Mechanistic Approach on Impact of Different Animal Models of Depression in Depressive State

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Abstract

One of the critical mental disorder is depression due to social and genetic reasons; depression is becoming a serious disability in the world. Animal models play a key task in the present comprehension about the pathogenesis of depression. There are many valid animal models with good predictive nature. Here we are presenting the stress induced animal models intended to explain the mechanism of antidepressive nature. It includes the both conventional and novel paradigms of depression. We highlight role of corticosteroids, GAD enzyme, glutamate, GABA and other neurotransmitters that involved in the pathogenesis of depressive state and the chief role of HPA axis in stress induced situations. Moreover a different animal model shows diverse mechanism where the targets of the mood disorders are entirely changed. This review can be used as a guide to develop an accurate and precise animal model before start of any research work in which resembles the human disease conditions. And we hope this will enrich the molecular knowledge about the behavioral models of depression.

Key words: Stress, Depression, HPA axis, Glutamate, GABA, Monoamines, Gene

1. INTRODUCTION

Depression is a mood disorder leading to the enhanced mortality rate. The mood issue are connected with the variation in different hormones, neurogenesis, neurotropic factors, monoaminergic, glutaminergic, GABAergic transmission.[1,2] In proof with reports of World Health Organization (WHO), depression will be the significant disability in the world by 2030.[3] In India, it is approximately, nearly one-third of patients could have indications like depression, and the crude prevalence rate of mood disorder was assessed to vary from as low as 0.5 to as high as 78 per 1000 population.[4] The genetic elements (about 40 %) as well as the other external factors are included in reason behind the beginning of depression.[5, 6] Current research on glutamate decarboxylase 1 (GAD1) and GAD2 genes, changes in mitochondrial DNA, for the genetic relationship with major depression and anxiety disorder.[7] One of the investigation concluded that the family risk issues, including parents, marital discord, parent-child dispute affectionless control, less family cohesion, and parental divorce were more widespread.[8] The most important environmental risk cause for depression is stress. The stress, hyper activates the hypothalamic-pituitary-adrenal (HPA) axis and it alters the expression and role of glucocorticoid receptors (GR). This is the basis for the climb of corticosterone (CORT) level during the depressive condition.[9] The symptoms of depressions are firmly identified with the dysregulation of limbic system and cortical region in brain.[10] The HPA axis will be activated during the stressful incidents, this leads to the advance discharge of GCs, one of the etiological factor for depression. GR is scattered throughout the hippocampus. Dysregulation of GR plays role in pathology of depression.[11]

2. VARIOUS DEPRESSIVE MODELS WITH MOLECULAR UNDERSTANDING

2.1 Maternal separation (MS) and models of early life stress

Maternal separation animal model of depression shows that, stress in the early life of pups could vary the HPA axis and cognition.[12] The consequence of MS on immobility time is check up by both tail suspension test and forced swim test. In light of the evidences i.e. the diminished expression of Brain Derived Neurotropic factor (BDNF) and neurofilament chain (NF-L), which are the neuroplastisity regulators, MS hinder the neuroplastisity and the cAMP responsive element binding protein (CREB)–BDNF signaling pathway.[13] This may reduce the expression of BDNF which is a neurotropin. GABA inhibitory system is influenced by MS due to neuronal excitation which assists for the GABA inhibitory system development.[14] GABA is an important factor for the brain development during the first postnatal week. MS influences the GABA inhibitory system. Repeated maternal separation [30 min] makes multiple times increment in the corticosterone (CORT) level and decline the GAD in neonatal mouse. GAD is a protein required for the production of glutamate from GABA. It leads to the fall of GABA level.[15,16] MS negatively influence on the maturation of GABAergic inter neurons which affects the growth of the neurons in hippocampus. It has been demonstrated that the early life stress make various impacts in the adulthood of animals on the expression of proteins looks after the glutamate/GABA cycling.[17] In another analysis, maternal behavior was experimentally induced by a brief 15-min separation between the mother and the pups during postnatal days 1 to 22. They reported that experimental and control dams levels of anxiety in the elevated plus maze (EPM) as well as the levels of receptors for estrogens (ERα, ERβ), oxytocin (OTR) and serotonin (5-HT1AR) in areas of the limbic system engaged with the regulation of maternal behavior.[18]
2.2 Chronic unpredictable mild stress (CUMS)

