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Review Article

Pathophysiology of depression: inflammation and its relation with oxidative stress and the hypothalamic-pituitary-adrenal axis

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ABSTRACT

Depression is well-known to be a widespread, disabling mental disorder. Despite the many theories that have been put forth to explain the underlying pathophysiology of depression, the exact pathophysiology remains uncertain. In this review, we aim to summarize pathophysiological pathways and experimental animal models for depression, focusing mainly on inflammatory pathways. Stress is a well-known predisposing factor for depression. So, we aim to demonstrate the link between stress and inflammation in depression pathophysiology, highlighting the role of microglia activation, the release of proinflammatory cytokines, and the production of neurotoxic metabolites. We also aim to show the link between inflammation and the disturbance of serotonin, which is also known as 5-hydroxytryptamine (5-HT), and norepinephrine (NE) levels in the brain. Activated microglia produce reactive oxygen species (ROS), which further enhances the inflammatory response. Additionally, we aim to illustrate the hypothalamic-pituitary-adrenal (HPA) axis hyperactivity that occurs as a result of stressful conditions and the consequent resistance of glucocorticoid receptors (GRs), leading to the failure of glucocorticoids to suppress inflammation. We also aim to demonstrate experimental animal models of depression that are based on psychological stress, such as the maternal separation model and the social defeat stress (SDS) model, as well as reviewing the lipopolysaccharide (LPS) inflammation-based model. We also aim to briefly review the widely used chronic unpredictable mild stress (CUMS) model.

Keywords: *Depression; Inflammation; Oxidative stress; Hypothalamic-pituitary-adrenal axis; Maternal separation model; Social defeat stress model; Lipopolysaccharide injection model.*

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1. Introduction

Depression is a highly prevalent mental disorder that can greatly affect the quality of life of patients. It presents with depressed mood, sadness, loss of pleasure in activities once enjoyed, low self-esteem, feeling worthless, excessive guilt, and feeling hopeless about the future. It can also cause difficulty thinking, concentrating, or making decisions. These problems can greatly impair the capability of the patient to carry out his or her daily tasks. Accordingly, depression can cause disruptions in productivity and social interaction. In the worst-case scenario, depression can cause the patient to commit suicide **[1, 2]**. Depression can also increase the burden on society and the health care system **[3, 4]**. Depression is causing an increasing concern for global health, and it is of growing concern in low-income countries in particular.

The World Health Organization predicts that by 2030, depression will account for the majority of disease burden globally **[5, 6]**.

Studies show that the cause of depression may be a complex combination of biological and psychosocial factors **[1, 7]**. Studies of depression pathophysiology are still in progress, and till now, the exact mechanism has not been completely explained owing to the complex nature of the biological processes involved in depression. Therefore, it is difficult to achieve extensive treatment effects **[2, 8]**. The traditional theory explains depression as a decrease in central monoaminergic function **[8, 9]**. The monoamine theory in itself could not provide a complete understanding of the pathophysiology of depression. Currently, the most commonly prescribed classes of antidepressants are those that depend on the monoamine theory in their mechanism of action. However, they have their drawbacks; usually, only 50% of patients achieve significant improvement in symptoms following antidepressant medication therapy **[9, 10]**. Therefore, there is a need to study how to prevent depressive symptoms by focusing on different possible mechanisms beyond the monoamine hypothesis.

There are numerous neuropharmacological theories other than the monoamine hypothesis to help explain the pathophysiology of depression. Some hypotheses emphasized the role of neurogenesis and neurotrophic factors, including the brain-derived neurotrophic factor, in disease pathogenesis. Other theories are also under investigation, some of which will be discussed in this review article. Stress is a well-known predisposing factor leading to depression, and there is a well-known relationship between stress and inflammation. Studies have demonstrated that inflammation is deeply involved in the pathophysiological mechanisms of depression. The production of reactive oxygen species (ROS) and the resulting oxidative stress have also been found to be involved in the pathophysiology of depression. Furthermore, hypothalamic-pituitary-adrenal (HPA) axis hyperactivity with the consequent glucocorticoid receptors (GRs) resistance is also commonly discovered in studies of depression **[9, 11-13]**. The effect of inflammation and inflammatory cytokines on serotonin, which is also known as 5-hydroxytryptamine (5-HT), and norepinephrine (NE), has received much attention. Several studies have demonstrated that proinflammatory cytokines can reduce 5-HT and NE levels, which in turn can contribute to the pathophysiology of depression **[14, 15]**.

