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Folic acid prevents depressive-like behavior induced by chronic corticosterone treatment in mice

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ABSTRACT

The objective of this study was to investigate the effects of folic acid on depressive-like behavior induced by chronic administration of corticosterone in mice. Corticosterone (20 mg/kg, p.o.) was administered once a day for 21 days. Folic acid (30 mg/kg, p.o.) or fluoxetine (10 mg/kg, positive control, p.o.) was administered immediately after corticosterone injection during the last 7 days of corticosterone treatment. On the 22nd day, animals were submitted to tail suspension test, open-field test and splash test. Corticosterone treatment caused a depressive-like behavior, evidenced by increased immobility time in the tail suspension test and decreased time in which mice spent grooming in the splash test. Repeated folic acid or fluoxetine administration significantly abolished corticosterone-induced depressive-like behavior. Chronic administration of corticosterone decreased levels of serum corticosterone in mice. Neither folic acid, nor fluoxetine treatment reversed this impairment. These findings indicate a robust effect of folic acid in reversing behavioral alterations induced by corticosterone model of depression in mice, suggesting that this vitamin may be an alternative approach for the management of depressive symptoms.

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1. Introduction

Depression is a chronic, multi-factorial and incapacitating psychiatric disorder often associated with high morbidity and mortality throughout the world (Nemeroff, 2007). Lifetime prevalence for depression varied from 4.4 to 20% in general population and it is commonly associated with increased physical illness and decreased social functioning (Nemeroff et al., 1998; Wong and Licinio, 2001; Nestler et al., 2002). A depressed patient may experience low mood, anhedonia, altered appetite and weight, irritability, sleep disturbances, and psychomotor agitation or retardation (Uher et al., 2014).

Numerous studies associate depression with stress by showing that stressful life events have an important causal relationship with the onset of depressive episodes (Heim and Nemeroff, 2001; Hammen, 2005). Several findings have shown hypothalamic–pituitary–adrenal (HPA) axis dysfunction in stress-related illnesses, including depression (Juruena et al., 2004; Swaab et al., 2005). The HPA axis receives information from other neural structures including hippocampus and amygdala, and its activity has direct action on glucocorticoids production. Rapid corticosteroid actions in the brain include, among others, a fast negative feedback at the level of the anterior pituitary gland, which leads to suppression of the activated HPA axis (Keller et al., 2006). Excessive activity of the HPA axis was pointed out as significant risk factor for depression (Sterner and Kalynchuk, 2010). Accordingly, clinical evidence has reported that cortisol levels are generally higher in depressed patients compared to healthy controls (Keller et al., 2006), an effect which is reduced by fluoxetine treatment (Piwowarska et al., 2012). Despite these findings, it is important to mention that depression is a heterogeneous disorder and that HPA axis function can be differently regulated in melancholic and atypical depression. A hypoactivation of the stress system, rather than sustained activation, is a consistent finding in patients with atypical and seasonal depression (Gold and Chrousos, 2002).

Preclinical studies corroborate the association between stress and depression. Mice repeatedly exposed to different stressors present depressive-like behavior (Zhao et al., 2008) generally associated with increased levels of serum corticosterone, the rodent homologue of cortisol (Gregus et al., 2005). Moreover, repeated corticosterone treatment in rats causes increase in immobility time in the forced swimming test (FST), an indicative of depressive-like behavior (Iijima et al., 2010). Exposing animals to chronic corticosterone also results in physiological alterations associated with depressive behavior, including reduced body weight gain and adrenal weights (Fernandez et al., 2001; Johnson et al., 2006), decreased hippocampal mRNA levels of BDNF and CREB (Chen et al., 2014) and altered dopaminergic and serotonergic neurotransmission in the medial prefrontal cortex (Inoue and Koyama, 1996). The

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corticosterone-induced depression model mimics the dysfunction of the HPA axis in depression and fulfills adequate face, construct and predictive validity as an animal model of depression (Iijima et al., 2010; Chen et al., 2014).

A wide range of effective treatments are available for depression, but several adverse events are associated with antidepressant therapy. Thus, alternative therapeutic agents or adjunctive strategies which could improve clinical outcomes are of great importance. Some naturally occurring compounds, including folic acid, are good candidates as an alternative and complementary approach to the management of depression (Manosso et al., 2013).

Folic acid (folate or vitamin B9), a water-soluble vitamin implicated in cell replication, has an important role in one-carbon metabolism, essential for neurological function (Kronenberg et al., 2009). Previous studies have shown that folate deficiency is associated with higher incidence of mental symptoms and cognitive decline in epileptic, neurological, psychiatric, and geriatric populations. Particularly in major depression, low plasma, serum or red blood cell levels of folate are frequently described in clinical studies (Reynolds, 2002; Abou-Saleh and Coppen, 2006; Sarris et al., 2009). Corroborating these findings, a variety of controlled and open-label studies have shown the efficacy of folic acid and L-methylfolate as augmentation agents of conventional antidepressants in patients with normo- and hypofolatemic status (Owen, 2013). Regarding preclinical studies, our group has previously shown that an acute oral and central administration of folic acid in mice elicits antidepressant-like effect in FST and tail suspension test (TST) (Brocardo et al., 2008b, 2009) and is able to prevent the depressive-like behavior induced by restraint stress (Budni et al., 2013), suggesting that folic acid may play a role in the modulation of depression. However, the ability of folic acid to counteract the depressive-like behavior induced by a model of depression that mimic the human disorder remains to be established.

