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Review

Experimental Models of Depression

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ABSTRACT

Depression is the most common disease among psychiatric disorders. Depression with anhedonia may lead to a weakening of social communication, an intense feeling of sadness, or it can lead to suicide. It has been observed that people who become depressed as a result of environmental factors outnumber people genetically prone to depression. One of the most important factors for depression is found as stress. As a result of stress, cortisol is secreted in our body. In prolonged stress situations, it has been observed that excessive secretion of cortisol causes depression in the prefrontal lobe. Based on this information, the application of experimental animal models are prominent in order to better understand the pathophysiology of the disease and to develop various treatments. Because of the importance of stress in depression, most of experimental animal models were created by exposing them under stress. The basis of all models is to expose the animal to a forced stress. And as a result, the animal is expected to imitate depression-like behaviors. In this review, alternative depression models such as chronic mild stress, learned helplessness, social stress, early life stress, olfactory bulbectomy and corticosteroid administration that can be used to create models of depression. In addition to the evaluation of animals using these models, forced swimming, which can be used to determine whether the animal is depressed or not as well as the tests such as tail hanging are included. These tests are based on the behavioral helplessness. In addition, validity criteria are very important in experimental depression models. Validity is chosen according to the goals of the model and can be tested in different ways.

Keywords: Animal models, depression, stress.

According to the data of the World Health Organization, depression is a very common psychiatric disease with a prevalence of 10% to 15%, affecting more than 264 million people. The disease progresses with anhedonia. In other words, activities that were done with pleasure and excitement in the past are no longer done or continue to be done without pleasure. Depression is characterized by feelings of hopelessness, worthlessness, and helplessness for a long time, feeling guilty, suicidal thoughts or attempts, sleep problems, appetite and weight changes. [1] Not every similar mood should be qualified as depression. Because the symptoms in depression are much more severe and long enough to last for weeks or even months. The main cause of the disease is thought to be a combination of genetic, environmental and physiological factors.[2,3]

Almost all psychiatric diseases are caused by insufficiency of the prefrontal cortex. The prefrontal cortex is the foremost part located behind the frontal lobe. This region is responsible for behaviors such as judgement, decision making, discerning right and wrong, and empathy. The most important symptom of prefrontal insufficiency is impaired ability to establish cause and effect between events. Studies have shown that the prefrontal lobes of depressed people are smaller than those who are not depressed.[4] It has also been shown that depression shrinks the hippocampus, which is the memory center of the brain, and causes glial cell loss.[5,6]

It has been shown that neurotransmitters, especially serotonin, play an important role in the etiology of depression.[5,6]

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BASIC NEUROTRANSMITS PLAYING A ROLE IN DEPRESSION

The most associated neurotransmitter with depression is serotonin (5-HT). It has a calm effect on the body. It is produced from the amino acid tryptophan, stored in vesicles and released into the synaptic cleft with a nerve impulse. It fulfills its function by connecting to receivers. Most of the serotonin absorbed by the reuptake pumps is broken down by the enzyme monoamine oxidase (MAO) and then aldehyde with aldehyde dehydrogenase to its main metabolite, 5-hydroxyindolacetic acid (5-HIAA). First, it passes into the cerebrospinal fluid (CSF), then into the blood and urine and is discharged from the body.[7]

Serotonin receptors regulate serotonergic neural transport. It has been known that there are currently 14 different serotonin receptor subtypes. However, only some of these receptor subtypes play a role in the physiological events of the brain. Serotonin subtypes that play an important role in depression and related disorders are 5-HT1A-B, 5-HT2A, 5-HT3.[8]

HTTLPR is a degenerate repeating polymorphic region in the gene (SLC6A4) encoding the Serotonin transporter (5-HTT). It has been shown that the short and long alleles in 5-HTTLPR affect the transcriptional rates of the 5-HTT gene.[9] Individuals with one or two copies of the short allele of the 5-HTTLPR polymorphism have been found to be much more depressed and prone to depression than individuals with the long allele.[10]

