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RESEARCH ARTICLE

Effect Of Serotonin Receptor Modulators On Depressive-Like Behavior In Animal Models

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Abstract: Depression is a complicated neuropsychiatric condition which is manifested by a persistent low mood, anhedonia, and neurochemical signaling abnormality, especially in the serotonergic system. Serotonin (5-HT) receptors are important targets in the regulation of mood and have emerged as central targets in the treatment of depression using antidepressants. The objective of the current research was to assess the impact of serotonin receptors modulators on depressive-like behavior in depression models in animals. To measure behavioral despair, male Wistar rats were exposed to forced swim test (FST) and tail suspension test (TST). There were animals that were used in vehicle, standard antidepressant (fluoxetine, 10 mg/kg), and the test serotonin receptor modulators (5-HT 1A agonist, 5-HT 2A antagonist, and 5-HT 9 inverse agonist). The therapy was undertaken over 14 consecutive days. There were behavioral parameters such as immobility, swimming, and climbing times. The findings showed that all modulators had a significant effect on the duration of immobility in reducing immobility in comparison with control ($p < 0.05$) and the 5-HT 1A agonist had the highest antidepressant-like effect similar to fluoxetine. The findings suggest that modulation of specific serotonin receptor subtypes can effectively ameliorate depressive-like symptoms, supporting their therapeutic potential as novel antidepressant agents.

Keywords: Serotonin receptors, Depression, 5-HT_1A agonist, 5-HT_2A antagonist, 5-HT_7 inverse agonist, Forced swim test, Tail suspension test, Antidepressant activity.

INTRODUCTION

Depression is a multifactorial neuropsychiatric disorder affecting millions of individuals globally, characterized by persistent low mood, loss of interest in pleasurable activities (anhedonia), cognitive deficits, fatigue, and disturbances in sleep and appetite. The disorder poses a substantial socioeconomic burden due to decreased productivity, impaired social functioning, and increased risk of suicide. Although the etiology of depression is complex, encompassing genetic, environmental, and psychological factors, alterations in monoaminergic neurotransmission particularly serotonergic signalling are recognized as central contributors to the pathophysiology of depression [1].

Serotonin (5-hydroxytryptamine, 5-HT) regulates mood, cognition, sleep, and appetite through multiple receptor subtypes in the brain. Among these, the 5-HT_1A receptor is predominantly involved in anxiolytic and antidepressant responses, 5-HT_2A receptors modulate emotional processing and cortical excitability, and 5-HT_7 receptors influence circadian rhythms and synaptic plasticity. Dysregulation of these receptors has been implicated in depressive disorders, making them attractive targets for novel pharmacological interventions [2]. Unlike traditional antidepressants such as selective serotonin reuptake inhibitors (SSRIs) that globally increase serotonin levels, receptor-specific modulators can provide targeted effects, potentially offering faster onset, improved efficacy, and fewer adverse effects.

Experimental models of depression, particularly the forced swim test (FST) and tail suspension test (TST), are validated paradigms for evaluating antidepressant-like activity. These models measure behavioral hopelessness, which is usually expressed in immobility and this is mitigated by antidepressant compounds [3]. They make it possible to determine the intensity and the appearance of drug action, which makes them appropriate to screen novel serotonergic modulators (Figure 1).