Different types of animal models of depression are available for use in laboratory investigations to explore the mechanisms that are involved in depression **[16, 17]**. In laboratories, models of depression that depend on psychological stress to induce depression in animals are probably the most widely used animal models for studying depression. For example, the maternal separation model is the most commonly used animal model that is based on early life stress. On the other hand, the social defeat stress (SDS) model is the most commonly used model based on social stress. Stress is known to have the ability to initiate the pathophysiology of depression. Stress is well-known to be an important predisposing factor leading to depression. Therefore, stress-induced animal models are believed to better demonstrate the neuropathology associated with depression compared to most other animal models **[2, 18]**. These manipulations have the potential to cause certain biological and behavioral outcomes that are linked to a variety of aspects of depression in terms of both symptoms and pathophysiology **[2, 18]**. One of the most widely used animal models for depression is the chronic unpredictable mild stress (CUMS) model. It mimics depression brought on by an inability to cope with stressful

situations in daily life by subjecting the animals to a series of mild, unpredictable stressors **[7, 17-19]**.

On the other hand, one of the most widely used depression models that depend on inflammatory challenges is the systemic administration of lipopolysaccharides (LPS). Systemic exposure to inflammatory challenges, such as LPS, not only causes systemic inflammation but also causes central neuroinflammation accompanied by depressive behavior **[18-20]**.

The purpose of this review article is to provide an overview of the role of inflammation in the pathophysiology of depression as a response to stress, highlighting the role of microglial activation and the production of proinflammatory cytokines, ROS, and neurotoxic compounds in the inflammatory pathway. We also aim to provide an overview of the roles of the HPA axis and oxidative stress in depression pathophysiology and their relation to inflammation. In this review article, we also show the effect of inflammation on 5-HT and NE. We also aim to review animal models that depend on psychological stress for the induction of depression. This stress can either be early life stress, which is used for the induction of depression in the maternal separation model, or adulthood stress, which is used for the induction of depression in the SDS model. One of the most widely used models for depression that depends on applying minor stressors, the CUMS model, is also reviewed here. Also, an LPS-based model is illustrated here to show the role inflammation plays in depressive disorder.

2. Pathophysiology of Depression

2.1. The Role of Inflammation in Depression

Studies have hypothesized that there is a strong link between inflammation and the pathophysiology of depression. Depression can be regarded as an inflammatory disorder caused by stress, characterized by increased proinflammatory cytokines **[1, 21]**. Stress is the most common cause of depression. Nearly all stressors can lead to depression. Both psychological and immune stressors are well known to be strongly associated with inflammation. Consistent with the idea that stress might provide a link between depression and inflammation, growing evidence suggests that psychological and emotional stress can trigger inflammatory reactions with the subsequent increased production of proinflammatory cytokines **[1, 22-24]**. There is an increasing recognition that psychosocial stressors can activate the inflammatory response **[23, 25]**.

Although the exact pathophysiological mechanisms underlying depression's pathogenesis in response to stress remain unclear, inflammation has been demonstrated to play a crucial role in the pathogenesis of depression in response to stress. In humans, stress has been proven to be highly associated with increasing the levels of proinflammatory cytokines **[23]**. Previous research findings have demonstrated that depression patients have elevated levels of proinflammatory cytokines, such as interleukin-1 β (IL-1 β) and tumor necrosis factor-α (TNF-α). In patients with depression, inflammation is found to be accompanied by an elevation in levels of ROS, which causes oxidative stress **[1, 11, 26-29]**.

In laboratory animal studies, it was found that exposure to psychologically stressful conditions caused an elevation in the levels of proinflammatory cytokines **[23, 27]**. These findings suggest that inflammatory pathway activation may play an important role in the pathophysiology of depression **[1, 26]**. Elevation of proinflammatory cytokines such as IL-1β and TNF-α within the central nervous system (CNS) is known to predispose a person to depression.

Accordingly, depression could be based on inflammatory changes **[1, 18, 24, 30]**.

