International Journal of Pharmacological Research
ISSN: 2277-3312 (Online)
Journal DOI: https://doi.org/10.7439/ijpr **Research Article**

Effect of sertraline and its interaction with imipramine on forced swimming induced immobility period in mice

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Abstract

Background: The treatment of depression relies on a varied group of antidepressant therapeutic agents, in part because clinical depression is a complex syndrome of widely varying severity. The objectives of the present study were (i) to study the possible mechanism of antidepressant action of sertraline in different models of mice using FST and (ii) to study the interaction of sertraline with imipramine in the above models.
Methods: Forced swimming test (FST) is a behavioral screening method used to test antidepressant activity in animals. Mice were divided into different groups on basis of drugs administration intraperitoneally (i.p.). Imipramine was administered 30 min, sertraline 60 min, clonidine 15 min and reserpine 4 hr and 24 hr prior to FST. Vehicle dimethyl sulphoxide (DMSO) 0.1 ml was administered 1 hr, 4 hr and 24 hrs prior to FST. Control group received 0.1 ml saline. Effects of different doses of sertraline and imipramine and its combination were evaluated on various models of depression using FST.
Results: Sertraline and imipramine dose dependently decreased the duration of immobility in control mice. However doses of sertraline (0.5 mg/kg) and imipramine (2.5 mg/kg) alone did not alter the duration of immobility; but in combination, they significantly decreased the duration of immobility in control mice, suggesting additive effect.
Conclusion: Sertraline when combined with imipramine, significantly enhanced reduction in immobility produced by imipramine in all the three models (i.e. control, clonidine treated and reserpine treated).
Keywords: Sertraline, Imipramine, Antidepressant.

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***Article History:**
Received: 20/10/2020
Revised: 30/11/2020
Accepted: 30/11/2020
DOI: https://doi.org/10.7439/ijpr.v10i11.5531

QR Code

How to cite: Domadia D, Patadia J and Bhabhor P. Effect of sertraline and its interaction with imipramine on forced swimming induced immobility period in mice. *International Journal of Pharmacological Research* 2020; 10(11): e5531. Doi: 10.7439/ijpr.v10i11.5531 Available from: https://ssjournals.com/index.php/ijpr/article/view/5531

1. Introduction

Depression, also known as depressive disorders or unipolar depression, is a mental state characterized by a profound and persistent feeling of sadness or despair and/or a loss of interest in things that were once pleasurable. Disturbances in sleep, appetite and mental processes are a common accompaniment.

Approximately 15 - 20% of the population experience a major depression episode at some point in life and 6 to 8 % of all outpatients in primary care setting satisfy diagnostic criteria for the disorder. Depression is often undiagnosed and even more frequently, it is treated inadequately. The presence of anxiety, panic or agitation significantly increases suicidal risk. Nearly 10 to 15% of patients whose depressive illness goes untreated will commit suicide. [1]

The use of drugs with demonstrated efficacy in broad range of severe psychiatric disorder has become widespread since the mid-1950s, leading to development of the subspecialty of psychopharmacology. Knowledge of the actions of various agents has greatly stimulated research in biological psychiatry aimed at defining pathophysiological changes. The treatment of depression relies on a varied group of antidepressant therapeutic agents, in part because clinical depression is a complex syndrome of widely varying severity.

Most antidepressants exert important actions on the metabolism of monoamine neurotransmitters and their receptors, particularly norepinephrine and serotonin. [2,3] Depressed patients usually respond to antidepressant drugs or, in severe or treatment - resistant cases, to ECT. [4]

Imipramine, a prototype of the class tricyclic antidepressant (TCAs) - is the first agent which elicited a wide range of neuropharmacological effects in addition to its presumed primary action of inhibiting norepinephrine and, variably, serotonin transport into nerve endings and to sustained facilitation of noradrenergic and perhaps serotonergic function in brain. [5]

Sertraline, a prototype of the class, selective serotonin reuptake inhibitor (SSRTs), inhibits reuptake of serotonin immediately, increases synaptic availability of serotonin and stimulates a large number of postsynaptic 5-HT receptor types, leading to complex secondary responses.[6]

There is no known animal condition corresponding to the inherited condition of depression in man, but various procedures have been described which produce typical human depression.[7] Animal models in psychopathology and psychopharmacology provide functional assessments of phenomena and hypothesized mechanisms that help to bridge the gap between more fundamental processes and the human behavior which the neuroscience seeks to understand,

In the present study we have used different animal models of depression. Reserpine and clonidine induced behavior models of depression were employed in our study. [8,9] Many CNS active agents, antidepressants are reported to be effective in the above models. [10]

The objectives of the present study were (i) to study the possible mechanism of antidepressant action of sertraline in different models of mice using FST and (ii) to study the interaction of sertraline with imipramine in the above models.