Neurotransmits are found in and released from vesicles within neurons. However, monoamine neurotransmitters (such as serotonin, dopamine, epinephrine) are transported to the vesicles by the vesicular monoamine transporter (VMAT). VMATs exist as two different isoforms: VMAT1 is mainly expressed in chromaffin and enterochromaffin cells, and VMAT2 is mainly expressed in monoaminergic neurons.[10] The monoamine binding affinity of VMAT2 is higher than that of VMAT1. This means that more serotonin goes to the vesicles and more is released. In addition, there is evidence that depression is linked to the genetic polymorphism of the VMAT2 gene.[11]

Glutamate

Glutamate, the most abundant neurotransmitter in the brain. It is mostly found in the cortex and hippocampus in the brain. It binds to the N-Methyl D-Aspartate (NMDA) receptor. Another cause of depression is an excess of glutamate. In mood disorders, glial cell loss causes changes in glutamate neurotransmission. Glial cells' glutamate reuptake is the mechanism that is effective in removing glutamate from the synapse. Therefore, a decrease in the number of glial cells may result in toxic extracellular glutamate accumulation.[12] Consequently, excessive stimulation of glutamate receptors causes cell death through the increase of intracellular calcium (Ca). Neuronal death due to glutamate exposure is largely NMDA receptor mediated. Ca increase in the cell initiates toxic cycles, leading to neuronal cell death through free radical production, lipid peroxidation, nitric oxide synthesis and release.[13]

Gamma aminobutyric acid (GABA) and cortisol

It is the most abundant and inhibitory neurotransmitter in the brain after glutamate. It has a calm effect, when it binds to its receptor, the chlorine channel, negatively charged chlorine flows to the neurons and the neurons become difficult to excite. Cortisol, which binds to the GABA receptor; known as the stress hormone, it is released from the adrenal glands and allows us to cope with stress. When cortisol increases the activity of GABA by binding to the GABA receptor, the situation reverses when it is excessively secreted and the amount of glutamate increases. It causes inflammation in the brain. In addition, prolonged depression or a stressful life causes excess cortisol secretion from the adrenal glands and naturally high levels of cortisol in the blood. It has been reported that high cortisol in the blood lowers the immune system and makes the person tired and sick more quickly.[14,15]

DEPRESSION AND STRESS RELATIONSHIP

There may be individuals who are genetically susceptible to depression, and compared to today, it has been observed that cases of depression due to environmental factors.

It has been shown that the inflammation caused by stress in the brain can cause depression. We should not think of stress as just exam stress or negative situations we face in life. Being sleep deprived due to long workload, exercising excessively, eating too little or more than necessary are also sources of stress for the brain.[15]

Based on this information, most of the experimental depression models were created in acute or chronic form with stress factors. In these models, behavioral and pathophysiological changes similar to depression symptoms in humans were obtained and treated with antidepressant drugs. Stress models are generally

accepted to have a good appearance, structural and etiological validity profile and are frequently used.[16]

PURPOSE OF ANIMAL MODELS

Like most mental illnesses, the pathophysiology of depression is still not clearly explained. Also, the number of patients still unresponsive to treatment and the length of treatment. It shows that current treatments are insufficient, and more research and different strategies need to be developed on this subject.[17,18] Preclinical studies with animal models are crucial to bring a different perspective to the underlying causes of the disease, to develop various treatments and to examine the relationship of depression with genetic or environmental factors. However, as in most mental illnesses, symptoms seen in depression are not uniform. Depression is a complex disease that includes psychological, physiological and behavioral symptoms, and unfortunately, there is no animal model that reflects all of the symptoms of psychiatric illnesses seen in humans. On the other hand, it is possible to produce some symptoms or pathophysiological changes specific to the disease seen in the clinic in experimental animals.[18-20]

Models developed in depression are intended to mimic certain symptoms seen in humans rather than meeting human depression as a syndrome. The most frequently cited principles about animal models were proposed by McKinney and Bunney.[21] The minimum criteria that animal models prepared by the authors must meet are shown in the table (Table 1).

