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Antidepressant effect of pramipexole in mice forced swimming test: A cross talk between dopamine receptor and NMDA/nitric oxide/cGMP pathway

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ABSTRACT

Pramipexole is a dopamine D2 receptor agonist indicated for treating Parkinson disorder. This study was aimed to investigate the effect of pramipexole in forced swimming test (FST) in mice and the possible involvement of activation of D2 receptors and inhibition of N-methyl-D-aspartate (NMDA) receptors and nitric oxide-cyclic guanosine monophosphate (NO-cGMP) on this effect. Intraperitoneal administration of pramipexole (1–3 mg/kg) reduced the immobility time in the FST similar to fluoxetine (20 mg/kg, i.p.). This effect of pramipexole (1 mg/kg, i.p.) was ceased when mice were pretreated with haloperidol (0.15 mg/kg, i.p,) and sulpiride (5 mg/kg, i.p) as D2 receptor antagonists, NMDA (75 mg/kg,i.p.), L-arginine (750 mg/kg, i.p., a substrate for nitric oxide synthase) or sildenafil (5 mg/kg, i.p., a phosphodiesterase 5 inhibitor). The administration of MK-801 (0.05 mg/kg, i.p., a NMDA receptor antagonist) L-NG-Nitro arginine methyl ester (L-NAME, 10 mg/kg, i.p., a non-specific nitric oxide synthase (NOS) inhibitor), 7-nitroindazole (30 mg/kg, i.p., a neuronal NOS inhibitor) and methylene blue (10 mg/kg, i.p.), an inhibitor of both NOS and soluble guanylyl cyclase (sGC) in combination with the sub-effective dose of pramipexole (0.3 mg/kg, i.p.) reduced the immobility. Altogether, our data suggest that the antidepressant-like effect of pramipexole is dependent on the activation of D2 receptor and inhibition of either NMDA receptors and/or NO-cGMP synthesis. These results contribute to the understanding of the mechanisms underlying the antidepressant-like effect of pramipexole and reinforce the role of D2 receptors, NMDA receptors and L-arginine-NO-GMP pathway in the antidepressant mechanism of this agent.

1. Introduction

Depression is one of the debilitating conditions mostly associated with the dysregulation of neurotransmitters like noradrenaline and serotonin (5-HT). The current therapy for depression is also based on these neurotransmitters like noradrenaline and/or 5-HT re-uptake inhibitors [1,2] . Drugs such as selective serotonin re-uptake inhibitors (SSRIs) like as fluoxetine, fluvoxamine or paroxetine are a suitable therapy as it mask the histaminic and muscarinic receptors affinity, however classical tricyclic antidepressants like imipramine have high affinity towards these receptors [3].

A large body of research focusing depression have reported that depression occurs as a consequence of impairment in dopaminergic system [4,5] . Certain classes of drugs that shows antidepressant activity both in laboratory animals and human beings are thought to activate dopaminergic (D) receptors [6,7] . Also it is reported that the antidepressant like effects of certain drugs in the FST is mediated by D1/D5 receptors subtypes [8–10], while others reported that D2/D3 receptor antagonist prevent the antidepressant like effect but not the D1/D5 receptor antagonist [11,12]. Moreover, the reduction in the immobility time during FST by dopamine reuptake inhibitors has been reported to be initiated by dopamine D1 and D2 receptor [9].

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Pramipexole as a dopamine D2 receptor agonist has been proved to be effective in treating diseases like Parkinson's disease and restless leg syndrome in patients who has proven antidepressant capacity [13,14]. Also It has been reported pramipexole augmented the antidepressive effects of other drugs which showed resistance in the treatment of major depressive disorders [15]. A recent study reported that patient with bipolar disorder, subjected to antidepressive treatment with additional pramipexole administration, showed significant improvement within 36 weeks of therapy [16].

Furthermore it is shown that pramipexole decreases the time of immobility during force swimming test in mice as well as rats [17–19] through the stimulation of D2 receptors [17]. Despite its interaction and known antidepressant effects, still we need to do more in order to uncover the exact mechanism as yet it's not fully elucidated.

Dopamine and glutamate are considered as an important and extensively studied neurotransmitter in the brain. Aside from their main physiological functions, any variation in the normal harmony of neurotransmitter release, can lead to various psych- cognitive abnormalities including depression. Also, it is reported that D2 receptor activation, decreased NMDA receptor phosphorylation which is mediated by protein kinase A (PKA) enzyme [20] and hence blocked the NMDA initiated Ca^{2+} signaling [21].