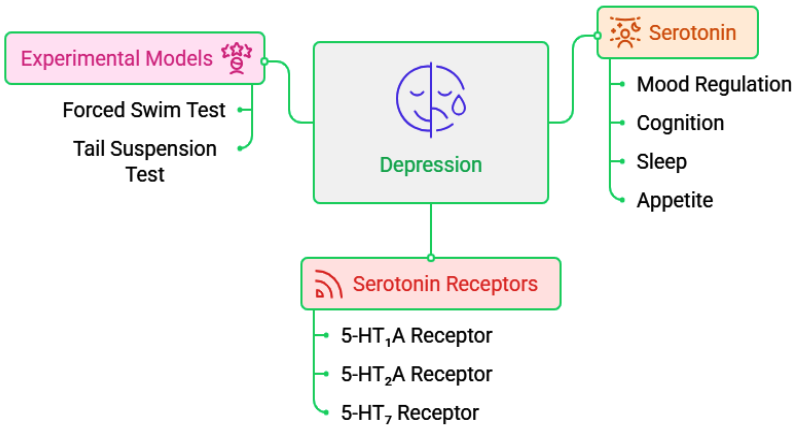


Figure 1: Serotonin Receptor Modulation in Depression Treatment

The current experiment aimed at determining the impact of selective serotonin receptor modulators on the depressive-like behaviors in Wistar rats. Three receptor-targeted compounds were evaluated, 5-HT 1 A receptor agonist, 5-HT 2 A receptor antagonist and 5-HT 9 receptor inverse agonist. Relative efficacy of the receptor-specific modulation was determined by comparison of the behavioral effects with that of fluoxetine which is one of the standard SSRIs [4]. The current study should inform the creation of receptor-targeted antidepressant interventions with faster acting mechanisms by explaining how the various subtypes of serotonin receptors contribute to antidepressant action.

MATERIAL AND METHODS

Chemicals and Reagents

The standard antidepressant was fluoxetine hydrochloride. A 5-HT 1A receptor agonist, 5-HT 2A receptor antagonist and 5-HT 9 receptor inverse agonist, which were acquired through certified chemical suppliers, were used as test compounds. Solvents and reagents were of analysis grade [5].

Experimental Animals

Wistar adult male (180220 g) were obtained and kept in the normal laboratory conditions (temperature 25±2^{0}C, relative humidity 5060, 12/12 hours light/dark cycle) with ad libitum food and water. The study protocol was approved by the Institutional Animal Ethics Committee (IAEC) and followed CPCSEA guidelines [6].

Experimental Design

Rats were randomly divided into five groups (n = 6 each) [7]:

- Group I: Normal control (vehicle, saline)
- Group II: Standard (fluoxetine 10 mg/kg, i.p.)
- Group III: 5-HT$_1$A receptor agonist (5 mg/kg, i.p.)
- Group IV: 5-HT$_2$A receptor antagonist (5 mg/kg, i.p.)
- Group V: 5-HT$_7$ receptor inverse agonist (5 mg/kg, i.p.)

Treatments were administered daily for 14 consecutive days prior to behavioral testing.

Behavioral Assessment

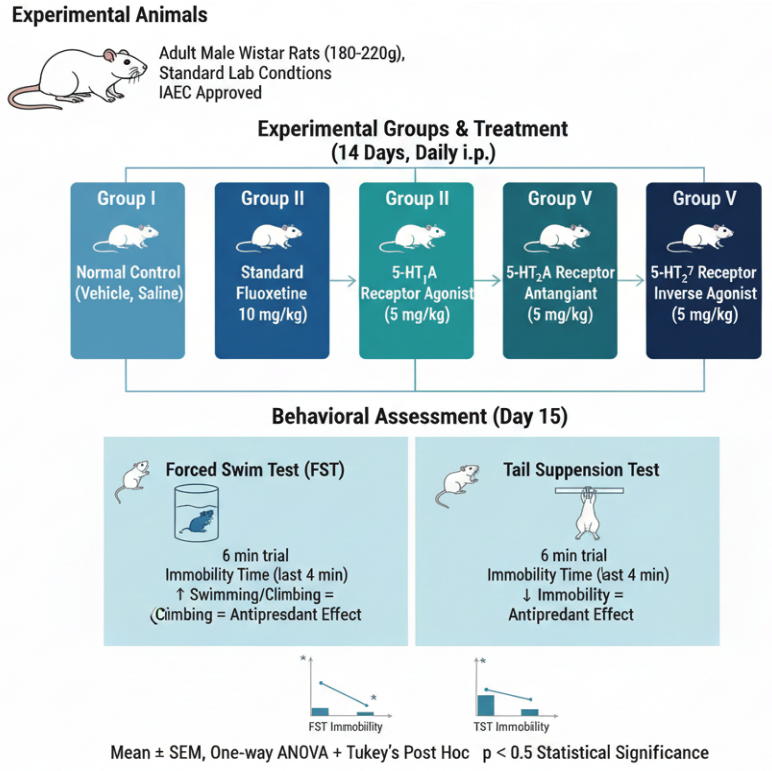
Behavioral despair was evaluated using two established models [8]:

