Pharmacology, Biochemistry and Behavior 132 (2015) 20–32

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Type 4 phosphodiesterase enzyme inhibitor, rolipram rescues behavioral deficits in olfactory bulbectomy models of depression: Involvement of hypothalamic–pituitary–adrenal axis, cAMP signaling aspects and antioxidant defense system

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ARTICLE INFO

Article history:
Received 12 June 2014
Received in revised form 15 February 2015
Accepted 17 February 2015
Available online 21 February 2015

Keywords:
Depression
Olfactory bulbectomy
Rolipram
Behavioral paradigms
Neurobiological markers
Oxidative stress

ABSTRACT

Olfactory bulbectomy (OBX) model has been proposed as a well documented model of depression. Accumulated evidences suggest that cAMP selective PDE4 enzyme plays an important role in the pathophysiology of depression disorder. Moreover, PDE4 inhibitors have shown antidepressant-like effect in behavioral despair models. However, the potential of PDE4 inhibitors to produce antidepressant-like effect in OBX model and their underlying mechanism(s) has not been adequately addressed. The present study was designed to investigate the possible antidepressant-like effects and underlying mechanism of rolipram in OBX model. The effects of rolipram were measured in a battery of behavioral paradigms, including hyperactivity in open field test (OFT), anhedonia behavior in sucrose consumption test, open arm activity in elevated plus maze test (EPM) and emotional scores in hyperemotionality test. The underlying signaling mechanisms were also investigated by measuring serum corticosterone (CORT), brain-derived neurotrophic factor (BDNF) and brain oxidant/antioxidant levels. Treatment with rolipram (0.5 and 1 mg/kg, p.o., 14 days) significantly improved the behavioral anomalies (decreased the hyperactivity, open arm activity and hyperemotionality scores, whereas, increased sucrose consumption). Further, rolipram significantly decreased the CORT level and increased cAMP, pCREB and BDNF levels. Additionally, rolipram reduced oxidative–nitrosative stress markers (lipid peroxidation and nitrite levels) and restored the antioxidant enzyme level, including reduced glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT), indicating attenuation of oxidative–nitrosative stress. Our results revealed that antidepressant-like effects of rolipram in OBX model may be mediated by modulating the hypothalamic–pituitary–adrenal (HPA) axis activity, increasing the cAMP signaling aspects and restoring the antioxidant mechanisms.

1. Introduction

Depression is a highly debilitating and frequently occurring psychiatric problem, which affects large population with a lifetime prevalence approximately 15–25% (Patten, 2008). The World Health Organization has indicated that the prevalence of depression is rising very rapidly and it will be the second largest burdensome disorder of society by the year 2020 (Manji and Duman, 2001; Nestler et al., 2002). Depression is clinically characterized by a pervasive low mood, reduced interest or pleasure in daily activities and low self-esteem (Hankin, 2006; Perahia et al., 2009). Despite, considerable research has been carried for the treatment of depression, the prevalence is still remaining high and therapeutic responses to currently available drugs are unsatisfactory. The etiological and pathological mechanisms underlying depression disorder are not well established. Recently, the neurogenesis hypothesis of depression has suggested that depression may be linked with neuronal degeneration (Stockmeier et al., 2004; Duman and Monteggia, 2006; Goshen et al., 2008).

Previous reports have showed a causal relationship between the incidence of depression disorder and hyperactivation of the HPA axis activity (Nikisch et al., 2005; Himmerich et al., 2007). The hyperactivation of the HPA axis leads to morphological changes in the hippocampal region (Li et al., 2007; Murray et al., 2008) and induces depression-like behavior in animals (Johnson et al., 2006; Murray et al., 2008).

Numerous studies have indicated that alterations in cAMP intracellular signaling cascade lead to neuronal degeneration, which is a recently explore feature of depression disorder (Castrén et al., 2007; Murakami et al., 2005). Clinical studies indicate that individuals with depression disorder have low serum BDNF level (Karege et al., 2005; Aydemir et al., 2007). However, it was observed that treatment with antidepressant restores the normal brain BDNF level (Başterzi et al., 2009).

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http://dx.doi.org/10.1016/j.pbb.2015.02.017
0091-3057/

Besides this, the postmortem analysis of brain tissues has also indicated a reduce brain BDNF level in depressed individuals (Castrén et al., 2007). Further, administration of BDNF in a rodent's brain produces antidepressant-like effects (Siuciak et al., 1997).

Additionally, an imbalance of oxidative–antioxidant system was found to be implicated in the etiology of depression disorder (Michel et al., 2007). High free radical generation affects the neuron morphology and can lead to neuronal degeneration (Fontella et al., 2005; Lucca et al., 2009). Earlier clinical and preclinical studies have demonstrated a close relationship between the patho-physiology of depression disorder and raise oxidative stress (Rothman and Mattson, 2010; Behr et al., 2012). The integration of HPA axis, cAMP signaling and oxidant/antioxidant systems, therefore, implicates in the regulation of neuronal plasticity and alteration of these signaling mechanisms can lead to neuronal degeneration, which may be responsible for the induction of depression.

OBX in rodents has been proposed as a valuable animal model with high predictive validity for screening of antidepressant/depressant-like activity (Kelly et al., 1997; Harkin et al., 2003). The bilateral removal of the olfactory bulb produces a wide variety of chronic behavioral, endocrine, neurochemical and immunological changes, similar to those observed in depressed patients (Van Reizen and Leonard, 1990; Song and Leonard, 1994). Moreover, ablation of olfactory bulbs results in disrupted connections between the bulbs and other brain regions, mainly the olfactory–limbic circuitry (Jesberger and Richardson, 1986; Kelly et al., 1997; Song and Leonard, 2005). In addition, OBX surgery in rodents also modulates several signaling mechanisms, which may be implicated in neuronal degeneration (Jarosik et al., 2007; Koo et al., 2010). In this respect, agents are expected to influence the intracellular signaling cascade, which is involved in the regulation of neuronal survival and synaptic plasticity may show a possible therapeutic efficacy in OBX model.