Considering this background, this study examined the effects of chronic corticosterone administration on behavioral parameters indicative of depressive-like behavior and serum corticosterone levels in mice, in order to validate this model. In view of the reported antidepressant-like effect of folic acid, we sought to investigate the ability of a 7-day administration of this vitamin to counteract the corticosterone-induced behavioral and biochemical alterations, comparing its effect to the one produced by fluoxetine.

2. Materials and methods

2.1. Animals

The behavioral experiments were conducted using female Swiss mice (30–40 g), maintained at 20–22 °C with free access to water and food, under a 12:12 h light/dark cycle, with lights on at 7:00 a.m. The animals were caged in groups of 15 in a 41 × 34 × 16 cm cage. All behavioral tests were carried out between 9.00 a.m. and 04.00 p.m. The animals were used according to the NIH Guide for the Care and Use of Laboratory Animals and the experiments were performed after approval of the protocol by the Ethics Committee of the Institution. All efforts were made to minimize animal suffering and to reduce the number of animals used in the experiments.

2.2. Drugs and treatment

To develop this study, mice were divided into six groups, as follows: (1) vehicle + vehicle; (2) vehicle + fluoxetine; (3) vehicle + folic acid; (4) corticosterone + vehicle; (5) corticosterone + fluoxetine; (6) corticosterone + folic acid. Corticosterone, folic acid and fluoxetine were obtained from Sigma Chemical Co., St. Louis, USA and administered orally (p.o.) in a volume of 1 ml/kg. Corticosterone (20 mg/kg) was dissolved in distilled water with 2% of Tween 80 and 0.2% of DMSO and administered once a day (between 9:00 a.m. and 10 a.m.) for 21 days. Folic acid (30 mg/kg) or fluoxetine (10 mg/kg) solutions were administered immediately after corticosterone administration during the last 7 days of corticosterone treatment. On the 22nd day, 24 h after the last treatment, animals were submitted to TST, open-field test and splash test. Mice were weighed once a week. All doses and times of administration were chosen based on dose–response pilot studies. Fig. 1 shows a schematic representation of the treatment regime, behavioral and biochemical evaluation in our experimental model.

2.3. Behavioral tests

Tail suspension test, open-field test and splash test were performed in the same group of animals, 10 min apart. Data from our laboratory do not show significant differences in the performance of control animals subsequently exposed to these tests compared with mice evaluated in independent groups.

2.3.1. Tail suspension test

The total duration of immobility induced by tail suspension was measured as previously described (Steru et al., 1985). Mice both acoustically and visually isolated were suspended 50 cm above the floor by adhesive tape placed approximately 1 cm from the tip of the tail. Mice were considered immobile only when they hung passively and completely motionless. Immobility time was manually recorded during a 6-min period by an experienced observer. The observer was in the room where experiments were performed and was blind to the animal condition.

2.3.2. Open-field test

Ten minutes after the tail suspension test, the locomotor activity was assessed in an open-field test as previously described (Moretti et al., 2011). The apparatus consisted of a wooden box measuring 40 × 60 × 50 cm high. The floor of the arena was divided into 12 equal squares. The number of squares crossed with all paws (crossings) was manually counted in a 6-min session. The light was maintained at minimum (~300 lx) to avoid anxiety behavior. The apparatus were cleaned with a solution of 10% ethanol between tests in order to hide animal clues.

2.3.3. Splash test

Ten minutes after the open-field test the splash test was carried out. This test consists of squirting a 10% sucrose solution on the dorsal coat of a mouse placed individually in clear Plexiglas boxes (9 × 7 × 11 cm) (Moretti et al., 2012). Because of its viscosity, the sucrose solution dirties the mouse fur and animals initiate grooming behavior. After applying sucrose solution, the time to start the first grooming and the total amount of time spent grooming were manually recorded for a period of 5 min as an index of self-care and motivational behavior, considered to be parallel with some symptoms of depression such as apathetic behavior (Willner, 2005). The apparatus was cleaned with a solution of 10% ethanol between tests in order to hide animal clues.

2.4. Corticosterone circulating levels

Mice were killed by decapitation 10 min after splash test and trunk blood was collected. Whole blood was centrifuged at 3000 ×g, at room temperature for 10 min and the obtained serum was used to measure corticosterone levels. Corticosterone levels were determined using commercially available enzyme immunoassay Kit (Assay Design, Inc., MI, USA), according to the manufacturer instructions.

2.5. Statistical analysis

All data are presented as mean ± SEM. Differences among experimental groups were determined by two-way ANOVA followed by Newman–Keuls' post-hoc test. A value of $p < 0.05$ was considered to be significant. In order to identify and, when appropriate, remove anomalous observations from behavioral data, detection of outliers was performed

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