An Overview of Antidepression Model

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ABSTRACT

Depression is a mental disorder categorized by a sense of despondency, inadequacy, pessimism, decreased activity, sadness, and anhedonia where these symptoms sternly disturb and negatively affect a patient's life, sometimes to the extent of developing suicidal tendencies or committing the act itself. It is often surrounded by common forms of psychiatric disorders and thus transforming itself into a significant factor for morbidity and mortality in today's life. Depression has been connected to social, cultural, lifestyle related, as well as biological factors. For a better understanding of the disease process as well as for developing newer and safer drugs, preclinical studies using various animal species are being conducted in various research labs all over the world. In this review article, we aim to summarize the findings of currently available animal models while discussing their potential to isolate the possible neurobiological basis of depression and highlight their impact on the development of novel treatment strategies. Animal models of depression give a promising approach to explore molecular & cellular pathways along with neural circuitry in a controlled environment.

INTRODUCTION

Depression is the most common mental and physical disorder all over the world. It could be a major reason for disability (1). Depressive illness comes in diverse forms, just as numerous other illnesses(2):

i. **Major depression** is manifested by a group of symptoms that obstruct one's ability to sleep, work, enjoy, and eat i.e. activities that once used to be satisfying. These disabling episodes of hopelessness can occur several times in a life span.

ii. **Dysthymia**, a milder form of depression; involving chronic, long-term symptoms that do not disable but remain you from feeling good.

iii. **Bipolar or Manic-depressive** is not as prevalent as depressive illnesses in other forms. It involves cycles of elation or mania and depression. More often than not, these mood switches are regular but rarely may also occur suddenly and dramatically. When in the depressed cycle, one can have depressive illness symptoms. When in the manic cycle, the person is overactive and often euphoric. It frequently affects social behavior, thinking, and judgment in ways that may cause solemn embarrassment and problems. (3)

Here are some signposts to recognize

• Depressed mood: For adolescents and children, this can be as subtle as an ill-tempered mood

• Loss of pleasure or Less interest in almost all work done (anhedonia)

• Appetite disturbance or considerable weight change

• Disturbance in sleeping (hypersomnia or insomnia)

• Retardation or Psychomotor agitation

• Loss of energy or Fatigue

• Feeling of worthlessness

• Indecisiveness; Decreased ability to concentrate or think

• Recurrent suicidal ideation without a specific plan, recurrent thoughts of death, or a specific plan for committing suicide or a suicide attempt (4)(5)

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It is extremely difficult to design an animal model that can perfectly replicate the symptoms of depression in human patients. In Animals, we cannot expect to find such self-awareness, self-reflection & consideration of others; let alone being conscious of depressed mood, low vanity, and suicidal thoughts. However, some of the manifestations of depression such as altered behavior in stress, impaired cognitive abilities, and dysfunctional reward-processing behavior can be easily modeled in animals(6) and these changes in behavior can be related to physiological, endocrine, and anatomical changes. (7). The model ought to (i) be moderately analogous to the human disorder in its symptomatology (face validity), (ii) reflect those behavioral changes which are undone by a similar treatment that is effective in humans (predictive validity) (8)(9). (iii) measures the construct, which it claims to do. (Construct Validity) (10). (iv) Assess operationalization skills to differentiate between groups that it should hypothetically be able to differentiate between (concurrent validity) (11).

ANTIDEPRESSANTS

The molecular pathology and complete mechanism behind the causation of depression are quite unknown. Pharmacological treatments are based on the monoamine theory of depression; which points towards the reduced levels of serotonin, dopamine, and noradrenaline in the brain being culpable (12). The main purpose of the antidepressant therapy is to increase levels of monoaminergic neurotransmitters in the synaptic cleft through inhibiting reuptake or by reducing their metabolism, which ultimately leads to an increase in the activity of the hypothalamic-pituitary-adrenal (HPA) axis (13)(14). The typical drawback of all these antidepressants is slow-onset and together with 60% of unresponsive patients to the first-line therapy (15) highlights the urgent need of discovering novel drug-targets and producing new therapeutic approaches in depression. A key area that we need to put more attention on is to develop and improve animal models of depression, to achieve these two goals. Although current models have helped us immensely over the last two decades in developing and evaluating current antidepressant therapies, we still need to address several limitations, to maximize our efficiency in the discovery of novel depressant drugs.