2.1.1. Proinflammatory Cytokines

Neuroinflammatory activation can be triggered by signals originating from both inside and outside the CNS **[24]**. Peripheral exposure to pathogens or injury/stress (sterile inflammation in the absence of infection) stimulates macrophages and monocytes **[24, 31, 32]**. Stress stimulates the macrophages and monocytes to release proinflammatory cytokines such as IL-1β and TNF-α **[24, 33]**. Cytokines are polypeptides of relatively large size, so they aren't able to freely cross the blood-brain barrier. However, limited amounts can enter the brain mainly via active transporters for specific cytokines like IL-1β and TNF-α or via areas lacking a fully functional blood-brain barrier. After crossing the blood-brain barrier, cytokines cause the activation of microglia **[4, 23, 32, 34-36]**. The effect of stress of peripheral origin on the release of inflammatory cytokines from stimulated macrophages, the entry of these cytokines to the brain, and microglial activation is illustrated in **(Fig. 1.)**.

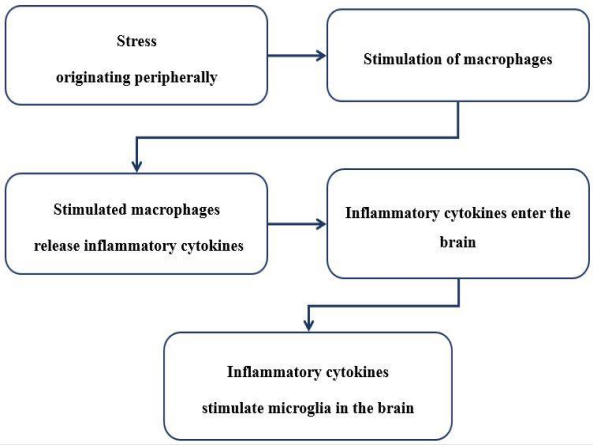

Fig. 1. Effect of stress originating peripherally on macrophages, the release of proinflammatory cytokines, and the subsequent activation of microglia in the brain.

CNS-localized injury also can cause persistent neuroinflammation through the activation of CNS microglia and the production of proinflammatory cytokines **[24, 31]**.

2.1.2. Microglia

Microglia are known to play a critical role in the pathophysiology of depression. Microglia are the macrophages of the CNS. Microglia usually respond to various neuropathological stimuli, including stress. When inflammatory signals from the periphery reach the brain, microglia are the main receivers. In the CNS, activation of microglia is the primary mediator of neuroinflammation **[25, 26, 31, 32]**.

Once activated by proinflammatory cytokines, microglia release proinflammatory cytokines, such as IL-1β and TNF-α. Activated microglia are also responsible for the generation of ROS **[9, 25, 31]**. The activated microglia are also responsible for the generation of neurotoxic compounds such as 3-hydroxykynurenine (3-OHK) and quinolinic acid (QA) **[13, 24, 35, 37, 38]**. It is considered that the released proinflammatory cytokines, ROS, and neurotoxic compounds contribute to cell death, which represents a possible factor associated with depression **[11, 29]**. The different roles of activated microglia are summarized in **(Fig. 2.)**.

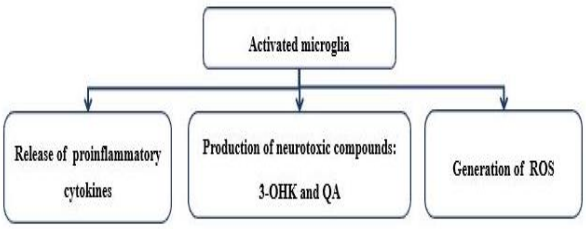

Fig. 2. Roles of activated microglia in depression pathophysiology.

Increased levels of proinflammatory cytokines, microglial activation, and their role in depression pathophysiology in response to stressors are supported by various animal studies using different animal models. Both psychologic and immune stressors can induce the inflammatory pathway **[39, 40]**. Maternal

separation is a depression animal model based on early life stress. This model has aided in the finding of data supporting the theory that inflammation has a major role in depression pathophysiology. The maternal separation model, which is based on psychological stress to induce depression, is evidenced by studies to cause elevations in levels of proinflammatory cytokines, IL-1β and TNF-α, in animals that went through this paradigm. Maternal separation animals exhibited increased microglial activation. These activated microglia caused an elevation of proinflammatory cytokines in the CNS, leading to depression **[39, 41]**. Other animal models based on psychologic stressors, such as the SDS model, also exhibited increased levels of brain proinflammatory cytokines and increased microglial activation in animals that were socially defeated **[18, 32, 42]**.

