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A REVIEW ON ANIMAL MODELS OF DEPRESSION AND THEIR VALIDITY

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ABSTRACT: Depression is a common long lasting and diverse psychiatric illness that is said to affect a person's thoughts, behavior feeling and sense of well-being. In order for the treatment and the complete pathological understanding of this illness some models are needed, this can express or display the same behavioral changes as that of the illness in question. Animal models can be appreciated for this but there has been some raised controversies in the interpretation of the read out in a number of tests. In this case it is not the way of modeling complex human disorder in animals but in a way the tests are conducted, selected, and interpreted. In this article we will be able to discuss further on various tests and models used, and their extent of validity in the long run for the effective treatment of depression.

***Index terms*: Depression ,Animal models, Tests, Models, Validity**

I. INTRODUCTION

Depression is regarded as the most common and serious medical illness which is said to have a negative effect on the brain and affects how we feel, the way we think, and how we act. It is said to be a state of low mood and displeasure or aversion to any activity. Depression is said to affect a person's thoughts, behavior, motivation, feelings, and sense of well-being. It can show features like sadness, difficulty in thinking and concentration, and an increase or decrease in appetite, and the time spent oversleeping or not sleeping at all (Insomnia). The core symptom of depression is said to be anhedonia which usually refers to loss if interest or pleasure in certain activities that usually bring joy to that particular individual. People with depression experience feelings of hopelessness, dejection, and may have reoccurring to constant exposure to suicidal thoughts. It can be either short term or long term.

Monoamine hypothesis: This was the first major hypothesis of depression which was proposed 30 years ago. It has proposed that depression symptoms are a result of a functional deficiency of monoaminergic neurotransmitters like norepinephrine, serotonin, and dopamine, whereas the excess of monoamines may cause mania.

Monoaminergic symptoms are responsible for many behavioural depressive symptoms like mood, vigilance, motivation, retardation and fatigue as the origin of noradrenergic, serotonergic and dopaminergic neurones in the brain and their projections into different part of the brain.

The Depressive symptoms are given below:

- Feeling sad or having depressed mood
- Lack of pleasure and interest in activities
- Weight gain
- Weight loss
- Trouble sleeping or sleeping too much
- Feeling worthless or guilty
- Difficulty in thinking, concentrating or making decisions
- Thoughts of death or suicide.

These symptoms may be shown at a mild to moderate to severe level. The symptoms must persist for about more than 2 weeks to be diagnosed with depression.

Table 1. Types of Depression

Major depressive disorder (MDD)	Also known as Clinical Depression whose symptoms are intense and overwhelming and might interfere with an individual's everyday life and lasts for more than two weeks.
Bipolar depression	People diagnosed with bipolar disorder have alternating periods of low mood which shows depression symptoms like feeling sad, losing hope and very low energy along with periods of extreme high energy also categorized as manic periods.
Perinatal and postpartum depression	Perinatal depression can occur during pregnancy. And it can continue for one year after birth of the baby. Symptoms include minor sadness, worry, and stress.
Persistent depressive disorder (PDD)	PDD is also referred to as Dysthymia. The symptoms associated with this disorder are less severe than major depression. The people with this disorder experience symptoms for two years or longer.
Premenstrual dysphoric disorder (PMDD)	This disorder affects woman in the days or weeks leading up to their menstrual period and it is a severe form of Premenstrual Disorder(PMS)
Psychotic depression	People with this depression have severe depressive symptoms or delusions and hallucinations. Hallucinations involve seeing, hearing and feeling touched by things that aren't actually there whereas delusions are the belief in things that are not real.
Seasonal affective disorder (SAD)	Usually starts in late fall or early winter and goes away during the spring and summer.

II. ANIMAL MODELS FOR DEPRESSION

It is very difficult to develop an animal model that perfectly reproduces the symptoms of depression just as in patients. Alot of animals lack self-consciousness, self-reflection, and moreover, hallmarks of the disorder such as depressed mood, low self-esteem or suicidality are barely accessible in non-humans. However, depression, as another mental disorder, consists of endophenotypes which can be reproduced independently and evaluated in animals.