- *Forced Swim Test (FST):* Rats were individually placed in a cylindrical container filled with water (25 ± 1°C, height 30 cm) for 6 minutes. Immobility time (duration spent floating without struggling) was recorded during the last 4 minutes. Increased swimming or climbing activity was considered indicative of antidepressant-like behavior.
- *Tail Suspension Test (TST):* Rats were suspended by the tail using adhesive tape attached 1 cm from the tip. Immobility time was recorded over a 6-minute period. Reduced immobility indicates antidepressant-like effects [9].

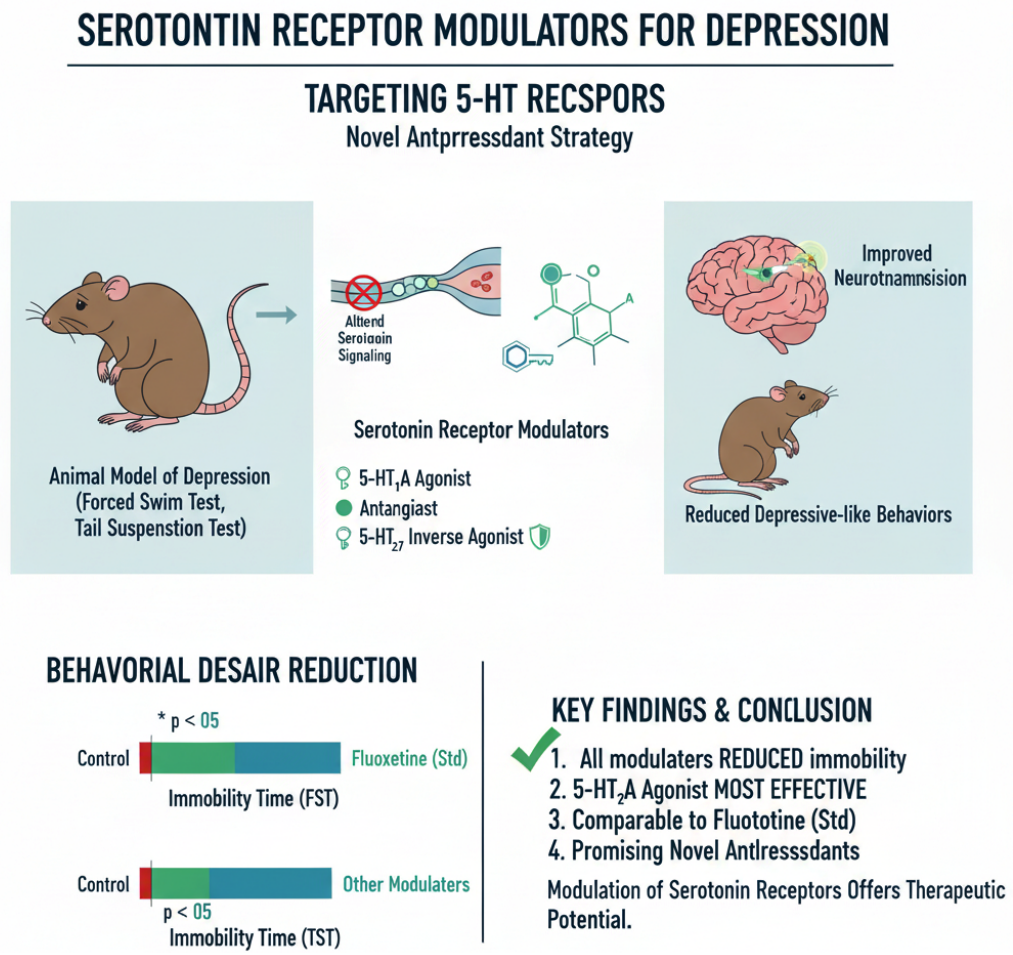
Data Analysis

Behavioral data were expressed as mean ± SEM. Statistical comparisons between groups were performed using one-way ANOVA followed by Tukey's post hoc test. A p-value < 0.05 was considered statistically significant (Figure 2) [10].

