Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2014, 6(10):123-130

Review Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Animal models of depression and their criteria of validation

Sajad Ahmad Bhat, Ab Latif Wani and Anjum Ara*

Section of Genetics, Department of Zoology, Faculty of Life Science, Aligarh Muslim University, Aligarh, Utter Pradesh, India

---

ABSTRACT

Major depressive disorder is a mental disorder which affect the mood of the person and also known as mood disorder. It is a brain disorder which generates major disability. Its etiology and molecular mechanism is not fully understood. However due to advances in the research in medical science various animal models are being used for studying the disease at the physiological and molecular levels. Animal model is a living, non-human animals used during the research and in the examination of various diseases of humans. For accomplishing better understanding of the disease animal models have played an unprecedented role without any danger of harming a human being during the process of research. Animal models are helping in research and may have an existing, induced disease or injury that is analogous to a human condition. In this article various types of animal models used for studying depression are reviewed. This article also highlights the validation criteria of many models used for studying depression. Both the advantages and drawbacks concerned with the use of animal models in studying depression are also evaluated in this article.

Key words: Depression, Animal Models, Validation, Disease, Drugs

---

INTRODUCTION

Major depressive disorder (MDD) (also known as clinical depression, major depression, unipolar depression, or unipolar disorder; or as recurrent depression in the case of repeated episodes) is a mental disorder which effects persons mood i.e. low mood and also known as mood disorder. It is a brain disorder which generates major disability. Its etiology and molecular mechanism is not fully understood. It is a leading cause of disability globally, with lifetime prevalence as high as 20% [1]. It is multifactorial disorders that differ in symptomology and most possibly in etiology. Major depressive disorder is a disabling state that badly affects a person's family, work or school life, biological clock or circadian rhythm and general health. Around 3.4% of people with major depression in the United States commit suicide, and up to 60% of people who commit suicide had depression or another mood disorder [2]. There are various symptoms of depression which include depressed mood, mood swing, loss of pleasure activities (anhedonia), inability to concentrate, lack of energy, disturbed sleep or appetite, feelings of worthlessness or guilt, and suicidal ideation and tendencies etc. [3].

Animal model is a living, non-human animals used during the research and in the examination of various diseases of humans, for the function of better consideration of the disease without any danger of harming a human being during the process of research. Animal models are helping in research and may have an existing, inbred or induced disease or injury that is analogous to a human condition. The animal selected generally meets a determined taxonomic equivalency to humans, so as to react to disease or its cure in a way that is similar to human physiology as required.

The use of animal models permit researchers and other workers to study disease states in a ways which would be difficult to get to in a human patient, using trials on the non-human animal that involve a level of harm which has some ethical issues.

There are several drugs, treatments available in market for human diseases which have been produced from time to time with the use of animal models.

ANIMAL MODELS

There are three major kinds of animal models used for to study the mental illness especially depression. Homologous, Isomorphic and predictive models.

Homologous models: It has identical causes, symptoms and treatment alternatives as would humans who have the same disease.

Isomorphic models It contributes to the same symptoms and treatments, only.

Predictive models: These are analogous to a particular human disease. Still, these are constructive in separating and making predictions about mechanisms of an onset of disease characteristics. When animals firmly exhibit only the treatment characteristics of a disease. This procedure is usually helpful when researchers do not know the origin and exact causes of a disease**.**

Animal models of depression have a function to replicate some known aspects of depression in preferred animal species (e.g. rodents). On this basis they can be used as an instrument for examining aspects of the neurobiology and pathophysiology of depression. They can be used as experimental models for studying the mechanism of action of antidepressant drugs and as screening tests for revealing antidepressant activity. Antidepressant drugs have slight or no function in healthy individuals. The number of validated animal models for affective disorders is great and still emerging.

