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Review Article

Etiopathogenesis of depression and experimental depression models used in preclinical studies*

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ABSTRACT

Depression is the most frequent psychiatric illness among mood disorders, affecting approximately 10% of adults. Especially recurrent and moderate/severe depression can become a serious public health problem by impairing people's life quality. The monoamine hypothesis is the most widely accepted hypothesis for clarifying the pathophysiology of depression. Depression's pathogenesis and etiology, however, are still poorly understood. Tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin or noradrenaline reuptake inhibitors, different atypical antidepressants, and electroconvulsive therapy are currently available therapies for depression. Although these treatment options are effective, a large number of patients do not respond to treatment or do not attain long-term remission. Furthermore, present antidepressants used in clinics have disadvantages such as delayed onset of effects, side effects, and patient compliance problems. Therefore, the discovery of new antidepressant medications is crucial. Animal models are critical in investigating the etiology of depression and developing novel treatments. Hence, in this review, the main mechanisms involved in the etiopathogenesis of depression and the experimental depression models used in preclinical studies have been demonstrated.

Keywords: Antidepressant, depression, depressive behavior, etiopathogenesis, experimental depression models

1. INTRODUCTION

Depression is a psychiatric disorder that ranks first among neurological and mental disorders [1,2]. Today, this disease, which can disrupt normal functioning in many societies worldwide, causes depressive thoughts, deterioration in cognitive and social functions, severely impair the patient's quality of life, and significantly increases morbidity and mortality [3-5]. Low socio-economic status, being divorced, unemployment, substance and alcohol addiction, anxiety disorders, history of depression, stress factors, childhood traumas, some drugs and diseases are the main risk factors for the development of depression [6,7].

Since depression is a heterogeneous and complicated disorder with multiple etiologies, the mechanisms involved in its pathophysiology are not fully understood [8]. Currently accepted mechanisms aiming to explain the etiopathogenesis of depression include the monoamine hypothesis, dysregulation of the hypothalamic-pituitary-adrenal (HPA) Axis, and involvement of environmental and genetic factors.

Other potential mechanisms involve impaired neurogenesis, enhanced inflammatory cytokine release, second messenger system abnormalities, and increased corticotropin-releasing factor (CRF) levels [8,9].

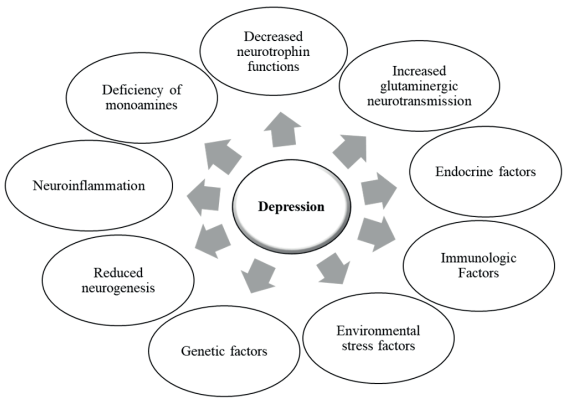

Figure 1. Pathophysiology of depression [8]

Animal models are crucial for understanding the pathogenesis of depression, as with most human diseases, and for developing new agents for its treatment. Although none of the models fully meets the symptoms of depression in human, numerous animal models resemble many of the symptoms observed in individuals with depression, and they are critical for investigating the disease's etiology, pathogenesis and treatment [10].

In this review, the main mechanisms included in the etiopathogenesis of depression and experimental depression models used in preclinical studies have been mentioned.

1.1. Etiopathogenesis of Depression

1.1.1. Biogenic Amines

The monoamine hypothesis is accepted as the most common hypothesis used to clarify the pathophysiology of major depressive disorder (MDD). The amount of monoamines such as noradrenaline, serotonin, and dopamine in the synaptic cleft are to be reduced during a depressive period [11]. Based on the monoaminergic deficiency theory, many antidepressants, such as tricyclic antidepressants, selective serotonin or noradrenaline reuptake inhibitors, and monoamine oxidase inhibitors, have been developed. Nevertheless, the specific mechanism of antidepressant efficacy and the molecular foundation of depression remain still unknown [12].

