Screening Models of Depression in Animals: A Review

Ramandeep Singh, Alok Sernwal and Satinder Kakar
1Department of Pharmacy, Himachal Institute of Pharmacy, Paonta Sahib (H.P), India
2Department of Pharmacy, Doon valley Institute of Pharmacy and Medicine, Karnal (Haryana), India

ABSTRACT
Depression is a chronic, recurring and potentially life-threatening illness that affects up to 20% of the population across the world. Despite its prevalence and considerable impact on human, little is known about its pathogenesis. One of the major reasons is the restricted availability of validated animal models due to the absence of consensus on the pathology and etiology of depression. Numbers of synthetic derivatives 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 that reputedly model some aspect of depressive illness. 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.

Key words: Depression, animal models, neurochemical, neurobiological


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, and suicidal ideation. 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. The interrelated suite of emotions and behaviors characterizing depression has been realistic in virtually all human societies. Major depressive disorder is a chief cause of disability worldwide, with a lifetime population occurrence as high as 20%. Women are about twice as likely to suffer from a major depressive event as men. Depression is the most common mental disorder leading to suicide, although substance abuse and schizophrenia are also major contributors. There is no single known cause of depression. Rather, it likely results from a combination of genetic, biochemical, environmental and psychological factors. Many types of depression tend to run in families, signifying a genetic link. However, depression can occur in people without family histories of depression as well. Genetics research indicates that risk for depression results from the influence of multiple genes acting together with environmental or other factors. In depression there is persistent weakening of the synaptic strength in the CNS of the human beings, the activation of NMDA and metabotropic glutamate receptors (mGluRs) occurs, respectively. The NMDA receptors are triggered by Ca2+ influx via NMDA channels and the subsequent activation of serine/threonine protein phosphatase. Whereas, the mGlurR is independent of calcium and serine/threonine phosphatase and may have a presynaptic mechanism of expression.

Depression models are generally evaluated for their reliability or reproducibility, 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). Utility of models to be discussed here is based on their predictive validity for pharmacological treatments act as an important tool for the management of depression\textsuperscript{17,11,19,20}.

PARAMETERS USED IN ASSESSING ANTIDEPRESSANT ACTIVITY

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\textsuperscript{17,18,21,22,24}. For the Study of antidepressant activity many animal models have been used. Methods that are used in study 5-hydroxytryptophan-induced behavioural syndrome, antagonism of reserpine-induced symptoms (mice and rats), olfactory bulbectomy, dopamine-induced depression of adrenergic nerve-mediated contraction of smooth muscle, apomorphine induced hypothermia in mice, isolation induced hyperactivity in rats.

ANIMAL MODELS

5-hydroxytryptophan-induced behavioural syndrome: The dose dependent head twitch response was produced by the 5-Hydroxytryptamine (5-HT) receptor agonists with the varying frequency. 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 and noradrenergic\textsuperscript{25,26,27,28,29} 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 mice were treated with the 5-HTP (5 mg kg\(^{-1}\)) 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 retraction\textsuperscript{30}.

Antagonism of reserpine induced symptoms (Mice and Rats): Reserpine obtained from Rauwalia Serpentina and it induces the syndrome of hypothermia, ptosis and akinnesia by nonselectively depleting the synaptic stores of brain monoamines (noradrenaline, dopamine and serotonine). A large No. of antidepressants like monoamine oxidase inhibitor and tricyclic antidepressants can reverse the effects of reserpine on motility in rats and mice\textsuperscript{31}.

Method: Intraperitoneal (i.p.) injection of reserpine 5 mg kg\(^{-1}\) in mice and 6 mg kg\(^{-1}\) in rats produces ptosis and akinnesia that are evaluated after 2 h. 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. For akinnesia, 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 akinnesia was expressed as ED\textsuperscript{50}, defined as the dose that antagonized the ptosis by 50% of the maximal obtainable score and as the dose that prevented the akinnesia 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, Dunnet’s method)\textsuperscript{32}.

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\textsuperscript{26,28,29,30}.

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\textsuperscript{33}. The antidepressants reverse the variety of behavioural changes, like irritability, hyperactivity and an elevation of circulating levels of plasma corticosteroids; as a result of their hyperactivity\textsuperscript{34}. The signal intensities in cortical, hippocampal, caudate and amygdaloid regions was demonstrated by imaging studies in olfactory bulbectomized animals compared with sham-operated controls\textsuperscript{35}.

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. The dopamine-receptor antagonists like haloperidol; phenolamine prevented the effect of dopamine\textsuperscript{36,40}.
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 De la Lande and Rand, and then perfused at a constant rate of 5 mL min⁻¹ with solution at 37°C. 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 Hukovic solution at 37°C with a resting longitudinal tension of 250 mg. The isotonic strain gauge was used to monitored 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 vasa deferens. To deliver trains of 1 ms wave pulses at 2 pulses sec⁻¹ and 70 v a grass S44 stimulator was used. The stimulating trains were for 12 sec every 200 sec and 5 sec every 80 sec 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 1.6 µg or gualanine sulphate 4 µg. Different drugs used were: dopamine hydrochloride (Sigma), haloperidol (Serenace, Searle), noradrenaline hydrochloride (Sigma) and phenolamine mesylate (Regitine, Ciba). Dopamine and noradrenaline were stored as 1 mg mL⁻¹ solutions in 0.001 N HCl and diluted into 0.9% w/v NaCl 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 phenolamine were diluted into saline commercially. With the help of the student t-test the differences of means were assessed.

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 symptoms of hypothermia. The hypothermic effect was due to the agonist action of the compound on dopaminergic receptors on noradrenergic terminals, preventing noradrenaline release.

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 h and the group I was given 1% gum acacia solution, group II-V were given 30,100 and 300 mg kg⁻¹ of IK and 30 mg kg⁻¹ of Imipramine, respectively. Then after 1 h, all the animals received apomorphine (16 mg kg⁻¹ s.c.). In all the mice the colon temperatures measurement was repeated after 1 h.

Isolation induced hyperactivity in rats: The separation of animals induced a hyperactivity behavior in them. Nicotine or other chemicals directly affect the brain of a depressed person. Nicotine may have antidepressant properties. A subtype selective nicotinic acetylcholine receptor agonist produced antidepressant like effect. Preclinical and clinical data regarding antidepressant action of nicotine are ambiguous.

Method: In this experiment, for a period of 15 days rats were socially deprived and housed singly in cages (38 x 26 x 20 cm) 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 photoactometer. As rat moved and crossed beam the locomotor activity was recorded on digital recorder. Reading was noted for 1 min every 10 min up to 50 min. The hyperactivity of the rats were compared with that of vehicle treatment and imipramine treated after isolation. In acute study, single dose of nicotine (subcutaneous) or nicotine (inhaletional) 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 (inhaletional) 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 (inhaletional) 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.

CONCLUSION

New Drug discovery and development consists of a series of processes starting with the demonstration of pharmacological effects in experimental cell and animal models and ending with drug safety and efficacy studies in human patients. From the above discussion it is concluded that, many of antidepressants have a no. 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 no. of animal models has been used which are discussed above.

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REFERENCES