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Nitric oxide involvement in additive antidepressant-like effect of agmatine and lithium in mice forced swim test

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ABSTRACT

Lithium is still the main agent in the management of mood disorders such as depression. Likewise, agmatine protects the central nervous system (CNS) against depression. The aim of the present study was to examine the possible additive antidepressant-like effect of agmatine and lithium in mice forced swim test (FST) as well as exploration of the probable involvement of nitric oxide (NO) pathway in this response. Results showed that pretreatment with a subeffective dose of agmatine (0.01 mg/kg) augmented the antidepressant-like effect of lithium subeffective dose (3 mg/kg) ($P < 0.001$). L-NG-nitroarginine methyl ester (L-NAME, nonspecific nitric oxide synthase [NOS] inhibitor) at doses of 10 and 30 mg/kg, and 7-nitroindazole (7-NI, neuronal NOS inhibitor) at doses of 15 and 30 mg/kg potentiated the antidepressant-like effect of the subeffective combination of lithium (3 mg/kg) and agmatine (0.001 mg/kg) ($P < 0.001$, $P < 0.01$, respectively). However, various doses of aminoguanidine (25 and 50 mg/kg, inducible NOS inhibitor) failed to alter the immobility time of the same combination ($P > 0.05$). Moreover, pretreatment with subeffective doses of L-arginine (substrate for NOS, 300 and 750 mg/kg) reversed the augmenting antidepressant-like effect of agmatine (0.01 mg/kg) on lithium (3 mg/kg) ($P < 0.001$). Our results revealed that agmatine enhances the antidepressant-like effects of lithium and the NO pathway might mediate this phenomenon. In addition, constitutive NOS plays a dramatic role in this response.

1. Introduction

Lithium is a typical medication for treatment of bipolar disease (Bourin and Prica, 2007). Meanwhile, some recent experiments reported the effectiveness of lithium in unipolar depressed patients (Freeman and Freeman, 2006; Souza and Goodwin, 1991). Furthermore, it is reported that lithium shows antidepressant-like properties in several animal models of depression including forced swim test (FST) (Ghasemi et al., 2008), tail suspension test (TST) (Cryan et al., 2002; Gould et al., 2008), and learned helplessness (Faria and Teixeira, 1993; Teixeira et al., 1995).

Lithium contributes in many neurotransmitters function in the brain (Wood et al., 1994). Nitric oxide (NO) is one of these neurotransmitters, which is a mediator for a several central (Ghasemi et al., 2008; Wegener et al., 2001) and peripheral (Sadeghipour et al., 2007) responses to lithium. Formerly, we reported the involvement of NO inhibition in antidepressant-like (Ghasemi et al., 2008; Ghasemi et al., 2009) and anticonvulsant (Bahremand et al., 2010) properties of lithium. Also, it is reported that acute administration of lithium inhibit the production of NO in brain (Maruta et al., 2005).

Nitric oxide/cyclic guanosine monophosphate (cGMP) regulates various physiological functions (Esplugues, 2002). Nitric oxide is suggested as a novel target for treatment of depression (Harkin et al., 1999; Inan et al., 2004; Yildiz et al., 2000), and experiments using mice FST, a common behavioral test for assessment of antidepressant-like activity have confirmed this matter (Borsini, 1995; Cryan et al., 2002).

Agmatine is a polyamine precursor that is the product of arginine decarboxylase enzyme, which decarboxylases L-arginine. Agmatine is shown to possess various biological actions in brain as a neurotransmitter (Bence et al., 2003; Reis and Regunathan, 2000). It has antidepressant-like effects (Zomkowski et al., 2002; Zomkowski et al., 2005; Zomkowski et al., 2004) and inhibits nitric oxide synthase (NOS)

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activity in various tissues (Abe et al., 2000; Feng et al., 2002; Galea et al., 1996). Pretreatment of mice with L-arginine, an NO precursor could completely reverse the antidepressant-like effect of agmatine (Zomkowski et al., 2002). Moreover, several studies have shown that agmatine augments the antidepressant effect of fluoxetine, paroxetine (Taksande et al., 2009), and imipramine (Zomkowski et al., 2002) in rodents.

Among all animal models, the forced swim test (FST) remains one of the most used tools for screening antidepressants (Petit-Demouliere et al., 2005). This method was described for the first time by Porsolt et al. in 1977. They reported that a depressed state could be induced in mice by forcing them to swim in a narrow cylinder from which they cannot escape. After a short period of swimming despair, animals adopt a characteristic immobile posture. Both antidepressants and psychostimulants could decrease this immobility time in FST, whereas only psychostimulants cause marked motor stimulation in behavioral tests that measure the total locomotor activity of animals, such as the open field test (OFT) (Porsolt et al., 1977). Regardless the few exceptions, the FST possesses a considerable level of predictive validity for discovering antidepressants, since it is reasonably sensitive to typical antidepressant drugs, which used in humans. Since changes in locomotor activity of animals may affect the swimming behavior of animals in the FST, so it is necessary to confirm the results of FST with other behavioral tests that measure the total locomotor activity of animals, such as OFT. Since FST does not represent the human condition exactly, it is more accurate that we use the term “antidepressant-like” for drugs show positive effectiveness is FST. Nevertheless, this limitation should not devalue the usefulness of FST as a drug discovery and validation tool (Can et al., 2012).

