

# Animal models of stress-based depression

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## Abstract

Depression is one of the most common psychiatric disorders. Despite the prevalence and serious effects of depression, the pathological studies of depression are still preliminary. The main reason for this is limited access to valid animal models. Using animal models, the underlying molecular changes and causal relationship between environmental or genetic changes and depression can be studied, which provides a better insight into the pathology of depression. The role of stress as a key factor in the etiology of depression is emphasized. Because of the importance of stress in creating depression disorder in this study, animal models of stress - based depression have been investigated. Animal models of stress - based depression are: 1- learned helplessness (LH) model 2- Models based on early-life stress 3- chronic mild stress (CMS) model 4- Social defeat stress model. Studies show that exposure to early life stress can continuously alter DNA methylation in the brain of adult mice or rodents. In this regard, we can mention the role of methylation of Nr3c1 gene in parts of the hippocampus of the brain, indicating that epigenetic changes may play a role in depressive like behavior. Also, an unpredictable chronic mild stress model in rodents shows that significantly reduced diffusion of astrocyte cell gap and abnormal ultrastructure gap junction in the prefrontal cortex (PFC) and low levels of adenosine triphosphate (ATP) in the mouse brain, are the cause of depressive like behavior.

**Keywords:** Animal models, Depression, Stress.

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## 1. Introduction and preliminaries

Depression is one of the most common psychiatric disorders. Recent estimates show that about 20 percent of the US population, especially women, will experience clinically significant depression over a period of their lives; it has increased dramatically over the past two decades and before it. In fact,

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depression is high to the extent that the World Health Organization has ranked depression as the most important disease regarded as disabilities in middle-aged people in the world [1].

Epidemiological studies show that depression is associated with poor physical health, particularly with regard to "fibromyalgia", a high rate of heart problems and a higher rate of smoking [2,3]. It is characterized by depressed mood, lack of interest or happiness, feelings of guilt or worthlessness, sleep or appetite disturbances, energy loss, low concentration and suicidal ideation [4]. These symptoms are often recurrent and chronic, and they fundamentally interfere with the individual's ability to adapt to daily life and create problems. Depression is considered as a stress-related disorder. The role of stress as a key factor in the etiology of depression is emphasized. Approximately 40-50 percent of the risk of depression is estimated to be genetic [5]. However, no sole factor has been identified as genetically susceptible, indicating a complex interaction of genetic and environmental factors in the etiology of this order [6].

Despite the prevalence and serious effects of depression, pathogenesis of depression compared to other common, chronic and potentially deadly multi-factorial conditions, such as diabetes and Parkinson is still preliminary. The main reason for this is limited access to validated animal models. Because, firstly, an ideal animal model provides an opportunity to understand molecular, genetic and epigenetic factors that may lead to depression. Using animal models, the underlying molecular changes and the causal relationship between environmental or genetic alterations and depression can be examined; it provides a better insight into the pathology of depression. Since no depression gene has been identified in animal models to produce depression symptoms in rats, stress is still considered a risk factor for depression [6]. Secondly, animal models of major depression are essential for identifying new treatments for depression [7]. Considering the importance of stress in the incidence of depressive disorder, this study investigates animal models of stress-based depression.

## **2. Animal models of stress-based depression**

### **a. Learned helplessness model (LH)**

Helplessness and feelings caused by it are the main symptoms of major depressive disorder (MDD), and they are among the topics thoroughly studied in clinical and preliminary research on depression. In humans, LH refers to the lack of control over annoying stimuli induced by previous exposure to uncontrollable annoying stimuli in humans [8]. LH as one of the first models of depression in animals is used to study the effects of uncontrollable stress [9]. Animals with learned helplessness are complex animal models of depression; this model has a good face, construct and predictive validity. In addition, several pathophysiological concepts of depressive disorders have been confirmed using this model [8,10].

The classical experimental design consists of three groups; out of which two are control groups. The first animals' control group is exposed to electrical shocks that can be controlled by activities such as escaping or pressing the lever. Animals of the second group are paired with animals of the first group, meaning that each animal relates to any animal in the first group in terms of amount, duration, design and pattern of electrical shocks received (it receives the same level of shock). Animals of the second group experience

uncontrollable stress as they have no control over the position because they receive electrical shocks in an unpredictable, uncontrollable and unavoidable manner. The third group of animals (the second control group) does not experience any stress. Therefore, in this experiment, animals are exposed to uncontrollable shocks which can be compared to animals that receive controlled shocks (physically identical), and there is a control group with no stress. Studies using this triple design have shown that stress-related complications are not only due to exposure to stress, but the uncontrollability of stress is an important factor in causing these complications [11]. Helpless behavior is assessed by analyzing the function of the active escape paradigm such as the reaction of pressing a lever or crossing the door [12].

