European Journal of Pharmacology 762 (2015) 411–418

Contents lists available at ScienceDirect

European Journal of Pharmacology

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

Behavioural pharmacology

Elevated level of nitric oxide mediates the anti-depressant effect of rubidium chloride in mice

Nastaran Kordjazy [a,b,c], Arya Haj-Mirzaian [b,c], Shayan Amiri [b,c], Sattar Ostadhadi [b,c], Mehdi Kordjazy [d], Mohammad Sharifzadeh [a], Ahmad Reza Dehpour [b,c,*]

[a] Department of Pharmacology and Toxicology, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[b] Experimental Medicine Research Center, Tehran University of Medical Sciences, Tehran, Iran
[c] Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, P.O. Box 13145-784, Tehran, Iran
[d] Department of Veterinary Sciences, Islamic Azad University Babol Branch, Babol, Iran

ARTICLE INFO

Article history:
Received 7 March 2015
Received in revised form
24 May 2015
Accepted 16 June 2015
Available online 20 June 2015

Keywords:
Rubidium chloride
Nitric oxide
Forced swimming test
Tail suspension test
Mice

Chemical compounds studied in this article:
Rubidium chloride (PubChem CID: 62683)

ABSTRACT

Rubidium has been used to treat psychiatric conditions including depression. We examined the anti-depressant activity of rubidium chloride (RbCl) in male mice and the possible interference of nitric oxide (NO) in this effect. Mouse forced swimming test (FST) and tail suspension test (TST) were used to evaluate the antidepressant-like effect of RbCl. These drugs were used in this study: N^G-L-arginine methyl ester (L-NAME), a non-selective nitric oxide synthase (NOS) inhibitor, 7-Nitroindazole and aminoguanidine, selective neuronal and inducible NOS inhibitors, respectively, and L-arginine, an NO precursor. We studied the changes of serum and hippocampus nitrite level after different treatments. RbCl (30 mg/kg), when administered 60 min before the tests, significantly reduced the immobility time. Non-effective doses of L-NAME (10 mg/kg) and aminoguanidine (50 mg/kg), co-administered with the effective dose of RbCl (30 mg/kg), reversed the anti-immobility effect of RbCl, while 7-NI (25 mg/kg) could not prevent the diminishing effect of RbCl on immobility time. Moreover, co-administration of non-effective doses of L-arginine (750 mg/kg) and RbCl (10 mg/kg) decreased the immobility time. None of the mentioned treatments altered the locomotor activity of mice in open-field test. Nitrite level was significantly increased in serum and hippocampus of animals after RbCl (30 mg/kg) administration and this nitrite level elevation was reversed by non-effective dose of L-NAME and aminoguanidine, but not 7-NI. Our data for the first time reveal the role of NO pathway in the antidepressant-like activity of RbCl, concluding that this effect results from elevation of NO through involvement of iNOS in mice.

1. Introduction

Major depression is a disease characterized by considerable effects on one's mood and behavior (Ma et al., 2013). It is one of the most common psychiatric disorders (Villanueva, 2013). Among the several commonly prescribed antidepressant medications which are mainly based on monoamine regulation, many lack the ability to show the desired effect, beside causing side effects with differing severities (Arroll et al., 2005). Thus, the importance of studies to discover new antidepressants with more favorable pharmacological properties and side effect profile is unquestionable.

According to Meltzer & Fieve, rubidium ions were used to treat several psychiatric and non-psychiatric conditions during the last century; including mania, epilepsy, and depression (Meltzer et al., 1969; Paschalis et al., 1978). Later studies confirmed the claims about the beneficial effect of RbCl in behavioral changes and reported long biological half-life and few side effects following RbCl administration (Paschalis et al., 1978). Antidepressant activity of RbCl has been studied through clinical trials (Brundusino and Cairoli, 1996; Placidi et al., 1988). Although the mechanisms of these actions of rubidium had not yet been clearly understood, a few hypotheses were proposed by scientists (Fieve, 1973; Gambarana et al., 1999, 1956; Placidi et al., 1988), none of which do provide sufficiently reliable information.

Rubidium is an alkali metal which belongs to the same periodic series as lithium. Even though they have, to some extent, similar properties, some of rubidium's neurophysiological and neurochemical actions differ distinctly from those of lithium (Carroll and

* Corresponding author at: Experimental Medicine Research Center, Tehran University of Medical Sciences, P.O. Box 13145-784, Tehran, Iran. Tel.: +98 2188973652; fax: +98 2166402569.
E-mail addresses: dehpoura@sina.tums.ac.ir, dehpour@yahoo.com (A.R. Dehpour).

http://dx.doi.org/10.1016/j.ejphar.2015.06.030
0014-2999/

Sharp, 1971; Fieve, 1973; Meltzer et al., 1969; Schildkraut et al., 1967). Accordingly, they may have opposite biochemical properties. Studies have shown that lithium exerts an antidepressant-like effect through the interference of nitrergic system (Ghasemi et al., 2008). Though, it is presently unknown whether rubidium chloride could affect depression by acting on this system.

Nitric oxide (NO), a signaling molecule, is involved in different biological functions in central and peripheral nervous systems (Dawson et al., 1996; Sadaghiani et al., 2011) and is also suggested to act as a neuromodulator (Esplugues, 2002). NO evidently regulates different processes in the central nervous system including depression (Dhir and Kulkarni, 2011). NO is synthesized in brain from L-arginine by nitric oxide synthase (NOS), an enzyme family consisting of three isoforms, iNOS (inducible), eNOS (endothelial) and nNOS (neuronal) (Esplugues, 2002). Some studies suggest that NOS inhibition in mice results in an antidepressant-like effect (Harkin et al., 1999; Joca and Guimarães, 2006; Wegener and Volke, 2010). On the other hand, another study expresses a dual role in modulation of depression for NO and brings evidence to indicate that either the synthesis of NO or the inhibition of its synthesis might result in antidepressant-like effect in behavioral tests (da Silva et al., 2000).