Studies show that the CUMS model, which relies on applying mild, unpredictable stressors over a relatively long period to induce depression, causes elevations in proinflammatory cytokines, such as TNF-α and IL-1β, in animals that go through this paradigm **[19, 43, 44]**.

On the other hand, systemic exposure to LPS (an immune stressor) also induces neuroinflammation. Researchers observed an increase in proinflammatory cytokine levels such as IL-1β and TNF-α in animals injected with LPS. LPS-injected animals also exhibit a high number of activated microglia in the brain. When proinflammatory cytotoxins are produced in excess by activated microglia, depression-like behavior may progressively develop **[9, 18, 19, 38, 45]**.

2.1.3. Inflammation and ROS

Inflammation and oxidative stress are interdependent and function complementarily in the pathophysiology of depression. Inflammatory responses are known to be accompanied by an elevation of ROS levels. ROS are generated by inflammatory cells **[46, 47]**. Activated microglia are one of the most prominent producers of ROS. Microglial activation by proinflammatory cytokines results in the release of large quantities of ROS by these microglia into the surroundings, so inflammation promotes increased ROS levels.

High levels of ROS promote oxidative stress. It is well known that oxidative stress has an important role in the pathophysiology of depression. Oxidative stress promotes the proinflammatory response in the CNS by enhancing the further production of proinflammatory cytokines **[46, 47]**. These elevated levels of ROS can also cause oxidation and damage to deoxyribonucleic acid (DNA), lipids, and proteins, leading to cellular damage and neuronal death **[22, 46]**.

2.1.4. Kynurenine Pathway

Currently, it is well known that proinflammatory cytokines, IL-1β and TNFα, can induce indoleamine 2,3-dioxygenase (IDO) and tryptophan dioxygenase (TDO) pathways. IDO is broadly distributed in the periphery and the microglial cells. TDO is mostly found in the liver. IDO and TDO enzymes metabolize tryptophan to kynurenine. Kynurenine is further metabolized to 3-OHK and QA, both of which are known to be neurotoxins **[37, 48-50]**.

In the brain, IDO is predominantly found in the microglia. This enzyme is the initial and rate-limiting enzyme of the kynurenine pathway. Proinflammatory cytokines that are elevated in the pathophysiology of depression activate the IDO pathway in the microglia to metabolize tryptophan to kynurenine **[19, 25]**. Microglia that are activated as a consequence of the inflammatory changes further metabolize kynurenine to 3-OHK and QA, which are neurotoxic **[13, 35, 37, 38]**. Both 3-OHK and QA are N-methyl-D-aspartate receptor agonists that

cause elevations in intracellular calcium levels and are therefore likely to induce neuronal apoptosis **[37, 49-52]**. Thus, the IDO pathway amplifies the consequences of inflammatory states **[49, 52]**. Induction of IDO by cytokines and its end products' neurotoxicity has been proposed as a mechanism by which inflammation causes depression **[45, 48]**.

2.1.5. The Effect of Inflammation on 5-HT and NE

It is believed that neurotransmitters are essential to the etiology of depression. The monoamine hypothesis states that depression symptoms are caused by deficient 5-HT and NE, two monoamine neurotransmitters, in the brain **[9, 53]**. Attention has been paid to the impact of inflammation and inflammatory cytokines on 5-HT and NE. Numerous human and laboratory animal investigations have shown that the 5-HT and NE levels are affected by proinflammatory cytokines **[14, 15]**.

Through the IDO pathway's activation, proinflammatory cytokines can influence 5-HT levels. IDO is activated by cytokines such as TNF-α and IL-1β. Relevant to 5-HT metabolism, IDO catabolizes tryptophan, which is the primary amino-acid precursor of 5-HT, into kynurenine. Cytokine-induced activation of IDO can lead to reduced tryptophan, which in turn can contribute to decreased 5-HT availability **[11, 14, 15, 54, 55]**.

Research has also shown that the cytokines TNF-α and IL-1β can raise the expression of the 5-HT and NE reuptake pumps (transporters), increasing the 5-HT and NE reuptake and lowering the availability of these neurotransmitters **[11, 14, 15, 54-56]**.

