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Brain-derived neurotrophic factor signaling plays a role in resilience to stress promoted by isoquinoline in defeated mice

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ABSTRACT

Certain stressful life events have been associated with the onset of depression. This study aims to investigate if 7-fluoro-1,3-diphenylisoquinoline-1-amine (FDPI) is effective against social avoidance induced by social defeat stress model in mice. Furthermore, it was investigated the effects of FDPI in the mouse prefrontal cortical plasticity-related proteins and some parameters of toxicity. Adult Swiss mice were subjected to social defeat stress for 10 days. Two protocols with FDPI were carried out: 1- FDPI (25 mg/kg, intragastric) was administered to mice 24 h after the last social defeat stress episode; 2- FDPI (1–25 mg/kg, intragastric) was administered to mice once a day for 10 days concomitant with the social defeat stress. The mice performed social avoidance and locomotor tests. The prefrontal cortical protein contents of kinase B (Akt), extracellular signal-regulated kinase (ERK), cAMP-response element binding protein (CREB), pro-brain-derived neurotrophic factor (proBDNF), $p75^{NTR}$, neuronal nuclear protein (NeuN) and nuclear factor-κB (NF-κB) were determined in mice. A single administration of FDPI (25 mg/kg) partially protected against social avoidance induced by stress in mice. Repeated administration of FDPI (25 mg/kg) protected against social avoidance induced by stress in mice. Social defeat stress decreased the protein contents of $p75^{NTR}$, NeuN and the pERK/ERK ratio but increased those of proBDNF and the pCREB/CREB ratio, without changing that of NF-κB. Repeated administration of FDPI modulated signaling pathways altered by social defeat stress in mice. The present findings demonstrate that FDPI promoted resilience to stress in mice.

1. Introduction

Stress is a major contributing factor for depression (Anisman and Matheson, 2005), the consequences of stress exposure, defined as disturbances of physiological homeostasis, include a detrimental impact on certain aspects of brain function (McEwen, 2007). The World Health Organization estimates that 350 million individuals of all ages suffer from depression (Organization, 2016).

Social defeat stress, widely used to mimic stressful situations in rodents, alters the motivation for social interactions in mice and characterizes the neurobiological mechanisms induced by psychosocial experience (Berton et al., 2006; Krishnan et al., 2007). The prefrontal cortex is the most sensitive region of the brain to the deleterious effects of stress exposure and regulates actions and emotions through extensive connections with other brain regions (Arnsten, 2009; McEwen et al., 2015). Furthermore, Razzoli et al. (2011) demonstrated that social defeat stress reduces the synaptic plasticity in the prefrontal cortex.

The neurotrophic hypothesis suggests that the opposing effects of stress and antidepressant drugs are mediated by modulation of mitogen activated protein kinases (MAPKs) as extracellular signal-regulated protein kinases (ERKs) (Duman et al., 1997; Duman and Monteggia, 2006). This protein family is involved in cell proliferation and neuroprotection by inducing changes in cAMP response element-binding protein (CREB), which leads to transcription of genes involved in stabilization of synaptic plasticity, among these brain-derived neurotrophic factor (BDNF) (Pittenger and Duman, 2008).

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Considering the fact that 7-fluoro-1,3-diphenylisoquinoline-1-amine (FDPI), a synthetic isoquinoline compound, elicits an antidepressant-like action (Mantovani et al., 2014; Pesarico et al., 2014) and is a serotonin uptake inhibitor in experimental models of stress (Pesarico et al., 2015, 2016a), the aim of this study was to investigate if FDPI is effective against social avoidance induced by the mouse social defeat stress model. Furthermore, it was investigated the effects of FDPI in the mouse prefrontal cortical plasticity-related proteins and some parameters of toxicity.

2. Experimental procedures

2.1. Animals

The behavioral experiments were carried out using male adult Swiss mice, 2 month-old (intruders, 25–35 g), and aggressive retired breeder male mice, 8 month-old (residents, 43–50 g). The resident mice were used as defeaters for the social defeat protocol. The animals were kept in a separate animal room in a temperature controlled environment (22–25 °C) and time controlled lighting system (12:12 h light/dark) with lights turned on every day at 7.00 a.m. Mice were housed in cages with free access to tap water and commercial food. All manipulations were carried out between 08.00 a.m. and 04.00 p.m. 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 #6835140116. 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 based on a previous study carried out by Mantovani (Mantovani et al., 2014). 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. All other chemicals used in this study were obtained commercially from Sigma-Aldrich, USA.