CUMS induced by different stressors for 21 to 28 days, randomly. CUMS procedure was continued for 28 days. Then the animals were subjected to behavioral evaluation. It was accounted for that stress initiates the HPA axis bringing about GC blood levels sufficiently raise to activate type II GR and generate adjustments in gene expression and it is a reason for harmful consequences for hippocampal functions as well as cognition. [19, 20] Dubey et al., followed the 21 day procedure for the CUMS induced depression. The CORT level is elevated for the stress induced rats. The treatment with chromium picolinate (16 g/ml) reverse the Chronic stress induced elevation in plasma CORT level. They also investigated about the reduced 5-HT in the CUMS induced depressive behavior. Chromium picolinate essentially expand 5-HT concentration in the discrete area of brain (cortex and cerebellum), which was significantly brought down in CUMS group expressing the expanded serotonergic transmission as one the significant factor in mediating antidepressant and anxiolytic actions. [21] Ma K et al., reported that, impairments in the GABAergic neurons and the production, discharge and uptake of GABA in the stress induced depressive mice. They found out the clear evidences for the impairments of GABA, such as the declined release at terminals in 3 weeks CUMS induced mice. It is because of the reduced expression of the GAD and the down regulation of the mRNA encoded for the GAD. And the stress creates imbalance between the GABAergic – glutamnergic neurons in the PFC, this investigation also shows that CUMS by means of CORT upregulates the degrees of mRNA as down regulates the expression of GAD-67, VGAT and GAT-3 genes and proteins, which slow down presynaptic GABA release and take-up. Hence, genes/protein expression and neuron atrophy, in which both presynaptic and postsynaptic segments in GABAergic neural connections are altered in the PFC [22]. The cytokine theory of depression, called attention to that pro inflammatory cytokines actuated by initiated macrophages or chronic stress can separate the input circle of the HPA Axis by over the top discharge of GC and down-direct GR in the hippocampus, which can bring about neuronal damage and neurotransmitter dysfunction. In fact, patients with significant discouragement display rise in proinflammatory cytokines and their dissolvable receptors in fringe blood and cerebrospinal fluid (CSF) [23, 24]. Chronic stress, explicitly atrophy and impairments in different area of brain such as prefrontal cortex and hippocampus which plays a role in the generation of depression and Alzheimer’s disease (AD). Cortical level has been elevated in CSF in dementia of AD. [25, 26], chronic stress leads to marked fall in BDNF levels in hippocampal CA1 with subsequent hinder of the restore procedure that aggravating the cluster of amyloid β [27].

2.3 Repeated restraint stress

The rats were forced into a restraint cone which is disposable for 2 hour to make animal immobile and it was reported about the alteration in dopamine concentration in nucleus accumbens. [28] In 2012 Petra et al., published a work on restrained stress i.e. keep the animal daily for 5 hours. For acute stress and chronic stress animal underwent restraint stress for 3 days and 21 days respectively. Restraint stress induces biphasic dynamic alteration in β-actin, cofilin and MAPK-1 transcription and protein translation selectively in the rat hippocampal region. The impacts caused by stress on these genes and proteins may contribute to variation in cell survival, synaptic plasticity, learning and neurogenesis, as a result of modifications in the cytoskeleton. Acute (3 days) and chronic (21 days) restrained stress become a reason for the fourfold and tenfold increases, respectively, in hippocampal β-actin mRNA expression. [29] CORT level were increased in the stress induced stress rats, which are the pre-treated with the diazepam. Repeated restrained stress was given for 5 days. And the diazepam was not effectively reduce the CORT level for stress induced rats. [30] The prolonged stress results in the elevation of corticotrophin releasing hormone (CRH) synthesis and the down regulation of GRs in brain due to HPA axis repeated activation. [31] For the induction of acute stress, rats were placed in polycarbonate cylinders for 1 hour and 4 hour for long term stress [32].

Acute restraint stress for 1 hour increases the glutamate efflux in the basolateral and central nuclei of the amygdala of the rat brain. In this case, the initial stress-mediated peak in glutamate efflux was followed by a decline in extracellular glutamate levels monitored throughout the later stages of stress session. These distinct outlines in stress-mediated changes in glutamate neurochemistry may have key implications for the ability of stress to generate disparate neuroanatomical and plasticity responses in the amygdala. And the study gave support for that the glutamergic system in the amygdala was a target centre for the stress induced depression. [33] Drop off in the glial cell densities viewed in depressive patients may result in diminished glial glutamate transporter expression, thereby reducing the capacity to regulate synaptic concentrations of glutamate. [34] Acute restraint stress for 30 min reduces the GABAergic inhibitory transmission in rats and it elevates increase in circulating CORT. The neural pathways activated during stress target KCC2 (transmembrane anion transporter) in neuroendocrine command cells in the PVN that control the output of the HPA axis. By compromising KCC2 activity, stress boosts intracellular Cl⁻, which is be a sign of depolarizing shift in the reversal potential for GABA mediated synaptic events, and profoundly weakens synaptic inhibition. Drop off KCC2 activity allows for the buildup of intracellular Cl⁻ during repetitive synaptic activation, which reverses the ionic flux through the receptor and supports the depolarization and results in the excitation of neuroendocrine cells. [35] The acute immobilization trim downs the postsynaptic NMDA receptor activity. It is also found that, in response to a stressor, CRH acts as an instructive signal that primes glutamate synapses in the PVN. This priming involves LTD (long-term depression) of NMDAR function that allows for the unmasking of
associative activity-dependent, short-term strengthening of glutamate synapses. [36]