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ANIMAL MODELS OF DEPRESSION

Table No. 1: Classification of current animal models of depression

MAIN CLASSES	MODELS	STRESSOR	REFERENCES
Acute and subchronic stress-induced	FST	Inescapable forced swimming.	(16)
	TST	Tail suspension.	
	LH	Inescapable electric shocks.	
Chronic stress-induced	CSI	Prolonged-chronic isolation	(17)
	CSD	Repeated bouts of social subordination.	
	CMS	Chronic exposes to alternate and variable stressors.	
Models of secondary depression	HPA axis dysregulation.	Administration of corticosterone.	(18)
	Retinoic acid model.	Prolong use of retinoic acid.	
	Immune system dysregulation.	Administration of pro-inflammatory cytokines.	
Immutable models	Olfactory bulbectomy.	Surgical removal of the olfactory bulb.	(19)
	Genetically modified models.	Genetically selected for hypersensitivity to drugs, receptor knockouts, etc.	

FST: forced swimming test, **TST**: tail-suspension test, **LH**: learned helplessness, **CSI**: chronic social isolation, **CSD**: chronic social defeat, **CMS**: chronic (unpredicted) mild stress

FORCED SWIMMING TEST (FST)

This test was initially developed by Porsolt and colleagues in 1977 for testing potential antidepressant-like compounds when a single drug was administered (20)(21). It has become the most widely used pre-clinical model of depression due to its ease of use and ability to

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predict a broad range of antidepressant activities (16). In this model, the rodents are placed into a cylinder with cold water and are forced to swim to survive from an inescapable situation. Immobility is used as the predominant index of the level of behavioral despair and, therefore, increased duration of immobility or counts of immobile activity are the characteristic of depressive-like behavior. The original description of the FST process in rats includes two stages, that is, placing the animal in an erasable water tank twice within 24 hours for 15 minutes and 5 minutes, followed by calculating the fixed time (22). The mouse FST model was modified by using only a single 15-minute session for testing the efficacy of potential antidepressant drugs to reduce immobility levels [22]. Because of its simplicity, this paradigm is considered the most suitable for the high-throughput in vivo tests of antidepressant compounds in mice. Recent modifications were introduced based on different observed activities, as well as differences in the behavioral pharmacology among drugs. Active swimming, such as diving, climbing, and swimming are now also routinely measured individually. It has been elicited that serotonergic and noradrenergic antidepressants influence the swimming and climbing behavior differently in this model. The serotonergic system is revealed to conciliate the swimming motion, while noradrenergic antidepressants improve the climbing performance (active movements with forepaws in and out of the water, usually touching the wall of the cylinder) (23). Therefore, the increase in movement can be confused with reduced immobile phase as an index of behavioral distress; open field arena test is being utilized in most studies along with the FST model to evaluate hyperactivity potential. All clinically used antidepressants show efficiency in the FST without affecting locomotion in the open field test, compared to the immobility scores and locomotion of non-treated controls (24), which indicate that the diving, swimming, and climbing behaviors in the FST can be improved without hyperactivity induction.

TAIL SUSPENSION TEST (TST)

TST is a general behavioral pattern used to estimate the antidepressant activity of investigational drugs. In this test, the animals are positioned in an inevitable yet unassuming distressing situation; the mice are suspended in the air by their tails. Every mouse is hung 50 cm from the ground, fixing it almost 1 cm over the tail tip. It is continuously suspended for 6 minutes (360 seconds) (25). The behavior of the mouse to escape this aversive situation is recorded during this time. The principle of both paradigms being identical, it is taken as an alternative for the FST. Mice, suspended by their tails, inherently make an effort to get away from this unfavorable situation. However, as an outcome of the futile attempt to get away, the

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mice get familiar with dejection and become motionless. The immobility extent is thought to be linked with the depression-like state of the mice and is considerably diminished by antidepressant treatments (26).

LEARNED HELPLESSNESS (LEARNED HELPLESS, LH)

Learned helplessness (LH) is a phenomenon that was discovered by Seligman and his colleagues during the 1970s in dogs (27) and is now frequently applied to rodents. According to Seligman, most (2/3rd) of the dogs subjected to the inescapable shock would learn helplessness and not attempt to escape the shock when placed in the escape shuttle box. One of the chief attractions of this paradigm is that it is obtained from the cognitive view of depression in which proceedings are viewed negatively and elucidated as not tractable, leading to feelings of nervousness and defenselessness when dealing with them. Later, this occurrence was functional in rodents and parallel results were established when these animals were subjected to random inescapable shock.

