IJPSR (2013), Vol. 4, Issue 10 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 19 May, 2013; received in revised form, 21 June, 2013; accepted, 13 September, 2013; published 01 October, 2013

A REVIEW ON ANIMAL MODELS OF DEPRESSION

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Keywords:

Depression, Animal models, Antidepressants, Neurochemical, Neurobiological, Etiology

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ABSTRACT: As described by the world health organization (WHO), depression is the most common and serious disorder leading to suicide. Numbers of synthetic drugs are available for the treatment of this fatal disease, but are associated with serious complications. A wide diversity of animal models has been used to examine antidepressant activity. These range from relatively simple models sensitive to acute treatment, to highly sophisticated models. The number of validated animal models for affective disorders is large and still growing. A basic understanding of the underlying disease processes in depression is lacking, and therefore, recreating the disease in animal models is not possible. For the animal model of depression, the relevance, reliability and reproducibility in laboratories need to be focused, currently used models of depression attempt to produce quantifiable correlates of human symptoms in experimental animals and the animal modeling remains a potentially important approach towards understanding neurochemical and neurobiological mechanisms in depression. Animal models of depression attempt to represent some aspect of the etiology, symptomatology and treatment of the disorders, in order to facilitate their scientific study. Hence, this review deals with animal models that are beneficial for evaluating the potential of antidepressants. The present review further discusses the ability of currently available animal models for depression to investigate the novel hypothesis.

INTRODUCTION: Major depressive disorder (MDD) is commonly referred as "depression" that is characterized by sad mood, loss of interest, unhappiness, change of appetite, somatic complaints (e.g., aches and pains), psychomotor changes (e.g., agitation), decreased energy and tiredness, a sense of worthlessness or guilt, impaired concentration, suicidal ideation [1] and cognitive deficits [2]. Moreover, depression is the most common of the affective disorders; it may vary from a very mild condition, bordering on normality, to severe psychotic depression accompanied by hallucinations and delusions [3].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.4(10).3731-37

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.4(10).3731-36

Depression has a high lifetime prevalence of 21% and it is among the severe psychiatric disorder [4]. Lower rates of fertility can occur with depression [5, 6]. Major depressive disorder is a chief cause of disability worldwide, by the year 2020 [7]. Women are about twice as likely to suffer from a major depressive event as men [8]. In a year, about 1 million lives are lost due to suicide i.e. 3000

suicide deaths every day [9]. This lethal disorder can be treated with antidepressants with response in patient 65 to 80% of the time [10].

Depression occurs due to the combination of various factors such as genetic, biochemical, environmental, and psychological factors. Different types of depression tend to run in families, signifying a genetic link related to BDNF alleles [11.] However, depression can occur in people without family histories of depression as well [12]. In recent findings majority of cases the depression illness has been associated with known effects on immune function [13]. It was reviewed that stress and the major depression cause the decrease in hippocampal neurogenesis [14, 15]. In depression there is persistent weakening of the synaptic strength in the CNS of the human beings, the activation of NMDA (N-methyl D-aspartate) [16] and metabotropic glutamate receptors (mGluRs) occurs [17, 18] respectively. Besides the mononergic system, the glutamatergic system helps in developing and understanding the mechanisms of new antidepressants [17, 19-21]. A large number of papers have been published on mGluR and depression [17, 18, 22, 23]. In animal models of depression mGlu2 and mGlu3 receptors have been shown to be altered [24].

Depression models are generally used for evaluating the potential of antidepressants and their ability to accurately predict outcome in humans (predictive validity), their ability to reproduce in animals aspects of the human illness (face validity), and the extent to which they model the true disease process or its etiology in humans (construct or etiologic validity) [25-27]. The antidepressant potential of some plant extracts and bioactive compounds has been studied by some researchers [28-33]. Utility of animal models of depression to be discussed here is based on their predictive validity for pharmacological treatments act as an important tool for the management of depression [34].

ANIMAL MODELS OF DEPRESSION:

It is an important procedure to select the animal model because no model adequately meets the requirement of human diseases [35]. Animal models of depression illness are used for variety of purposes: as screening tests to find out the novel antidepressant drug therapies; as simulations for investigating aspects of the neurobiology of depressive illness and as experimental models within which the neuropharmacological mechanisms associated with antidepressant treatments [25, 36-38].