Serotonin

Serotonin is an essential neurotransmitter that regulates various physiological functions such as pain, sleep, appetite, and mood. Any abnormality in serotonin synthesis, metabolism or reuptake has been reported to be partly responsible for specific symptoms of depression, schizophrenia, learning problems, and compulsive disorders [13,14].

Several investigations have demonstrated that the serotonergic system plays an essential role in the pathophysiology of depression. Scientific research has shown that the function of serotonergic neurons decreases in depression. Postmortem and positron emission tomography imaging studies demonstrate that depressive people who do not use medications have lower presynaptic and postsynaptic serotonin levels and fewer serotonin transporter binding sites in the amygdala and midbrain. Furthermore, low levels of 5-hydroxyindole acetic acid, the major serotonin metabolite, were identified in the cerebrospinal fluid (CSF) of patients with suicidal depression [15]. Various antidepressant medications used in the clinic today are known to target serotonin receptors [14].

Noradrenaline

The noradrenergic system appears to be involved in a wide variety of brain activities, including stress response, arousal, attention, enhancement of memory, immunological response, endocrine functions, sleep/wake cycle, mood, and regulation of pain threshold [16-18].

Noradrenaline's role in depression and stress response is related to the neuroanatomical structure of the central noradrenergic system. Noradrenergic neurons are found in two main areas of the brain. These are the locus coeruleus (the region with the highest concentration of noradrenaline-producing neurons) in the brainstem and the lateral tegmental area. The locus coeruleus sends multiple projections to the brain's fear-related parts, including the

cortex, amygdala, thalamus, hippocampus, and hypothalamus. All of these regions are critical to comprehending the anatomical basis of stress-related disorders and depression [19].

In patients with MDD, a reduction in central noradrenaline level leads to depletion of positive emotional resources such as decreased enjoyment, happiness, alertness, interest, vitality, and loss of trust. Postmortem investigations in depressed patients have reported enhanced conformation of central α_2-adrenergic autoreceptors. It has been additionally found that the mRNA levels of α_2-adrenergic autoreceptors are elevated in the frontal cortices of patients with MDD who committed suicide. These findings have been associated with hypersensitive presynaptic α_2-adrenergic autoreceptors contributing to the decline in the release of noradrenaline and serotonin [20].

Dopamine

Dopamine is an essential neurotransmitter in the central nervous system. The mesolimbic pathway, one of the dopaminergic pathways in the brain, plays a vital role in emotional behavior. Anhedonia and altered reward systems in depressed patients are thought to be primarily caused by the hypoactivity of this dopaminergic pathway [21,22].

Postmortem studies in patients with severe depression have shown decreased levels of dopamine metabolites in both CSF and brain areas that regulate mood and motivation. The effectiveness of drugs that acts directly on dopaminergic neurons or receptors, such as pramipexole (D_2/D_3 receptor agonist) and monoamine oxidase inhibitors, suggests the existence of subtypes of depression caused by dopamine dysfunction [23-21].

The prevalence of depression in schizophrenia and Parkinson's disease, which are diseases caused by central dopaminergic system dysfunction, is another evidence of dopaminergic system alteration seen in depression. In addition, an increase in postsynaptic D_2/D_3 receptor density has been found in depressed patients in neuroimaging and postmortem studies. These data indicate that dopamine neurotransmission is reduced in depressed patients [15,24].

Numerous studies in neuroscience suggest that in addition to monoamines, other neurotransmitter systems involve the neurobiological features of mood disorders. The contribution of amino acid neurotransmitters like gamma-aminobutyric acid (GABA) and glutamate in depression is better-understood by recent preclinical and clinical investigations [25].

1.1.2. GABAergic system

GABA is abundant and widely distributed in the healthy human brain. About one-third of all synapses are estimated to be GABAergic. GABA, which is closely related to other neurotransmitter systems in terms of its function, is well known to interact with monoaminergic and cholinergic pathways. GABA modulates several behavioral and physiological mechanisms through its interactions with other neurotransmitter systems and its role as the major inhibitory neurotransmitter in the brain [25,26]. According to the GABAergic deficiency hypothesis of depression, decreased GABA concentration in the brain, dysfunction of GABAergic interneurons, changed expression and function of GABAA receptors, and alters in GABAergic transmission caused by disrupted chloride homeostasis may all contribute to the etiology of depression [25,27-29].

