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Research report

Involvement of dopamine (DA)/serotonin (5-HT)/sigma (σ) receptor modulation in mediating the antidepressant action of ropinirole hydrochloride, a D_2/D_3 dopamine receptor agonist

Ashish Dhir, S.K. Kulkarni *

Pharmacology Division, University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh-160014, India

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Abstract

Multiple lines of investigation have explored the role of dopaminergic systems in mental depression. Chronic treatment with antidepressant drugs has been reported to alter dopaminergic neurotransmission, most notably a sensitization of behavioural responses to agonists acting at D_2/D_3 dopamine receptors within the nucleus accumbens. Recent clinical evidences have shown that ropinirole, a D_2/D_3 dopamine receptor agonist, augments the action of various standard antidepressant drugs in treatment-resistant depression. The present study was undertaken to elucidate the possible mechanism of antidepressant action of ropinirole employing various behavioral paradigms of despair supported by the measurements of neurochemical changes in the tissue contents of dopamine (DA) and serotonin (5-HT) in the whole brain using high-performance-liquid chromatography (HPLC) with electrochemical detectors (ECD). In the mouse forced swim test (FST) or tail-suspension test (TST), ropinirole (1–10 mg/kg, i.p.) produced S-shaped dose–response curve in the percentage decrease in immobility period. Compared with vehicle, ropinirole (10 mg/kg., i.p.) had a significant anti-immobility effect without affecting locomotor activity. The reduction in the immobility period elicited by ropinirole (10 mg/kg, i.p.) in the FST was reversed by dopaminergic and sigma receptor antagonist, haloperidol (0.5 mg/kg, i.p.), and specific D_2 dopamine receptor antagonist sulpiride (5 mg/kg i.p.), but not by SCH 23390 (0.5 mg/kg i.p), a D_1 dopamine receptor antagonist. Rimcazole (5 mg/kg i.p.) (a sigma receptor antagonist), progesterone (10 mg/kg i.p.) (a sigma receptor antagonistic neurosteroid), BD 1047 (1 mg/kg i.p.) (a novel sigma receptor antagonist with preferential affinity for sigma-1 sites) also reversed the anti-immobility effect of ropinirole (10 mg/kg i.p.). The neurochemical studies of whole brain revealed that ropinirole at 10 mg/kg i.p. did not affect the tissue levels of dopamine but significantly increased serotonin levels. The study indicated that ropinirole possessed anti-immobility activity in FST by altering dopaminergic, serotonergic or sigma receptor function.

Keywords: Ropinirole; Forced swim test (FST); Tail suspension test (TST); Dopaminergic modulation; Serotonergic modulation; Sigma receptors

1. Introduction

The catecholamine and indoleamine hypotheses of depression [56,4] spurred research into abnormalities of noradrenergic and serotonergic transmission as causes of mental depression. Subsequently, a dopamine hypothesis of depression was put forward [49]. Since then, multiple lines of investigations have explored the role of dopaminergic systems in depression [26,16]. A deficiency of mesolimbic dopamine (DA) is a leading candidate for the etiology of certain symptoms of depression. Studies have revealed that a decrease in dopamine and its metabolite homovanillic acid (HVA) in the cerebrospinal fluid of depressed patients [63]. The drugs which increased dopamine levels in brain either by inhibiting the dopamine reuptake (e.g. bupropion or nomifensine) or dopaminergic agonistic action have been shown to be potent antidepressants [34,2]. Piribedil and bromocriptine, directly acting DA agonists [15] possessed antidepressant activity. Among all the dopamine receptors, D_2 and D_3 receptor type have been considered as particularly important in affective disorders due to their localization in the limbic region of the brain along with serotoninergic transmission of the CNS [2,67]. A recent double-blind study found that pramipexole, a very selective D_3-preferring D_2/D_3

* Corresponding author. Tel.: +91 172 2534114/2541142; fax: +91 172 2541142.
E-mail address: skpu@yahoo.com (S.K. Kulkarni).

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receptor agonist to have comparable antidepressant efficacy as compared to fluoxetine, a selective serotonin reuptake inhibitor (SSRI) [36]. When pramipexole was combined with fluoxetine, it enhanced its action suggesting the functional interaction between dopamine and serotonin system [53]. Standard antidepressants such as fluoxetine or imipramine are also known to modulate the dopaminergic system. In one of the studies, a single injection of 2.5 mg/kg (i.p.) of fluoxetine significantly increased the number of spontaneously active DA neurons in rat brain suggesting the role of dopamine in mediating antidepressant action [57].

