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Involvement of nitric oxide-cyclic guanosine monophosphate pathway in the antidepressant-like effect of tropisetron and ondansetron in mice forced swimming test and tail suspension test

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ABSTRACT

Antidepressant-like effects of 5-hydroxytryptamine subtype 3 (5-HT_3) antagonists including tropisetron and ondansetron have been previously demonstrated in the literature. It was reported that stimulation of 5-HT_3 receptors activate the nitric oxide-cyclic guanosine monophosphate (NO-cGMP) pathway, which is involved in regulation of behavioral and emotional functions. In our study, treating animals with tropisetron (5, 10, and 30 mg/kg) and ondansetron (0.01 and 0.1 μg/kg) significantly decreased the immobility time in forced swimming test (FST) and tail-suspension test (TST). Co-administration of subeffective doses of tropisetron (1 mg/kg) and ondansetron (0.001 μg/kg) with subeffective dose of L-NAME (10 mg/kg, nonselective NO synthase (NOS) inhibitor) and 7-nitroindazole (25 mg/kg, neural NOS inhibitor) exerted antidepressant-like effect in FST and TST, while aminoguanidine (50 mg/kg, inducible NOS inhibitor) did not enhance the antidepressant-like effect of 5-HT_3 antagonists. Besides, L-arginine (750 mg/kg, NO precursor) and sildenafil (5 mg/kg, phosphodiesterase inhibitor) suppressed the antiimmobility effect of 5-HT_3 antagonists. None of the treatments altered the locomotor behavior of mice in open-field test. Also, hippocampal (but not cortical) nitrite level was significantly lower in tropisetron and ondansetron-treated mice compared with saline-injected mice. Also, co-administration of 7-nitroindazole with tropisetron or ondansetron caused a significant decrease in hippocampal nitrite levels. In conclusion, we suggest that antidepressant-like effect of tropisetron and ondansetron are partially mediated by modulation of NO-cGMP pathway.

1. Introduction

Depression, one of the most common psychiatric disorders, has become a public health concern (Silva et al., 2014). In view of the fact that the prevalence of depression is progressively high (Compton et al., 2006), increasing attention is paid to treatment of patients with depression. Amongst the several routine prescribed antidepressant medications, which are mainly based on monoamine regulation, few are highly expected to show the desired outcomes (Arroll et al., 2005; Berton and Nestler, 2006). Thus, finding new antidepressants with favorable pharmacological properties is advantageous.

5-hydroxytryptamine 3 (5-HT_3) receptors are the only ligand-gated ion channel subtype among the 5-HT receptor family (Hoyer and Schoeffter, 1991). Tropisetron and ondansetron are highly selective competitive inhibitors of 5-HT_3 receptors (Broocks, 1992). These receptors are widely distributed in the central nervous system and play a pivotal role in regulation of a variety of processes in different brain structures including hippocampus. Evidence indicates that tropisetron and ondansetron exert antidepressant-like properties in rodent behavioral tests such as forced swimming test (FST), tail suspension test (TST), and learned helplessness (Bravo and Maswood, 2006; Martin et al., 1992; Nakagawa et al., 1998; Ramamoorthy et al., 2008). Also, several clinical investigations have assessed the beneficial effects of

Abbreviations: 5-HT, 5-hydroxytryptamine; NO, nitric oxide; NOS, nitric oxide synthase; iNOS, inducible nitric oxide synthase; nNOS, neuronal nitric oxide synthase; cGMP, cyclic guanosine monophosphate; FST, forced swimming test; TST, tail suspension test; OFT, open-field test; i.p., intraperitoneal; NIH, National Institutes of Health; L-NAME, N^G-L-arginine methyl ester; 7-NI, 7-nitroindazole; L-arg, L-arginine; PDE, phosphodiesterase; ANOVA, analysis of variance; PFC, prefrontal cortex

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ondansetron and tropisetron in psychiatric conditions including anxiety and depression (Haus, 2000; Hewlett et al., 2003; Lecrubier et al., 1993). These 5-HT_3 antagonists have desirable pharmacological profile and cause few adverse effects, and are consequently well-tolerated in patients (Greenshaw and Silverstone, 1997; Rajkumar and Mahesh, 2010).

It has been reported that nitric oxide (NO) is involved in many physiological functions of the 5-HT_3 receptors. In this context, activation of 5-HT_3 receptors has been reported to stimulate nitric oxide synthase (NOS) as well as cyclic guanosine monophosphate (cGMP) pathways (Giordano and Schultea, 2004; Wetzel et al., 1998). The NO–cGMP pathway is known to be implicated in regulation of various (patho)physiologic behavioral and emotional functions (Denninger and Marletta, 1999), and has been suggested as a therapeutic target for depression (Harkin et al., 1999). In this regard, many studies demonstrated that NOS and cGMP inhibition produce antidepressant-like effects in FST and TST (Heiberg et al., 2002; Zomkowski et al., 2010).