Validity in animal models

Validity is the main criteria for using animal models. In experimental depression models, validity is chosen according to the goals of the model and can be tested in different ways. This concept was first proposed by Mc Kinney and Bunney in 1969.[21] Then, in 1984, Paul Willner mentioned the importance of at least three criteria related to the validity of experimental depression models.[22]

Table 1. Minimum criteria that animal models used in depression studies should meet[21]

- It should be reasonably similar to the symptoms of depression seen in humans
- Must be observable behavioral changes that can be objectively assessed
- Independent observers must adopt objective criteria to draw conclusions in subjective situations
- Treatments that reverse depression in humans should also reverse changes in animals.
- The model must be reproducible by different researchers

These criteria's are following:

1. Behavioral phenotype and clinical symptoms are similar in the animal (apparent validity),
2. How accurately the mechanism and processes of etiological factors known to play a role in the development of the disease can be imitated by the model (Structural validity),
3. Understanding that a drug that is effective in a model animal will also be effective in humans (predictive validity). In addition to these, etiological validity, which was added later, is a concept close to structural validity. It is related to the similarity between the etiology of the disease between the model and the person it models.[16,22,23]

DEPRESSION MODELS CREATED BY STRESS

Chronic unforeseen mild stress

The chronic unpredictable mild stress model is considered to be one of the most widely used depression models with the best validity profile.[24] In the model; experimental animals are chronically exposed to a variety of environmental stressors in an unpredictable manner. In order for the experimental animals not to adapt to the stresses, they are exposed to one or two of the stressors in a way that the same stressor is not applied on consecutive days and without following a certain order among the stressors.[25,26]

It is possible to produce anhedonia (decreased pleasure and interest in hobbies), which is one of the most important symptoms of depression in humans in experimental animals. In addition, it has been shown that the chronic unpredictable mild stress model reduces sexual, aggressive, investigative behaviors and locomotor activities.[27] Neurologically, impairments in the hypothalamus-pituitary-adrenal (HPA) axis, decrease in hippocampal neurogenesis, increase in microglial activation, decrease in 5-HT neurotransmission in the forebrain and decreases in dendritic branching were also observed.[28]

When examined historically, this model was first used by Katz et al. It has been proposed by rats were exposed to severe stressors intermittently for 3 weeks. If we give an example of these stressors; unpredictable electric shock exposure for 60 minutes,

water deprivation for 40 hours and then food deprivation for 40 hours, flotation in cold water (4°C), exposure to high heat stress (40°C), cage shaking stress for 30 minutes, day/night cycle reversal. Different stressors were applied in different orders in order to prevent the experimental animal from predicting stressors and adapting to stress. As a result of the experiment, an increase in the level of corticosteroids and a decrease in sugar water consumption as an example of anhedonia were observed.[24-26]

Katz et al. Based on their studies, Willner et al. developed a longer-lasting modification by alleviating stressors (such as night lighting, cage bending, cage mate change). These stressors were applied alternately for several hours. This application can take weeks or months. The lighter weight of this study and longer duration of stress factors have higher predictive validity in terms of its adaptability to humans.[29]

The improvement of anhedonia-like behaviors in experimental animals with the model with chronic antidepressant treatment, as in humans, increases the validity profile of the model.[16]

The main parameter that associates the chronic unpredictable mild stress model with depression is hedonic activity. Whether the experimental animal exhibits anhedonia-like behavior can be understood by looking at its preference for Sucrose, a reward-based test. Rodents instinctively love sugar and sugar-based foods. Preferring normal water to sucrose (sugar) water indicates anhedonia.[24] Criticism of the test has suggested that the reduction in sucrose water consumption is a reduction in overall water consumption. However, in most of the studies conducted, there was no change in general water consumption and it was confirmed that this preference was specific to sucrose and this preference was not affected by the state of being hungry or full. The weight loss observed in the model was thought to be caused by one of the stressors, but weight loss was observed when different stressors were used. Studies have shown that the reward effect of eating is lost rather than changes in the amount of food. This is another evidence that anhedonia develops.[25,29,30]