2.2. The Role of Oxidative Stress in Depression

The high ROS levels and inflammation have been linked to the pathophysiology of depression. Increased amounts of ROS are known to accompany inflammatory reactions. High levels of ROS generation induce oxidative stress, which is a key factor in the pathophysiology of depression. Excessive oxidative stress and a heightened inflammatory response are two key components of depression pathogenesis. Preclinical and clinical studies have shown that increased generation of ROS and exhaustion of antioxidative defenses are responsible for depression **[22, 46, 57]**.

2.2.1. ROS in Physiological Conditions

Under physiological conditions, ROS are counterbalanced by defense pathways. Scavenger antioxidants may remove ROS through scavenging radicals. Scavenger antioxidants include vitamins A, C, and E, as well as reduced glutathione. Reduced glutathione is considered to be the most important nonenzymatic endogenous scavenger antioxidant. Antioxidant enzymes like superoxide dismutase, glutathione peroxidase, and catalase are also responsible for neutralizing ROS such as superoxide anion and hydrogen peroxide **[22, 46]**.

2.2.2. ROS in Pathophysiological Conditions

Oxidative stress occurs when there is an excess of ROS or in situations where defenses are compromised by lowered antioxidant capacity. When oxidative stress occurs, ROS can react with proteins, lipids, and DNA, damaging these substrates **[22, 46]**. Research indicates a correlation between depression and reduced consumption of antioxidants, such as vitamins A, C, and E. An inadequate diet may also lead to glutathione deficiency. Decreased levels of antioxidants lead to decreased protection against ROS; in such cases, ROS are generated without counterbalance and restraint, leading to an elevation in ROS levels and oxidative stress **[16, 46, 58]**.

It is well recognized that the overproduction of ROS and the subsequent oxidative stress are

key components in the pathophysiology of depression. Physical and psychological stress-induced depression animal models have shown that oxidative stress is involved in the pathogenesis. These models show increased inflammation, which is accompanied by the generation of ROS **[22, 57]**. These elevated levels of ROS cause disruption of DNA, lipids, and proteins, leading to cell death **[11, 22, 46]**.

Oxidative stress and inflammation function in a complementary manner in the depression pathophysiology. Activated microglia are the major sources of ROS in the brain. When microglia are activated, they release large quantities of ROS, so inflammation promotes an increase in ROS levels and consequently oxidative stress **[11, 46, 47]**. On the other hand, oxidative stress enhances proinflammatory factor production, promoting neuroinflammation **[46, 47]**. One of the ways through which oxidative stress may contribute to the pathogenesis of depression is the enhancement of the inflammatory pathway, which is accompanied by higher cytokine levels that act as inducers on the IDO pathway, which eventually results in neurotoxic catabolites such as 3-OHK and QA **[22, 47]**. The relation between oxidative stress and inflammation in the pathophysiology of depression is illustrated in **(Fig. 3.)**.

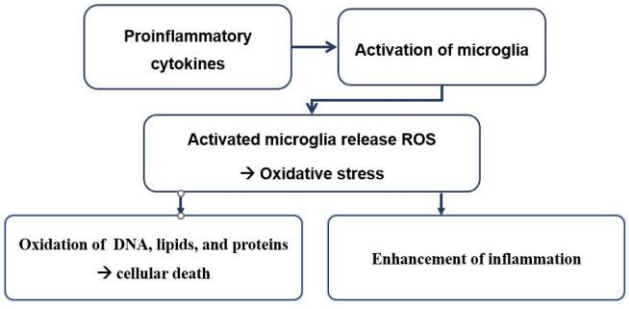

Fig. 3. Relationship between oxidative stress and inflammation in depression pathophysiology.

2.3. The HPA Axis

Virtually all stressors can induce HPA axis and inflammatory changes. Chronic stress and HPA-axis hyperactivity are frequently proposed as primary players in the development of depression **[28, 59]**. Early life stress can cause increased reactivity of the HPA axis, which is related to the development of depression. This is in accordance with findings from the maternal separation model. Patients with depression exhibit reduced HPA negative feedback due to GRs resistance **[17, 18, 39, 44, 60]**.

2.3.1. Physiology of the HPA Axis

The importance of the role that the HPA axis plays in stress response has long been recognized. Stressors of all sorts, physical and psychological, can stimulate the hypothalamus to release corticotropin-releasing hormone (CRH). CRH induces the pituitary gland to release adrenocorticotropic hormone (ACTH). Subsequently, ACTH stimulates the adrenal cortex to release glucocorticoids (cortisol in humans and corticosterone in mice and rats) **[40, 47, 61]**. Glucocorticoids mediate the suppression of the HPA axis by interacting with GRs in the HPA axis. The glucocorticoids function as feedback inhibitors of the production of ACTH by the pituitary gland and the production of CRH by the hypothalamus **[9, 62, 63]**.