Although the antidepressant-like effect of tropisetron and ondansetron in the FST and TST has been reported in rodents, underlying mechanisms through which these drugs exert these antidepressant-like effects are not well defined. In this study, we investigated the possible participation of NO–cGMP pathway in the antidepressant effect of ondansetron and tropisetron in mice.

2. Materials and methods

2.1. Animals

The animals used for this study consisted of male NMRI mice (20–30 g) brought from the Pasteur Institute, Tehran, Iran. All animals were housed in groups of four or five, and were kept at the temperature of 21–23 °C under 12 h regular light/dark cycle. Mice were given access to food and water ad lib. All experiments were carried out between 10:00 and 14:00. All procedures were performed in accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23, revised 1978) and the institutional guidelines for animal care and use (Department of Pharmacology, School of Medicine, TUMS, No. 91-01-159-18022) (ethical permit number: 3186). All experimental groups included 6–8 animals and full efforts were made to minimize the use of animals and to optimize their comfort (number of animals in each experimental group were shown in Fig. captions).

2.2. Drugs

The following drugs were used in this study: tropisetron, ondansetron, fluoxetine, N^G-L-arginine methyl ester (L-NAME), aminoguanidine, 7-Nitroindazole (7-NI), L-arginine (L-arg), and sildenafil (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 and were prepared immediately before the experiments. All drugs were injected through intraperitoneal (i.p.) route and with a volume of 5 ml/kg body weight (Turner et al., 2011).

2.3. Open field test (OFT)

The OFT was used to evaluate the locomotor behavior of animals (Haj-Mirzaian et al., 2015a; Kulesskaya and Voikar, 2014). The open-field apparatus was made of white opaque Plexiglas (50 cm × 50 cm × 30 cm) which was dimly illuminated. Each mouse was placed gently on the center square (30 cm × 30 cm), and behaviors were recorded by a camera for 5 min and were analyzed by Ethovision software version 8 (Noldus, Netherlands). The total distance moved (horizontal activity) in the OFT was evaluated to ensure that the decrease or increase in animal's motionlessness in FST/TST is not due to the alterations in locomotor activity.

2.4. Forced swimming test (FST)

For conducting the FST, the animals were placed in an open cylinder-shaped flask (diameter 10 cm, height 25 cm) filled with 19 cm water at 24 ± 1 °C. The FST was used to assess behavioral immobility of mice as a selective standard animal test for antidepressant treatment (Haj-Mirzaian et al., 2015b; Porsolt et al., 1977). Being allowed to swim for 6 min, each mouse was assumed immobile when stopped struggling and floated motionless in the water, making only the movements for keeping its head above water. The time of remaining immobile within the last 4 min of the test was recorded.

2.5. Tail suspension test (TST)

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 measured for a 6 min observation period. Mice were considered immobile only when they hung down passively and were completely motionless (Cryan et al., 2005; Steru et al., 1985). Compounds that decrease immobility and increase active behaviors in FST and TST are considered to suppress indices of depression.

2.6. Treatments

First, we studied the effects of tropisetron and ondansetron on the FST, TST, and OFT. Intraperitoneal injection of ondansetron (0.001, 0.005, 0.01, and 0.1 μg/kg) and tropisetron (1, 5, 10, and 30 mg/kg) 30 min before the behavioral tests was performed to evaluate the effective and subeffective doses of these drugs. These doses and times of administration were based upon our pilot studies and previous reports (Bravo and Maswood, 2006; Ramamoorthy et al., 2008). Fluoxetine (20 mg/kg), a selective serotonin reuptake inhibitor, was used as a standard antidepressant drug. Fluoxetine was administered intraperitoneally 30 min before the tests and the results were considered as the positive control group (Haj-Mirzaian et al., 2014; Kordjazy et al., 2015; Moretti et al., 2012). Also, in order to exclude the effect of saline administration on behavioral tests, saline (5 ml/kg) was injected 30 min before the tests into control group.

In the same way, we assessed the effects of L-NAME (a non-selective NOS inhibitor, 10 mg/kg, 45 min prior to behavioral tests), aminoguanidine (a selective inducible NOS or iNOS inhibitor, 50 mg/kg, 45 min prior to behavioral tests), 7-NI (a selective neuronal NOS or nNOS inhibitor, 25 mg/kg, 30 min prior to behavioral tests), L-arg (an NO precursor, 750 mg/kg, 45 min prior to behavioral tests), and sildenafil (a selective phosphodiesterase (PDE)-5 inhibitor) (5 mg/kg, 30 min prior to behavioral tests) on behaviors of mice in the FST, TST, and OFT. The doses were based on a pilot study and also previous studies (Amiri et al., 2015a; da Silva et al., 2000; Ghasemi et al., 2008; Harkin et al., 2004; Kordjazy et al., 2015; Sadaghiani et al., 2011). To exclude the effect of vehicle administration on behavioral assessments, saline or Tween80 1% (5 ml/kg) were injected 30/45 min before the tests into control groups.

Further, the probable involvement of nitrergic system on the antidepressant-like activity of these 5-HT_3 antagonists was