2. Material and methods

2.1 Animals

Albino mice of laka strain of either sex, weighing 25-30 g were kept in the departmental animal house at room temperature (25° C to 30° C) and were given regular laboratory diet with water and libitum except during the experiments. All the experiments were carried out between 09.00 hr and 17.00 hr at ambient temperature.

2.2 Forced Swimming Test (FST)

This test was based on the method described by Porsolt *et al* [11]. The mice were forced to swim individually in a glass jar (19cm x 29cm x 21cm) containing water to a 9cm height and maintained at room temperature (22 ± 1°C) for 6 min session daily for 2 days. [8]

On the 1st day mice placed in the glass jar, were initially highly active, rigorously swimming in circles, trying to climb the wall of glass jar, diving to the bottom. After 2 to 3 min, the activity began to subside and was interspersed with phases of immobility of floating of increased length. The mice were judged to be immobile whenever they remained floating passively in the slightly hunched but upright position, their head just above the surface. This constituted the 'Pretest' session.

The immobility period increased in control mice and immobility reached a plateau where mice remained immobile for approximately 80% of the time in each successive session. Twenty-four hour later, each animal was again forced to swim for period of 6 min in a "Test session".

During 6-min test session following parameters were noted. Anxiety was calculated as mobility and depression (decrease in functional activity) as immobility.

2.3 Schedule of drug administration

Mice were divided into different groups on basis of drugs administration. Drugs were administered intraperitoneally (i.p.). Imipramine was administered 30min, sertraline 60min, clonidine 15 min and reserpine 4hr and 24hr prior to FST. Vehicle dimethyl sulphoxide (DMSO) 0.1ml was administered l hr, 4 hr and 24 hrs prior to FST. Control group received 0.1ml saline.

Animals were divided into different groups as mentioned below:

Group I: Receiving either normal saline or DMSO

Group II: Receiving different doses of sertraline (0.5mg/kg, 1 mg/kg, 5 mg/kg and l0 mg/kg)

Group III: Receiving different doses of imipramine (2.5mg/kg, 5 mg/kg and 10mg/kg)

Group IV: Receiving combination of imipramine (2.5mg/kg) and sertraline (0.5mg/kg)

Group V: Receiving clonidine (0.15mg/kg) 15min prior to FST

Group VI: Receiving combination of imipramine (1 mg/kg) and clonidine (0.15mg/kg)

Group VII: Receiving combination of sertraline (1 mg/kg or 5mg/kg) and clonidine (0.15mg/kg)

Group VIII: Receiving combination of imipramine (2.5mg/kg), sertraline (0.5mg/kg) and clonidine (0.15mg/kg)

Group IX: Receiving reserpine (2mg/kg) 4hr and 24hr prior to FST

Group X: Receiving combination of imipramine (10mg/kg) and reserpine (2mg/kg)

Group XI: Receiving combination of sertraline (1 mg/kg or 5mg/kg) and reserpine (2mg/kg)

Group XII: Receiving combination of imipramine (2.5mg/kg), sertraline (0.5mg/kg) and reserpine (2mg/kg)

2.4 Drugs

The solutions of each drug were prepared fresh on the day of experiment. Fresh solutions of imipramine

hydrochloride [Sun Pharmaceutical Industries, Vadodara] and clonidine hydrochloride [Boehringer Ingelheim, W. Germany] were prepared in normal saline, while that of sertraline hydrochloride [Sun Pharmaceutical Industries, Vadodara] and reserpine hydrochloride [Loba-chemie, Bombay] were prepared in dimethyl sulphioxide.

2.5 Statistical analysis

All data are expressed as mean ± standard error of mean (S.E.M.) as immobility period. For comparison between any of the two groups, students' t test was employed. Values of P less than 5% (P <0.05) were considered to be statistically significant.

3. Results and discussion

None of the vehicles (i.e. normal saline or dimethly sulphoxide (DMSO) administered at intervals of 1 hr, 4hr or 24hr modified the duration of immobility in mice. Sertraline (10 mg/kg) produced significant peak inhibitory effects on the duration of immobility at an interval of 60 min. Therefore the time interval of 60 min was selected for the study pertaining to sertraline. (Table 1)

Sertraline and imipramine produced dose dependent decrease in the duration of immobility in mice as compared to their respective values in the vehicle treated groups (Table 2).

