Evaluation of antidepressant activity of ondansetron in rodent models of depression

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ABSTRACT

Background: At present, there is an escalating concern regarding possible role of 5-HT3 receptor in psychopharmacology and the therapeutic potential of their antagonists. Moreover, inclusion of 5-HT3 receptor antagonist may curtail the antidepressant-induced LTP decrease causing memory deficits, thereby improving efficacy of current antidepressants. Aim and Objective: This study aims to evaluate the antidepressant activity of 5-HT3 antagonist, that is, ondansetron (OND) in rodent models of depression. Materials and Methods: Male Swiss albino mice (20–30 g bw) and Wistar rats (100–200 g bw) were divided into five groups. Animals received either OND p.o. (0.1, 0.5 and 1 mg/kg), venlafaxine (10 mg/kg), or vehicle (1 ml distilled water p.o.) in control. Tail suspension and forced swim test were used to evaluate the effects of drugs and control after 60 min of their administration. Furthermore, assessment of locomotor activity (LA) was done by photoactometer after 24 h of drug administration. Results: Ondansetron exhibited significant antidepressants activity (P < 0.05) in rodent models. However, LA was not significantly altered by OND. Conclusion: Ondansetron exhibited significant antidepressant activity in rodent models hence paving the way for exploration of 5-HT3 receptor antagonist in future researches and its therapeutic application in depression.

KEY WORDS: 5-HT3; Antidepressants; Psychopharmacology; Long-Term Potentiation

INTRODUCTION

Among all the psychiatric disorders, depression and anxiety are the most commonly encountered entities.¹ As per the data from the National Health and Nutrition Examination Survey in American population, females (10.4%) were found to suffer more than males (5.5%) and approximately 8.1% of adults have episodes of depression in between 2013 and 2016.² Moreover, depression accounts for 60% of all suicidal deaths³ that alarm its early diagnosis and treatment in current scenario.⁴ The National Mental Health Survey 2015–2016 in India revealed that 9.8 million teenagers in the age group 13–17 years suffer depression and other mental health disorders and entails timely intervention.⁵ Commonly prescribed medication in depression are tricyclic antidepressants, MAO inhibitor, selective serotonin reuptake inhibitors, atypical antidepressants, and majority of these acts by increasing the concentration of monoamines in synapse directly or indirectly.⁶ Limited utility of currently used
antidepressants for the psychiatric disorders is attributed to longer duration of treatment and its associated adverse effects as well as effectiveness. At present, it is hypothesized that 5-HT3 receptor is implicated in the psychopharmacology and pathophysiology of major depression. A study shows that shrinkage of the hippocampus and prefrontal cortex of depressed patients is associated with loss of neurons and glia. Hippocampus and prefrontal cortex are rich in GABAergic interneurons that express 5HT3 receptors. Furthermore, 5-HT3 receptor agonist reduces the hippocampal transmission in vivo as well as reduces the hippocampal plasticity by decreasing the long-term potentiation (LTP) in vitro while 5-HT3 receptor antagonists are found to induce an increase in LTP induction along with positive effect on memory which might be useful if added with currently used antidepressants that are found to have inhibitory effect on LTP. Hence, the study was done for exploration of antidepressant activity of a 5-HT3 antagonist, namely, ondansetron (OND).

MATERIALS AND METHODS

A written consent was obtained from Institutional Animal Ethics Committee before conduct of the study and animals were maintained according to the CPCSEA guidelines. Animals were kept in 12 h light and dark cycle and were housed in groups of five. The food and water were allowed ad libitum. All behavioral tests were conducted during daytime between 00600 and 1800. Male Wistar rats 100–200 g and Swiss albino mice weighing 20–40 g were divided into five study groups, six animals each tested for forced swim test (FST) and tail suspension test (TST) respectively. The antidepressant activity was determined primarily by behavior-based models, FST and TST to achieve a level of accuracy in predicting clinical activity that could not be assessed by a single test alone. Group I served as control and received 1 ml dw p.o., Groups II–IV received OND 0.1 mg/kg, p.o., 0.5 mg kg, p.o., and 1 mg/kg, p.o., respectively, and Group V received venlafaxine 10 mg/kg, p.o. as a standard antidepressant. Drugs which decrease immobility and increase active behaviors in both FST and TST are considered to suppress depression. These tests were performed after 1 h of drug administration.

Forced Swim Test (FST)

The FST is reliable with strong predictive validity for antidepressants. The adult male rats were individually forced to swim in a cylinder (40 cm × 18 cm) filled with water 23–25°C with no escape over a period of 6 min. A mouse is considered immobile when it floats motionlessly or made only those moments necessary to keep its head above the water surface as a survival instinct. This behavior reflects a state of despair in rats, which can be decreased by various clinically effective antidepressants. Time was noted when the animals become immobile. The total duration of immobility was measured in the past 4 min of the trial.

Tail Suspension Test

The mouse was individually hung by the tail with an adhesive tape tied to a stand (distance from tip of the tail was approximate 1 cm), 75 cm above the surface in upside down posture such that its nostril touches the water surfaces in a container. Initially, the animal tried to escape by making vigorous movements, but was unable to escape and become immobile. This inescapable and unavoidable stress reflecting the behavior despair in mice which, in turn, may reflect the depressive disorders in human. The period of immobility during 6 min observation period was noted.