Animals with learned helplessness showed several neurovegetative changes indicating depression, such as rapid eye movement sleep, weight loss, decreased sexual behavior and high levels of corticotrophin-releasing factor (CRF) and corticosterone [13,14,15]. Recently, studies have shown that repeated use of antidepressants (Ads) or electroconvulsive seizure therapy (ECS) decreases delayed escape (observed in animals with learned helplessness) as well as the number of animals with learned helplessness [16,17]. This response (compared to Ads) is so effective that at present, no antidepressant compound has been clinically unsuccessful in relieving helplessness [18].

In contrast, a wide range of medicinal compounds (including benzodiazepine anxiolytics, typical neuroleptic chlorpromazine, psychostimulants such as caffeine, amphetamine, phenobarbital, and ethanol) is not effective in relieving helplessness. This indicates that the learned helplessness model at least as a model of the function of Ads has partially predictive validity [16]. In addition, studies show that treatment with Ads reduces different comorbid neurogenetic disorders in these animals [19].

#### **b. Models based on early-life stress**

Early-life stress models are based on the fact that unpleasant events and experiences occurring during a critical early-life may result in various types of illnesses such as depression and psychosis in later life [20,21]. These models are based on preliminary studies on rodents and nonhuman primates [22,23,24,25]. In recent decades, evidence resulted from epidemiological studies has shown that environmental factors in prenatal and postnatal are fundamentally related to the etiology of neuropsychiatric disorders. Early-life negative experiences such as parental absence, abuse, emotional and physical neglect significantly increase the risk of emotional disturbance in later life [26,27,28]. Today, many experimental approaches aimed at causing stress in early life have been investigated in critical periods of life of rodents and nonhuman primates. Many of these manipulations (experiments) cause physical and behavioral changes that continue into adulthood and represent a risk factor for psychopathology [29,30].

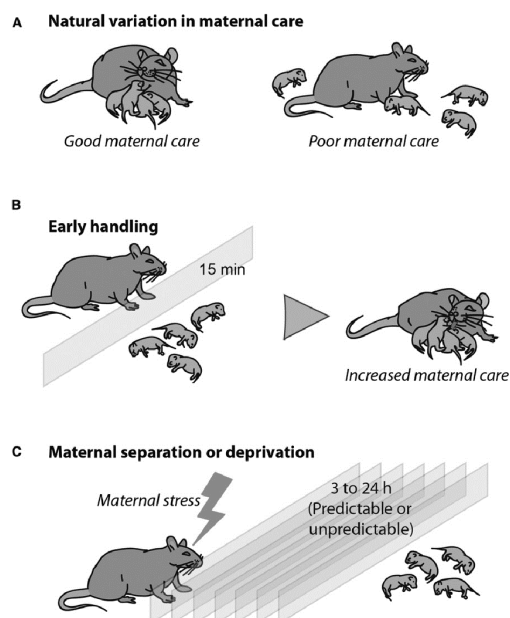
Maternal separation is a widely used experimental method in this field. Numerous studies conducted on rats have shown that one-time or repeated maternal separation leads to acute or chronic physical and behavioral effects in rats. Although maternal separation is the most popular model of disruption of the mother-offspring relationship, reports on the effects of this model show contradictory findings for almost all parameters and components examined [31,32]. One possible explanation for this paradox is that the

concept of maternal separation has become a generic term for very different experimental manipulations [32]. For example, stress resulted from maternal deprivation as a model of parental neglect leads to lasting structural and functional consequences [33,34]. In contrast, maternal care increases in the repeated maternal separation model. Obviously, this model is less stressful for children [35,36]; therefore, the results are often compared with effects in contrast to deprivation models. The maternal separation model directly disrupts normal mother-child interaction, and it also disrupts the hypothalamic-pituitary-adrenal axis (HPA) [30,35,37,38,39]. HPA function and stress responsiveness are relatively low during early postnatal life [40,41], but this is much more prominent in later life. Interestingly, early-life stress in a short time, such as manipulating and creating a situation in which mother leaves her children to find food, not only reduces HPA function but also decreases anxiety-like behavior in adulthood [40,42]. This is appropriately consistent with stress.