Lower dose of imipramine (2.5mg/kg) or sertraline (0.5 mg/kg) per se did not alter the duration of immobility; however combination of the above low doses of both the drugs produced significant decrease in the duration of immobility as compared to their values in vehicles, imipramine or sertraline-treated group (Table 3). Thus the immobility reducing effect was observed after concomitant administration of lower doses of both the drugs, suggesting additive effect.

In the control and clonidine treated groups imipramine (10 mg/kg) produced equivalent decrease in the duration of immobility (Table-4), while in the reserpine treated group it produced further significant reduction in the duration of immobility at an interval of 4 hr and 24 hr as compared to the value in control group.

In the control and clonidine treated groups sertraline (lmg/kg and 5mg/kg) produced significant decrease in the duration of immobility; however sertraline produced comparatively more decrease in the duration of immobility in clonidine treated group as compared to the value in the control group. Sertraline (lmg/kg and 5mg/kg) did not modify the duration of immobility in reserpine treated animals (Table 4) as mentioned earlier.

Combined treatment produced equivalent decrease in the duration of immobility in the control and clonidine treated mice; however in the reserpine treated mice at an interval of either 4 hr or 24 hr there was less decrease in the duration of immobility as compared to the value in the control group (Table 4).

Table 1: Effects of vehicles, sertraline (10 mg/kg, i.p.) on forced swimming - induced immobility in control mice

Treatment	N	Latency Time (HR)	Duration of Immobility (SEC)
Saline Treated	18	0.5	215.56 ±3.26
DMSO Treated	6	01	218.66 ±3.14
DMSO Treated	6	04	217.60 ±3.45
DMSO Treated	6	24	219.50 ±4.33
Sertraline	3	0.5	169.66 ±5.55 ***
Sertraline	6	1	124.17 ±4.44 ***
Sertraline	3	2	156.00 ±5.36 ***
Sertraline	3	3	182.00 ±3.47 ***

*** P < 0.001 as compared to vehicle treated group; Values are Mean ± SEM; DMSO = Dimethyl Sulphoxide

Table 2: Effects of different doses of sertraline and imipramine on forced swimming - induced immobility in control mice

Treatment (mg/kg, i.p.)	N	Duration of Immobility (sec)
Vehicle (DMSO) Treated	6	218.66 ±3.14
Sertraline (0.5)	6	222.50 ± 4.44
Sertraline (1.0)	6	175.83 ±3.94***
Sertraline (5.0)	6	133.83 ±4.44 ***
Sertraline (10.0)	6	124.17 ±4.44 •*•
Vehicle (Saline) Treated	18	215.56 ±3.26
Imipramine (2.5)	6	210.00 ±3.05
Imipramine(5.0)	6	155.67 ±2.85 M*
Imipramine (10.0)	6	135.33 ±4.92 ***

*** P < 0.001 as compared to vehicle treated group; Values are Mean ± SEM; DMSO = Dimethyl Sulphoxide

Table 3: Effects of imipramine and sertraline on forced swimming - induced immobility in control mice

Treatment (mg/kg, i.p.)	N	Duration of immobility (sec)
Vehicle (DMSO) Treated	6	218.66 ±3.14
Sertraline (0.5)	6	222.50 ± 4.44
Imipramine(2.5)	6	210.00 ±3.05
Sertraline (0.5) + Imipramine (2.5)	6	150.83 ±2.77 ***ab

Values are Mean ± SEM; *** P < 0.001 as compared to vehicle treated group; a P < 0.001 as compared to sertraline treated group; b P < 0.001 AS compared to imipramiine treated group; DMSO = Dimethyl Sulphoxide

Table 4: Effects on change in forced swimming - induced immobility after various treatments in control, clonidine and reserpine treated mice

Group	Change in duration of immobility (sec)			
	Imipramine	Sertraline		Imipramine + Sertraline
	10 mg/kg	1 mg/kg	5 mg/kg	2.5 mg/kg + 0.5 mg/kg
Control	77.17 ±3.68	38.33 ± 6.22	84.5 ± 5.46	67.5 ± 7.45
Clonidine Treated	80.66 ±3.31	61.5 ±3.13*	110.33 ±2.45*	65.17 ±2.45
Reserpine 4 H	109.83 ±4.77*	6.0 ± 3.27 *	4.33 ±3.73*	28.66 ±2.95*
Treated 24 H	100.83 ±2.09*	-4.0 ±1.46*	-10.33 ±2.5*	30.83 ± 3.26 *
One way ANOVA f (df)	19.23 (3,20)	58.33 (3,20)	250.6 (3,20)	22.17(3,20)
P	< 0.0001	< 0.0001	< 0.0001	< 0.0001

Values are Mean ± SEM; * P Value as compared to their corresponding control value