The major drawback of the model is its low repeatability. Compared to other models, it is time consuming, difficult to build and requires a large laboratory space. Nevertheless, the chronic unpredictable mild stress model is frequently preferred as it is considered to provide the best criteria for appearance, etiological predictive and structural validity among existing depression models.[16,31]

Social stress

Deficiencies in social interaction are known to be an important environmental factor that plays a role in the development of depression, and various depression symptoms such as introversion, feeling lonely, anxiety, and decreased self-esteem have been observed in individuals who have been socially defeated.[32,33]

When animals stay in groups, a hierarchy forms between them. In these populations, differences in behaviors of dominant and non-dominant populations, as well as significant negative outcomes related to the health status of non-dominant individuals were shown.[34]

In this model, the experimental mouse is placed in the home cage of an aggressive resident mouse for 10 minutes a day. The experimental animal is attacked by the resident mouse and can be injured in some cases.[35] The lab mouse sees the aggressive mouse, smells it and is forced to hear it for the rest of the day, but there is no physical contact. After 10 days, social defeat was created in the animal, especially anhedonia and social avoidance; It has been shown that changes reflecting the depression picture such as anxiety, decrease in sexual activity, weight loss, decreased motor activity and exploratory behavior, and changes in sleep physiology occur.[18,34,36] As the neurobiological effects of social defeat related to depression, disruptions in the prefrontal cortex lead to increased amygdala activity.[37]

The prolonged continuation of anhedonia and social avoidance behaviors that occur with the model, as in humans, and their recovery only with chronic antidepressant treatment are among the features of this model that increase predictive and appearance validity.[18,34]

Early life stress

Traumatic or negative experiences in early life; It is accepted that it increases the susceptibility to stress-related pathologies such as depression in adulthood and therefore it is one of the important risk factors that play a role in the development of depression.[38,39]

Maternal separation (MS) and maternal deprivation (MD) protocols are widely used in mice and rats as an early life stress model. MS, postnatal 2-14. 3 hours

of weaning repeatedly every day on days; On the other hand, MD is defined as a one-time 24-hour weaning period on the postnatal 9th day. This model; It is based on the imitation of the early period stress, which reflects the loss of parents or the relationship between the mother and the newborn and has a negative effect on the developmental process.[40,41]

While the separation of rat pups from their mothers individually from the postnatal 2nd day to the 11th day causes disorders in cortical functions, it has been reported that cortical disorders were not observed in the offspring that were reunited after the 11th day.[42]

Depression-like behaviors such as a decrease in movement, play behavior, social interaction and consumption of water and food were observed in the puppies experiencing early life stress. HPA axis hyperactivity and decreased neurotrophic support have been reported.

In this respect, the model is reported to have a good validity and reliability profile.[46] Some of the problems with this model are; The examination of different protocols under the same heading is that the duration of separation of the offspring from the mother can vary between studies and therefore, sometimes conflicting results are reported regarding the model.[16]

Learned helplessness

One of the important and common symptoms of depression is the feeling of helplessness. The learned helplessness model, first defined by Overmier and Seligman, is the most widely researched animal depression model.[47]

Test animal in the learned helplessness model; In a mechanism where escape is not possible, it is repeatedly subjected to electric shock stress from the foot. Then, when the experimental animal is subjected to the same electric shock in a system where escape is possible, it is seen that it exhibits the escape behavior insufficiently or not at all. This behavior is accepted as the equivalent of learned helplessness in depression in animals.[46,48,49]

