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Research report

A novel isoquinoline compound abolishes chronic unpredictable mild stress-induced depressive-like behavior in mice

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HIGHLIGHTS

- FDPI has been reported as antidepressant-like effect in acute model.
- FDPI protected against CUMS-induced depressive-like behavior.
- FDPI reversed CUMS-caused alterations in prefrontal cortex of mice.

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ABSTRACT

Chronic unpredictable mild stress (CUMS) elicits aspects of cognitive and behavioral alterations that can be used to model comparable aspects of depression in humans. The aim of the present study was to investigate the antidepressant-like potential of 7-fluoro-1,3-diphenylisoquinoline-1-amine (FDPI), a novel isoquinoline compound, in CUMS, a model that meets face, construct and predictive criteria for validity. Swiss mice were subjected to different stress paradigms daily for a period of 35 days to induce the depressive-like behavior. The animals received concomitant FDPI (0.1 and 1 mg/kg, intragastric) or paroxetine (8 mg/kg, intraperitoneal) and CUMS. The behavioral tests (splash test, tail suspension test, modified forced swimming test and locomotor activity) were performed. The levels of cytokines, corticosterone and adrenocorticotropic (ACTH) hormones were determined in the mouse prefrontal cortex and serum. The synaptosomal [^{3}H] serotonin (5-HT) uptake, nuclear factor (NF)-κB, tyrosine kinase receptor (TrkB) and pro-brain-derived neurotrophic factor (BDNF) levels were determined in the mouse prefrontal cortex. CUMS induced a depressive-like behavior in mice, which was demonstrated in the modified forced swimming, tail suspension and splash tests. FDPI at both doses prevented depressive-like behavior induced by CUMS, without altering the locomotor activity of mice. FDPI at the highest dose prevented the increase in the levels of NF-kB, pro-inflammatory cytokines, corticosterone and ACTH and modulated [^{3}H]5-HT uptake and the proBDNF/TrkB signaling pathway altered by CUMS. The present findings demonstrated that FDPI elicited an antidepressant-like effect in a model of stress-induced depression.

1. Introduction

Depression is an incapacitating psychiatric disorder that has been estimated to affect 16% of the world population [1]. It is characterized by a pervasive low mood, loss of interest in common activities, anhedonia and withdrawal of interest [2]. Although most studies focus on the monoamine theory [3], recent evidence has been found to suggest that patients with major depression commonly present activated inflammatory pathways [4] and that the deregulation of hypothalamic-pituitary-adrenal (HPA) axis plays a role in the manifestation of depressive symptoms [5].

The appearance of depression has been also associated with the accumulation of stressful life events [6,7]. In this context, the HPA axis [8] is modulated by anti- and pro-inflammatory cytokines, which are central regulators of stress response. Some researchers

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have demonstrated that the nuclear factor (NF)-κB, a major mediator of inflammatory pathways, is activated by stress [9,10].

Neurobiological theories have also demonstrated the decreased expression of mature brain-derived neurotrophic factor (mBDNF) in depressive disorders [11]. The mBDNF supports neuronal survival by activating its tyrosine kinase receptor (TrkB) [12]. However, proBDNF, the precursor of mBDNF, binds with the p75 neurotrophin receptor ($p75^{NTR}$) [13] inducing neuronal atrophy, apoptosis and dendritic pruning, which cause a depressive response [14,15].

Although there are classic antidepressants not all depressed patients respond to these drugs and only some of drug-responsive patients achieve full remission of symptoms [16]. Therefore, the development of novel pharmacological treatment strategies for depression is required.

Chronic unpredictable mild stress (CUMS) is a widely used rodent model to elicit depression-related behavior, which consists of repeated exposure to an array of varying and unpredictable mild stressors over a sustained period of time [7]. Most effects of CUMS can be reversed by antidepressant agents, illustrating a strong predictive validity of this model [17,18].

In the search for a novel pharmacologically active drugs isoquinoline derivatives have gained attention in view of their antitumoral, antibacterial, neuroprotective, anti-addictive and antidepressant-like activities [19–22]. This way, 7-fluoro-1,3-diphenylisoquinoline-1-amine (FDPI), a synthetic isoquinoline compound, has some of specific molecular targets and mechanisms of action that accredit this compound for more detailed studies as a future antidepressant drug. Similar to some commercially available antidepressants, FDPI is an inhibitor of monoamine oxidase, an antioxidant [23], an modulator of serotonergic and dopaminergic systems and an antidepressant-like compound in the forced swimming test (FST) and tail suspension test (TST) [23,24].