It has been suggested that glutamate is involved in pathophysiological conditions like depressive disorders [22,23] . Furthermore, it was also affirmed by other research group, which reported that a high level of glutamate was found in the frontal cortex of post mortem, who was suffering from major depressive disorder [24]. Also pharmacological inhibition of NMDA receptor through antagonist like ketamine, has an excellent clinical outcome in depressive patients [25,26] . Reports from experimental data are also in line with the above results, where it shows that drugs which block the NMDA receptors have antidepressant like activity [27–30]. Similarly, high doses of antidepressant drugs have intense effect on NMDA receptor activity [22,23].

It is well established that NMDA receptor activation can mimic the activity of nitric oxide synthase (NOS), which in turn catalyze the synthesis of nitric oxide NO from L-arginine [31,32]. The nitric oxide mediated cGMP synthesis is an essential signaling involved in pathogenesis of depression [33]. Nitric oxide in brain is also found to perform other important functions such as neurotransmitter release, pain perception, synaptic plasticity and depression [32]. In recent years, nitric oxide, where decline in the NO level was found to have antidepressant, thus supporting that NO is important determinant in the instigation of depression [34]. Nitric oxide is powerful modulator of cGMP, which is implicated in the manifestation of depression in experimental animals [35]. Recent literature on the blockage of NOS activity reported that it can enhance the antidepressant activity of SSRI's and other agents [36–38].

Taken together these observations, in current study we tried to uncover the potential mechanism for the antidepressant-like activity of D2 receptor agonist pramipexole, in the mouse FST. This test is a reliable model, widely used for the assessment of antidepressant-like activity of drugs [39]. In order to uncover this antidepressant-like mechanism, we focused on the following components as an important determinant of such effect.

- The involvement of dopamine D2 receptor in the antidepressant- like effect of pramipexole
- A cross talk with NMDA receptor and Nitrergic system, possibly through neural NOS (nNOS) inhibition, in the antidepressant-like effect of pramipexole.

2. Materials and methods

2.1. Animals

Adult male NMRI mice,aged 11–13 weeks, were obtained from the Pasteur Institute of Iran, within the range of 20–30 g and. All animals were kept under standard conditions of temperature 21± 2 °C and light/dark cycle of 12-h each. Freely access to food and water was given except for the period of experimentation outside the cage. Four to five animals were housed in a single cage. Full efforts were paid to conduct the experiments within 08:00am to 16:00 pm. In each group there were 8–10 animals and experiments were performed by strictly following the institutional guideline of animal care and use committee (Department of Pharmacology, School of Medicine, Tehran university of Medical Sciences). This study was ethically approved by the International Campus research Committee of Tehran University of Medical Sciences.

2.2. Open-field test (OFT, locomotor activity test)

The locomotor activity of animals was determined through a well-known test i.e. open-field test, immediately followed by FST as described previously [27,40]. Briefly the apparatus consist of a box made of wood with dimension of 40 cm × 60 cm × 50 cm. The base of the box is divided equally into 12 small squares. At the start of each trial a mouse was placed in the left corner of the field. The number of squares were counted, when crossed with all paws for a period of 6-min. After every session for each animal the apparatus was washed with a 10% ethanol solution.

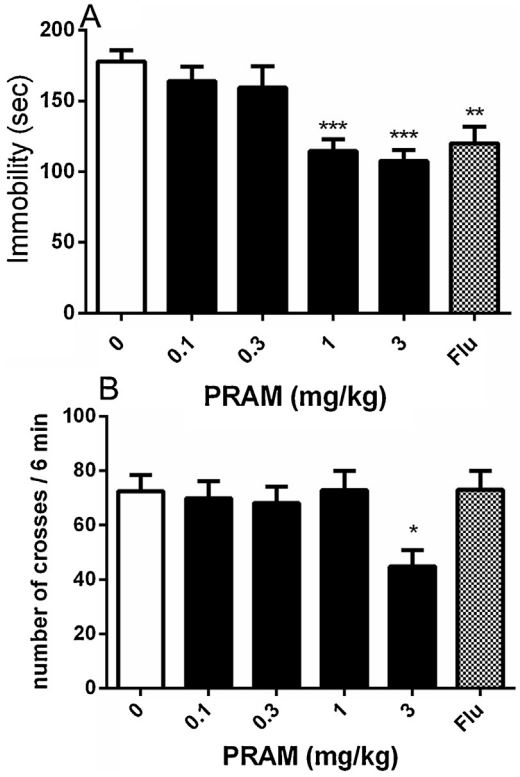

Fig. 1. Effect of i.p administration of pramipexole (PRAM) and fluoxetine (Flu, 20 mg/kg, i.p.) on FST (A); and OFT (B) in mice. Values are expressed as mean +SEM (n=8). $^{*}P < 0.05$ $^{***}P < 0.001$ as compared with the vehicle-treated control.