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Repeated paroxetine treatment reverses anhedonia induced in rats by chronic mild stress or dexamethasone

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Abstract The present study was designed to assess the effect of dexamethasone, a synthetic glucocorticoid receptor agonist, in the sucrose preference test in rats. Rats treated acutely with dexamethasone (5–10 mg/kg) showed a significant decrease in sucrose preference (anhedonia) in comparison to vehicle treated rats, although 1 mg/kg dexamethasone did not alter the sucrose preference. Daily paroxetine treatment (10 g/kg, i.p., 14 days) reversed the anhedonic effect of acute dexamethasone (5 mg/kg), while causing no increased sucrose preference in rats that received dexamethasone vehicle. The paroxetine vehicle treated rats showed anhedonia even 14 days after acute dexamethasone administration. Paroxetine (10 mk/kg, i.p. for 28 days) also reversed anhedonia induced by chronic mild stress (8 weeks). In conclusion, acute dexamethasone induced an enduring anhedonic state that was reversed by repeated paroxetine treatment. Thus, the present study adds new data to the evidence supporting an important role for glucocorticoid in depression.
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1. Introduction

The precipitation of a depressive episode has been linked to stressful life events (Paykel, 2003), which can activate the hypothalamic–pituitary–adrenal (HPA) axis leading to an increase in plasma cortisol. Furthermore, dysregulation of HPA; such as lack of cortisol suppression by dexamethasone administration, increased cortisol secretion and blunted adrenocorticotropic hormone response to exogenous corticotropin-releasing hormone; are frequently associated with depression, suggesting that depression is related to a failure in HPA negative feedback, which would result in higher cortisol levels (Checkley, 1992; Holsboer, 2001; Barden, 2004; Juruena et al., 2004). This stress-induced increase in cortisol secretion is one underlying mechanism proposed for the stress-depression association (Holsboer, 2001; Mello et al., 2003; Paykel, 2003). The hippocampus, which shows signs of atrophy in patients with prolonged depression (Campbell and MacQueen, 2004), is vulnerable to stress and increased glucocorticoid levels (Campbell and MacQueen, 2004; McEwen, 2005). Since the hippocampus exerts a negative control over the hypothalamic–pituitary–adrenal (HPA) axis, its atrophy may induce impairment in HPA control, leading to cortisol hypersecretion (Holsboer, 2001; Barden, 2004). Thus, glucocorticoid is thought to play a major role in hippocampal

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atrophy and depressive symptoms. In this context, chronic antidepressant administration was shown to increase corticosteroid receptors, which can restore HPA negative feedback and normalize cortisol levels and HPA function (Barden, 2004). Furthermore, an abnormal dexamethasone suppression test after treatment-induced clinical improvement is associated with a higher risk of relapse and may present prognostic value for treatment (Dratcu and Calil, 1989; Ribeiro et al., 1993). Thus, it appears that there is an interrelationship between stress, high glucocorticoid levels and depression.

Several animal models of depression, such as the forced swim test, learned helplessness and anhedonia induced by unpredictable chronic mild stress, involve behavioral responses to stressful procedures. The anhedonia induced by unpredictable chronic mild stress consists in the repeated exposure of animals to unpredictable mild stress: tilted cage, food deprivation, paired caging, reduction of cage area, etc.; leading to a reduction in self-stimulation of rewarding areas or in the consumption of palatable food or liquids, i.e. anhedonia. This model yields good similarity with clinical depression, since it was found that stressful life events frequently precede major depression episodes (Paykel, 2003; Willner, 2005). This model has also good face validity, since anhedonia, described as a marked diminished interest or pleasure in events that would normally be enjoyable, is a core symptom of major depression episodes according to DSM-IV criteria (American Psychiatric Association, 1994; Willner, 2005). Furthermore, the reversal of anhedonia induced by unpredictable chronic mild stress requires 2–4 weeks of daily antidepressant treatment (Willner, 1997; Stout et al., 2000; Willner, 2005), again showing good parallels with clinical data. Therefore, the chronic mild stress paradigm is adequate for providing insight into the neurobiology of depression (Willner, 1997, 2005). However, the anhedonia induced by unpredictable chronic mild stress was not reliably observed in some experiments (Harris et al., 1997; Nielsen et al., 2000; Bielajew et al., 2002). Another problem is that although some studies found an increase in plasma corticosterone in this model (Ayensu et al., 1995; Harris et al., 1997; Bielajew et al., 2002; Froger et al., 2004; Grippo et al., 2005a; Song et al., 2006), this effect was not consistently observed (Harris et al., 1997; Stout et al., 2000; Grippo et al., 2005b). Although these inconsistencies could be related to the strain of the experimental animals or procedural differences (e.g. nature, duration or frequency of stress) among the studies, they may be also related to individual variability and styles of coping with stress (Nielsen et al., 2000; Bielajew et al., 2002; Veenema et al., 2003; Anisman and Matheson, 2005). The administration of exogenous glucocorticoid would avoid some of these variables in the study of the role of glucocorticoid in stress-induced depression.