1.1.3. Glutamatergic system

Glutamate, the brain's principal excitatory neurotransmitter, contributes to learning and memory processes, brain development, neuronal life, neuronal differentiation, neuronal migration, and axon formation [30]. Changes in glutamatergic neurotransmission have been proposed to have an essential role in the pathophysiology of depression. Reduction of glutamate release or receptor function is a promising mechanism for developing more effective antidepressant therapies [31,32].

The rapid, potent and safe antidepressant effect of a single intravenous administration of the NMDA receptor antagonist ketamine in patients with treatment-resistant depression has led to the expansion of research into new glutamate-based therapeutic targets [33,34]. Intranasal esketamine spray, in addition to standard antidepressant

therapy, has recently been approved in the USA and Europe for the treatment of antidepressant-resistant depression [35,36].

1.1.4. Neuropeptides

Neuropeptides are short-chain proteins with neuromodulatory and neurohormonal functions as well as local neurotransmitter functions [37]. Neuropeptides have potential clinical importance in treating psychiatric disorders due to their neuromodulatory properties [38].

It has been reported that neuropeptides are changed in some brain regions as well as classical neurotransmitters in depression. In MDD, it has been shown that neuropeptides such as CRH, substance P, and thyrotropin-releasing hormone are hyperactive, while neuropeptides such as galanin and neuropeptide Y are hypoactive [39].

1.1.5. Neurotrophic factors

Neurotrophic factors, which nourish neurons and promote their development, survival, and regeneration [40], are known to act in the pathophysiology and treatment of depression [41,42].

Brain-derived neurotrophic factor (BDNF) levels have been reported to be decline in serum and brain areas such as the amygdala and hippocampus in depressed patients [43,44]. Tyrosine kinase (Trk) B mRNA levels have also been shown to be less in postmortem samples of depressive people, and genetic variations in the TrkB gene NTRK2 have been linked to suicide attempts [44]. Reduced levels of neurotrophic factors seen in depressed people are thought to lead to the atrophy of specific limbic tissues, such as the prefrontal cortex and hippocampus [45]. Other growth factors, including fibroblast growth factor-2, insulin-like growth factor-I, neurotrophin-3, glial cell line-derived neurotrophic factor, and artemin, may also affect neurogenesis, and there is evidence that these growth factors are diminished in depressed people [46,47].

1.1.6. Stress and neuroendocrine regulation

The HPA axis is a complicated system interacting with psychosocial, genetic, and developmental factors. This system assists humans in responding to acute stress and undergoes over time alterations in response to chronic stress exposures. These long-term changes may be significant in the etiology of depression [48].

In vulnerable people, stressful life experiences can trigger depressive episodes, and childhood trauma in the form of neglect or abuse raises the probability of depression later in life. In depressed patients, various abnormalities in the HPA axis related to stress response have been observed. These changes include excessive CRF secretion from the hypothalamic paraventricular nucleus, defective negative feedback mechanism of the HPA axis, hypertrophic adrenal glands and hypercortisolemia [49]. Chronic stress has been demonstrated to degenerate some prefrontal cortical layers, reduce pyramidal neuron dendritic density, and enhance the transcriptional function of GABA interneurons in the medial prefrontal cortex. Additionally, it has been hypothesized that higher cortisol levels disrupt the hippocampus's ability to adjust to a changing environment [49-51].

1.1.7. Inflammation and depression

Systematic reviews and meta-analyses demonstrate that depressed patients have higher concentrations of circulating C-reactive protein and other inflammatory indicators than healthy controls [52]. In major depressed patients, inflammatory markers in the peripheral blood have been indicated to be elevated. Inflammatory cytokines reaching the brain have been shown to interact with almost every pathophysiological event known to be associated with depression, involving neuroendocrine functions, neurotransmitter metabolism, and neural plasticity. Activation of inflammatory pathways in the brain has been shown to cause oxidative stress resulting in excitotoxicity and loss of glial elements, consistent with neuropathological findings in depressive disorders. Inflammation may also result in diminished neurotrophic support and alterations in glutamate release or reuptake [53].

