Anitta Augustine et al /J. Pharm. Sci. & Res. Vol. 12(6), 2020, 757-762

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

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

Anitta Augustine, Jinu Avarachan ,Pallavi Mahadev Shinde, Venkatesh Gunasekaran*

Department of Pharmacology, KMCH College of Pharmacy,
Tamil Nadu Dr MGR Medical University, Tamil Nadu, Coimbatore, India.

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 neuroplasticity 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 antianxiety 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 GABA ergic – glutamanergic 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 bluster 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 restraint stress induced 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 was lessen in CMS induced group and after two week CORT is elevated in resilient rats. The hippocampal serotonin level has no remarkable change. But the intraneuronal serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) has a significantly drop off among the stressed group and non stressed groups. [38] In 2019, the impact of prolactin receptor (PRLR) on CMS- induced depression was studied on the impact of PRLR gene on BDNF expression and hippocampal neuron cell death, these points giving another and viable restorative alternative for depression. PRLR gene was accepted to take part in growth of depression by directing the JAK - STAT pathway. Alongside increased expression of BDNF and Bcl-2, PRLR gene silencing brings about the inhibition of hippocampus neuron apoptosis and lightening of CMS-induced depression by inactivating the JAK2-STAT5 signaling pathway [39]

2.5 Social isolation (SI)

Social isolation in animal models induced behaviors relevant to depression and anxiety. SI boosts the risk of developing stress .The elevated adult neurogenesis in the grouped animals were decreased when the animals were isolated. The prolonged exercise of the animals results in the enhanced neurogenesis and the significant increase in the volume of brain region (hippocampus)The SI can also affect the stress hormones like GC was increased in individually isolated animals, this have a negative influence on the neurogenesis in hippocampus. [40] Results of a chronic SI study shows the declined glutamate and glutamine may put forward the neuron glial integrity was implicated by stress caused chronic SI. It leads to the neurochemical and biochemical changes which results in behavioral abnormalities. The range of glutamate and glutamine in the dorsal hippocampus was significantly reduced. But they maintained stable in the cerebral cortex because oxidative stress has high impact 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 Sprauge –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 cortiocsterone 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.