2.3. Drugs and treatments

This study was divided in two protocols; the first protocol aimed to investigate the effect of a single effective antidepressant-like dose of FDPI (Pesarico et al., 2014) on the social avoidance induced by the social defeat stress in mice. FDPI at a single dose of 25 mg/kg (n = 8 animals/group) or vehicle (canola oil) was administered to the intruder mice 24 h after the end of social defeat stress protocol. The mice performed the behavioral tests 30 min after vehicle or FDPI administration (Fig. 1A).

In the second protocol, it was investigated whether different doses of FDPI (1, 10 and 25 mg/kg) would be effective in social avoidance. FDPI at doses of 1–25 mg/kg (n = 8 animals/group) or vehicle was administered to the intruder mice once a day during 10 days concomitant with the social defeat stress protocol (Fig. 2A).

Only the samples obtained from animals of the second protocol (groups: vehicle, FDPI 25 mg/kg, social defeat/vehicle and social defeat/FDPI 25 mg/kg) were used for the western blot analyses. The

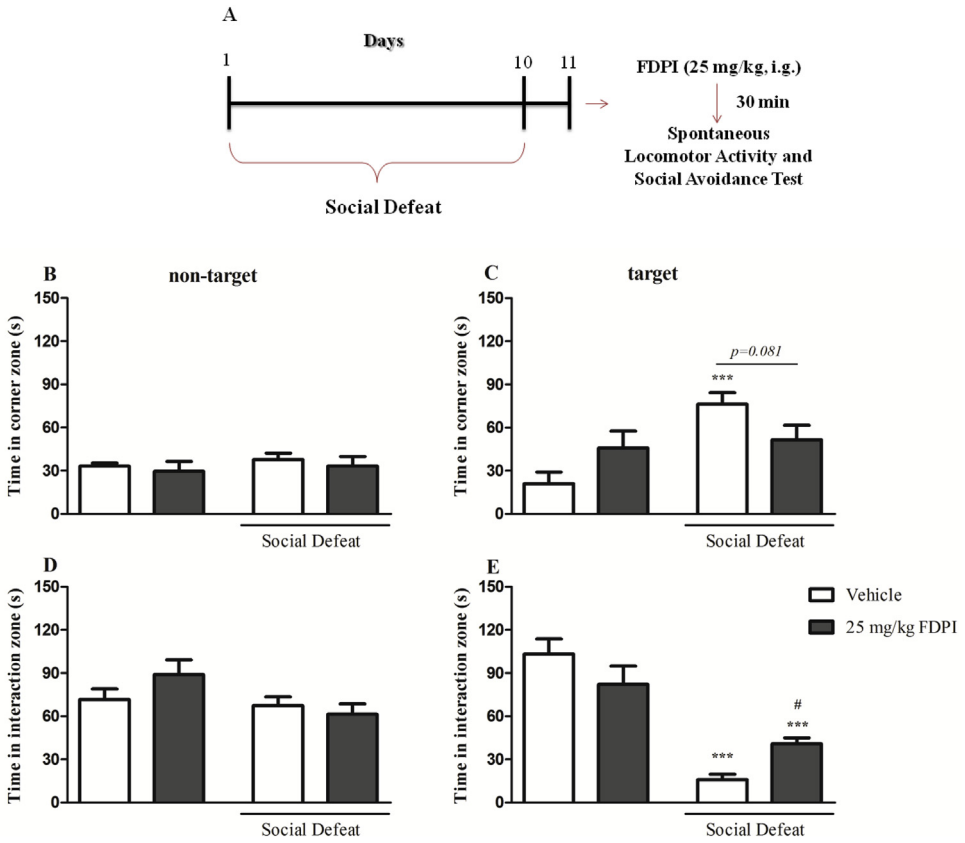

Fig. 1. Schematic representation of the experimental protocol of this study (A). Effects of FDPI (25 mg/kg, i.g.) on time in the corner zone (non-target B and target C), time in the interaction zone (non-target D and target E) of mice subjected to the social defeat stress. Bars represent means ± S.E.M. of 8 mice. Statistical analysis was performed by two-way ANOVA followed by the Duncan's test (***$p < 0.001$ compared with the vehicle group and #$p < 0.05$ compared with the social defeat/vehicle group).