2.4 Chronic mild stress (CMS)
Faramawy et al., study the changes in the glutamate metabolism in CMS rat hippocampus, assessment on old and control rodents, treated with the neuronal nitric-oxide synthase enzyme inhibitor, 7-nitroindazole (20 mg/kg/day i.p.). Hippocampus glutamate levels and GAD actions were resolved and tau protein phosphorylation was evaluated. Age was a major aspect for the variation in glutamate level in young control and old control rodents, separately. Old rodents presented to CMS were risk factor to create anhedonia. There was noteworthy lessening in GAD chemical movement and expanded tau protein hyperphosphorylation in mature rodents exposed to CMS. After the treatment, CMS-induced mature rodents fundamentally boost GAD action, diminished glutamate levels and phosphorylation of tau proteins contrasted with CMS induced rodents. GABA levels didn't show huge changes over the study groups. [37] The impact of CMS for 2 weeks on sucrose Consumption, serum CORT Concentration, and CORT receptor levels in rat hippocampus were estimated that the serum CORT level Concentration, and CORT receptor levels in rat hippocampus were estimated that the serum CORT level

2.5 Social isolation (SI)
Social isolation in animal models induced behaviors relevant to developing stress. The elevated adult neurogenesis in the group animals were decreased when the animals were isolated. The prolonged exercise of the animals results in the hippocampus than in cortex in terms of the alterations in antioxidant enzymes. [41] The raised neuronal excitability results to the decline of GABAergic tone elicited by SI. The 5-HT3 receptor is a ligand-gated ion channels that is permeable to Na+, K+, and Ca2+ ions, expressed on GABAergic neurons in the hypothalamic region, the release of GABA is elevated when the 5-HT3 receptor expressed on GABAergic neurons to repress neuronal excitation caused reduced extent of SI by GABA antagonists. [42] SI employs as a depression model can reduce the function of the serotonergic system. Stress induced by SI inhibits the serotonin discharge with the help of chronic selective serotonin reuptake inhibitors (SSRIs) treatment. [43] It has been reported that the effect of chronic SI for 90 days on anxiety related behaviors. The end results of long-term social deprivation surprisingly diminish anxiety related behaviors and reduced level of serotonin but levels of dopamine and metabolites of these neurotransmitters 5HIAA and DOPAC, respectively, remained unaffected. [44].

2.6 Olfactory bulbectomy model (OBX)
Bilateral OBX has been used as an animal model for major depression that results in behavioral, neurochemical, and neuroendocrinological changes were reversed by chronic treatment with antidepressants, including fluoxetine. The study results revealed that OBX caused a reduction in the volumes of the CA1/2, CA3, and dentate gyrus regions after 4 weeks OBX without fluoxetine treatment. The treatment did not reverse neuron loss in whole hippocampal regions 12 weeks after OBX. Therefore, they suggest that the OBX rat model should not be used to detect the antidepressant activity of various pharmacological agents such as fluoxetine. [45] However, OBX induced rodents shows some changes in practices like, increment immobility time, ambulatory and rearing behaviors significantly, decline BDNF level, 5-HT, DA,NE and antioxidant parameters alongside raised serum CORT, IL-6, and TNF-α in hippocampus and cerebral cortex. OBX exploited rodents demonstrated critical decrement in both catalase (CAT) activity and glutathione (GSH ) substance in hippocampus. There was an increase GR and BDNF expression in the hippocampus subsequent to the treatment and could also satisfies CRH expression in hypothalamus, as well as reducing significantly the levels of serum CORT. [46]

