Neurosci Bull August 1, 2010, 26(4): 327-337. http://www.neurosci.cn
DOI: 10.1007/s12264-010-0323-7

·Minireview·

Behavioral animal models of depression

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Abstract: Depression is a chronic, recurring and potentially life-threatening illness that affects up to 20% of the population across the world. Despite its prevalence and considerable impact on human, little is known about its pathogenesis. One of the major reasons is the restricted availability of validated animal models due to the absence of consensus on the pathology and etiology of depression. Besides, some core symptoms such as depressed mood, feeling of worthlessness, and recurring thoughts of death or suicide, are impossible to be modeled on laboratory animals. Currently, the criteria for identifying animal models of depression rely on either of the 2 principles: actions of known antidepressants and responses to stress. This review mainly focuses on the most widely used animal models of depression, including learned helplessness, chronic mild stress, and social defeat paradigms. Also, the behavioral tests for screening antidepressants, such as forced swimming test and tail suspension test, are also discussed. The advantages and major drawbacks of each model are evaluated. In prospective, new techniques that will be beneficial for developing novel animal models or detecting depression are discussed.

Keywords: depression; animal models; learned helplessness; chronic mild stress; social defeat; forced swimming test; tail suspension test

1 Introduction

1.1 Depression: an unmet medical need Depression is one of the most serious mood disorders and affects up to 20% of the global population[1-3]. The World Health Organization predicts that major depression will be the second leading cause of global disability burden by 2020[4]. Besides, the depression-caused economic burden is estimated to be as high as $83 billion per year in the United States[5]. Although great development has been achieved since the first introduction of pharmacological antidepressant (AD) medications in the 1950s, there are still many patients whose illness cannot be alleviated by current ADs including tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and selective serotonin and/or norepinephrine reuptake inhibitors (SSRIs and/or SNRIs). Moreover, for the case of response, the mood improvement starts only after 3-6 weeks of AD medication. These unmet medical needs require more efforts in finding novel and efficacious strategies for depression treatment.

1.2 The importance of modeling depression in animals Despite the prevalence of depression and its serious impacts, studies on the pathogenesis of depression are still preliminary compared to those on the pathogenesis of other common chronic and potentially fatal multi-factorial conditions, such as diabetes and Parkinson's disease. The major obstacle is the restricted availability of validated animal models. Firstly, an ideal animal model offers an opportunity to understand molecular, genetic and epigenetic factors that may lead to depression. By using animal models, the underlying molecular alterations and the causal relationship between ge-

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Article ID:1673-7067 (2010) 04-0327-11
Received date: 2010-03-24; Accepted date: 2010-06-04

netic or environmental alterations and depression can be examined, which would afford a better insight into pathology of depression. Since no "depression gene" has been identified to generate depressive symptoms in mice, stress still remains a risk factor for depression[2]. Secondly, improved animal models of depression are indispensable for identifying novel therapies for depression.

1.3 The criteria for the "ideal" model of depression Ideally, an appropriate animal model of human depression should fulfill the following criteria as much as possible: strong phenomenological similarities and similar pathophysiology (face validity), comparable etiology (construct validity), and common treatment (predictive validity)[6-8]. Unfortunately, depression is a heterogeneous disorder[9] and its many core symptoms (e.g., depressed mood, feeling of worthlessness, and recurring thoughts of death or suicide) are hard to be mimiced in laboratory animals. The question therefore remains whether we can know a mouse is "depressed". Actually, few models of depression fully fit these validating criteria, and most models currently used rely on either actions of known antidepressants or responses to stress[2]. Of note, it is not necessary for an "ideal" animal model of depression to exhibit all the abnormalities of depression-relevant behaviors, just like that the patients do not manifest every possible symptom of depression. In fact, anhedonia is the core symptom of depression[3] and most of the current models only mimic anhedonia.