In this study, we examined the antidepressant activity of rubidium chloride in the mouse forced swimming test (FST) and tail suspension test (TST), commonly used models for depression (Porsolt et al., 1977b). Plus, the possible involvement of NO pathway in this effect of rubidium chloride is also evaluated.

2. Materials and methods

2.1. Animals

All animals used for this study consisted of male NMRI mice, brought from the Pasteur Institute, Tehran, Iran. All animals weighting 20–30 g, were housed in groups of four to five, and were kept at the temperature of 21–23 °C under a twelve-hour regular light/dark cycle. Mice were given access to food and water ad lib, excluding the temporary time of being removed from their cages for conducting the tests. All experiments were carried out between 12:00 and 18:00 h. The whole procedure was performed in accordance with the institutional guidelines for animal care and use (Department of Pharmacology, School of Medicine, TUMS). All experimental groups included 6 to 8 animals and each mouse was used only once and full efforts were made to minimize the use of animals and in order to optimize their comfort.

2.2. Drugs

The following drugs were used in this study: rubidium chloride, fluoxetine, N^G-L-arginine methyl ester (L-NAME), aminoguanidine, 7-Nitroindazole (7-NI), and L-arginine (All were purchased from Sigma, St Louis, MO, USA). Except 7-NI which was dissolved in tween80 1% solution, all drugs were freshly dissolved in physiological saline, being prepared immediately before the experiments. All injections were through intraperitoneal (i.p.) route and with a volume of 5 ml/kg body weight.

2.3. Open field test

Testing was routinely gotten started with the open-field test to rule out possible alterations in locomotion that might affect FST and TST. The device consisted of a wooden box measuring 50 cm × 50 cm × 30 cm. The ground of the arena was separated into 12 equal squares. Each mouse was placed gently on the central zone (30 × 30 cm^2) and behaviors were recorded by a camera for 5 min and were analyzed by Ethovision software version 8 (Noldus, Netherlands). The total distance moved (vertical activity), and number of rearing (horizontal activity) was evaluated in this test. The open-field test is usually performed to ensure that the decrease or increase in animal's motionlessness in FST and TST is not due to alterations in locomotor activity (David et al., 2003; Haj-Mirzaian et al., 2013). The floor of the apparatus was usually cleaned with 10% ethanol between tests.

2.4. Forced swimming test

Immediately after the open-field test, the animals were placed in an open cylinder-shaped flask (diameter 10 cm, height 25 cm) which contained 19 cm water at 25 ± 1 °C, undergoing the forced swimming test. The FST was used to assess behavioral immobility of mice as a selective standard animal model for antidepressant treatment (Haj-Mirzaian et al., 2014; Porsolt et al., 1977a). Being allowed to swim for 6 min for habituation with the condition, each mouse was regarded as immobile when stopped struggling and floated still in the water. The duration of remaining immobile within the last 4 min of the test was recorded. Reduced immobility in this test has predictive validity for antidepressant drug action. Conversely, increased immobility has been proposed as an index of behavioral despair in animals.

2.5. Tail suspension test

This test relies on the fact that animals when facing the inescapable stress of being suspended by their tail will develop an immobile posture. In brief, each mouse was suspended on the edge of a rod 50 cm above a table top using adhesive Scotch tape, placed approximately 1 cm from the tip of the tail. Tail climbing was prevented by passing the mouse's tail through a small plastic cylinder prior to suspension. The duration of immobility was manually scored for a 6-minute observation period. Mice were considered immobile only when they hung down passively and were completely motionless (Cryan et al., 2005; Steru et al., 1985).

2.6. Treatment

First, we studied the effects of RbCl on the FST, TST, and open field test. Intraperitoneal injection of rubidium chloride (10, 30, and 50 mg/kg) an hour before performing the behavioral tests was performed to evaluate the effective and non-effective doses. Also, RbCl 30 mg/kg was administrated 30, 60, and 120 min before the behavioral tests to obtain the best time of action for our following experiments. These doses and times of administration were based upon our pilot studies with rubidium chloride. Fluoxetine 20 mg/kg, a selective serotonin reuptake inhibitor, was used as a standard antidepressant drug (Haj-Mirzaian et al., 2014; Moretti et al., 2012). This drug was administered 30 min before behavioral tasks and the results were considered as the positive control group.

In the same way, we assessed the effects of L-NAME (a non-selective NOS inhibitor, 10 mg/kg), aminoguanidine (a selective iNOS inhibitor 50 mg/kg), 7-NI (a selective nNOS inhibitor, 25 mg/kg), and L-arginine (an NO precursor, 750 mg/kg) in the mouse FST and TST (Ghasemi et al., 2008; Harkin et al., 2004). All drugs were administered 45 min before the tests except 7-NI which was administered 30 min prior to behavioral tests. The times of administration were based on a pilot study and also previous studies.

Further, the probable involvement of NO in the antidepressant-like activity of RbCl was examined through separately co-administering the non-effective doses of L-NAME, aminoguanidine, and 7-nitroindazole along with the effective dose of RbCl. Forced swimming and tail suspension tests were conducted 45 min past L-NAME/ aminoguanidine injection and 30 min past 7-NI injection.