Uncontrollable stressful events, which precipitate depression-like behaviors observed in rodents, similarly precede the onset of some clinical depression in humans are some similarities between the LH animal and human depression (28)(29). Furthermore, the subjection of animals to parallel but convenient events does not create related behavioral changes (30)(31). Numerous of the chief symptoms that distinguish clinical depression is perceived in harassed animals. These include decreased motor activity (32)(31), decreased eating and drinking, weight loss/lack of weight gain (33), decreased grooming (34).

Recently, utilized congenitally learned helpless (cLH) rats and found that β-CaMII expression was significantly up-regulated in the LH animals, and down-regulated by antidepressants. Adverse regulation of β-CaMKII levels, by obstructing its activity or its intent molecule GluR1, upturned the depressive indications. This study provided new insights into the molecular mechanism for depression based on the learned helplessness rodent model (35), decreased competitive behavior (30)(36), increased errors in a choice/discrimination task (37), decreased response to rewarding brain stimulation, and sleep disturbances (31). These indications strongly resemble those typically used for the analysis of depression.

CHRONIC SOCIAL ISOLATION (CSI)

It is proposed that social isolation is of special significance for adolescent/juvenile mice and rats; this method is also used for adult rats (38). Contrary to other pressure-induced

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paradigms, this paradigm has hardly attracted attention due to data placement errors (22). The consumption of sucrose is reduced if the long-term social lack of contact of adult rats occurs (39). The socially isolated animals avoided the open testing center area and spent longer swimming time and resting period in the FST. Compressed animals also show significant adrenal cortex hypertrophy with a decrease in serum corticosterone levels. While the molecular flexibility marker, PSA-NCAM continued to increase in the remote rat's hippocampus, it was also noted that the successful treatment of fluoxetine restored it to control levels (22)(40). The elevation in PSA-NCAM, a molecular plasticity indicator in the hippocampus of constantly remote rats was also noticed while succeeding treatment with fluoxetine brought back to the control level (22)(40). Chronic stress up-regulated the serum corticosterone level of a single animal and reduceed the hippocampal GR, but not in groups of animals (41). After the half, a day of social offscouring give rise to behavior similar to depression in mice, restored the forgotten prejudice (i.e., negative price) task, and improved corticosterone amount, (42). Frustration behavior is particularly important for social isolation because 12 hours of crowding can neither persuade this behavior nor improve recovery, improved recovery, although corticosterone levels have increased, just like social isolation. After the situational fear condition was damaged, a 6-hour social quarantine was carried out immediately, and the fear was calculated 48 hours after the destruction of the situational memory. The depletion of BDNF mRNA in the hippocampal CA3 and dentate gyrus area was estimated immediately after separation (43). After performing a related fear adjustment, social offscouring for about 180 minutes can also improve IL-1β protein in the cerebral cortex, and hippocampus (44)(45). Compared with male mice reared in groups, solitude mice flashed to immedicable mild stress expressed elevated basal corticosterone and lower IL-2 and IL-4 and splenocyte multiplication (46). Compared with the balance of anti-inflammatory cytokines, social isolation has increased, and the metabolism of kynurenine has changed, and the neuroprotection rate of rats has decreased (22)(47).

CHRONIC SOCIAL DEFEAT

The social frustration stress model involves produces high physical strength bellicose animals into the home coop of a native animal daily for several weeks (48). Research mice are forced to maintain physical contact with their attackers in hearing, sight, and smell, to be in existence for the leftover day. This sequence repeats for ten days, with a new challenger daily. After ten days, the animals manifested conduct regarding anhedonia and solitariness.

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Social offscouring will manufacture various MDD related neurobiological changes, for instance, increased amygdala activity lead by prefrontal cortex (PFC) dysregulation (49), The pro-inflammatory cytokines (50), hypercortisolemia (51) release, and neurotrophins changes (52)(53). Even though this process is more suitable for male rodents because the process of social offscouring in females is more complicated due to the ferocity of females, contemporary research proclaimed that alternative occurrences of social offscouring encourage behavior similar to depression in female mice. The immedicable social offscouring paradigm is perceptive to immedicable SSRIs (53)(54) and acute ketamine treatment (44).