We previously showed that antidepressant-like effects of lithium in FST could be mediated by NO signaling. Combination treatment with lithium and other drugs that can affect this signaling pathway may provide a new insight into the treatment of mood disorders (Ghasemi and Dehpour, 2011). Since both lithium and agmatine possess antidepressant-like effects and inhibit NOS, the aim of the present study was to investigate the possible synergistic antidepressant-like properties of these agents through inhibition of NOS. For this purpose, we used the model of FST in mice and examined the possible mediation of neural NOS isoenzyme in this response.

2. Materials and methods

2.1. Chemicals

Drugs used in the present study were as below: fluoxetine (20 mg/kg), lithium chloride (3–30 mg/kg), agmatine sulfate (0.001–10 mg/kg), L-arginine, L-NG-nitroarginine methyl ester (L-NAME, 10 and 30 mg/kg), 7-nitroindazole (7-NI, 15 and 30 mg/kg), L-arginine (300 and 750 mg/kg), and aminoguanidine (25 and 50 mg/kg). All drugs were purchased from Sigma-Aldrich, St. Louis, MO, USA. All drugs were injected intraperitoneally (i.p.). 7-NI was suspended in a 1% aqueous solution of Tween 80, and the other drugs were dissolved in normal saline.

2.2. Animals

We used male Naval Medical Research Institute (NMRI) mice weighing 23–30 g (Pasteur Institute). Mice were kept in groups of four or five and had ad libitum access to chow food and water except for the short time of test with a light/dark cycle of 12 hours, at a temperature of 22 ± 2 °C and 80% humidity. All procedures were conducted in accordance with experimental protocols and approved by the local ethics committee at Tehran University of Medical Sciences. Moreover, we tried to diminish animal suffering as well as to use the minimal number of mice necessary to obtain reliable scientific data.

2.3. Open field test (OFT)

The ambulatory behavior of mice was evaluated in the OFT (Stanford, 2007). We carried out this test immediately prior to the FST to ensure that alterations in motor activity are not responsible for the changes in duration of immobility time, based on our previous reports (Haj-Mirzaian et al., 2016a; Haj-Mirzaian et al., 2016b; Nikoui et al., 2016; Ostadhadi et al., 2016a). The apparatus consisted of a wooden box measuring 40 cm × 60 cm × 50 cm. The bottom of the arena was divided into 12 equal squares. The mice were mildly placed in the center of the field and the number of squares crossed with all paws was measured in a 6 min period.

2.4. Forced swim test (FST)

The despair behavior of mice was assessed in the FST (Porsolt et al., 1977). In this test, based on our previous reports (Abbasi-Maleki et al., 2017; Haj-Mirzaian et al., 2014; Ostadhadi et al., 2017; Ostadhadi et al., 2016b), mice were placed in an open cylinder (diameter 10 cm, height 25 cm), containing 19 cm of water at temperature of 23 ± 1 °C, and were allowed to swim for a 6 min session. Two experienced raters blinded to drug treatment, performed the test. Mice were judged immobile when they stopped struggling and remained floating motionless in the water, making only those movements essential to keep their head above water. The period of immobility was recorded during the last 4 min of the test.

2.5. Experimental groups

We used 170 mice in experiments. Fluoxetine (20 mg/kg) (Nazari et al., 2016; Ostadhadi et al., 2016d), a standard antidepressant drug, was used as a positive control group in our experiment. Fluoxetine was injected to mice and FST was performed after 30 min (Haj-Mirzaian et al., 2015; Kordjazy et al., 2016). We used the subeffective dose of lithium (3 mg/kg) based on our previous report (Mohseni et al., 2017). As a result of previous report, the effective and subeffective doses of agmatine were obtained as 10 and 0.001 mg/kg, respectively (Mohseni et al., 2017). In the first experiment, we evaluated the possible synergistic effect between different subeffective doses of agmatine (0.001 and 0.01 mg/kg) with a subeffective dose of lithium (3 mg/kg). We injected agmatine immediately prior lithium administration and 30 min before FST. The second experiment was carried out to study the impact of the NO precursor, L-arginine (300 and 750 mg/kg) (Ergün and Ergün, 2007; Kaster et al., 2005) on the antidepressant-like effect of combination of agmatine (0.01 mg/kg) and lithium (3 mg/kg). We injected L-arginine 15 min before the either of agmatine or saline and 45 min prior to the FST (Khan et al., 2016), while corresponding control groups were treated by various combinations of saline and/or lithium (3 mg/kg) and/or agmatine (0.01 mg/kg) prior to the FST. The third experiment examined the effect of the NOS inhibitor, L-NAME (10 and 30 mg/kg) (Ghasemi et al., 2008) on co-administration of lithium (3 mg/kg) and agmatine (0.001 mg/kg). Corresponding groups received saline or L-NAME, 15 min before agmatine and/or lithium administration and 45 min before the test (Ostadhadi et al., 2016c). The corresponding control groups were injected by various combinations of saline and/or lithium (3 mg/kg) and/or agmatine (0.001 mg/kg) prior to behavioral tests. In the fourth experiment, we studied the role of the selective nNOS inhibitor 7-NI (15 and 30 mg/kg) in the synergistic antidepressant-like properties of lithium (3 mg/kg) and agmatine (0.001 mg/kg) in both FST and OFT (Ostadhadi et al., 2016a,d). For this purpose, we treated mice with either of saline or 7-NI, immediately before injection of agmatine and/or lithium and 30 min prior FST.

In the fifth experiment, we studied the role of the selective iNOS inhibitor aminoguanidine (25 and 50 mg/kg) in the synergistic antidepressant-like properties of lithium (3 mg/kg) and agmatine (0.001 mg/kg) in both FST and OFT (Ostadhadi et al., 2016a,d). For this