4. Discussion

Forced - swimming test method (a behavioral screening method) is used to evaluate the antidepressant activity. [12,13] Forced - swimming test (FST) is based on the behavioral responses. Behavior despair was proposed as a model to test antidepressant activity by Porsolt *et al*. [11] In our present study, Porsolt method was employed to study the antidepressant activity of sertraline & its interactions with imipramine in different models of depression [9,14]

In FST method, behavioral state resembling depression is induced by exposing the animals to a mildly aversive situation from which there is no possibility of escape. Preliminary experiments showed that prolonged exposure to such situation produced increasing periods of virtually complete immobility which contrasted markedly with the vigorous attempts to escape observed when the animals were first introduced to the situation. These behavioral observations suggested that the animals, on finding that escape was impossible, gave up trying and resigned themselves to the experimental condition. [13] The immobility observed in FST was a reflected state of despair and various CNS active agents and antidepressants are reported to reverse this behaviour, which are therapeutically effective in depression. [10-16]

FST is one of the best animal behavior tests at predicting clinical activity of antidepressants [17]. The FST appears to model "behavioral despair" [13], passive coping strategies in response to stress [18] or entrapment through uncontrollable exposure to severe stress [19] in rodents and similar behavioral processes are thought to be part of clinical depression.

Imipramine, a prototype of the class tricyclic antidepressant (TCA) agent, is a potent inhibitor of neuronal transport (reuptake) of norepinephrine and variable blockade of serotonin transport. [5, 20] Thus increased synaptic availability of 5-HT and NE stimulate number of postsynaptic 5-HT and AI receptors. [6] Kaur & Kulkarni, *et al* reported decrease in forced swimming immobility period with imipramine (10 mg/kg, i.p.).[21] Also Chaturvedi *et al* reported a dose dependent decrease in immobility period with imipramine. [22] Our results pertaining to imipramine study are in accordance with the above studies.

Sertraline, a selective serotonin reuptake inhibitor blocks neuronal transport of serotonin immediately and apparently indefinitely, leading to complex secondary responses. [5,23,24] Increased synaptic availability of serotonin stimulates a large number of postsynaptic 5-HT receptor types. Fluoxetine, a SSRI has been reported to produce its antidepressant action by inhibition of 5-HT uptake because prior depletion of 5-HT by PCPA (paracholoro phenylalanine) completely blocked the decrease in immobility period by fluoxetine. Kulkarni *et al* reported decrease in total duration of immobility during 6 min test with fluoxetine (5 mg/kg).[8] In our study sertraline 10 mg/kg i.p. produced maximum decrease in immobility at 60 min which was dose dependent. It is suggested that the above effects of sertraline may be mediated through its selective 5-HT uptake inhibitory property as reported above.

Clonidine, stimulates the CC_2A subtype of 0:2 - adrenergic receptors in the brainstem resulting in a reduction in sympathetic outflow from the CNS which suppress the release of NE pre synaptically. Gurpreet *et al* and Parale *et al*

also reported increase in the immobility duration in behavior despair test. [9, 21] Our results are in accordance with the above studies. The reversal of clonidine induced behavioral despair by imipramine indicated the facilitation of noradrenergic activity by its interaction with presynaptic α_2 adrenoceptors.

Similarly, reversal of clonidine induced behavioral despair by sertraline suggested involvement of presynaptic noradrenergic mechanisms in antidepressant action of sertraline.

Reserpine depletes catecholamine or lowers noradrenergic turnover in the brain and produces depression like syndrome in animals. Kaur *et al* and Kulkarni *et al* reported increase in immobility period after 4hr and 24hr of treatment. [8, 21] Our results are in accordance with the above studies.

Imipramine, acting through noradrenergic or serotonergic mechanisms reversed reserpine induced immobility, suggesting the involvement of both of these transmitters in reserpine induced immobility in the behavioral despair model. This is in accordance with the fact that reserpine is known to deplete both NA and HT.

Sertraline was ineffective in the reserpinised model, however lower doses of sertraline when combined with lower dose of imipramine, produced significant decrease in immobility suggesting synergistic action. Thus sertraline facilitates the effects of imipramine in this model. The mechanism of action for the above effect could not be ascertained at present. Further work is needed to delineate the probable mechanism involved in the above interaction.

4. Conclusion

From the present study it is concluded that sertraline reduced immobility in FST employed in the control and clonidine treated mice however it was ineffective in the reserpinised mice. Sertraline when combined with imipramine, significantly enhanced reduction in immobility produced by imipramine in all the three models (i.e. control, clonidine treated and reserpine treated).

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