REFERENCES

1. Angst F, Stassen HH, Clayton PJ, Angst J. Mortality of patients with mood disorders: follow-up over 34-38 years. J Affect Disord. 2002 Apr;68(2-3):167-81.
2. Kendler KS, Kuhn J, Prescott CA. The interrelationship of neuroticism, sex, and stressful life events in the prediction of episodes of major depression. Am J Psychiatry. 2004 Apr;161(4):631-6.
3. Krishnan V, Nestler EJ. The molecular neurobiology of depression. Nature. 2008 Oct 16;455(7215):894-902.
4. Uchida S, Hara K, Kobayashi A, Otsuki K, Yamagata H, Hobara T, Suzuki T,Miyata N, Watanabe Y. Epigenetic status of Gdnf in the ventral striatum determines susceptibility and adaptation to daily stressful events. Neuron. 2011 Jan 27;69(2):359-72.
5. Hettema JM, An SS, Neale MC, Bukszar J, van den Oord EJ, Kendler KS, Chen X.Association between glutamic acid decarboxylase genes and anxiety disorders, major depression, and neuroticism. Mol Psychiatry. 2006 Aug;11(8):752-62.
6. Fendrich M, Warner V, Weissman MM. Family risk factors, parental depression, and psychopathology in offspring. Developmental Psychology. 1990 Jan;26(1):40.
7. Gold PW. The organization of the stress system and its dysregulation in depressive illness. Mol Psychiatry. 2015 Feb;20(1):32-47.
8. Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of depression. Neuron. 2002 Mar 28;34(1):13-25.
9. Leuchter AF, Cook IA, Hunter AM, Cai C, Horvath S. Resting-state quantitative electroencephalography reveals increased neurophysiologic connectivity in depression. PLoS One. 2012 Feb 24.
10. Stahl SM. Placebo-controlled comparison of the selective serotonin reuptake inhibitors citalopram and sertraline. Biol Psychiatry. 2000 Nov 1;48(9):894-901.
11. Anacker C, Zunszain PA, Carvalho LA, Pariante CM. The glucocorticoid receptor: pivot of depression and of antidepressant treatment? Psychoneuroendocrinology. 2011 Apr;36(3):415-25.
12. Stepanichev M, Dygalo NN, Grigoryan G, Shishkina GT, Gulyaeva N. Rodent models of depression: neurotrophic and neuroinflammatory biomarkers. BioMed research international. 2014;2014.
13. Bian Y, Yang L, Wang Z, Wang Q, Zeng L, Xu G. Repeated three-hour maternal separation induces depression-like behavior and affects the expression of hippocampal plasticity-related proteins in C57BL/6N mice. Neural plasticity. 2015;2015.
14. Bonhoeffer T. Neurotrophins and activity-dependent development of the neocortex. Curr Opin Neurobiol. 1996 Feb;6(1):119-26.
15. Cellot G, Cherubini E. Functional role of ambient GABA in refining neuronal circuits early in postnatal development. Front Neural Circuits. 2013 Aug 13;7:136.
16. Katahira T, Miyazaki N, Motoyama J. Immediate effects of maternal separation on the development of interneurons derived from medial ganglionic eminence in the neonatal mouse hippocampus. Development, growth & differentiation. 2018 Jun;60(5):278-90.
17. Martisova E, Solas M, Horrillo I, Ortega JE, Meana JJ, Tordera RM, Ramírez MJ. Long lasting effects of early-life stress on glutamatergic/GABAergic circuitry in the rat hippocampus. Neuropharmacology. 2012 Apr;62(5-6):1944-53.
18. Stamatakis A, Kalpachidou T, Raftogianni A, Zografou E, Tzanou A, Pondiki S, Stylianopoulou F. Rat dams exposed repeatedly to a daily brief separation from the pups exhibit increased maternal behavior, decreased anxiety and altered levels of receptors for estrogens (ERα, ERβ), oxytocin and serotonin (5-HT1A) in their brain. Psychoneuroendocrinology. 2015 Feb 1;52:212-28.
19. Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. Biol Psychiatry. 2006 Jun 15;59(12):1116-27.
20. Dubey VK, Ansari F, Vohora D, Khanam R. Possible involvement of corticosterone and serotonin in antidepressant and antianxiety effects of chromium picolinate in chronic unpredictable mild stress induced depression and anxiety in rats. J Trace Elem Med Biol. 2015 Jan;29:222-6.
21. Ma K, Xu A, Cui S, Sun MR, Xue YC, Wang JH. Impaired GABA synthesis, uptake and release are associated with depression-like behaviors induced by chronic mild stress. Transl Psychiatry. 2016 Oct 4;6(10):e910.