In the present study, the antidepressant-like potential of FDPI was investigated in the mouse chronic unpredictable mild stress, a model that meets face, construct and predictive criteria for validity.

2. Methods

2.1. Animals

The behavioral experiments were conducted using sixty three male adult Swiss mice (25–35 g). The animals were maintained at 22–25 °C with free access to water and food, under a 12:12 h light/dark cycle, with lights turned on every day at 7:00 a.m. All manipulations were carried out between 08.00 a.m. and 04.00 p.m. All experiments were performed on separate groups of animals. The present experimental study was approved by the Institutional Ethics Committee on Care and Use of Experimental Animal Resources from the Federal University of Santa Maria, Brazil and registered under the number of 047/2014. All efforts were made to minimize animals suffering and to reduce the number of animals used in the experiments.

2.2. Chemicals

FDPI was prepared and characterized in our laboratory by the method previously described by Mantovani, Pesarico [23]. Analysis of the ^{1}H NMR and ^{13}C NMR spectra showed analytical and spectroscopic data in full agreement with its assigned structure. The chemical purity of studied compound (99.9%) was determined by gas chromatography–mass spectrometry. FDPI was dissolved in canola oil and given to mice in a constant volume of 10 ml/kg of body weight. All other chemicals were of analytical grade and obtained from Sigma-Aldrich, USA.

2.3. Drugs and treatment

FDPI and paroxetine (positive control) were administered to mice once a day during 35 days concomitant to the CUMS procedure (Fig. 1). The doses of FDPI (0.1 and 1 mg/kg) were administered intragastrically (i.g) [24] and paroxetine (8 mg/kg) was intraperitoneally (i.p.) injected [25] in mice. All drugs were administered to mice in a volume of 10 ml/kg. The vehicles of FDPI and paroxetine were canola oil and saline, respectively. The intragastric procedure is commonly used to delivery oil-soluble drugs, compounds were administered by using a gastroesophageal probe that releases them directly into the stomach.

Animals were randomly allocated to one of the following seven groups: (a) canola oil (vehicle), (b) 0.1 mg/kg of FDPI, (c) 1 mg/kg of FDPI, (d) canola oil + CUMS, (e) 0.1 mg/kg of FDPI + CUMS, (f) 1 mg/kg of FDPI + CUMS and (g) 8 mg/kg of Prx + CUMS.

2.4. CUMS procedure

The CUMS procedure was performed as previously described with minor modifications [16,17]. Briefly, the non-stressed control animals were housed in groups of five per cage, in standard plastic cages, and they had no contact with the stressed groups. For another four groups, mice were housed five per cage and exposed to the stress protocol.

Animals were exposed to the weekly stress regime consisting of 18 h food deprivation/water deprivation, 10 min tail pinch (1 cm from the end of the tail), and 16 h wet wood shavings/box housing tilted (45°), 2 h physical restraint, 48 h isolation and overnight illumination. One of these stressor episodes was applied daily, at different time every day, in order to minimize its predictability.

2.5. Behavioral tests

The locomotor activity, tail suspension and splash tests were carried out at day 1 after the end of CUMS procedure. At day 2 after the end of CUMS procedure, the modified FST was performed (Fig. 1). The number of mice assigned to each experimental group was eight and the same mice were used for all behavioral tests. The mouse behavior was recorded by an observer who was blind to the treatment condition to which the animal was exposed.

2.5.1. Spontaneous locomotor activity

With the purpose of excluding sedative or motor abnormality, the mouse spontaneous locomotor activity was performed. The animals were exposed to the chamber before testing, and activity was monitored under light and sound-attenuated conditions. Testing took place in a clear acrylic chamber (500 × 480 × 500 mm) equipped with 16 infrared sensors for the automatic recording of horizontal activity (Model EP149, Insight Instruments Ltda, Sao Paulo, BR). Each animal initially was placed in the center of the testing chamber and allowed to freely move while being tracked by an automated tracking system. The data (rearing, distance, velocity and crossings) were collected and recorded during 4 min.

2.5.2. Modified forced swimming test (FST)

The modified mouse FST was conducted as described by Detke et al. [26] and Porsolt et al. [27], with some modifications [28]. Briefly, mice were individually forced to swim in an open cylindrical container (12 cm in diameter and 30 cm in height), containing 20 cm of water at 25 ± 1 °C. In the test, the time of climbing, swimming and immobility was measured during a 6-min period. Climbing behavior consisted of upward directed movements of the forepaws along the side of the swim chamber. Swimming behavior was defined as movement (usually horizontal) throughout the swim chamber, which also included crossing into another quadrant.