2.3.2. Pathological Response of the HPA Axis to Stress

In depression patients, the HPA axis is found to be overactive under stressful conditions. Elevated cortisol production and insufficient inhibition of the HPA axis by GR regulatory feedback are common features of depression **[11, 40]**. Long-term exposure to stress leads to HPA axis hyperactivity and increased levels of cortisol. The persistent hypercortisolism due to stress in depressed patients leads to GRs resistance. This resistance decreases the glucocorticoid-mediated feedback inhibition of HPA, causing persistent HPA axis hyperactivity

in depressed patients **[9, 11, 40, 58, 64]**.

All physical and psychological stressors are accompanied by immune activation and proinflammatory cytokines production. Glucocorticoids are known to be anti-inflammatory hormones. They exhibit their anti-inflammatory effect by suppressing the production of proinflammatory cytokines. It would have been expected that the persistent hypercortisolism associated with stress would result in the suppression of the immune system in patients with depression. However, GRs resistance applies not just to their regulatory role in the HPA axis but also to other GRs functions. In this case, GRs may also lose their ability to perform anti-inflammatory activities, allowing inflammation to occur **[12, 13]**.

In the case of depressed patients, persistent hypercortisolemia with subsequent repeated stimulation of GRs results in resistance of GRs of immune cells, such as macrophages. The GRs resistance leads to a decrease in the inhibitory effect of glucocorticoids on inflammatory responses, causing unrestrained inflammation and increased release of proinflammatory cytokines, adding to the pathophysiology of depression **[12, 13, 24, 58, 62]**. The effect of long-term stress on the HPA axis and its relation to inflammation in the pathophysiology of depression is expressed in **(Fig. 4.)**.

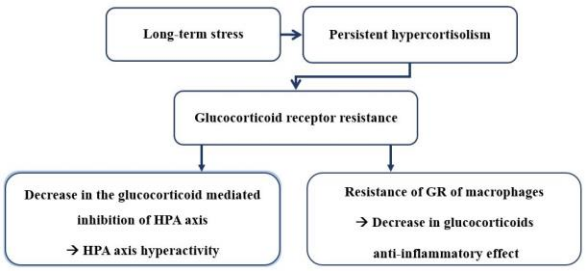

Fig. 4. Effect of long-term stress on the HPA axis and its relation to inflammation in depression pathophysiology.

3. Animal Models of Depression

3.1. Maternal Separation Model

Early-life stress and a history of childhood stress have been identified by clinical studies as two of the most potent risk factors for depression. Depression patients who were exposed to stressful conditions in childhood show clinical features such as early age of onset, severe depressive symptoms, and reduced efficacy of common antidepressants. Children who have endured family violence, parental absence, or parenting characterized by rejection are at an increased risk of developing depression compared to children without those early life stresses **[2, 39, 65]**. It is still unclear exactly how early-life stressful experiences lead to depression in terms of pathophysiology.

3.1.1. Maternal Separation of Laboratory Animals

One of the main risk factors for depression development is early-life adverse experiences **[44, 66]**. Maternal separation, in particular, has been suggested to be a significant animal model for studying the pathophysiology of depression. The maternal separation model is, in fact, the most popular early-life stress model **[44, 66]**.

Maternal care is extremely important for rodents. Therefore, early maternal separation can have a biological and behavioral impact on the offspring. The most widely used procedure for maternal separation consists of a 3-hour daily separation from the second to the 12th day postpartum **[18, 39]**.

3.1.2. Mechanisms Involved in the Maternal Separation Model

In animals exposed to maternal separation, the pathophysiology of depression was found to involve the HPA axis and inflammation modulation. Early psychological stress activates the HPA axis, as demonstrated by the maternal separation model **[39, 65]**. The hyperactive HPA axis leads to increased corticosterone levels and consequent resistance of GRs **[17, 18, 44, 60]**.