Measurement of Locomotor Activity (LA)

The assessment of behavioral activity based on immobility time measurement may give false-positive results due to general increase or decrease in LA shown by neuropharmacological studies. For this reason, the basal LA was assessed to find out the effects of drug treatment as compared to control on locomotor scores. To rule out any effects of the drugs on motor activity, horizontal LA of control and test animals was recorded for a period of 5 min using photoactometer.

The photoactometer consisted of a square arena (30 cm × 30 cm) with walls painted black and having photocells above the floor level. Before starting the test, photocells were checked. The principle of photocell is that the rays of light falling on the photocells are cut off by the animals crossing the beam of light and photocell activated, a count is recorded by an electronic automatic counting device in the form of number of cutoffs.

The animals were placed individually in the photoactometer cage and after initial familiarization period of 2 min, digital locomotor score was recorded for the next 5 min. The experiment arena was cleaned with dilute alcohol (70% v/v) and stays dried between the tests.

Statistical Analysis

Data were analyzed using SPSS (20.0) software. The results were expressed as Mean ± SD. One-way analysis of variance (ANOVA) test was applied for statistical comparison. For all tests, significant main effects or interactions were resolved using post hoc ANOVAs with adjusted P-values and/or post hoc test (Tukey’s HSD). The level of significance was set at P < 0.05.

RESULTS

In the present study, we found that OND in all given doses decreased the immobility time and increased the swimming time depicting antidepressant activity. Reduction of immobility in FST and TST methods was statistically significant (P < 0.0001). In FST, immobility time reduction...
was more in dose of 1 mg/kg (74.50 ± 4.086) than 0.5 mg/kg dose (121.00 ± 4.690) and 0.1 mg/kg (138.83 ± 4.792) dose of OND as compared to control (161.00 ± 3.619) [Figure 1]. Reduction in immobility in TST was also observed and was more evident with the test dose of 1 mg/kg of (74.50 ± 4.056) of OND as compared to lower dose of 0.5 mg/kg (85.00 ± 4.419), and 0.1 mg/kg (94.33 ± 4.020) and control (122.67 ± 5.551) [Figure 2]. These observations were also significant in between test doses and the results showed that effects were dose dependent. The results showed that venlafaxine also significantly reduced the immobility duration in both FST (55.00 ± 3.464) and TST (55.00 ± 3.410) as compared to control (161.00 ± 3.619) in FST and control (122.67 ± 5.551) in TST indicating antidepressant activity of the drug. Observations with OND in dose of 1 mg/kg showed lesser antidepressant activity in comparison to the venlafaxine 10 mg/kg in both FST and TST that were statistically significant ($P < 0.0001$). In our present study, spontaneous horizontal LA was not significantly affected by OND in all test doses (0.1, 0.5, and 1 mg/kg p.o.), as well as with the venlafaxine (10 mg/kg p.o) [Figure 3], suggesting independence between swimming and LA.

**DISCUSSION**

Development of antidepressants in the past five decades has been mainly based on monoaminergic hypothesis. In our study OND, a 5HT3 antagonist reduced the immobility time in a dose-dependent manner which was statistically significant ($P < 0.0001$) in both experimental methods.

Ondansetron exhibited greater reduction in immobility time in dose of 1 mg/kg p.o. although it was not equivalent to venlafaxine. We observed that spontaneous horizontal LA was not significantly altered by OND, indicating that the antidepressant effect of was not merely due to increased motor activity. Reduction of immobility time in both tests by OND is likely to be due to antidepressant effect of drug and supported by study of Shrivastava et al. and Mahesh et al. In their randomized controlled trial, Johnson et al. found that OND reduces mood disturbance among biologically predisposed, alcohol-dependent individuals. In patients with chronic hepatitis C and in bulimic patients, OND also reduced depressive symptoms which are in accordance with our study. In an animal experimental study, Kurhe et al. and Gupta et al. found that OND reverses the comorbid depression and anxiety associated with obesity and diabetes and have a role in facilitating serotonergic neurotransmission. Using a novel 5-HT3 receptor antagonist, Bhatt et al. found that concentration of serotonin was raised at the synapse by 6P and the antidepressant-like activity of OND might be attributed to selective 5-HT3 receptor blockade modulating neuronal release of neurotransmitters. However, preclinical studies have shown that addition of a 5-HT receptor agonist or antagonist with existing antidepressants regime improves the effect and reduced the delay in response as compared to currently prescribed antidepressants.
5-HT3 receptor has role in the neurotransmission regulation which was relevant to many psychiatric diseases.[12,33] In the present study OND, a 5HT3 receptor antagonist exhibited antidepressant activity in a dose-dependent manner although not equivalent to standard drug venlafaxine suggesting blockade of serotonergic receptors and may be associated with lesser adverse effects as compared to currently prescribed antidepressants. The hippocampal LTP is inhibited by antidepressants medicines[13] as well as by the 5-HT3 receptor agonists due to reduction in hippocampal transmission and plasticity causing effect on memory in the form of deficit.[11-13] These antidepressants induced LTP reduction[15] might be prevented by addition of 5-HT3 receptor antagonist lead to increasing the effect of existing antidepressants and improve the deficit of memory.[20] Even though, the exact molecular mechanism behind antidepressant action of OND is not known and yet to establish.

CONCLUSION

It is likely that additional exploration of 5-HT3 receptor and their molecular structure, function, and regulation with understanding of several responses of antagonist may offer new therapeutic opportunities. Further studies are required to explore before it finds utility in practice.

REFERENCES