Interestingly, a disruption of dopaminergic transmission is implicated in the depressed mood displayed both by Parkinson and by non-Parkinson patients [67,30,64]. Ropinirole is a nonergoline dopamine D_2–D_3 dopamine receptor agonist indicated in Parkinson's disease and its use has been associated with a lower risk of dyskinesias and valvular regurgitation [29]. Recent clinical evidences have shown that ropinirole augments the antidepressant effects of many standard drugs such as tricyclic antidepressants (TCA) or selective serotonin reuptake inhibitors (SSRI) [7]. Besides, ropinirole has been reported to possess anxiolytic and antidepressant profile in various animal paradigms in mice, rats and common marmoset [52].

Various preclinical studies have indicated the role of sigma receptors in depression [3,61]. Sigma receptors are non-opioid, non-phencyclidine receptors and consist of two subtypes: sigma-1 and sigma-2. Sigma-1 receptors exist mainly in the central nervous system, but also in the periphery. Many pharmacological and physiological actions have been attributed to sigma-1 receptors [20]. These include the regulation of IP_3 receptors and calcium signaling at the endoplasmic reticulum, mobilization of cytoskeletal adaptor proteins, modulation of nerve growth factor-induced neurite sprouting, modulation of neurotransmitter release and neuronal firing, modulation of potassium channels as a regulatory subunit, alteration of psychostimulant-induced gene expression, and blockade of spreading depression [62]. These receptors are known to modulate the dopaminergic and serotonergic system in the brain [22,27]. Behavioral models used to test potential antidepressants have shown that ligands that bind to sigma receptors possessed "antidepressant-like" properties. Sigma ligands have potential as antidepressant medications with a fast onset of action as they produced a rapid modulation of the serotonergic system in the dorsal raphe nucleus (DRN) and the glutamatergic transmission in the hippocampus [3]. One of the earlier studies from our laboratory has indicated the involvement of sigma-1 receptors in modulating the antidepressant effect of neurosteroids in forced swim test in mice and the test was carried out using NE-100, a sigma-1 receptor antagonist [51]. Recently, we have shown the involvement of sigma-1 receptors in the antidepressant action of venlafaxine in mouse FST [11]. As these effects of sigma ligands may produce antidepressant properties by completely novel mechanisms of action, they may provide an alternative to the antidepressants currently available and may prove to be beneficial in treatment-resistant depressed patients [3].

As sigma receptors are known to modulate the dopaminergic and serotonergic system in the brain [3,22,27] and this interaction between dopaminergic agonists and sigma receptors may constitute a possible mechanism for their neuropharmacological effects in depression. However, there is little evidence to support this hypothesis. Therefore, it is speculated that ropinirole may be having antidepressant action possibly by acting through sigma receptors.

The antidepressant profile of ropinirole and its exact mechanism of action have not been worked out. The test models of depression (forced-swim test and tail-suspension test) are based on the observation that rats or mice when forced to swim or suspended in a restricted space from which there is no possibility of an escape, eventually cease to struggle, surrendering themselves (despair or helplessness) to the experimental conditions. Porsolt et al. [45] and Steru et al. [60] suggested that this helplessness or despair behavior reflected a state of lowered mood in laboratory animals and could serve as a valuable test for screening antidepressant drugs [28].

With this background, the present study was designed to elucidate the anti-immobility profile of ropinirole in various behavioral paradigms of despair (FST and TST) and to elucidate the possible neurochemical mechanism of action of its antidepressant activity.

2. Materials and methods

2.1. Animals

Male albino mice (Laca strain) weighing between 22 and 30 g bred in Central Animal House (CAH) facility of the Punjab University, Chandigarh were used. The animals were housed under standard laboratory conditions and maintained on natural light and dark cycle, and had free access to food and water. Animals were acclimatized to laboratory conditions before the experiment. Each animal was used only once. All the experiments were carried out between 0900 and 1500 h. The experimental protocols were approved by the Institutional Animal Ethics Committee (IAEC) and conducted according to the Indian National Science Academy (INSA) Guidelines for the use and care of experimental animals.

3. Experimental protocol

3.1. Behavioral parameters

3.1.1. Forced swim test

The test procedure was carried out according to the previously standardized and validated animal model in our laboratory [51,11,28,42,12,13]. In brief, mice were individually forced to swim inside a rectangular glass jar ($25 \times 12 \times 25\ cm^3$ containing 15 cm of water maintained at 23–25 °C). After the initial 2–3 min of vigorous activity the animals showed period of immobility by floating with minimum movements. An animal is considered to be immobile whenever it remained floating passively in the water in a slightly hunched but upright position, its nose above the water surface. The total immobility period for the period of 6 minutes was recorded with the help of stop-watch [28].

3.1.2. Tail suspension test (TST)

The total duration of immobility induced by tail-suspension was measured according to the method of Steru et al. [60] and validated in our laboratory [12,13]. Mice both acoustically and visually isolated were suspended 50 cm above the floor by adhesive tape placed approximately 1 cm from the tip of the tail. Immobility period was recorded during a 6-min test. The total immobility was recorded for a period of 6 min with the help of stop-watch. A mouse