It has been reported that there is positive feedback between inflammation and depression. While psychological stress increases cytokine production, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, and IL-6, and inflammation leads to depression and psychological stress. The

bidirectional association between inflammation and depression parallels the clinical link between inflammatory and depression diseases. Depression rates are higher in individuals suffering from an inflammatory disease. It has also been indicated that anti-inflammatory agents can be successfully used in addition to treatment with antidepressants [49].

1.1.8. Genetic, environmental and psychosocial factors

Family-based research has shown that the contribution of genetic factors to the risk of developing depressive disorders is significant. According to studies, family members of individuals with major depression have a 2-3 fold increased risk of developing depression [54,55]. Environmental factors are frequently stressful events such as bad childhood experiences, child sexual abuse, other lifelong traumas, a lack of social support, marital issues, and divorce [56]. Environmental factors (i.e., trauma, stressful life experience) raise the risk of depression by changing the brain's structure, chemistry and function [28].

Various genes and genetic polymorphisms have been linked to the development of MDD. Some of these genes are tryptophan hydroxylase 1 gene (TPH1), noradrenaline transporter gene (SLC6A2), dopamine transporter gene (SLC6A3), serotonin transporter gene (SLC6A4), serotonin receptor gene (HTR1A, HTR2A, HTR1B, HTR2C), dopamine receptor gene (DRD4) catechol-o-methyltransferase (KOMT), MAO-A and tyrosine hydroxylase (TH) gene. Apolipoprotein E (APOE ε2 and APOE ε4), guanine nucleotide binding protein (GND3), and the methylenetetrahydrofolate reductase gene (MTHFR 677T) are some of the other genes that have been investigated. Polymorphic variations related to point mutations or tandem repeat polymorphisms have been reported in depressed patients for each of these genes [8,54].

1.2. Experimental Models of Depression

Depression symptoms such as depressed mood, anhedonia, somnipathy, appetite/weight alterations, and psychomotor changes can be easily evaluated in animals [57].

Current depression models are based on manipulating the environment or biological functions of rodents [57]. Regardless of the used method, it has been suggested that a valid animal model must meet at least three essential criteria; appearance, structural and predictive validity. Etiological validity has been added to these criteria later [58-61].

Many experimental depression models are based on the implementation of various stressors. Some models also target other potential etiologies of depression (they directly target biological substrates that cause changes in various pathways, stress axis and immune system in the brain) [57]. Some of the experimental depression models are displayed in Table 1.

In this section, some of the most widely used experimental depression models are discussed.

Table 1. Experimental models of depression [10,57,62]

1. Adulthood stress models
• Learned helplessness
• Social isolation
• Chronic mild stress/Chronic unpredictable mild stress
• Repeated restraint stress
• Chronic social defeat stress
• Social instability stress
2. Early-life stress models
• Prenatal stress
• Maternal separation
• Post-weaning social isolation stress
3. Lesion-induced depression model
• Olfactory bulbectomy
4. Pharmacological models
• Reserpine-induced depression model
• Corticosterone-induced depression model
• Lipopolysaccharide-induced depression model
5. Genetic models
• Wistar Kyoto (WKY) model
• Genetically-selected Flinders Sensitive Line (FSL) rat model
• The Fawn-Hooded (FH/Wjd) rat
• Holtzman Albino rat model
• Transgenic model

1.2.1. Learned helplessness model

The "learned helplessness" model is one of the oldest models used to explore the consequences of uncontrollable stress in animals [63-65]. In the learned helplessness model, one of the well-validated animal models, uncontrollable and unexpected electrical foot shock stress leads to a depression-like condition in the experimental animal. Experimental animals exposed to unavoidable electric shocks develop "helplessness" behavior when exposed to the same shocks again. When animals are exposed to the same electric shock again in an environment where they can easily escape, it is observed that the animals delay their escape behavior or stop escaping completely this time [66]. The feeling of helplessness is among the main symptoms of MDD and is among the subject extensively researched in preclinical and clinical studies on depression [67].