Figure 2: **Experimental Animals** **Experimental Design**



Graphical Abstract:



RESULTS AND OBSERVATIONS:

The effects of serotonin receptor modulators on depressive-like behavior in rats were evaluated using the forced swim test (FST) and tail suspension test (TST).

Forced Swim Test (FST)

The control group exhibited high immobility time (198.3 ± 6.4 s), indicating depressive-like behavior. Treatment with fluoxetine significantly reduced immobility (112.5 ± 5.2 s, $p < 0.01$). Among the test compounds, the 5-HT$_1$A receptor agonist showed the most pronounced reduction in immobility (118.6 ± 4.9 s), comparable to fluoxetine. The 5-HT$_2$A receptor antagonist and 5-HT$_7$ inverse agonist also significantly decreased immobility (142.8 ± 5.5 s and 130.4 ± 5.1 s, respectively), demonstrating antidepressant-like effects.

Tail Suspension Test (TST)

In the TST, control animals showed immobility of 210.7 ± 7.1 s. Fluoxetine-treated rats displayed significantly lower immobility (118.2 ± 5.3 s, $p < 0.01$). Similar to the FST results, the 5-HT$_1$A agonist markedly reduced immobility (123.4 ± 4.7 s), while the 5-HT$_2$A antagonist and 5-HT$_7$ inverse agonist also exhibited significant reductions (138.9 ± 5.4 s and 129.7 ± 5.0 s, respectively) (Table 1, Figure 3).

Table 1: Effect of Serotonin Receptor Modulators on Immobility Time in FST and TST

Group	Treatment (mg/kg, i.p.)	Forced Swim Test (Immobility, s)	Tail Suspension Test (Immobility, s)
I	Control (Saline)	198.3 ± 6.4	210.7 ± 7.1
II	Fluoxetine (10)	112.5 ± 5.2**	118.2 ± 5.3**
III	5-HT$_1$A Agonist (5)	118.6 ± 4.9**	123.4 ± 4.7**
IV	5-HT$_2$A Antagonist (5)	142.8 ± 5.5*	138.9 ± 5.4*
V	5-HT$_7$ Inverse Agonist (5)	130.4 ± 5.1**	129.7 ± 5.0**

*Values are expressed as mean ± SEM, n = 6.

*Significant at $p < 0.05$, **highly significant at $p < 0.01$ compared to control (ANOVA followed by Tukey's test).

