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Short Communication

INVOLVEMENT OF OPIOIDERGIC SYSTEMS IN THE ANTIDEPRESSANT EFFECT OF 5-AMINOINDAZOLE

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ABSTRACT

Objectives: The present study was designed to investigate the anti-depressant activity of 5 – aminoindazole and the possible mechanism involved.
Methods: Anti-depressant activity was evaluated in mice by employing forced swim test. The involvement of opioidergic system was investigated by using naloxone.
Results: 5 - aminoindazole exhibited a significant and dose dependent reduction in period of immobility in the forced swim test. Pretreatment with naloxone attenuated the reduction in immobility period produced by 5 - aminoindazole.
Conclusion: The investigated 5 - aminoindazole exhibited promising anti-depressant activity in animal models of depression. The participation of opioidergic mechanism in the antidepressant activity of 5 - aminoindazole was elucidated from the results.
Keywords: Anti-depressant activity, 5 - aminoindazole, Forced swim test.

INTRODUCTION

Depressive disorders are predicted to become the second leading cause of disability by the year 2020 (Kessler et al., 2005). These disorders are severe types of psychiatric conditions that affect about 16 % of the population during their lifetime. A report indicates that approximately 63% of patients fail to respond to the first line therapy with selective serotonin reuptake inhibitors (Rush et al., 2006). In addition, the delayed onset of resolution of depressive symptoms and serious adverse effects associated with the currently used antidepressant. Hence, there is an urgent need to search for a safe and potent antidepressant.

Indazoles are emerging as pharmaceuticals with specific use in certain diseases. Investigations carried out in recent decades have identified the potential usefulness of these compounds in several biological conditions such as inhibition of apoptosis (Jin et al., 2002), treatment of rheumatoid arthritis (Robert et al., 2004), anti-proliferative activity (Vasiliki et al., 2007), treatment of hypertension (Jesse et al., 2006), hypotensive activity (Thomas et al., 2003), treatment

of obesity (Andrew et al., 2005), tumor cell cytotoxic assays (Jian et al., 2007), anti - hyperlipidemic activity (Wyrick et al., 1984), trichomonacidal activity (Aran et al., 2005). The above interesting biological activities of indazoles kindled an interest whether 5 - aminoindazole could be a potential source for antidepressant drug. Hence, in the present study, 5-aminoindazole has investigated for potential antidepressant effect in mice by employing forced swim test. In addition, the possible mechanisms involved in the antidepressant effect of these compounds were also considered for investigation.

MATERIALS AND METHODS

Animals:

Adult Swiss albino mice of either sex weighing 25 to 30g were selected for the study and were sourced from the institutional animal house. The animals had free access to food and water ad libitum under strict hygienic conditions and maintained in room temperature of 25±1°C, relative humidity 45- 55% and a 12:12h light/dark cycle. To avoid circadian variation and to maintain uniformity, all the experiments were carried out between 9.00 and 13.00 hours. The experimental protocol was approved by the institutional animal ethics committee (BR/COL/3401/2015).

Drugs and chemicals:

5-aminoindazole was purchased from Sigma Aldrich, USA and prepared as a fine suspension in 0.5% carboxy methyl cellulose (CMC) and injected i.p in doses ranging from 25 - 100 mg/kg, 30 min prior to the test procedures. Imipramine (Torrent Pharmaceuticals, India), naloxone hydrochloride (Endo Labs USA) were used in the present study.

Forced swim test:

Forced swim test was proposed as a model to test for anti-depressant activity by Porsolt et al., (1978). In this test, the mouse is forced to swim inside a vertical open cylindrical container (height - 35 cm, diameter – 15cm) with 25cm of water (depth) at 20 ± 1.5°C. Initially the mouse swims vigorously and tries to climb the wall. After a minute, the activity begins to subside and replaced with phases of immobility or with only minimal movements to keep its head above the water level. A decrease in the duration of immobility is indicative of an antidepressant effect. 5 - aminoindazole was administered i.p in doses of 25, 50 or 100 mg/kg to different groups of mice, 30min prior to the test. Imipramine 20mg/kg i.p was used for comparison in a separate group of mice.

Opioid mechanism:

In order to investigate the participation of opioid system in the anti-depressant action of 5 - aminoindazole, mice were pretreated with naloxone 5mg/kg i.p, (Fichna et al., 2007) and after 15 min the animals received an injection of 5 - aminoindazole in a dose of 100 mg/kg i.p. The anti-depressant effect was recorded 30 min later using forced swim test.

Statistical analysis:

ANOVA, Dunnett's't' test and unpaired "t" test (SPSS 16 software) were used to analyze the data obtained from various experiments. A probability value less than 5% was considered to be statistically significant.