The model may differ between laboratories. But the basic logic is the same; It is based on the principle that the animal is placed in a mechanism that will not like and cannot escape. It can be made with two compartments (shock is applied on one side, not applied on the other) or it can be done by placing a pedal in one compartment to terminate the shock with the intervention of the animal.[48-50]

By repeating stimuli such as light and sound before an electric shock is delivered, animals can learn to prevent shock. When two experimental groups exposed to shock with similar intensity and frequency (those without control over shock and the control group) are compared, it is seen that animals without control over shock remained more passive than control groups in later trials where they can prevent shock. In addition to this passivity, animals show neurovegetative symptoms similar to those in depression. These; appetite and weight loss, decreased mobility, loss of motivation, decreased sexual behavior and change in sleep patterns.[50]

The disadvantages of this model, which decrease the predictive validity, are that the behaviors that do not disappear after 2-3 days after the electric shock is given and the behaviors that do not disappear with the acute antidepressant treatment in contrast to the chronic treatment applied in humans.[51]

Olfactory bulbectomy

It is created by surgically removing the olfactory bulbs. Olfactory is the basic sensory modality for rodents. It has been observed that the sensory deprivation caused by this loss causes depression-like behaviors. These behaviors are anhedonia, increased motor activity, disruption in exploratory and social behavior, and learning-memory loss. However, in another study where the sense of smell was damaged by chemical means, similar behavioral responses were not obtained. Therefore, it is a model with low validity.[52,53]

Corticosteroid application

Corticosteroids are released from the HPA axis due to stress in healthy individuals. However, under pathological conditions, higher concentrations of glucocorticoids can cause brain damage, decrease in hippocampal neurogenesis, and decrease neuronal branching in the CA3 region in the hippocampus and in the prefrontal cortex.[54,55] The model was made by adding high levels of glucocorticoid or injecting corticosterone in the drinking water of animals. In the forced swimming test, depression-like behaviors were observed, such as increased inactivity and a decrease in sucrose water consumption as an indicator of anhedonia.[56]

DEPRESSION TESTS

Compulsory Swimming test

Learning experiments conducted by Porsolt were developed by observing that mice that could not

find the platform in the Morris water tank remained inactive after a while, and with some modifications, today, it is often preferred to determine whether the test animal is depressed and to evaluate its antidepressant activities.[46,57]

It is based on the principle of floating a certain amount of mice or rats in water in the cylindrical arrangement. In order to create an unavoidable stress on animals, the device must be such that the mouse or rat cannot escape or cling to one place. It is seen that mice trying to get rid of water at first swim actively (moving part), then only exhibit enough movement to keep their head above the water (immobile part). The model differs between mice and rats.[57,58]

The rats are floated as a training session for 15 minutes the day before the test is administered. In this way, it has been reported that more efficient results were obtained in the test. After 24 hours, it is floated under the same conditions for 5 minutes and the periods of inactivity are calculated.[46]

There is no need for a training session in mice, clear data were obtained in the first application. In the test carried out, 6 cm of water (21-23°C) was added to the mechanism, which was 25 cm in height and 10 cm in diameter, and followed for 6 minutes. In the first two minutes, only the last four minutes are considered as there is minimal inactivity. The scores of inactivity time per minute were recorded. It has been observed that when a mouse considered to be sedentary stops fighting, it remains immobile in the water and only exhibits the movements necessary to keep its head above the water.[57,58]

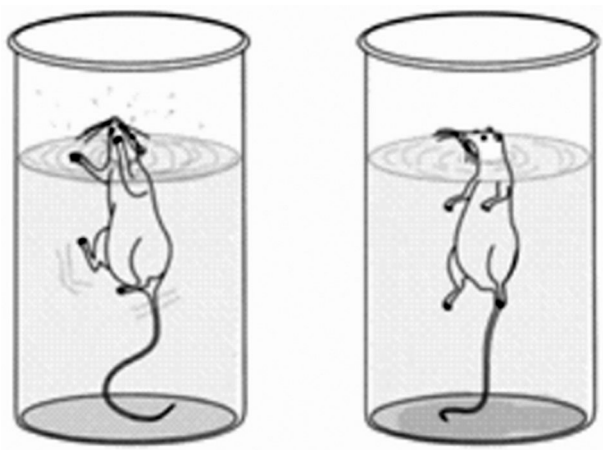

Figure 1. Schematic representation of mobility and immobility in the forced swimming test.[46]