CHRONIC MILD STRESS (CMS)

The CMS paradigm involves adult rats and mice exposed to various relatively mild and impulsive stressors in a haphazard sort over several weeks (39)(55)(56)(57). It is mostly intended to provide the symptoms of anhedonia and general loss of interest towards rewards, as understood in mostly depressive patients. In this animal model, the behavioral insufficiencies are induced above a period of 3 - 9 weeks by commanding a diversity of stressors in a semi-random routine intermitted by abundant intervals, therefore delaying the probable development of adaptation mechanisms that are regularly perceived with the constant presence of a solitary stressor(58). Stress sources include grouping and isolation, intermittent lighting and overnight lighting, lack of food and water, cage tilt, cold stress (4°C), restraint, forced swimming, and white noise. As a consequence, neuroendocrine, functioning, neuroimmune, and neurochemical changes, together with nap disturbances, depression, and anhedonia are exhibited by these animals in the long-term, similar to those observed in patients with depression. Long-term but not acute antidepressant treatment can make changes caused by long-term trauma (59). CMS notably governs the endurance of granular cell level latest cells; however, it will not affect their differentiation or multiplication (60).

HPA AXIS DYSREGULATION

The "cortisol," theory suggests that in certain depressive disorders, the Hypothalamus-Pituitary-Adrenal axis probably plays a role in disease manifestations, by
(1) decreasing negative feedback expressed by glucocorticoids in the brain and thus,
(2) increasing the production of hypothalamic corticotropin releasing factor (CRF)(61).

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Clinical investigations have revealed that a few patients with depression (mainly patients with severe depression and psychotic symptoms) have HPA axis dysregulation (62), and these patients may benefit greatly from pharmacological antagonists of glucocorticoid receptors (63). It is often perceived that dejection is an adverse effect of long-term glucocorticoid therapy and gives important clues for the presence of signs of psychosis in Cushing's syndrome, which is manifested as hypercortisolemia secondary to corticotrophic hyperplasia of the adrenal or pituitary. Therefore, the negative consequences of increased HPA axis activity are at least partly related to the adverse effects of glucocorticoids themselves (64)(65).

ISOTRETINOIN

A retinoic acid imitative, Isotretinoin, is tremendously effectual in the therapy of severe acne and depression, and suicide (66). Mice treated with isotretinoin recovered the increase in FST and TST tranquility, so the long-term agreement with decreased neuron production and hippocampal metabolism (67)(52)(68). Isotretinoin is known to bind to and activate the retinoic acid receptor (RAR) that is widely spread in the brain of an adult. RAR belongs to the nuclear hormone receptor family of transcription factors, and the transcriptional significance of exposure to isotretinoin surrounding the limbic brain area remains to be studied (69).

IMMUNE SYSTEM DYSREGULATION

In the three decades since the first seminal findings in 1990 showed that major depression is associated with inflammation and T cell activation (70); since then, the link between major depression and inflammation has become widely established and accepted (71)(72). Several immune system-based models have been developed to study major depression and other psychiatric disorders (such as maternal immune activation (73)(74) and the administration of lipoglycan endotoxins such as lipopolysaccharide S (75) or proinflammatory cytokines such as interferon-α) (76). The subjection of rodents to social trauma has been frequently demonstrated to lead to constant neuroinflammation connected with neuropeptide systems and multiple neurotransmitters alterations; these alterations probably underlie, at least in part, the behavioral phenotype observed following stress exposure (77). One mechanism through which social stress-induced release of proinflammatory cytokines into the bloodstream (78) is thought to lead to neuroinflammation involves a reduction in the integrity of the blood-brain barrier, specifically due to the loss of claudin 5 (an endothelial cell tight junction protein)

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(79). Though, external immune activation strategies are improbable to mirror the low-grade auto-inflammation observed in persons with foremost depression. Despite this limitation, the findings linking major depression and inflammation show the importance of investigating cross-compartmental mechanisms in the preclinical models utilized for research (80).

OLFACTORY BULBECTOMY (OBX) MODEL

The olfactory bulbectomy procedure involves the bilateral surgical ablation of the olfactory bulbs in rodents. Fourteen days later, the rodents display hyperactive behaviors in the novel environment, and increased susceptibility to trauma troubled sleep cycles and momentary hypohedonia, weight loss, and distress, like that in an MDD patient are noticed. The brain contents of serotonin and 5-HIAA are fairly diminished. In the same way, inflammation and corticosterone elevated levels have been found (81). Chronic (2-4 sennights) but not acute or sub-chronic treatments with classical ADs work against the behavioral alteration(82) and the levels of serotonin and 5-HIAA are also conversed (83).