With the learned helplessness model, in which animals are exposed to highly stressful and uncontrollable events, an animal model similar to human depression is obtained. Decreased body weight, appetite, locomotor activity, libido and grooming, as well as cognitive impairments and abnormalities, have been exhibited by helpless animals in this model [62,66,68]. The learned helplessness model has the advantages such as replicating the symptoms seen in severe depression patients, and most symptoms ameliorate with antidepressant medication. The learned helplessness model has high face validity and predictive validity, making it a reliable model for investigating the etiopathogenesis of depression. The model's major disadvantage is that most of the depression-like symptoms do not remain long enough after the shock stimulus is discontinued [66,69].

1.2.2. Early life stress models

Early life and adolescence are considered sensitive periods for depression and affective behaviors [70]. Difficult early life experiences are the main risk factors for developing psychiatric disorders like major depression. The early postnatal period is critical in the formation and plasticity of the nervous system. Therefore, the early postnatal environment is of great importance in terms of affecting adult behavior. Preclinical studies have shown that early life stress increases susceptibility to stress and causes permanent changes in the HPA axis [66].

As a type of neonatal stress, the separation stress model from the mother is frequently used in behavioral research to explore the impacts of early life stress and to model the pathology of some psychiatric disorders [71]. Rodents are highly dependent on maternal care after birth. The most common maternal separation protocol consists of a 3-hour separation per day from the second postnatal day to the 12th day. Biological and behavioral outcomes in animals are then evaluated in adulthood. This experimental manipulation leads to depression-like and anxiety-like behaviors and impaired memory and learning. Maternal separation is a traumatic occurrence that simulates early life neglect/parent loss in humans and can influence offspring's behavioral and biological phenotypes in adulthood. This model has been defined as a sensitive model for drug addiction, depression, anxiety, and stress-related illness [66]. Although maternal separation is a popular depression model used in the deterioration of the mother-offspring relationship, it has disadvantages, such as obtaining inconsistent findings about the investigated parameters and the different times of separation of the offspring from the mother in studies [67].

1.2.3. Social defeat stress model

Social defeat stress is a prolonged and recurrent arousal. In real-living conditions, most cases of depression are induced by high social pressure rather than direct neural circuit damage [72]. The social defeat model causes emotional and psychological stress by utilizing social disagreement as a source of stress. In this paradigm, another male rodent (test animal) is placed in the cage of an older, aggressive and dominating male rodent for 10 minutes per day. The test animal attacked and sometimes injured by the resident animal in the cage is defeated. This process is repeated every day for ten days with a new competitor. Then the animal is tested for different behavioral experiments. After ten days, these animals usually exhibit social withdrawal and anhedonia behavior. In addition, several physiological changes have been observed in animals, including decreased sexual behavior, increased defensive behavior and

anxiety, reduced locomotor or exploratory activity, changes in circadian rhythm, nutrition and body weight, sleep disturbances, and impaired immune functions. Similar to other depression models, the HPA axis has been demonstrated to be activated in defeated rodents. The social defeat also causes some neurobiological changes related to MDD, such as the release of proinflammatory cytokines, hypercortisolemia, and neurotrophin changes [57,62].

The advantage of the model is that it can be created in an average of 20 days with a simple method. It is accepted that female mice and rats have low aggression, and male-to-female attack is uncommon in both species. Therefore, the main disadvantages of this model based on regional aggression between males are that it cannot be studied in female subjects, and the subjects are limited to adult animals [62,72,73].

1.2.4. Chronic unpredictable mild stress model

The Chronic Unpredictable Mild Stress (CUMS) model is a widely used, well-validated, and realistic depression model [67,74,75].

The first chronic stress model based on the development of anhedonia has been created by Katz and Hersh (1981). The initial protocol, which has lasted for three weeks, used more severe stressors such as intense electric shock and prolonged food and water deprivation. In animals exposed to stress were reported to display increase in plasma corticosteroid levels, decrease in reward sensitivity, and decrease in sucrose preference which is indicative of the development of anhedonia [76,77]. Later, Willner updated this model by utilizing mild stressors that lasted longer and were more realistic, and the model was named CUMS [67,78].