Thus, the main objective of the present study was to evaluate the effect of acute administration of dexamethasone, a synthetic glucocorticoid that binds to glucocorticoid receptors, on the sucrose preference of rats; a measure of anhedonia. If the dexamethasone-effect on anhedonia plays a significant role in depression neurobiology, it should be reversed by repeated antidepressant administration. Therefore, the influence of chronic treatment with paroxetine, a clinically effective antidepressant drug, regarding the effect of dexamethasone on anhedonia was also studied.

2. Methods

2.1. Subjects

Adult male Wistar rats weighing between 200 and 300 g were used. The rats were housed in polypropylene cages with wood shavings as bedding, under controlled room conditions of light (12-h light–dark cycle, lights on at 7:00 a.m.) and temperature (22 ± 2 °C), with free access to food and water, except prior to the sucrose preference test or when they were submitted to chronic mild stress (see below). Two rats were housed in each cage (cage size: 41 × 32 × 16.5 cm) but they were isolated by a central aluminum wall, which divided the cage in two equal compartments and permitted minimal contact between them, but neither one consumed the food or water/sucrose solution of the other. Thus, the rats were not absolutely isolated. All procedures were carried out in compliance with the NIH Guide for the Care and Use of Laboratory Animals (Committee to Revise the Guide for the Care and Use of Laboratory Animals, 1996).

2.1.1. Drugs

Paroxetine (Eurofarma, São Paulo, Brazil) was dissolved in distilled water. Dexamethasone-acetate (DEG, Curitiba, Brazil) was suspended in saline containing 0.2% Tween 80. The vehicle of each drug was administered in the respective control rats. All drugs were administered intraperitoneally (i.p.) at a constant volume of 1.0 ml/kg. Dexamethasone or its vehicle was administered once, while paroxetine or its vehicle was administered for 14 (dexamethasone-induced anhedonia) or 28 days (chronic mild stress experiment). The paroxetine dose was chosen on the basis of previous studies in our laboratory (Consoni et al., 2006; Beijamini and Andreatini, 2003).

2.2. Sucrose preference test

In all experiments, prior to the first sucrose preference test, all the rats were submitted to 48 h of forced exposure to 1% sucrose solution in order to habituate to it, during which sucrose solution was the only fluid available for consumption, followed by two days of free access to food and water. After this, the rats were submitted to water deprivation for 16 h prior to performing the sucrose preference test; baseline test at day zero. The sucrose preference test was performed in the rat's home cage: two pre-weighted bottles, one containing tap water and another containing 1% sucrose solution, were presented to each rat. The bottles were weighed again after 1 h and the weight difference was considered to be the rat intake from each bottle. The sum of water and sucrose intake was defined as total intake and the sucrose preference was expressed as the percentage of sucrose intake from the total intake following the formula:

$$\%\ \text{sucrose preference} = \text{sucrose intake} \times 100 / \text{total intake}$$

All tests were carried out weekly (each Tuesday) between 8:00 and 10:00 am, with a variable sequence of bottle positioning (for each rat, the side of sucrose or water bottles were changed from one test to another), in order to avoid habituation. After the sucrose preference test, all the rats received free access to food and water. After the baseline sucrose preference test, and prior to drug treatment or stress administration, the rats were paired according their preference and then distributed in experimental groups to form paired (matched) groups.

2.3. Chronic mild stress (experiment 1)

The rats were initially divided into two groups: stressed and nonstressed. The stressed group received a stress regimen over an eight-week period, consisting of weekly "unpredictable" (in fact, a pseudorandom sequence) mild stress, such as food and/or water

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