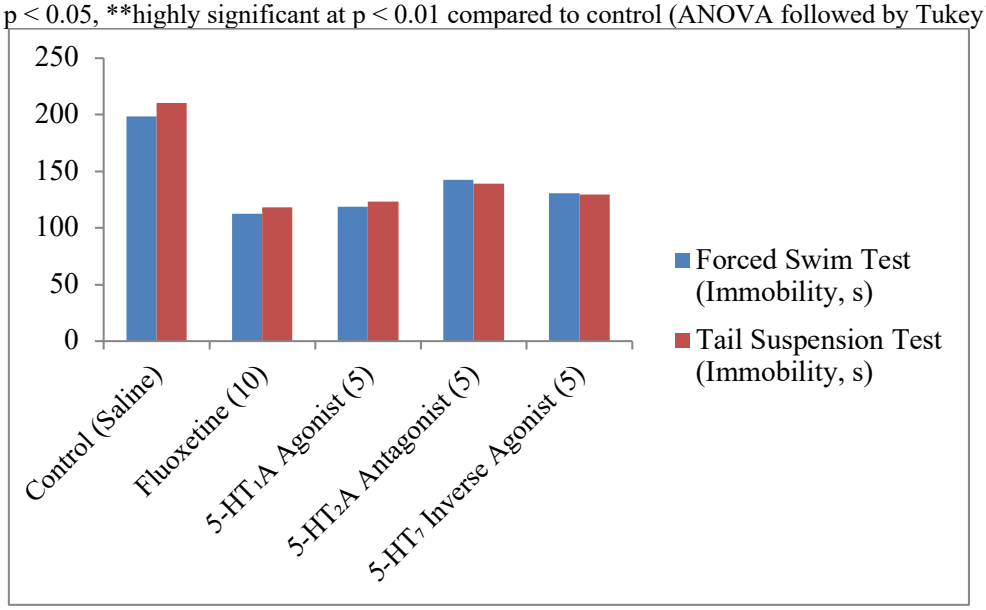


Figure 3: Graphical presentation of Serotonin Receptor Modulators on Immobility Time in FST and TST

All serotonin receptor modulators demonstrated significant antidepressant-like effects by reducing immobility in both behavioral models. The 5-HT$_1$A receptor agonist exhibited the most potent effect, comparable to the standard drug fluoxetine. These results suggest that modulation of specific serotonin receptor subtypes effectively alleviates depressive-like behavior in rats.

DISCUSSION

The present study demonstrated that selective serotonin receptor modulators significantly ameliorate depressive-like behavior in rat models, as evidenced by reduced immobility in the forced swim test (FST) and tail suspension test (TST). Such behavioral paradigms are highly tested in measuring the antidepressant like behavior where immobility is a measure of behavioral hopelessness and decreases a measure of possible antidepressant action [11].

The antidepressant effect of the 5-HT 1A receptor agonist was the most significant, as with the familiar drug fluoxetine. By activating, these receptors enhance serotonin signaling in the brain which leads to elevations in serotonin in areas such as the

hippocampus and prefrontal cortex- areas that play a major role in the regulation of emotions and mood. This increase in serotonin activity is probably the cause of the betterment of depressive symptoms. This is probably due to the mechanism responsible in reducing the immobility and the rise in the active behavioral responses [12].

Likewise, the 5-HT 2A receptor antagonist exhibited great antidepressant-like effects. It blocks 5-HT 2A receptors and, as such, regulates the downstream signaling pathways including glutamatergic and dopaminergic pathways, which can provide positive mood and cognitive function. Moreover, the 5-HT 7 receptor inverse agonist was also discovered to decrease the immobility implying that the receptor has a part in regulating circadian rhythms, synaptic plasticity, and neuronal excitability which are all associated with the effects of antidepressants. [13].

The specificity of the receptor subtypes, the distribution of the brain regions, and the pharmacokinetics of the test compounds may be considered as the reasons of the different efficacies. The findings confirm that antidepressant effects of conventional SSRIs can be observed through the specific regulation of serotonin receptor subtypes that could be even faster acting and with fewer side effects [14].

In general, the results allow to conclude that the therapeutic potential of serotonin receptor modulators exists as new antidepressant agents. Additional mechanistic work is justified such as neurochemical studies and receptor occupancy studies that will clarify the exact mechanisms involved and how these compounds can be optimized in clinical use [15].

CONCLUSION

The current work has shown that selective serotonin receptor modulators have great antidepressant-like effects on animal depression models. The 5-HT 1A receptor agonist was the most potent with its effect similar to that of fluoxetine, and the 5-HT 2A receptor antagonist and 5-HT 9 inverse agonist had significant effects on immobility in forced swim and tail suspension tests. These results demonstrate that the subtypes of serotonin receptors play a crucial role in mood control and that specific receptor-based interventions can be an effective approach to the development of new antidepressive treatments. Research investigations are still justified in order to explain the exact molecular processes and to test clinical perspectives of these receptor-targeted compounds.

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