Models:

1. 5-hydroxytrytophan induced behavioral syndrome.
2. Antagonism of reserpine-induced symptoms (mice and rats).
3. Olfactory bulbectomy.
4. Dopamine-induced depression of adrenergic nerve-mediated contraction of smooth muscle.
5. Apomorphine induced hypothermia in mice.
6. Isolation induced hyperactivity in rats.

1. **5-hydroxytrytophan-induced behavioral syndrome:** The head twitch response was produced by the 5-Hydroxytryptophan (5-HTP) [39]. This effect provides a model for the study of antidepressants. This model proved an attractive model for the study of transmitter interactions with 5-HTergic mechanisms and verified a role for dopaminergic [40] and noradrenergic [41-43] mechanisms in the modulation of the 5-HTergic head-twitch response. This test provides a relatively rapid and accurate index of SSRI potency in vivo.

Method: The method mentioned elsewhere by [44] and is adopted with some modifications [45].

The mice were treated with the 5-HTP (5 mg/kg) and after fifteen min, the observation recorded were the number of head twitches exhibited by the mice, which was recorded as the head twitch score. The head twitch response was characterized by abnormal lateral movements, which may or may not be accompanied by body twitches and hind limb retractions.

2. **Antagonism of reserpine induced symptoms (mice and rats):** Reserpine obtained from *Rouwolfia Serpentina* and it induces the syndrome of hypothermia, ptosis and akinesia

by nonselectively depleting the synaptic stores of brain monoamines (noradrenaline, dopamine and serotonin). A large number of antidepressants like monoamine oxidase inhibitor and tricyclic antidepressants can reverse the effects of reserpine on motility in mice and rats [46].

Method: This test was performed effectively as described by [47].

Intraperitonial (i.p.) injection of reserpine 5 mg/kg in mice and 6 mg/kg in rats produces ptosis and akinesia that are evaluated after 2 hrs. Hypothermia was to evaluated using rectal thermometer before and 4 h after the reserpine treatment. No significant change in temperature was found in rats administered reserpine. The degree of ptosis was measured according to the following rating scale: 0, eyes open; 1, eyes half closed; 2, eyes completely closed; 3, eyes three-quarters closed; 4, eyes completely closed [48]. For akinesia, mice were placed at the center of a circle (9.5 cm in diameter) on white paper whereas rats on home cage and were judged to be akinetic, on an all-or-none basis, if they remained within the circle for 15 s or more.

The effect of test compound on ptosis and akinesia was expressed as ED50, defined as the dose that antagonized the ptosis by 50% of the maximal obtainable score and as the dose that prevented the akinesia in 50% of animals, respectively. The effect on hypothermia was expressed as the lowest dose that produced a statistically significant prevention compared with reserpine-treated control (MED; $P < .05$, Dunnett's method).

3. **Olfactory bulbectomy:** Olfactory bulbectomy in the rat were associated with changes in exploratory behavior that are reversed by chronic, but not acute treatment with antidepressant drugs [49-51].

Method: First of all the rats were anesthetized with tribromoethanol and then the skull was exposed with holes which were drilled anterior to bregma on the either side of the midline at a point which was corresponding to the posterior margin of the orbit of the eye. With the help of the suction process the olfactory bulbs were removed, after that the bleeding were controlled with the help of haemostatic sponge which was filled in the holes and the scalp was sutured, Sham-operated animals also received the same surgical treatment, but the bulbs were left intact and further subjected to open field and passive avoidance test [52]. The antidepressants reverse the variety of behavioral changes, like irritability, hyperactivity and an elevation of circulating levels of plasma corticosteroids; as a result of their hyperactivity [25].

The signal intensities in cortical, hippocampal, caudate and amygdaloid regions was demonstrated by imaging studies in olfactory bulbectomized animals compared with sham-operated controls [53].

4. **Dopamine-induced depression of adrenergic nerve-mediated contraction of smooth muscle:** The low concentrations of dopamine depress the transmitter overflow from the rabbit ear artery [54]. In animal models of depression D1 and D2 receptor agonists, as well as drugs that increase dopamine function, have an antidepressant-like profile [55].

Method: By the procedure of the cervical dislocation the adult albino rabbits of weight (2.0-2.5 kg) were killed. After that the rabbit ear arteries were prepared as described by [56] and then perfused at a constant rate of 5 ml/min with [57] solution at 37ºC. With the help of changes in the perfusion pressure via a pressure transducer coupled to the perfusion system distal to the pump the vasoconstriction was monitored. Without the removal of the mesenteric investment the vasa deferentia were dissected free of the hypo gastric ganglia and mounted vertically in [58] solution at 37°C with a resting longitudinal tension of 250 mg.