Considerable research has revealed that PDE4 enzyme inhibitors increase intracellular cAMP level and influence cAMP-mediated and other signaling cascades, which regulate the neuronal survival and synaptic plasticity (Manji and Duman, 2001). Thus, considering the findings mentioned above PDE4 inhibitor, like rolipram may influence the signaling cascades and produce antidepressant-like effect in OBX model of depression. In addition, extensive reports already have addressed the antidepressant-like effect of PDE4 inhibitors in behavioral despair models of depression. To the best of our knowledge, no study has explored adequately the role of rolipram on the behavioral paradigms and underlying mechanisms in OBX model of depression. Therefore, the present study was designed to investigate the effect of rolipram on OBX-induced depression-like behaviors. In addition, the underlying mechanisms were evaluated by measuring serum CORT level, cAMP signaling aspects and brain oxidant/antioxidant markers in OBX rats.

2. Material and methods

2.1. Animals

Behavioral experiments were carried out using male Wistar rats (250–275 g), procured from Lala Lajpat Rai University of Veterinary and Animal Sciences, Hissar, Haryana, India. Animals were housed under standard laboratory conditions (temperature 23 ± 2 °C and room humidity 60 ± 5%), maintained on 12:12 h light/dark cycle with free access to standard diet and filtered water. The experimental procedures on animals were in compliance with the Institutional Animal Ethics Committee of Birla Institute of Technology and Science, Pilani, India (protocol no. IAEC/RES/14/03/REV/16/08).

2.2. Schedule for drug administration and behavioral tests

Rolipram was procured from the Sigma Aldrich, USA. Fluoxetine was procured from Glenmark Pharmaceuticals Ltd., India as gift samples. Rolipram and fluoxetine were dissolved in distilled water before administration. After a postsurgical rehabilitation period of 14 days, administration of rolipram (0.5 and 1 mg/kg, p.o.) and fluoxetine (10 mg/kg, p.o.) was started once a day for the next 14 days (15th to 28th day). After 14 days of treatment, the first behavioral test was performed 20 h after the last drug/vehicle administration to avoid the acute effect of drug treatment on the behavior. The schedule of OBX surgery, drug treatment and behavioral test was carried out as reported earlier (Pandey et al., 2008; Jindal et al., 2012).

2.3. Olfactory bulbectomy

2.3.1. Surgery

Bilateral OBX was performed according to the method described, elsewhere (Kelly et al., 1997; Ramamoorthy et al., 2008; Jindal et al., 2012). Briefly, rats were anesthetized with the cocktail of xylazine and ketamine (5 and 75 mg/kg, i.p., respectively). The rats were fixed in a stereotactic frame (Inco, Ambala, India) and a midline incision was made in the skull. Two burr holes (2 mm in diameter) were drilled 8 mm anterior to bregma and 2 mm on either side of the midline. The olfactory bulbs were removed by suction, the holes were then filled with hemostatic sponge to control excessive bleeding and the scalp was sutured. To prevent post-surgical infection, the animals were given Sulprim injection (0.2 ml/300 g), once a day for 3 days. The detail of surgical process and treatment schedule is mentioned in Table 1.

2.4. Experimental design

After 14 post-operative days (recovery period), 48 rats (six rats in each group) were randomly divided into eight different groups. Group I consisted the sham control rats and no treatment was given; Groups II, III and IV consisted of sham control rats treated with rolipram 0.5, 1 and fluoxetine 10 mg/kg, respectively for 14 days; Group V comprised of OBX control rats; Groups VI and VII consisted of OBX rats treated with rolipram 0.5 and 1 mg/kg, respectively for 14 days and Group VIII consisted of OBX rats, treated with fluoxetine (10 mg/kg) for 14 days. Sham-operated rats were subjected to the same surgical procedure, including piercing of the dura mater but their bulbs were left intact. Sham control and OBX control groups received the p.o. administration of water.

2.5. Behavioral assessments

2.5.1. Modified open field test

The OBX/sham rats were subjected to an open field exploration test on the 29th day post-surgery and 15th day of chronic drug treatment according to the method described by Kelly et al. (1997) with slight modifications (Ramamoorthy et al., 2008). The apparatus consisted of a circular (diameter: 90 cm) arena with 75 cm high aluminium walls and floor equally divided into 10 cm squares. A 60 W light bulb was positioned 90 cm above the base of the arena, which was the only source of illumination in the testing room. On the 29th day, each animal was individually placed in the center of the open field arena and the ambulation scores (number of squares crossed), rearing and fecal pellet were counted for 5 min. After each test, the apparatus was sprayed with alcohol and wiped thoroughly to eliminate residual odor.

2.5.2. Elevated plus maze test

The test was performed essentially as described previously (Pellow et al., 1985) on the 30th day post-surgery. The plus maze consisted of two opposite open arms (50 × 10 cm^2) and two opposite enclosed arms (50 × 10 × 50 cm^3). The four arms were joined by a central platform (10 × 10 cm^2), which was open to all the arms. The entire apparatus was elevated to a height of 60 cm above the floor. The apparatus was indirectly illuminated with a ceiling-suspending lamp (60 W) placed at a height of 100 cm above the apparatus. At the beginning of the test, the animal was placed in the central platform facing an open