Animal models offer a strong methodology for examining the disease problems and enlarge some therapies. Homologous models are very uncommon in the field of neuroscience. There are some isomorphic models which are more universal, but they show analogous symptoms. Animal models have got two main uses in the field of neuroscience research, first is the development and testing of theory about neurological and Neuropsychiatric disorders and second is the improvement of drugs and relevant therapies [4]. It has been demonstrated that these two currently available models do not meet these two requirements. Animal models provide explanations for two main symptoms of depression, one is depressed and other is loss of attention or pleasure which is also known as anhedonia. There are some symptoms in animals which can be simply modeled, for example alteration in body weight, psychomotor mental retardation and anhedonia, while as other cannot. Thus one of the most essential disadvantages of animal models of depressions comes from the unfeasibility to translate into verbal behavior of animal symptoms, suicidal ideation and tendencies feeling of guilt, or worthlessness lack of concentration and appetite, mood swing, disturbed sleep etc. Hence animal models can only generate some characteristics of depression. [4,6-8]. A perfect animal model recommends chances to know genetic, molecular and epigenetic factors that may lead to depression. Therefore, by using animal models, the basic molecular modifications and the fundamental association between genetic or environmental variations and depression can be studied, which would meet the expense of a better future into pathology of depression. Besides, animal models of depression are very important for discovery of innovative therapies for major depressive disorder.

Another demerit of offered animal models for depression lies in the fact that they make use of normal mice, while on the other hand, depression most likely needs a genetic susceptibility in most cases.

A major idea in depression research is lack of validated animal models in animal models. Many core symptoms of depression e.g. depressed mood, feelings of worthlessness, and suicidality cannot be easily considered in laboratory animals. Also, the lack of known depression susceptibility genes means that genetic causes of depression cannot be simulated in animals. As a result all the available models of depression rely on one of two fundamentals: action of known antidepressants or responses to stress [9-12]. Force swim test has been very useful at expecting the efficacy of antidepressant action and responses to stress.

Validity are the main criteria for right to use animal models .Validation criteria are the essential values that are applicable to the evaluation of any animal model and are distinct by many ways. The problem in all animal models, and especially models for psychiatric conditions which are in part distinct through subjective experience, is to describe clear criteria that allow stating the validity of the model. McKinney and Bunney 1969 proposed some of the least requirements more than 25 years ago [13]. These should be considered for choosing and selecting for an animal model of depression, such requirements are as follows.

(A) there is a 'logical analogy' to the human disorder in its expression or symptomatology (B) there is a behavioral modification that can be revealed objectively (c) the behavioral modifications observed should be reversed by the same treatment that are effective in humans and (D) the model should be reproducible between investigators. A major problem in depression research is the shortage of validated models. Many of the symptoms of depression (e.g. depressed mood, feelings of worthlessness, suicidality) cannot easily be measured in laboratory animals.

Flow chart of tests used in studying depression in various Animals Models

Validity types ➢ Face validity ➢ Construct Validity ➢ Predictive Validity
Various models in depression research 1) Acute stress :The learned helplessness model 2) Genetic model The genetic model involves three processes ➢ HPA Transgenic (HPA stands for hypothalamic pituitary axis) ➢ 5-HT Transporter knockout (5-HT stands for serotonin transporter) ➢ Tachykinin receptor knockout
Free Swim Test (FST)
Tail suspension test (TST)
Olfactory Bulbectomy (OB)
Fear conditioning
Neonatal clomipramine administration
Selective breeding
Stress model (Three types of stress model) ➢ Chronic mild stress ➢ Social stress ➢ Early life stress

VALIDITY OF ANIMAL MODELS

Willner [6] refined McKinney and Bunney criteria [13] and proposed many types of validity: face validity, construct validity and predictive validity.

(A) FACE VALIDITY: Face validity is a type of validity which is defined as the resemblance between the behaviors modeled in the animal and the symptoms of depression. A model which parallels numerous symptoms of human depression is considered important. It is well known that animal models should contribute to phenomenological resemblances isomorphism with the human pathology to be modeled. In other words we can say that it is phenomenological similarities between the behavior shown by the animal model and the particulars symptoms of the human condition [14].The face validity of animal model of depression is a determination of the models capability to replicate core symptoms of the disease [5].

In using the face validity of animal models of depression, anhedonia which is a loss of pleasure activity as a result assumes an important position. Anhedonia is also a most important symptom of psychosis. In case of animal models drug promote reversal of anhedonia, while greatly encouraging, should be considered in relation to DSM-IV criteria for both depressive illness and schizophrenia.

