociceptive behavioral response that was induced by dentin hypersensitivity after dental erosion in rats that exhibited depressive-like behavior induced by unpredictable chronic mild stress (UCMS). The UCMS procedure is a classic animal model of depression (D'Aquila, Brain, & Willner, 1994; Forbes et al., 1996; Papp, Willner, & Muscat, 1991). Dentin hypersensitivity was evaluated, and depressive-like parameters were assessed by evaluating sucrose preference and immobility in the forced swim test. We also determined plasma tumor necrosis factor α (TNF-α) and corticosterone levels and astrocytic glial fibrillary acidic protein (GFAP) expression in the prefrontal cortex, hippocampus, amygdala, and hypothalamus.

2. Material and methods

2.1. Animals

Thirty-five male Wistar rats, weighing 320–350 g at the beginning of the experiments, were used. The rats were housed in polypropylene cages (38 cm × 32 cm × 16 cm, 5 rats/cage) at a controlled room temperature (22 ± 2 °C) with artificial lighting (12 h/12 h light/dark cycle, lights on at 8 A.M.) with free access to Nuvilab rodent food (Nuvital, São Paulo, Brazil) and filtered water or acidic solution.

Sterilized and residue-free wood shavings were used as animal bedding. The experiments began at least 10 days after the rats arrived in the laboratory. The animals were maintained in accordance with the guidelines of the Committee on the Care and Use of Laboratory Animal Resources of Paulista University, São Paulo, Brazil (protocol no. 227/14, CEUA/ICS/UNIP). These guidelines conform with those of the National Research Council (Committee, 2011).

2.2. Dental erosion and dentin hypersensitivity test

Erosion was assessed by offering the rats an acid solution (Gatorade®, lemon flavor, pH 2.7) as drinking water for 30 or 45 days. DH test was performed by cold water stimuli (jet of cold water 4 °C, 0.5 ml, assessed by a syringe provided with a metal cannula), applied for 5 s, on the labial surface of molars (the rearmost teeth in the mouth). Three days before the test, the rats were daily habituated to the test manipulation. The animal's response to nociceptive stimulus was scored (0 = no response; 0.5 = slight contraction of the body; 1 = body contraction; 2 = strong body contraction and a short vocalization; 3 = strong body contraction and a prolonged vocalization). The scores were independently attributed by two observers and the mean score attributed by each one was employed in the DH evaluation. This method was previously validated in our laboratory (Bergamini et al., 2014).

2.3. Unpredictable chronic mild stress procedure

The UCMS procedure is used to induce a depressive-like state in rats (D'Aquila et al., 1994; Forbes et al., 1996; Papp et al., 1991). We adapted this method based on Forbes et al. (1996). Briefly, the stressors were unpredictable with regard to their nature, duration, and frequency. The procedure lasted for 30 days and consisted of one different stressor each day. It included 24-h water deprivation, 24-h deprivation of acidic solution or food, 5-min swimming in 4 °C water, heating the paws at 45 °C, restriction of movements and shaking, 5-min stressful handling, exposure to a dirty cage, 1 h ventilation cageless (turn off the ventilation of the cage which increases the smell of the ammonia and other wastes), 1-min tail grip clamp, and 24-h exposure to a wet cage. The stressors were presented in a pseudo-random order. To evaluate depressive-like behavior that was caused by UCMS, the rats were subjected to the Porsolt forced swim test (Porsolt, Anton, Blavet, & Jalfre, 1978) and sucrose preference test (Pollak, Rey, & Monje, 2010).

2.4. Forced swim test

The forced swim test is used to evaluate the antidepressant efficacy of drugs and experimental manipulations that seek to cause or prevent depressive-like states (Slattery & Cryan, 2012). Exposure to the swim tank 24 h before the test session is required to discern antidepressant and depressant effects. In the afternoon on the last day of the UCMS procedure, the rats were trained to swim for 10 min in a 20 cm diameter cylindrical tank that was filled with 26 °C water to a depth of 30 cm. The wall of the tank was sufficiently high that the rats could not escape. The next day, the rats were placed again in the tank for a 5 min test session. The latency to immobility and time spent immobile were measured (in seconds).

2.5. Sucrose preference test

Before the UCMS and dental erosion procedures, the animals were trained to consume increasing concentrations of sucrose up to 2%. Baseline sucrose preference over a 48-h period was determined. Afterward, the UCMS procedure was conducted for 4 weeks. Sucrose consumption was evaluated again 48 h after the UCMS procedure was completed. The sucrose preference test was conducted at 9:00 A.M. in the rats' home cage following 24 h of water deprivation. Two rats per cage were presented simultaneously with two bottles, one that contained 2% sucrose solution and one that contained water. The percentage of sucrose preference was calculated according to the following formula: *% sucrose preference = (sucrose solution consumption/[sucrose solution consumption + water consumption]) × 100.*