Meaney & Szyf (2005) found that corticosterone and adrenocorticotrophic hormone (ACTH) has been significantly increased in blood serum of rodents separated from mothers during the first two weeks of neonatal life, whereas the status of glucocorticoids receptors in hippocampus and prefrontal cortex was significantly changed [43]. A large number of studies on repeated maternal separation during the first two weeks of neonatal life shows depression and anxiety-like behaviors in adulthood [44,45,46,47]. Recent studies also indicate that exposure to early-life stress consistently can change DNA methylation (an epigenetic phenomenon that is created by adding Methyl group (CH<sub>3</sub>) to cytosine which is a nucleotide and part of DNA and RNA structure) in the brain of rats or adult rodents [48].

Weaver et al. (2004) reported that low maternal care such as licking, treating and nursing puppies alters DNA methylation in Nr3c1 gene promoter segments of a child's hippocampus which consistently influences patterns and stress responsiveness in adulthood [49]. Another study by Kemper et al. (2012) confirmed the role of Nr3C1 gene methylation in parts of the hippocampus in male rats separated from his mother, and it showed that epigenetic alterations may play a role in depressive like behavior [50].

**Figure 1.** Maternal separation model [51].



### **c. Chronic mild stress (CMS) model**

The chronic mild stress model is often recognized as a primary model [52,53]. In this model, rats are chronically and consistently exposed to unpredictable micro-stressors, which results in increased behavioral changes and decreased response to rewards; this is the main clinical sign of depression, namely anhedonia. In the standard design of this model, the sensitivity to reward is measured by periodic tests in which the animal is given access to a sweet solution that is completely preferred, or a choice between a sweet solution and water is given. Intake or preference of the sweet solution decreases over several weeks of animal's exposure to stress, but it can be returned to normal levels using chronic treatment by antidepressants [54]. The origin of chronic mild stress (CMS) model is in a series of studies conducted by Katz et al. published in the early 1980s in which rats were exposed to a variety of severe stressors. Most of these studies have investigated the effects of stress using changes in explicit behavior. According to reports, these effects have been counteracted, in particular, by chronic treatment using antidepressants rather than non-antidepressants [55,56,57,58].

Neurobiologically, severe stressors activate HPA and subsequently increase blood glucocorticoids. High levels of glucocorticoids may lead to atrophy and apoptosis (cell death) in the hippocampus and prefrontal cortex of the brain. Depression-related cognitive impairment changes with the release of corticosterone and decrease of glucocorticoid receptor regulation [59]. Animals with unpredictable chronic mild stress (UCMS) show a significant decrease in diffusion (molecular diffusion), astrocyte gap and ultrastructure abnormal gap junction in PFC. Antidepressants improve the dysfunction of gap junction and connexin 43 gene expression (connexin protein) (gene expression: the process of using intra-gene data) [60]. A study by Crema et al. (2010) based on the UCMS model in rodents indicates that low levels of Adenosine triphosphate (ATP) in rat's brain cause depressive-like behavior. In other words, stimulation and subsequently ATP release in astrocytes result in a function similar to that of antidepressants [61].

### **d. The social defeat stress model**

Social defeat stress paradigm is often used in rodents [62,63]. In this model, at the first stage, laboratory male animals are exposed to intruding male animals. The intruding animals are quickly identified, attacked and defeated by resident animals. To ensure the desired outcome of social conflict, resident animals are usually overweight and accustomed to fighting. These animals usually belong to a breed with a relatively high level of intrusion [64]. After a few minutes of physical interaction, residents and intruding animals are usually separated by a porous plastic wall by which a 24-hour period of visual, olfactory and auditory contacts and communications can be possible. Laboratory rodent animals are exposed to a different aggressive animal for several successive days [62,63].