Depression patient on average needs chronic drug treatment so far pharmacotherapy is concerned; the validity of animal models is called into question by an acute response to tricycle antidepressant treatment. Chronic treatment effects may be linked with drug adaptive changes in neurotransmitter receptor intervene symptoms, rather than amplified drug level in plasma. Thus in comparison to chronic treatment effects, an acute response in an animal model may be opposite; orthogonal (it is a sensory map in the brain which has superimposed stimulus coding (for instance place and quality), due to its side effects, like sedation which means the process of decreasing irritability.

Apart from, how it responds, to acute antidepressant treatment, to be valid an animal model if depression must respond to chronic treatment. This test has been generally used to animal models of depression but in general, those models to which the test has been applied have passed it, though tolerance to antidepressant effects has been observed in some behavioral models.

(B) CONSTRUCT VALIDITY: This type of validity is wholly based on analogous theoretical rationale (homology) So far the pathology in animals and humans are concerned. A perfect model would need to be analogous to the disorder it models so far its etiology, biochemistry, symptomatology, and treatment are concerned. The construct validity has been declared as the most vital criteria to label a good animal model [15].

Measurement of this type of validity requires a comparison of the casual pathology of the disease state and the cellular and neurochemical mechanisms underlying the model. There is a dearth in literature about biochemical markers or neurochemical anomalies related with depression that can be used to give a standard against which to validate animal models [5]. Besides there is diversity of psychological factors used in the etiology of depression, bad childhood experiences, difficult life events, some personality traits. Akiskal [16] declared that there are some biological factors like genetic influences and a diversity of physical illness and medications which should be also considered. The best parts of animal models of depression are dependent on response to stressors, but there is a wide array of animal models modeling other kinds of factors in the etiology of depression. Some confronts have made to use the theoretical rationale of animal models and are limited by this lack of theoretical structure at the clinical level; a number of general ideas are possible. Whereas, measurement of theoretical rationale of animal models of depression is restricted by paucity, of theory, construct validity can be studied at the level of constructs – that is whether the behavioral facts are correctly explained. This approach is best understood by good experimental analysis of whether learned helplessness model is a precise and exact term to enlighten the damage of escape learning that follow exposure to unavoidable electric shock.

(C) PREDICTIVE VALIDITY

This type of validity is based on the capacity to expect drugs or successful treatment in animal models to be strong in human .The predictive validity of animal models of depression is decided exclusively by their response to different antidepressant drugs. A suitable test should be responsive and precise. It should respond to valuable treatment of antidepressant plus electroconvulsive shock (ECS), and should be unsuccessful to respond to unsuccessful agent.

A model with superior predictive validity should therefore make best use of recognition of both true positives and true negatives, but must reduce identification of false positives and false negatives. Besides, positive responses ought to occur at behaviorally fixed doses (i.e., those which do not usually interrupt behavior nor bring motor injury) that are within or close to the clinical range, and should be certain within a range of morphologically dissimilar compounds. It has been observed that no animal model has a 100% prediction rate, while as some multifaceted experimental paradigms have approached this level of predictive capability.

There are some phases of the difficulties, lies not so much with the preclinical model but with a number of older areas in the clinical literature where it is not known whether few drugs contain antidepressant activity or not. It is usually approved that the most efficient treatment for depressive disorders is electroconvulsive therapy (ECT) which is the most important and advanced therapy for the treatment of neuropsychiatric disorders especially major depressive disorder what we call depression. A stimulation of electric current is passed through brain which is able to control the process of neurotransmission in turn control neurotransmitter which is known as ECT. An appropriate starting point to check out the validity of an animal model must then able to show a positive response to recurring electroconvulsive seizure (ECS). Letdown to respond properly to ECS would sternly question the predictive validity of the animal model of depression research.

There are various models used in depression research, which are in detail given below.

(1) Acute – stress: **The learned helplessness model**: This model can be explained as in which animal is exposed to unpreventable footshock takes a longer time to escape or fail to get away wholly, when subsequently exposed to escapable foot shock antidepressants acutely decrease escape latency and failures. It is totally based on the observations that animal exposed to excess amount of stress generally electric shocks are damaged in learning to escape shock, an effect that is not observed in animals exposed to equal or really identical, pattern of uncontrollable

shock. The self-protective effect of control seems to result from lower levels of fear, which raises important questions about the relationship between depression and anxiety. It has been studied by Seligmen that exposure to uncontroballe stress gives the basis, in animals as in people, for learning that stress is hard to control (helplessness).The leaned helplessness test can be seen as analogous to the forced swim test and tail suspension tests, while the previous involves a series of stresses and antidepressant treatments, even though only over a few hours or days.