There is mounting evidence that inflammation plays an important role in response to early-life stress and the development of depression. Individuals who have experienced maternal separation usually have elevated proinflammatory cytokines levels and are more likely to develop depression **[18, 39]**. The maternal separation model exhibits depression-like behavior, which is linked to increased proinflammatory cytokines such as TNF-α and IL-1β in the brain and exhibits greater microglial activation and increased IDO activation and production of 3-OHK and QA **[9, 39, 41]**.

3.2. The SDS Model

It is widely accepted that one of the most common key risk factors leading to the development of depression in humans is recurrent social stress **[2, 16]**. In humans, loss of social control is associated with a high risk of depression. Humans who experience social defeat exhibit increased depression symptoms. Because the majority of stress stimuli in humans that cause psychopathological changes are social, the process of losing control is critical to an individual's psychosocial situation.

The most widely used model of social defeat is the SDS model, which is thought to be relevant to the human situation **[2, 7, 67]**. The SDS model socially simulates the majority of human depression cases **[2, 16]**. It has been demonstrated that the SDS model results in behavioral and physiological consequences that closely resemble those resulting from stress in humans **[2, 18]**.

3.2.1. Social Defeat of Laboratory Animals

The SDS animal model is based on the resident-intruder paradigm in promoting the pathogenesis of depression **[7, 68]**. Social conflict between members of the same species is necessary for the generation of emotional and psychological stress in the SDS model **[7, 68]**. The central theme in this model is to allow subjects to socially and physically interact **[7, 17, 18, 67]**.

Customarily, in this model, the test intruder male mouse will be transferred into the home cage of another male, the resident, for 10 min. daily. In all settings, the intruder is investigated, attacked, and defeated by the resident **[7, 17, 18, 67]**.

In addition to the physical stress during social encounters, the psychological stress of sensory contact can also be added, through which the intruder is housed in the same cage as the resident counterpart, separated by a wall made of transparent acrylic with small holes that would allow for the odors and vocalizations to circulate, allowing for sensory interaction and exposure to the stressful psychological signals emitted by the resident without fighting **[7, 17, 18]**. This sequence is repeated for 10 days, with a novel opponent each day. SDS-induced depressive behavioral changes in the test animal are comparable to those of human depression **[17, 18, 67]**.

3.2.2. Mechanisms Involved in the SDS Model

According to research, social defeat causes significant hyperactivity of the HPA axis in rodents, with a significant elevation in corticosterone levels **[18, 68]**. Social defeat was found to elicit neurobiological changes relevant to increased brain proinflammatory cytokines, increased microglial activation, and IDO pathway activation with consequent production of 3-OHK and QA **[18, 32, 42]**.

3.3. The LPS Injection Model

The pathophysiology of depression is heavily influenced by inflammatory activation caused by various stressors. Systemic administration of LPS is one of the most widely used methods to achieve inflammation-induced depression **[19,**

45]. The major component of the outer membrane of gram-negative bacteria is LPS **[19, 45]**. Animal studies demonstrated that systemic administration of LPS and consequent inflammation reliably triggered depressive-like behaviors in rodents **[18, 30, 38]**. Systemic LPS administration is commonly used to make rodents go through depressive-like states, simulating human depressive symptoms brought on by immune stressors **[16, 19]**.

3.3.1. LPS Injection in Laboratory Animals

A single injection of LPS, typically ranging from 0.5 to 0.83 mg/kg, is commonly used to induce depressive-like states in rodents and to generate an inflammation-related model of depression **[18, 19]**. Single systemic LPS administration is known to cause depressive states in rodents **[19, 26]**.

3.3.2. Mechanisms Involved in the LPS Model

Systemic exposure to inflammatory challenges as LPS not only causes peripheral systemic inflammation with increased production of proinflammatory cytokines but also induces central neuroinflammation, reflected by activation of brain microglia with elevation of proinflammatory cytokines, like TNF-α and IL-1β, in the brain **[18, 19, 31, 38, 45]**. Gradually, depression-like behavior emerges as activated microglia increase proinflammatory cytokine levels, thereby augmenting inflammation. Proinflammatory cytokines lead to the activation of microglial IDO **[19, 37, 38, 51]**. The activation of microglial IDO generates neurotoxic metabolites, 3-OHK and QA, in the brain **[19, 37, 38, 48]**.