Easy applicability, low cost and repeatability of the test; It is a good alternative for new antidepressant applications. Various antidepressants used in the test (such as selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants) were found to both shorten the immobility periods and prolong the time to inactivity (Figure 1).[46,57]

Tail Hanging Test

Another depression test that is the tail hanging test is done by hanging the animals from their tails with a tape so that they cannot escape. As with the forced swimming test, the animals' ability to cope with stress is assessed. However, it is recommended that this test be performed on mice only. The test takes 6 minutes and the time the animal spends immobile is measured. This inactivity is interpreted as a measure of depressive behavior. It has been observed that various antidepressant drugs shorten the inactivity time and encourage escape-oriented behaviors.[31,46,59]

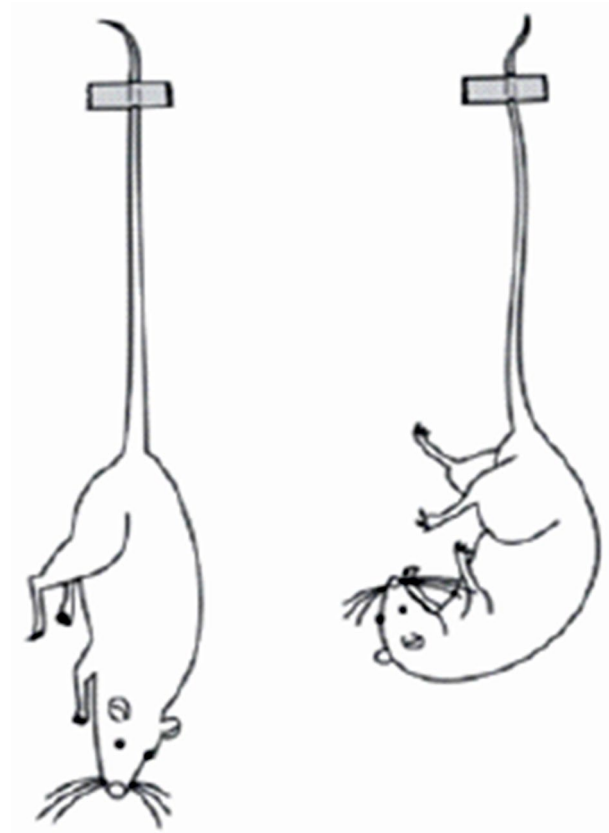

Figure 2. Schematic representation of immobility and mobility in the tail hanging test.[46]

Both tests have problems with structural validity. Depression-like behaviors, called behavioral hopelessness, are criticized for the animal being inactive in order not to expend more energy.[60] However, it continues to be widely used in the examination of antidepressant activities due to its high predictive validity and both its ease of application and practicality (Figure 2).[46,60]

RESULT

These experiments demonstrated the importance of stress and how negatively it can affect life. Although it is not possible to provide all the human symptoms of depression in experimental animals, most of the basic symptoms of depression have been shown in them. The most basic problems in stress-induced depression models that while improvement is observed in humans as a result of chronic use of antidepressant treatment, short-term improvement is seen in animals and there is difficulty in treatment studies due to much shorter effects. This difficulty shows that current models are inadequate. Different strategies should be used in studies to overcome the deficiency. One of the reasons why depression is so common today may be that people live more stressful lives than in the past. Studies on how to cope with stress and how to control stress may produce more beneficial results than studies of treating depression.

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