The main fault of all the tests is that they involve short term stress applied to normal rodents which is very different from human depression in which a primary genetic inclination combines with stochastic and chronic environmental exposures to create long lasting behavioral pathology. In the same way, the capabilities of antidepressants to generate a rapid response after single doses in these tests make a distinction considerably with the well predictable need to use antidepressants chronically (weeks-months) to get a clinical response in humans. It also remains puzzling whether these tests are susceptible to non-monoaminergic mechanisms of antidepressant action. Still these weaknesses, the forced swim, tail suspension, and learned helplessness tests are used, all too often without remark, to disagree that a genetic mutation or other experimental treatment has generated a depression- or antidepressant-like effect in rodent animals.

(2) Genetic models: There are large number of genetic models has been recently proposed from time to time for their possible meaning to depression. While their success is yet limited. The genetic model involves three processes.
(A) HPA transgenic.

(**B)** 5HT Transporter knockout.

(**C)** Tachykinin receptor knockout.

(A) HPA Transgenic (**Hypothalamic pituitary axis)**
The discharge of CRH corticotrophin releasing hormone from the par-ventricular nucleus of the hypothalamus is run by a glucorticoid receptor- mediated inhibitory feedback.

Finally, a number of a pattern or model has disturbed an animal's glucocorticoid homeostasis, based on the HPA axis derangement. In some models, animals are treated persistently with glucocorticoid. In others, genetic mutant mice express irregular levels of glucocorticoid receptors in brain to stop the normal feedback inhibition that occurs. These models reveal that anhedonia that is reversible with action of antidepressants treatment. On the other hand, anomalies in the HPA axis are extremely unpredictable in human depression, which means that, by means of HPA axis defect to disagree for construct or face validity should clearly shield these choices and perfectly depend on superfluous validators.

(B) 5HT Transporter knockout
The serotonin reuptake transporter 5-HT is very important in the inactivation and management of seroternergic neurotransmission and obstruction of serotonin transporter is the main target of tricyclic antidepressants (TCA), selective serotonin reuptake inhibitor (SSRI), selective nor -epinephrine reuptake inhibitor (SNRI) drugs. The seroternergic transporter, while not a model of depression, may give hope to the adaptive mechanisms related with the everlasting lack of serotonin reuptake. There are some new studies proposed that 5-HTT knock-out mice shows provincial differences from wild type mice in terms of 5-HT1A receptor protein and mRNA expression which is well-known to be strongly condensed in dorsal raphe, hypothalamus, amygdale, and septum, but improved in hippocampus that are related with decreased functional sensitivity to the hypothalamic effects of the 5-HT1A-receptor agonist 8-Hydroxy-2- (di-n-propylamino) tetraline (8-OH-DPAT).In the same way, 5-HT2A- receptor density is also decreased in 5-HT1 knockout mice .Keenly, the negative reaction of the 5-HT1A auto receptor in 5-HTT knockout mice is further enhanced by experiencing to stressful conditions.

(C) Tachykinin receptor knockout:
The NK1 receptor is expressed in brain regions linked with the control and management of depressive illness, stress, anxiety. Mostly, antagonists at the NK1 receptor have been determined as a powerful antidepressant drug with an original mode of action. The NK1- receptor knockout mice is not an animal model of depression. To some extent, these mice show signs of behavioral changes analogous to those shown by antidepressants in normal mice, including less immobility in the forced swim test and tail suspension test. NK1- receptor knockout mice also demonstrated a

loss of satisfying assets of morphine, in concert with decreased physical response to opiate withdrawal, but their response to cocaine is unaffected, signifying that this may reproduce a more meticulous interaction with opid system, relatively than a general effect on brain mechanisms.