The model is based on the unpredictable exposure of experimental animals to a range of mild stressors over several weeks or even months. Various stressors such as social isolation or crowded housing, water or food deprivation, changing the light/dark cycle, cage tilting, and wet bedding are chronically applied to experimental animals throughout the CUMS protocol [67]. Since repeated exposure to identical stressors may lead to adaptive behavior in animals, stressors are administered to experimental animals in an unpredictable order [66]. Experimental animals constantly exposed to mild stressors develop many behavioral changes, and "anhedonia" occurs, one of the main clinical symptoms of depression. Periodic tests based on the choice between a sweet solution and tap water are used in the model to assess reward sensitivity. Consumption or preference for the sweet reward has been reduced following weeks of stress exposure but can be restored to normal levels with chronic treatment with antidepressant medication [67,78].

In experimental animals for which a CUMS model has been created have been observed changes in various molecular parameters that are important in the neurobiology of depression. Some of these changes include an increase in HPA axis activity, a decrease in hippocampal neurogenesis, an increase in microglial activation, a decrease in serotonin neurotransmission in the forebrain, a decrease in neurotrophin levels, especially BDNF, reduced dendritic branching in the hippocampus and some frontal areas, increase in corticosterone levels and adrenal gland weight, reduction of antioxidant enzymes activity, and increase in proinflammatory cytokines [57,66].

Many alterations seen in animals exposed to stress procedures, confirming face validity and structural validity, are reversible after chronic administration of various clinically effective antidepressant class drugs. Thus it can be declared that this animal model also has predictive validity. The advantage of the model is that it causes long-term changes in behavioral, neuroimmune, neurochemical, and neuroendocrinological parameters similar to the abnormalities seen in depressive cases. However, the CUMS model has two essential disadvantages. Firstly, it is a labor-intensive procedure that requires a large experimental space in the laboratory, and it is physically and practically difficult to perform long-term CUMS experiments. Another problem is that it can be difficult to create the model in a new laboratory environment, and it can be challenging to maintain a consistent standard among laboratories [66,67,72].

1.2.5. Reserpine-induced depression model

According to the monoamine hypothesis, depression is induced by a decrease in the levels of noradrenaline, serotonin, and dopamine neurotransmitters. VMAT2 (vesicular monoamine transporter 2) is known to cause cytosolic monoamine accumulation in presynaptic vesicles. It has been proven that disruption of VMAT2 expression has been shown to limit active reuptake and storage of monoamines. Reserpine is an alkaloid that prevents serotonin and catecholamines from being stored in vesicles at the presynaptic terminal, resulting in monoamine depletion and depression-like symptoms in animals [79,80]. Pretreatment with antidepressants can reverse the depression caused by this model. This finding suggests that the reserpine-induced depression model can be used to assess the effectiveness of antidepressants. Despite being quickly developed, the model has disadvantages such as significant animal loss and an inability to fully explain depression pathophysiology [10,72].

1.2.6. Glucocorticoid/corticosterone-induced depression model

High levels of glucocorticoid administration produce effects similar to chronic stress in animals. Corticosterone can be administered to animals for weeks to months via subcutaneous injection, osmotic pump implantation, drinking water, or feeding [10]. Chronic corticosterone administration results in many behavioral abnormalities in rodents, including anhedonia, reduced grooming, increased immobility time in the forced swimming test, memory impairment in the Morris Water Maze and T maze tests, and anxiety-like behaviors in the open field test. Furthermore, long-term corticosteroid administration causes structural alterations in rodent brains, including a reduction in hippocampus volume [10,62]. On the other hand, chronic corticosterone administration has been demonstrated to generate several biochemical and metabolic abnormalities outside the brain, impacting animal behavior differently than human depression [10].

1.2.7. LPS-induced depression model

A single injection of the bacterial endotoxin lipopolysaccharide (LPS) at a dose of 0.5 to 0.83 mg/kg has created a model of inflammation-related depression [57]. LPS is a lipophilic compound that can pass to the brain via the blood-brain barrier (BBB) or circumventricular organs [81]. The secretion of proinflammatory cytokines in the blood reaches its peak about 2 hours after systemic LPS treatment, and illness behavior is noticed after 6 hours, followed by depression-like behavior (such as a decrease in sucrose preference and an increase in helplessness behavior) 24 hours later. LPS stimulates the immune system, leading to microglial activation and increased expression of proinflammatory cytokines such as IL-1 and TNF-α in the brain [57,82].