Table 2. Endophenotypes in animal models of depression

S.no	**Name of Endophenotype**	**Description**
1.	Anhedonia	The lack of interest is known as the core symptom of depression. In rodents it can be assessed by sucrose preference or by intracranial self-stimulation.
2.	Neuroanatomy	Depressed subjects tend to show a decrease in the hippocampal volume. Whereas in rodents, when they are subjected to chronic stress and an excess amount of glucocorticoids, they show similar loss of hippocampal neurons.
3.	Alterations in sleeping schedule	Disturbances in the sleep architecture and circadian rhythm are mostly seen which in the case of rodents it can be examined by electroencephalography (EEG).
4.	Behavioural Despair	In rodents, some of the tests like forced swimming test and tail suspension test might lead to behavioural despair which can be evaluated properly.
5.	Changes in appetite	In rodents changes in appetite and weight gain can be easily measured which is said to be associated with depression.
6.	Anxiety related behaviour	Often, there is a display of altered anxiety related behaviour in animal models of depression.

By using animal models, we are able to understand the molecular, genetic, epigenetic factors which may lead to depression. Thus, implying a better insight into the pathology of depression. Experimentally induced defeat or despair in the animal is the main aim even though this aspect of mammalian behaviour is likely physiological (i.e., adaptive). Presently depression models are quite often evaluated by fulfilling the three main criteria (a) face validity (the requirement of symptomatic homology), (b) construct (etiological) validity (the requirement of similar causative factors), and (c) pharmacological validity (requires the reversal of depressive symptoms by available antidepressants).

Table 3. Depression models

Name of the test	Description	Advantages	Disadvantages
Anxiety induced depression models			
Despair based			
Forced swimming test	Forced-swimming test (FST) is based on the observation that animals can develop an immobile posture in an unescapable cylinder filled with water. In this test, immobility is interpreted as a passive stress-coping strategy or depression-like behaviour (behavioural despair). After antidepressant administration, the animals will actively perform escape-directed behaviours with longer duration than animals with control saline treatment.	-low cost -fast process -easy to handle -strong predictive validity	-acute treatment only -poor face and construct validities
Tail suspension test	In the TST, the mice are suspended by their tails using adhesive tape onto a horizontal bar for a couple of minutes, and the time of immobility is recorded. Typically, the suspended rodents perform immediately an escape-like behaviours, followed by developing an immobile posture. If antidepressants are given prior to the test, the subjects will be engaged in escape-directed behaviours for longer periods of time than after saline treatment, exhibiting a decrease in duration of immobility.	-simple & Inexpensive	-restricted to mice -limited for strains -acute treatment only
Anxiety-based			
Novelty induced hypophagia	Hypophagia,is one of the anxiety symptoms in rodents, and is defined as the reduction in feeding in response to novelty, and it can be evoked by various novel features of the environment, including the novel food, novel testing environment and novel food containers. Novelty-induced hypophagia (NIH) is very recently developed test, that measures the latency and consumption of food in a novel and unfamiliar environment. This test rather reflects the anxiolytic effects of antidepressants, and response is seen only after chronic treatment with antidepressants rather than acute.	-improves practicality, Sensitivity and reliability	-reflects only the anxiolytic effects of antidepressants -seen only after chronic treatment not acute