(3) Force swim test (FST). The forced swim test initiated firstly by Porsolt et al. [17] and is most often used and also known as Porsolt test. This test involves putting a rat or a mouse in a tall cylinder of water from which it cannot run away, so that it must swim or float to stay alive. It is a behavioral test in which antidepressants extremely increase the time an animal struggles in a chamber of water; deficiency of struggling thought which correspond to a state of depression. This is despair based.

(4) Tail suspension test: **(TST)** This was given by Cryan et al. [18] and is recommended to have larger sensitivity. Treatment of antidepressants raises the time of animals spend in active behaviors'. The tail suspension test is the second most generally used test for depression, is theoretically analogous to the FST. This test is most frequently used in mice, because it is very not easy to apply in rats. It is a behavioral test in which antidepressants extremely raises the time an animal struggles when suspended by tail, deficiency of struggling thought which signify a situation of depression. So this also despair based.

(5) Olfactory bulbectomy (OB): This is a behavioral test in which surgical lesions or chemicals of the olfactory bulb cause behavioral modifications, some of which can be reversed by the treatments of antidepressants.

(6) Fear conditioning: Animal show fear like responses when exposed to previously neutral cues e.g. tone that has been linked with an aversive stimulus e.g. shock.

(7) Neonatal clomipramine administration: When exposed to neonatal clomipramine, adult animals show a many symptoms analogous to depression, including decreased reward seeking, aggressiveness and sexual behavior. By the application of antidepressants which can reverse behaviours [19].

(8) Selective breeding: This model concentrates on individual differences in vulnerability to depression or depression-like behavior.

There are some genetic factors and in addition to it, numerous studies have implicated environmental modifications together with stressful life events with the development of affective disorders [20,21]. In experience to stress or to traumatic life events which has a powerful impact on the appearance of depression, signifying a damage of proper stress-coping approaches in depressed patients [22,23]. So, depression is also considered as a stress-related disorder, and, as a result, several of the animal models of depression are based on the exposure to different types of acute or chronic stressors. On the other hand, till to date small agreement exists on the meaning of stress. There are many studies which interpret the existence of a stress response, manifest in an abrupt boost of corticosterone, as a sign of stress exposure. Likewise, appetitive and rewarding situations for instance sexual behavior and pleasing a social interaction bring out HPA axis responses that are analogous in magnitude as extremely aversive situations like social defeat [24]. It should be noted that the physiological response does not essentially implies a state of stress. Koolhaas and other researchers satisfied on the opinion that stress should be measured as a cognitive sensitivity of uncontrollability and/or uncertainty that is expressed in a physiological and behavioral response. Therefore, an unpredictable situation should be characterized by the absence of a defensive response, but unmanageable can be explained as a decreased recovery of the neuroendocrine reaction [24] In that feature the most important models which are known as stress models and are of three types

Stress model (Three types of stress model)
(a) Chronic mild stress
(b) Social stress
(c) Early life stress
(a) Chronic mild stress: Animal exposed repetitively to some unpredictable stresses cold, disruption of light dark cycle footshock resistant etc. showed decrease sucrose preference and sexual behavior; still these endpoints have been complex to duplicate, mainly mice. While chronic stress has been implicated in the commencement of psychiatric disorders, it should be kept in mind that not all individuals exposed to rigorous stress will progress to disease. In that sense, it is also pretty doubtful that a lone genetic variant which is wholly responsible for a specific disorder. Hence, it is of great need to know the cause of individual differences and the consequences of difference in

susceptibility, with respect to disease development. It is ampiclear that most important efforts should be directed towards the amalgamation of genetic changes and environmental variations in the same subject. Such prompt of gene-environment interactions is more possibly to reveal the pathophysiological mechanisms of depression. There are many studies which have already valuable this notion by subjecting transgenic lines to chronic social stress trials [25]. These studies give further proof that disease-linked genetic alterations do not have to be pathological/beneficial under normal conditions, but in amalgamation with chronic stress can either cause susceptibility or resilience towards the progression of depression-like phenotypes.

(b) Social stress: This is a behavioral test in which animal is exposed to diverse type of social stress proximity to dominant males, shows behavior anomalies while on the other hand, such abnormalities have been complicated to replicate predominantly mice.