2.7 Learned helplessness model
Rats that developed learned Helplessness had increased GABA A receptor density in septum over controls but not match up to other rats that had been stressed. There was no changes in receptor density were found in any other brain regions studies. But GABA B receptor significantly lower in septum of rats that received inescapable stress, but did not react by becoming helpless. [47] Animals with learned helplessness shows many Neurovegetative changes that are reminiscent of depression, elevated levels of Corticotrophin-releasing factor (CRF) and CORT. [48]
Animals were not able to get away from the inescapable shock, but the 5-HT in the brain section such as amygdala not remains regular during this time. 5-HT neuronal activity were inhibited by the 5-HT binding to these receptors in dorsal raphe nucleus, 5-HT releases from the axon collaterals from nearby 5-HT cells. Thus, the activation of a dorsal raphe nucleus 5-HT neuron to the inhibition of its neighbors, and so dorsal raphe nucleus 5-HT activity is under self- leads restraint. High levels of 5 HT desensitized or down regulated by these receptors. Thus, 5-HT discharged within the dorsal raphe nucleus during the strong 5-HT activation bring on by inescapable shock desensitize these receptors. This leading to a loss of the normal inhibitory restraint on these cells, there by sensitizing them. [49] The expression of BDNF in the hippocampus was elevated by the treatment , thus accelerating fear memory extinction and progressing depression like behavior induced by learned helplessness [inescapable stress]. And this mechanism was mediated by stimulating the Akt-mTOR signaling pathway. [50]

2.8 Electric shock induced stress
There are many benefits for electric shock induced models, one is the animals generally do not habituate to electric foot shocks, when judge against to other stressors routines.[51] The relationship between the strength of electric shock stimulus and the mice response were reported by Yerkes and Dodson.[52] And the other advantage is to manage the intensity and duration of parameters, therefore by changing those parameters it is possible to create different models. Inescapable shock produce a state of ‘animal hypnosis’, which in turn studied as a model of human catalepsy, suggesting the non specificity of the model.[53] Different studies in electric foot shock shows that the low intensity;0.3 mA was enough to induce the involuntary behaviors in animals, take account of the tail flinch response, body movements etc.[54]. When the animals undergo the inescapable foot shock, it will cause the learned helplessness. It was comparable to the depressive behavior in humans.[55] It has good predictive validity as sub-chronic treatment with a variety of clinically employed antidepressants, to effectively repeal the learned helplessness behavior. [56] Electric foot shock stress produces the neuroendocrinological changes by the activation of the HPA axis. These changes including the raise in plasma corticosterone and ACTH levels. This experiment shows a unilateral stimulation of the amygdaloid complex in unanesthetized monkeys is associated with marked rise in pituitary-adrenal cortical activity by plasma I7-hydroxycorticosterone levels.[57] Furthermore, stress leads to the activation of amygdala activates the adrenocortical cells, suggesting the direct involvement of amygdala in HPA axis activation. [58] Electric shock induced learned helplessness is responsible of the activation of central dopaminergic system. [59] Many evidences shown that the female rats is not responsive similar to the male rats. This is a most important problem for the validity of foot shock-induced learned helplessness model of depression in females.[60] In this model, the glutamate intensity of the stress induced group is raised in hippocampus while compare with the PFC. And the GABA concentration in hippocampus is enhanced in stress induced animals. [61]

2.9 Witness social defeat
Only a few studies reported that social defeat witness stress model, yet it has been shown that witness stress results in the emergence of robust anxiety-and depressive-like behaviors . This model as follows, i.e. 2 rats are kept together inside a cage. One in the Sprague –Dawley rat is consider as the intruder and kept the rat in the resident rat’s cage during acclimatization period. After this a partition using a perforated plexiglass was kept between them to avoid the defeats, but this allows for the sensory interactions. The other rat is consider as trauma witnessing rat, set aside as it witnessed social defeat of the cage mate for 5 min. This will generate a visual stress in trauma witnessed rat. The plasma corticosterone level is enhanced in both Rats intruder and trauma witnessed rats. In case of the animals housed individually, plasma corticosterone level was increased contrast to the animals housed grouped. [62] The witnessing of social defeat fills in as an intense stressor in grown-up male mice equipped for actuating durable dysregulation in a few functional yields. Exposure to stress changes in weight gain, serum CORT levels, anxiety-like behavior, and social interaction. Therefore suggestive enduring dysregulation of the HPA axis was shown after exposure to emotional stress. [63]

CONCLUSION
Many behavioral models reproduce the pathophysiological conditions found in the humans. Most of the physiological conditions in humans can be related to the experimental studies conducted in animals. Here we can found stress induced animal models in relation with the pathophysiology of the depressive behavior. Presently animal models have many drawbacks, majority of the current behavioral models could not replicate the clinical conditions as in human, and there was not much attempts to create the models of female animals or to develop drug treatments that are related to gender. Moreover a different animal model shows diverse mechanism where the targets of the mood disorders are entirely changed. These results can be used as a guide to develop an accurate and precise animal model before start of any research work in which resembles the human disease conditions. Thus we can create a more accurate, effective and safe decision in relating animal studies with clinical information.

Conflict of Interest
Authors declare no conflict of research interests.

Acknowledgement
No funding support for this study. Thanks for the KMCH college of Pharmacy and Management for the free journal access facilities.
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