22. Huang TL, Lee CT, Liu YL. Serum brain-derived neurotrophic factor levels in patients with major depression: effects of antidepressants. Journal of psychiatric research. 2008 Jun 1;42(7):521-5.
23. Zunszain PA, Hepgul N, Pariante CM. Inflammation and depression. Curr Top Behav Neurosci. 2013;14:135-51.
24. Li K, Yan L, Zhang Y, Yang Z, Zhang C, Li Y, Kalueff AV, Li W, Song C. Seahorse treatment improves depression-like behavior in mice exposed to CUMS through reducing inflammation/oxidants and restoring neurotransmitter and neurotrophin function. Journal of Ethnopharmacology. 2020 Mar 25;250:112487.
25. Popp J, Wolfsgruber S, Heuser I, Peters O, Hüll M, Schröder J, Möller HJ, Lewczuk P, Schneider A, Jahn H, Luckhaus C, Perneczky R, Frölich L, Wagner M, Maier W, Wiltfang J, Kornhuber J, Jessen F. Cerebrospinal fluid cortisol and clinical disease progression in MCI and dementia of Alzheimer's type. Neurobiol Aging. 2015 Feb;36(2):601-7.
26. Aleisa AM, Alzoubi KH, Gerges NZ, Alkadhi KA. Chronic psychosocial stress induced impairment of hippocampal LTP: possible role of BDNF. Neurobiol Dis 2006 Jun;22(3):453-62.
27. Catania C, Sotiropoulos I, Silva R, Onofri C, Breen KC, Sousa N, Almeida OF. The amyloidogenic potential and behavioral correlates of stress. Mol Psychiatry. 2009 Jan;14(1):95-105.
28. Ye M, Jang D, Kim JS, Kim K, Shim I. Effects of Camellia Sinensis Extract on Repeated Restraint Stress-Induced Ovariectomized Female Rats. BioMed research international. 2019;2019.
29. Sántha P, Pákáski M, Fazekas OC, Fodor EK, Kálmán S, Kálmán J Jr, Janka Z, Szabó G, Kálmán J. Restraint stress in rats alters gene transcription and protein translation in the hippocampus. Neurochem Res. 2012 May;37(5):958-64.
30. Kalman BA, Kim PJ, Cole MA, Chi MS, Spencer RL. Diazepam attenuation of restraint stress-induced corticosterone levels is enhanced by prior exposure to repeated restraint. Psychoneuroendocrinology. 1997 Jul;22(5):349-60.
31. Jankord R, Herman JP. Limbic regulation of hypothalamo-pituitary-adrenocortical function during acute and chronic stress. Ann N Y Acad Sci. 2008 Dec;1148:64-73.
32. Viviana Vargas-López a,c Q , Angélica Torres-Berrioa,b, Lina González-Martínez a,b, Alejandro Múneraa,c, Marisol R. Lampreaa, Restraint Stress-Induced Changes in Saccharin Preference: The Effect of Antidepressive Treatment and Diazepam .Behavioural brain research,2015,.
33. Reznikov LR, Grillo CA, Piroli GG, Pasumarthi RK, Reagan LP, Fadel J. Acute stress-mediated increases in extracellular glutamate levels in the rat amygdala: differential effects of antidepressant treatment. European Journal of Neuroscience. 2007 May;25(10):3109-14.
34. Hamidi M, Drevets WC, Price JL. Glial reduction in amygdala in major depressive disorder is due to oligodendrocytes. Biol Psychiatry. 2004 Mar 15;55(6):563-9.
35. Hewitt SA, Wamsteeker JI, Kurz EU, Bains JS. Altered chloride homeostasis removes synaptic inhibitory constraint of the stress axis. Nat Neurosci. 2009 Apr;12(4):438-43.
36. Kuzmiski JB, Marty V, Baimoukhametova DV, Bains JS. Stress-induced priming of glutamate synapses unmasks associative short-term plasticity. Nat Neurosci 2010; 13: 1257-1264.
37. El-faramawy YA, El-Banouby MH, Sergeev P, Mortagy AK, Amer MS, Abdel-tawab AM. Changes in glutamate decarboxylase enzyme activity and tau-protein phosphorylation in the hippocampus of old rats exposed to chronic mild stress: reversal with the neuronal nitric oxide synthase inhibitor 7-nitroindazole. Pharmacology Biochemistry and Behavior. 2009 Jan 1;91(3):339-44.
38. Zurawek D, Gruca P, Antkiewicz-Michaluk L, Dziedzicka-Wasylewska M. Resilient Phenotype in Chronic Mild Stress Paradigm Is Associated with Altered Expression Levels of miR-18a-5p and Serotonin 5-HT_{1a} Receptor in Dorsal Part of the Hippocampus. Mol Neurobiol. 2019 Nov;56(11):7680-7693.
39. Tian RH, Bai Y, Li JY, Guo KM. Reducing PRLR expression and JAK2 activity results in an increase in BDNF expression and inhibits the apoptosis of CA3 hippocampal neurons in a chronic