(c) Early life stress: This is a test in which animals detached from their mothers at a young age show some continuous behavioral and HPA axis anomaly as adults, some of which can be reversed by the treatment of antidepressants or antipsychotics. This includes maternal deprivation. The maternal deprivation model is the most commonly accepted early life stress model.

CONCLUSION

Although there are many animal models of depression, together with some that have predictive, face, and construct validity within the same model. There are many limitations which restrict their utility. It is noteworthy that all animal models of depression have added to a better understanding of the neurobiology of the depression, and recommend new pharmacological targets for treatment. However, the progress of a model that represents most symptoms of depression and meet all criteria for animal model validity should be given priority.

REFERENCES

[1] RC Kessler; WT Chiu; O Demler; EE Walters. *Arch Gen Psychiatry*., **2005**, 62(6), 617- 627.
[2] DH Barlow; and VM Durand. *Abnormal psychology: An integrative approach (5th ed.)*. Belmont, CA, USA: Thomson Wadsworth. ISBN 0-534-63356-0, **2005**
[3] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5Th ed. Washington, DC. **2013**
[4] MA Geyer; A Markou. (**2002**) The role of preclinical models in the development of psychotropic drugs. In: Davis KL, Coyle JT, Nemeroff C, editors. Psychopharmacology: the Fifth Generation of Progress. Philadelphia: Lipincott, Williams and Wilkins. **2002** pp. 445–455.
[5] PJ Mitchell; and PH Redfern. *Current Pharmaceutical Design*., **2005**, 11, pp.171-203
[6] P Willner. *Psychopharmacology*, **1984**, 83, 1-16.
[7] P Willner, M Wilkes, A Orwin. *Journal affect disord*., **1990**, 18, 281-287
[8] A Frazer; DA Morilak. *Neurosci Biobehav Rev*., **2005**., 29, 515-523.
[9] P Willner. *Adv Biochem Psychopharmacol*., **1995a**, 49, 19-41.
[10] R Hitzermann. *Alcohol Res. Health.*, **2000**, 24, 149–158.
[11] RD Porsolt. *Rev in the Neurosc.*, **2000**, 11 (1), 53-58
[12] I Lucki. *Behav pharmacol*., **1997**, 8, 523-532
[13] WT McKinney Jr; anWE Bunney Jr. *Arch Gen Psychiatry*., **1969**, 21(2), 240-8.
[14] MA Geyer; and A Markou. (**1995**) Animal models of psychiatric disease. In: Bloom, F.E., and Kupfer, D.J., eds. *Psychopharmacology:* The Fourth Generation of Progress. New York: *Raven Press.* **1995**., pp. 787–798.
M Sarter; JP Brumo. Animal models of biological psychiatry. In biological psychiatry Eds H.D' haenen, J.A den Boer and P.Willner) *John Williner and sons. New York and sons*. **2002** pp, 47-49.
[15] HS Akiskal. *Psychopharmacology Bull*., **1986**, 22(3),579-586
[16] RD Porsolt; M Le Pichon; M Jalfre. *Nature.,* **1977a**, 266, 730–732
[17] JF Cryan; C Mombereau; A Vassout. *Neurosci Biobehav Rev*., **2005**, 29, 571-625
[18] G Vogel D Neill, D Kors; M Hagler. *Neurosci Biobehav Rev*., **1990**, 14, 77-83
[19] L Pezawas, J Angst, S Kasper. *Int Rev Psychiatry.*, **2005**, 17, 63-70.
[20] M Ising; F Holsboer. *Dialogues Clin Neurosci.*, **2006**, 8, 433-444.
[21] RC Kessler. *Annu Rev Psychol*., **1997**, 48, 191-214.
[22] ER de Kloet; M Joels; F Holsboer. *Nat Rev Neurosci*., **2005**, 6, 463-475.

[23] JM Koolhaas; A Bartolomucci; B Buwalda; SF de Boer; G Flugge; SM Korte; P Meerlo; R Murison; B Olivier; P Palanza; G Richter-Levin; OA Sgoif; T Steimer; O Stiedl; DG van; M Wohr; E Fuchs, *Neurosci Biobehav Rev.*, **2011**, 35, 1291-1301.
[24] Berton; C McClung; R DiLeone; V Krishnan; W Renthal; S Russo, et al. *Science.*, **2006**, 311, 864–868.