INNATE PARADIGM

Depression has an unquestionable hereditary component; many studies have attempted to modify gene expression associated with susceptibility to MDD. Many transgenic strains of target genes related to the norepinephrine and serotonergic systems and HPA axis regulation have been produced. Additionally, the genetic paradigm includes strains selected based on stress sensitivity, for illustration, Wistar Kyoto rats that exhibit improved stress response and mood (84)(85), and special strains based on stress inhibition sensitivity (i.e., competition) to corticosterone. Increased reproduction in reactive mice was observed (86). Of course, in some behavioral examinations, mice with high responsiveness (HR) are hyperactive with their peers with low responsiveness (LR) and intermediate (IR), while a small number of depression subjects show psychomotor restlessness. Besides, even cLH rats that have not suffered electric shocks and other traumas failed to escape(87), they showed the same applicable neuronal changes as major depression, their ACC and foot canal activity increased, and depression-like behavior (88)(89). Another attractive method is to use knockout mice for gene transformation (knockout 5-HT system: 5-HT2B, 5-HT transporter, 5-HT1B, 5-HT1A, P11; HPA axis: CRHR1 or FKBP1; other systems: CB1, MIF, vGlut, OCT2 or DBH). Extensive re-evaluation of this different paradigm is beyond the scope of this article, because they may be different depending on the target system and the paradigm used. These animals all show resistance to treatment and increased sensitivity to stress (90). However, what I want

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to introduce is that depression is a polygenic disease, in which the influence of genes strongly reacts with environmental factors. A genetic paradigm with a single mutation on a given gene cannot summarize the genetic cause of MDD. Also, this genetic manipulation should be linked to exposure to a stressful environment to summarize the role of stress vulnerability in activating clinical situations (44).

DISCUSSION AND CONCLUSION

Even though there are a few restrictions in the ongoing depression rodent paradigm, such that the feelings of suicidal thoughts, sadness, guilt cannot be fully detained, the ongoing paradigm of depression does give to some level the essential tools for examining molecular, epigenetic, genetic, and environmental risk factors in understanding the pathogenesis of depression. (91) While no solitary animal paradigm is the one-size-fits-all wrap up respond for studying depression, the different paradigms have advantages over others for studying precise aspects of the disease. In recent years, inflammation (92), apoptosis, stress-signaling pathways (93), growth factors, genetics and epigenetic regulation (94)(95), environment and nutrition (96)(97) along with other compounding diseases and comorbidities (98) all contributed to the symptomatic pathophysiological state collectively known as depression.

ABBREVIATIONS

ABBREVIATIONS	FULL FORMS
FST	Forced Swimming Test
TST	Tail-Suspension Test
LH	Learned Helplessness
CSI	Chronic Social Isolation
CSD	Chronic Social Defeat
CMS	Chronic (Unpredicted) Mild Stress
HPA axis	Hypothalamic–Pituitary–Adrenal Axis
cLH	Congenitally Learned Helpless
β-CaMKII	Beta Calmodulin-Dependent Protein Kinase II
GluR1	Glutamate Receptor 1

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PSA-NCAM	Polysialylated Neuronal Cell Adhesion Molecule
GR	Glucocorticoid Receptors
BDNF	Brain-Derived Neurotrophic Factor
mRNA	Messenger RNA
CA3	Cornu Ammonis 3 (Hippocampus)
IL-1β	Interleukin 1 Beta
IL-2 / IL-4	Interleukin-2 (IL2) / Interleukin-4 (IL4)
MDD	Major Depressive Disorder
PFC	Prefrontal Cortex
SSRIs	Selective Serotonin Reuptake Inhibitors
CRF	Corticotropin Releasing Factor
RAR	Retinoic Acid Receptor
HR	High Responsiveness
LR	Low Responsiveness
IR	Intermediate
ACC	Anterior Cingulate Cortex
HT	Hydroxytryptamine
HT2B	5-Hydroxytryptamine Receptor 2B
HT1B	5-Hydroxytryptamine Receptor 1B
HT1A	5- Hydroxytryptamine Receptor 1A
P11	Small Protein 11
CRHR1	Corticotropin-Releasing Hormone Receptor Type 1
FKBP1	FK506 Binding Protein 1
CB1	Cannabinoid Receptor 1
MIF	Migration Inhibitory Factor
vGlut	Vesicular Glutamate Transporter

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OCT2	Organic Cation Transporter 2
DBH	Dopamine-B-Hydroxylase

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