The isotonic strain gauge was used to monitor the longitudinal contractions and the Pt ring electrodes which was 10 mm in diameter and 5 mm apart were used for the stimulation of intramural adrenergic nerves, which were positioned around the proximal end of the artery and the urethral end of the vas deferens. To deliver trains of 1 m square wave pulses at 2 pulses/s and 70 volts a grass S44 stimulator was used. The stimulating trains were for 12 s every 200 seconds and5 s every 80 seconds with the arteries and the vasa deferentia respectively.

Due activation of adrenergic axons and not to activation of the smooth muscle cells the

contractile responses were obtained, the responses were abolished by tetrodotoxin 1.6µm or guanethidine sulphate 4 µm. Different drugs used were: dopamine hydrochloride (Sigma), haloperidol (Serenace, Searle), noradrenaline hydrochloride (Sigma) and phentolamine mesylate (Regitine, Ciba). Dopamine and noradrenaline were stored as 1 mg/ml solutions in 0.001 N HCI and diluted into 0.9% w/v NaCI solution (saline) on the day of use. The saline which was used contained 0.6 mm ascorbic acid. On the day of use the haloperidol and phentolamine were diluted into saline commercially. With the help of the student t-test the differences of means were assessed.

5. **Apomorphine induced hypothermia in mice:** Apomorphine, being a dopamine agonist has been reported to play a pivotal role in the pathogenesis of depression. High dose of Apomorphine has been evident to produce the symptom of hypothermia [59]. The hypothermic effect was due to the agonist action of the compound on dopaminergic receptors on noradrenergic terminals, preventing noradrenaline release [60].

Method: The Albino mice were divided into twelve groups. By using commercially available digital thermometer, the temperatures of the mice colon were recorded. In the study the mice with body temperature between 37 and 38.4°C were included. The initial temperature was measured after 1 hr and the group I was given 1% gum acacia solution, group II – V were given 30,100 and 300mg/kg of IK and 30mg/kg of Imipramine respectively. Then after 1hr, all the animals received apomorphine (16mg/kg s.c.). In all the mice the colon temperatures measurement was repeated after 1 hr [61-64].

6. **Isolation induced hyperactivity in rats:** The separation of animals from each other induces hyperactivity behavior in them. Nicotine or other chemicals directly affect the brain of a depressed person. Nicotinic receptor agonist increases the locomotor activity due to the modulation of dopamine release mainly in the mesolimbic pathway [65, 66]. Nicotine with imipramine decrease the isolation induced hyperactivity in rats [67].

Method: In this experiment, for a period of 15 days rats were socially deprived and housed singly in cages (38cm × 26cm × 20cm) without any visual or auditory contact with their normally housed counter parts. Then after 15 days of isolation the locomotor activity score was tested by keeping the rat in actophotometer. As rat moved and crossed beam the locomotor activity was recorded on digital recorder.

Reading was noted for1minute every 10 minutes up to 50 minutes. The hyperactivity of the rats was compared with that of vehicle treatment and imipramine treated after isolation. In acute study, single dose of nicotine (subcutaneous) or nicotine (inhalational) were administered at the end of 7-days of administration of imipramine and effect on locomotor activity and behavioral changes was observed. In chronic study, imipramine was administered for 7 consecutive days with nicotine (subcutaneous) or nicotine (inhalational) and effects on locomotor activity and behavioral changes were observed at the end of treatment.

By using actophotometer the locomotor activity score was tested, with vehicle, imipramine, nicotine (subcutaneous) and nicotine (inhalation) after 15 days of isolation and after isolation the effect of combination of acute and chronic administration of nicotine with imipramine was studied on locomotor activity. In all the study groups simultaneously behavior parameters i.e. sleep reduced response to external stimuli; ambulatory behavior, stereotypy and posture were studied [68].

CONCLUSION: From the above discussion it is concluded that, many of antidepressants have a number of side effects. So to overcome the side effects of those antidepressant drugs we have a need to target on the herbal as well as synthetic antidepressants and for evaluating the potential of novel antidepressants a large number of animal models has been used which are discussed above.

ACKNOWLEDGEMENT: The author is highly thankful to the Director, Rayat Institute of Pharmacy and the management for providing us all the facilities.

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How to cite this article:
Devi M and Sharma R: A Review on animal models of Depression. *Int J Pharm Sci Res* 2013: 4(10); 3731-3737. doi: 10.13040/IJPSR. 0975-8232.4(10).3731-37