This method can lead to many behavioral changes compared to the control group, including decreased social interaction, lack of pleasure with physiological, neuroendocrinal and neurobiological consequences and social stress [62,63,65]. These changes are considered as indications of certain aspects of human depression [64]. Previous studies have shown that behavioral and pharmacological approaches in treating human depression are also useful in reducing behavioral, physiological, neuroendocrinal and

neurobiological changes after social defeat. Sleep deprivation, antidepressants such as clomipramine, imipramine, fluoxetine as well as social interaction can prevent many consequences of social stress [62,63,65,66,67]. Therefore, social defeat stress is generally interpreted as a model of human depression. In addition, this model suggests that treatment with antidepressants can improve social incompatibility just chronically and not acutely [68]. However, this model has two major drawbacks; one is that short-term pattern is more likely to show anxiety phenotype (not depression), and the other is that only male rodents can be used in this model because female rats do not fight each other in resident-intruder confrontation [69,70].

Figure 2. Social defeat stress model (71).



### 3. Conclusion

Depression is one of the most common psychiatric disorders. In fact, depression is high to the extent that the World Health Organization has ranked depression as the most important disease regarded as disabilities in middle-aged people in the world [1]. Despite the prevalence and serious effects of depression, pathogenesis of depression compared to other common, chronic and potentially deadly multi-factorial conditions is still preliminary. The main reason for this is limited access to validated animal models. Using animal models, the underlying molecular changes and the causal relationship between environmental or genetic alterations and depression can be examined; it provides a better insight into the pathology of depression [6]. The role of stress as a key factor in the etiology of depression is emphasized.

Since no "depression gene" has been identified in animal models to produce depression symptoms in rats, stress is still considered a risk factor for depression [6]. This reflects the complex interaction of genetic and environmental factors in the etiology of this disorder. Due to the importance of the role of stress in depression disorder, animal models of stress-based depression are investigated in this study; these models include 1. Learned helplessness (LH) model, 2. Early-life stress models, 3. Chronic mild stress (CMS) model, 4. Social defeat stress model. LH as one of the first models of depression in animals is used to study the effects of uncontrollable stress [9]. Animals with learned helplessness are complex animal models of depression; this model has a good face, construct and predictive validity. In addition, several pathophysiological concepts of depressive disorders have been confirmed using this model [8,10]. Early-

life stress models are based on the fact that unpleasant events and experiences occurring during a critical early-life may result in various types of illnesses such as depression and psychosis in later life [20,21]. Today, many experimental approaches aimed at causing stress in early life have been investigated in critical periods of life of rodents and nonhuman primates. Many of these manipulations (experiments) cause physical and behavioral changes that continue into adulthood and represent a risk factor for psychopathology [29,30]. Maternal separation is a widely used experimental method in this field [31,32]. The maternal separation model directly disrupts normal mother-child interaction, and it also disrupts the hypothalamic-pituitary-adrenal axis (HPA) [30,35,37,38,39]. A large number of studies on repeated maternal separation during the first two weeks of neonatal life shows depression and anxiety-like behaviors in adulthood [44,45,46,47]. Recent studies also indicate that exposure to early-life stress consistently can change DNA methylation in the brain of rats or adult rodents [48].

Weaver et al. (2004) reported that low maternal care alters DNA methylation in Nr3c1 gene promoter segments of the child's hippocampus which consistently influences patterns and stress responsiveness in adulthood [49]. Another study by Kember et al. (2012) confirmed the role of Nr3C1 gene methylation in parts of the hippocampus in male rats separated from his mother, and it showed that epigenetic alterations may play a role in depressive like behavior [50].

In the CMS model that rats are chronically and consistently exposed to unpredictable micro-stressors, a significant decrease in diffusion (molecular diffusion), astrocyte gap and ultrastructure abnormal gap junction in PFC are shown. Antidepressants improve the dysfunction of gap junction and connexin 43 gene expression (connexin protein) [60].

A study by Crema et al. (2010) based on the UCMS model in rodents indicates that low levels of Adenosine triphosphate (ATP) in rat's brain cause depressive-like behavior. In other words, stimulation and subsequently ATP release in astrocytes result in a function similar to that of antidepressants [61]. In the social defeat stress paradigm in which rodent animals are in resident-intruder confrontation, many behavioral changes are observed compared to the control group, including decreased social interaction, lack of pleasure with physiological, neuroendocrinal and neurobiological consequences and social stress [62,63,65]. These changes are considered as indications of certain aspects of human depression [64]. This model suggests that treatment with antidepressants can improve social incompatibility just chronically and not acutely [68].

### **Conflict of interest**

No competing financial interests exist.

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