RESULTS

Forced swim test:

The immobility period recorded in vehicle treated control animals was 190.14 ± 5.8 sec. A significant reduction in immobility period was observed in imipramine (20 mg/kg) treated mice and the mean value was 8.57 ± 1.12 sec (Fig. 1). A dose proportionate reduction in immobility period compared to vehicle treatment was observed after treatment with different doses (25, 50 & 100 mg/kg i.p) of 5 - aminoindazole. The maximum reduction in immobility period in a dose of 100mg/kg of 5 - aminoindazole was 28.05 ± 2.14 (Fig. 1).

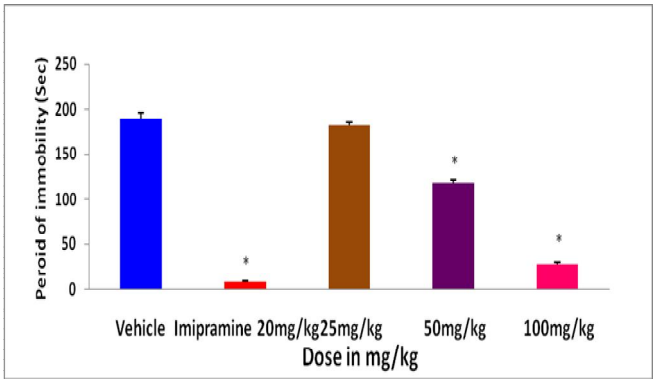

Fig. 1: Effect of 5 – aminoindazole on mice in forced swim test. Each value represents the mean ± SEM of six values, *P <0.05 compared to vehicle treatment (ANOVA, Dunnett's test)

Involvement of opioid system:

Naloxone (5mg/kg i.p) treatment per se did not significantly alter the immobility period of mice in forced swim test.

However, a significant reversal of the reduction of immobility period of mice was evident in animals treated with *5* - aminoindazole (Fig. 2).

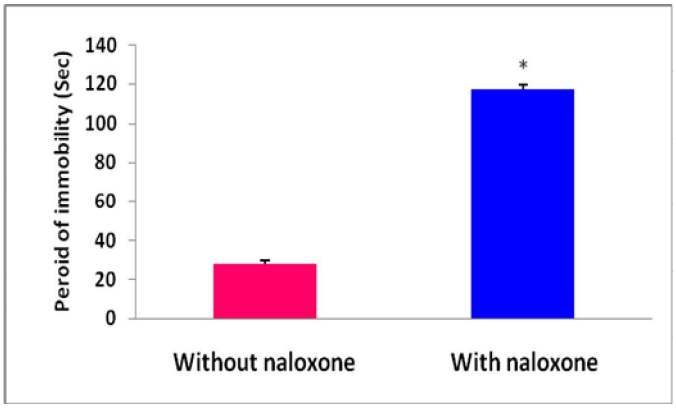

Fig. 2: Effect of naloxone on period of immobility produced by *5* – aminoindazole. Each value represents the mean ± SEM of six values, *P <0.05 compared to vehicle treatment (unpaired "t" test)

DISCUSSION

Mood and anxiety disorders are the most common psychiatric illnesses widely presented to clinicians. The manifestations of depression may be mild and self limiting or they may be extremely severe with high suicide potential, psychosis and serious functional impairment. Even though social awareness has improved the attitude of public to seek medical attention for depressive disorders, the duration and adherence to treatment remain questionable. This is also compounded by considerable delay in diagnosis and inadequate treatment of depression (O'Donnell and Shelton, 2011). More over intolerable side effects associated with the use of currently employed anti depressant drugs also necessitates the development of new drugs with minimal side effects. Hence, there is always a need for newer antidepressant drugs with maximum efficacy and minimal side effects.

The results of the present study clearly indicate that, the period of immobility in the forced swim test is decreased in a dose dependent fashion in mice treated with *5* – aminoindazole (Fig. 1). The reduction in immobility period was significantly evident only in 50mg/kg and 100 mg/kg of tested compound in forced swim test. The above findings clearly indicate an antidepressant effect of *5* – aminoindazole.

Darko et al., (1992) and Djurovik et al., (1999) found the decreased serum β – endorphin levels in patients with severe depression. Many opioid drugs such as oxycodone, oxymorphone and buprenorphine have shown their efficacy in refractory depression patients (Bodkin et al., 1995). Moreover, central administration of endogenous peptides like endomorphin - 1 and endomorphin - 2 have been shown to possess antidepressant activity in mice (Fichna et al., 2007). All these evidences indicate a prominent role for opioid system in the development of depression. Hence, it was considered interesting to investigate the possible role of opioidergic in the antidepressant effect of the *5* - aminoindazole. Naloxone, a non specific opioid antagonist was used for this purpose. In the present study, naloxone administration reversed the reduction in immobility period produced by *5* - aminoindazole. The results thus indicate that the antidepressant effect of the investigated *5* - aminoindazole due to the involvement of opioid mechanism.

In conclusion, the present study has identified the novel antidepressant activity of *5* - aminoindazole. The role of opioid mechanism in the antidepressant effect of *5* - aminoindazole was also revealed. Future investigations have required to finding out the other mechanisms involved in the antidepressants effect of *5* - aminoindazole.

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