Elevated plus maze	For the elevated plus maze test, the rodents are placed at the intersection of the four arms of the maze (two open, two closed),and facing the open arm. The number of entries and the time spent in each arm is recorded accordingly and valid results are obtained in a single, 5-minute testing session. An increase in the open-arm time is an index of anti-anxiety behaviour of rodents.	-quick and easy	-Mainly concerns with anxiolytics use
Stress induced depression models			
Learned helplessness model	This model is based on observation that, animals also develop deficits in escape, cognitive and rewarded behaviors when they have been subjected to various repeated unavoidable and certain uncontrollable shocks. This model is induced in one day or over other several days of repeated inescapable stress by the means of treating of tail shock or foot shock in shuttle boxes. Helpless behavior is evaluated by analyzing the performance in an active escape test, such as the latency to press a lever or cross a door.	-Helps to understand the depressive symptomatology in humans -Excellent phase and predictive validities	- Needs very strong stressors to induce the behavioral endophenotypes. -Symptoms do not persist long enough
Chronic Mild stress:	In this model it involves the exposure of animals to a series of mild and unpredictable stressors (periods of food and water deprivation, small temperature reductions, changes of cage mates, and other similar individually innocuous manipulations) during at least 2 weeks. The model has been reported to result in long lasting changes of behavioural, neurochemical, neuro immune and neuroendocrinological variables resembling reward functions including decreased intracranial self-stimulation, reflecting anhedonia that is reversed by chronic however not by acute antidepressant treatment.	-good predictive validity (behavioural changes are reversed by chronic treatment with a wide variety of antidepressants), face validity (almost all demonstrable symptoms of depression have been reproduced), and construct validity	-very labour intensive, and demanding of space, and of long duration -procedure may be difficult to establish and data can be hardly replicated
Social defeat stress	During the stress period, t male rodent will be introduced into a different territory of other cospecific males for each day as an intruder, that cause it to be investigated, attacked and defeated by the residents. The consequent behaviour changes in the subject caused by SDS, like decreased social interaction or lack of interest, are similar to some parts of human depression, and behavioural treatment and antidepressants can be reversed in SDS model	reversed by chronic treatment with a wide variety of antidepressants), face validity (many symptoms of depression have been reproduced), and construct validity (causing a generalized decrease in responsiveness to rewards) and gives another validity that only chronic but not acute antidepressant administration can reverse	female rodents can not fight each other in a resident–intruder confrontation -period of it should last at least 20 days otherwise only the anxiety symptoms could be induced

Olfactory Bulbectomy	The olfactory bulbectomy in rodents results in a disruption of the limbic-hypothalamic axis with the consequence of behavioural, neurochemical, neuroendocrine and neuroimmune changes, of which many resemble changes seen in depressed patients.	-shows high predictive validity as it mimics the slow onset of antidepressant action reported in clinical studies,	-responds to chronic but not subchronic antidepressant treatment with no response to other drugs

III. Validity

In general, it is accepted that the three criteria that can be used to assess the reliability of an animal model of depression: the phenomenological or morphological appearances (face validity), a similar etiology (construct validity), and therapeutic similarities (predictive validity).A debate remains regarding the validity of this approach because it does not reflect the complexity and intensity of symptoms in patients. The majority of the animal models of depression obey validity criteria, as defined by construct, and the face and predictive validity. Indeed, they mimic depressive phenotypes and induce neuronal changes similar to those observed in humans, reversed by classical anti-depressants. However, to date, this approach has failed to lead to the development of new treatments and the biological mechanisms of depression are still poorly understood. Moreover, these three conventional validities have some defects, such as low practicality, measurement difficulties, and gene-environment incompatibility. Some neurocircuit manipulations can be done on the rat, however this will affect only a particular area of the brain for depression and not work on the disorder as a whole. In depression there is no specific neuronal circuit involved in its pathophysiology, but an intricate network of multiple alterations. This explains why neuronal manipulations projected only on some areas of the brain can unravel only singular abnormalities of the disease, rather than providing a unified explanation of the pathological mechanisms of depression.

IV. CONCLUSION

It is difficult to predict the therapeutic effect by using only a single animal model. The pharmacologic model is said to have low reliability but high efficiency, which enables it be used to select antidepressants. The learned helplessness, chronic mild stress, and social defeat stress models have high specificity, which indicates that these animal models can manifest symptoms that are similar to those of depression in humans. These three methods may benefit investigators who study the etiology , or perform drug research in depression. However, to date, this approach had failed to lead to the development of new treatments and the biological mechanisms of depression are still poorly understood. Thus, future research should focus not only on the presence or absence of depressive symptoms but also on the biological features underlying the clinical signs.

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