3.4. The CUMS Model

The CUMS model is one of the most commonly used animal models for depression. It is believed that depression results from an inability to handle stressful situations in daily life. CUMS is used to mimic this effect in animals **[7, 17-19]**. Under the CMS paradigm, animals are subjected to a series of mild stressors in an unpredictable way over an extended period. Animals exposed to CUMS exhibit depression-like behavior. The neurobiological changes induced by this model are similar to those observed in cases of depression **[7, 18, 19]**.

3.4.1. CUMS of Laboratory Animals

Rodents in this model are exposed to a wide range of stressors. These stressors ought to be mild in intensity, applied over a relatively prolonged period, and occur unpredictably **[7, 17, 18]**. A variety of stressors, including changing lighting, tilting cages, and damp sawdust, can be applied **[18]**.

3.4.2. Mechanisms Involved in the CUMS Model

This model induces neuroinflammation by elevating proinflammatory cytokine levels and microglial activation **[18, 19]**. When an animal is exposed to CUMS, TNF-α and IL-1β levels are typically elevated **[19, 43, 44]**. Additionally, these animals exhibit elevated IDO activity **[19, 69]**. Moreover, animals exposed to CUMS exhibit hyperactivity of the HPA axis, resulting in markedly elevated corticosterone levels and GRs resistance **[18, 44, 70-72]**.

Conclusion

In summary, depression is one of the most common mental disorders. The most common risk factor for depression is stress. Inflammation in response to stressors appears to be strongly linked to depression. Inflammation is implicated in the pathophysiology of depression, according to both clinical and pre-clinical evidence. The relationship between inflammation and depression is still being investigated. Preclinical evidence suggests, however, that elevated proinflammatory cytokines are involved in mechanisms that cause depression. Proinflammatory cytokines such as TNF-α and

IL-1β have potent effects on activating microglia and inducing the IDO pathway, with the consequent formation of neurotoxic tryptophan catabolites, 3-OHK, and QA. The inflammatory response in depression is accompanied by increased oxidative stress, which also promotes neuroinflammation. These factors, combined, play a role in cell death. Additionally, stress triggers the HPA axis to release large amounts of glucocorticoids, which leads to the development of GRs resistance, which fails glucocorticoids to inhibit the HPA axis, and the failure of glucocorticoids to inhibit inflammation. Proinflammatory cytokines were proven to have an impact on 5-HT and NE levels in numerous studies. Proinflammatory cytokines activate the IDO pathway, which catabolizes tryptophan, the main amino acid precursor of 5-HT, causing a reduction in tryptophan levels and a consequent reduction in the availability of 5-HT. Proinflammatory cytokines also increase the expression of reuptake transporters of 5-HT and NE, causing an increase in the reuptake of these neurotransmitters with a consequent decrease in their availability. Different types of animal models of depression can be used in laboratory studies to look into the mechanisms underlying depression. The most widely used animal models of depression are those that are based on psychological stress, such as the SDS and the maternal separation stress model. These models can exhibit signs of inflammation and a dysregulated HPA axis. The LPS injection model is also useful in studying inflammatory roles in depression in response to immune stressors. CUMS is one of the most well-known models for depression that depends on applying mild stressors that are unpredictable over some time. Signs of inflammation and dysregulation of the HPA axis were also found in animals exposed to this model. More studies are still needed to fully understand the pathophysiology of depression to find an effective treatment.

List of abbreviations

ACTH, Adrenocorticotropic hormone; CNS, Central nervous system; CRH, Corticotropin-releasing hormone; CUMS, Chronic unpredictable mild stress; GR, Glucocorticoid receptor; DNA, Deoxyribonucleic acid; HPA axis, Hypothalamic-pituitary-adrenal axis; 5-HT, 5-hydroxytryptamine; IDO, Indoleamine 2,3-dioxygenase; IL-1β, Interleukin-1β; LPS, Lipopolysaccharide; NE, Norepinephrine; SDS, Social defeat stress; TDO, Tryptophan dioxygenase; TNF-α, Tumor necrosis factor-α; 3-OHK, 3-hydroxykynurenine; ROS, Reactive oxygen species; QA, Quinolinic acid.

Declarations

Consent to publish

All authors have read and agreed to the published version of the manuscript

Ethics approval and consent to participate

Not applicable.

Availability of data and material

All data generated or analyzed during this study are included in this published article in the main manuscript.

Conflict of Interest

The authors assert that there are no conflicts of interest.

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Authors Contribution

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