The LPS model has some limitations over the traditional animal model of depression in that it cannot more accurately mimic the depression phenotype [83]

1.2.8. Lesion-induced depression model- olfactory bulbectomy model

The olfactory bulbectomy model is a depression model that was developed surgically first by Leonard in 1984 by removing the bilateral olfactory bulb [84]. Removing the olfactory bulb in rats causes loss of smell (anosmia) and inhibits the perception of pheromones. Pheromones are chemical signals that carry information about an animal's behavioral and physiological state. Pheromones are crucial in reproductive behavior, sex recognition, aggressive behavior, male rodent social dominance, and avoidance behavior in rats. However, anosmia generated by bulbectomy is not the only mechanism contributing to behavioral problems [85].

Bilateral olfactory bulbectomy causes abnormalities in behavioral, immune, endocrine, and neurotransmitter systems similar to those in major depressed patients. The rat's olfactory system is part of the limbic area. The major mechanism underlying the behavioral alterations and other symptoms is bulbectomy-induced disruption of the cortical-hippocampal-amygdala circuit. These neuroanatomical areas have been reported to be dysfunctional in depressed persons [85]. Animals demonstrated hyperactivity in the open field test, poorer memory in the Morris Water Maze and 8-arm radial maze tests, higher open-arm entries in the elevated plus maze test, and alterations in food-conditional behavior after bilateral olfactory bulbectomy. Olfactory bulbectomy is also associated

with changes in the serotonergic, noradrenergic, cholinergic, glutamatergic, and GABAergic neurotransmitter systems. Following olfactory bulbectomy, various immunological alterations such as decreased lymphocyte count, increased leukocyte aggregation and neutrophil count, and changes in acute phase proteins are observed. Additionally, in bulbectomized rats has been reported an increase in nocturnal corticosterone production [86].

The limitations of this model are its low predictive validity and high morbidity rate [72].

1.2.9. Genetic models

Mutant methods provide a possibility to identify potential risk factors for depression. For instance, α_{2A} adrenergic receptor knock-out mice and mice with high cAMP response element binding protein expression may become more susceptible to developing depressive symptoms when exposed to stress [72]. Flinders Sensitive Line (FSL) rats with high muscarinic receptor densities in the striatum and hippocampus exhibit hypoactivity in the forced swim and open field tests. FSL rats exhibit a more pronounced decline in their sucrose preference when under acute or chronic stress. Holtzman Albino rats are especially preferred in investigations of learned helplessness. Wistar-Kyoto rats are the genetic models used in post-traumatic stress disorder, hyperactivity disorders, and anxiety research, in addition to being a good model of endogenous depression [10,62].

2. CONCLUSION

Depression is one of the primary disorders contributing to the global disease burden [87]. In this study, the general etiopathology of depression, experimental depression models that are widely used in research, and the advantages and disadvantages of these models are mentioned.

For many years researchers have focused on the monoamine hypothesis of depression, and they have conducted many studies to treat symptoms by increasing the concentration of monoamines. However, it is now recognized that depression is a considerably more complicated phenomenon. Inflammation, stress signaling pathways, growth factors, genetic and epigenetic regulation, environment, diet, other existing diseases and comorbidities have all been linked to depression's symptomatology and etiology [62].

Most of the available information on the pathogenesis of mood changes, impaired concentration, and neurovegetative symptoms observed in patients with major depression has been derived from animal models [88]. Animal models are very important because they allow researchers to examine brain circuits, molecular and cellular pathways in a controlled setting. In addition, manipulation and gene editing with pharmacological agents have been accepted methods to study depression in animal models [62].

Depression models can be categorized as genetic models, models caused by acute and chronic stressful situations, models caused by changes in brain neurotransmitters or specific brain injuries, and models induced by pharmacological agents [10]. A valid animal model must meet the face, structural, predictive, and etiological validity criteria [61,89].

The value of experimental animal models in studying the etiology of depression is well known. Once the underlying mechanisms of the depressive disorder are better understood, individualized treatment options can be planned [62].

Ethical approval

Not applicable, because this article does not contain any studies with human or animal subjects.

Author contribution

Concept: ÜK; Design: ÜK; Supervision: ÜK; Materials: ÜK; Data Collection and/or Processing: ÜK; Analysis and/or Interpretation: ÜK; Literature Search: ÜK; Writing: ÜK; Critical Reviews: ÜK.

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