mild stress model of depression. Brain Res.2019 Dec 15;1725:146472.
40. Stranahan AM, Khalil D, Gould E. Social isolation delays the positive effects of running on adult neurogenesis. Nat Neurosci. 2006 Apr;9(4):526-33.
41. Shao Y, Yan G, Xuan Y, Peng H, Huang QJ, Wu R, Xu H. Chronic social isolation decreases glutamate and glutamine levels and induces oxidative stress in the rat hippocampus. Behav Brain Res. 2015 Apr 1;282:201-8.
42. Shekhar A, Katner JS. Dorsomedial hypothalamic GABA regulates anxiety in the social interaction test. Pharmacol Biochem Behav. 1995 Feb;50(2):253-8.
43. Dankoski EC, Agster KL, Fox ME, Moy SS, Wightman RM. Facilitation of serotonin signaling by SSRIs is attenuated by social isolation. Neuropsychopharmacology. 2014 Dec;39(13):2928-37.
44. Shams S, Chatterjee D, Gerlai R. Chronic social isolation affects thigmotaxis and whole-brain serotonin levels in adult zebrafish. Behav Brain Res. 2015 Oct 1;292:283-7.
45. Yurttas C, Schmitz C, Turgut M, Strekalova T, Steinbusch HW. The olfactory bulbectomized rat model is not an appropriate model for studying depression based on morphological/stereological studies of the hippocampus. Brain research bulletin. 2017 Sep 1;134:128-35.
46. Yang SJ, Yu HY, Kang DY, Ma ZQ, Qu R, Fu Q, Ma SP. Antidepressant-like effects of salidroside on olfactory bulbectomy-induced pro-inflammatory cytokine production and hyperactivity of HPA axis in rats. Pharmacol Biochem Behav. 2014 Sep;124:451-7.
47. Kram ML, Kramer GL, Steciuk M, Ronan PJ, Petty F. Effects of learned helplessness on brain GABA receptors. Neurosci Res. 2000 Oct;38(2):193-8.
48. Yan HC, Cao X, Das M, Zhu XH, Gao TM. Behavioral animal models of depression. Neuroscience bulletin. 2010 Aug 1;26(4):327-37.
49. Rozeske RR, Evans AK, Frank MG, Watkins LR, Lowry CA, Maier SF. Uncontrollable, but not controllable, stress desensitizes 5-HT1A receptors in the dorsal raphe nucleus. Version 2. J Neurosci. 2011 Oct 5;31(40):14107-15.
50. Yang SJ, Song ZJ, Wang XC, Zhang ZR, Wu SB, Zhu GQ. Curculigoside facilitates fear extinction and prevents depression-like behaviors in a mouse learned helplessness model through increasing hippocampal BDNF. Acta pharmacologica Sinica. 2019 Oct;40(10):1269-78.
51. Glanzman DL, Mackey SL, Hawkins RD, Dyke AM, Lloyd PE, Kandel ER. Depletion of serotonin in the nervous system of Aplysia reduces the behavioral enhancement of gill withdrawal as well as the heterosynaptic facilitation produced by tail shock. J Neurosci. 1989 Dec;9(12):4200-13.
52. Yerkes RM, Dodson JD. The relation of strength of stimulus to rapidity of habit-formation. Journal of comparative neurology and psychology. 1908 Nov;18(5):459-82.
53. Bali A, Jaggi AS. Electric foot shock stress: a useful tool in neuropsychiatric studies. Rev Neurosci. 2015;26(6):655-77.
54. MASTERSON FA, CAMPBELL BA. Techniques of electric shock motivation. InMethods in psychobiology 1972 Jan 1 (pp. 21-58). Academic Press.
55. Overmier JB, Seligman ME. Effects of inescapable shock upon subsequent escape and avoidance responding. J Comp Physiol Psychol. 1967 Feb;63(1):28-33.
56. Willner P. Validation criteria for animal models of human mental disorders: learned helplessness as a paradigm case. Prog Neuropsychopharmacol Biol Psychiatry. 1986;10(6):677-90.
57. Mason JW. Plasma 17-hydroxycorticosteroid levels during electrical stimulation of the amygdaloid complex in conscious monkeys. Am J Physiol. 1959Jan;196(1):44-8.
58. Goldstein LE, Rasmusson AM, Bunney BS, Roth RH. Role of the amygdala in the coordination of behavioral, neuroendocrine, and prefrontal cortical monoamine responses to psychological stress in the rat. J Neurosci. 1996 Aug 1;16(15):4787-98.
59. Chrapusta SJ, Wyatt RJ, Masserano JM. Effects of single and repeated footshock on dopamine release and metabolism in the brains of Fischer rats. J Neurochem. 1997 May;68(5):2024-31.
60. Steenbergen HL, Heinsbroek RP, Van Hest A, Van de Poll NE. Sex-dependent effects of inescapable shock administration on shuttlebox-escape performance and elevated plus-maze behavior. Physiol Behav. 1990 Oct;48(4):571-6.
61. Gao J, Wang H, Liu Y, Li YY, Chen C, Liu LM, Wu YM, Li S, Yang C. Glutamate and GABA imbalance promotes neuronal apoptosis in hippocampus after stress. Med Sci Monit. 2014 Mar 27;20:499-512.
62. Patki G, Solanki N, Salim S. Witnessing traumatic events causes severe behavioral impairments in rats. Int J Neuropsychopharmacol. 2014 Dec;17(12):2017-29.
63. Warren BL, Vialou VF, Iñiguez SD, Alcantara LF, Wright KN, Feng J, Kennedy PJ, Laplant Q, Shen L, Nestler EJ, Bolaños-Guzmán CA. Neurobiological sequelae of witnessing stressful events in adult mice. Biol Psychiatry. 2013 Jan 1;73(1):7-14.