It should be noted that there is a difference between a model and a test. A model can be defined as an organism (non-human) or a particular state of an organism that reproduces aspects of human pathology, providing a certain degree of predictive validity. A test, on the other hand, provides only an end-point behavioral or physiological measure (read-out) designed to assess the effect of a genetic, pharmacological or environmental manipulation[10]. In the present review, the currently used animal models of depression are summarized and the advantages and drawbacks of them are discussed individually.

2 Animal models of depression

2.1 Learned helplessness Certain types of human depression are precipitated by stressful life events, and vulnerable individuals experiencing these stressors may develop clinical depression. In this aspect, stress can be used to induce depression-like symptoms in rodent animals. One of the well-validated animal models is learned helplessness, in which the depressive-like state in animals is induced by uncontrollable and unpredictable electrical foot-shock stress[11-15]. Learned helplessness was first observed in the early 1960s when Richard L. Solomon, a graduate student of Dr. Mowrer, was testing whether or not the 2 processes of classical Pavlovian conditioning and instrumental learning were in principle operationally separable and independent. He observed that moderately-extended experience with uncontrollable traumatic events resulted in later unexpected behavioral changes. Thereafter, Overmier and Seligman found that exposure to an uncontrollable traumatic event for a total of 3-5 min distributed over the course of a couple of hours resulted in dramatic deficits in behavioral coping, associative learning, and emotional expression, and they called these phenomena "learned helplessness". According to the protocols from different laboratories, learned helplessness is induced in one day or over several days of repeated exposure[16]. Among the various methods of inescapable stress application, the well-established one is the use of tail shock[17,18], a triadic design (escapable shock, yoked-inescapable shock, and restrained control)[19] or foot shock in shuttle boxes[20,21]. Helpless behavior is evaluated by analyzing the performance in an active escape paradigm, such as the latency to press a lever or cross a door[14]. For this model, the differences between mice and rats should be noted. The shuttle box paradigm is commonly applied in mice[21], while in rats, the experiment incorporates lever press[22]. Animals with learned helplessness show several neurovegetative changes that are reminiscent of depression, such as altered rapid eye movement sleep[23], reduced body weight[24], diminished sexual behavior[24], and elevated levels of corticotrophin-releasing factor (CRF) and corticosterone[25]. By selectively breeding learned helpless and non-learned helpless animals, 2 different lines of rats could be established: rats that show congenital learned helplessness (cLH) and rats that show relative resistance to learned helplessness (cNLH)[26]. The cLH rats show learned

helplessness without experiencing uncontrollable shock and they exhibit anhedonia and/or anergia under baseline conditions. On the other hand, the cNLH rats are resistant to the effects of inescapable shock[27]. The establishment of cLH rats is a validation of the congenitally helpless strain, and serves as a useful model to study the underlying mechanisms of depression[6].

Currently, studies have indicated that repeated dosing with ADs[28] or electroconvulsive seizure therapy (ECS)[29] reduces the latency to escape and decreases the number of animals that show learned helplessness. The specificity of this response appears to be very high and presently no compound that is clinically effective has failed to reverse helplessness[30]. In contrast, a wide range of compounds (including benzodiazepine anxiolytics, typical neuroleptic chlorpromazine and psychostimulants, caffeine, amphetamine, phenobarbital and ethanol) are not effective in ameliorating helplessness, suggesting that learned helplessness has some predictive validity at least as a model of ADs action[28]. Furthermore, treatment with AD is also reported to reduce various neurovegetative concomitants in these animals[31].

One advantage of learned helplessness as a model is that its symptoms are parallel to those of major depression, and most of them can be reversed by multiple acute (subchronic) treatment with AD (typically for 3-5 d)[32]. In addition, the cognitive (e.g., learning) and other behavioral outcomes (e.g., neurovegetative abnormalities) seem to be correlated, thus helping to understand the depressive symptomatology in humans. These excellent face and predictive validities make learned helplessness an interesting model to explore the pathophysiology of depression[30]. Besides, this model can also be generally used to measure the escape performance of mice with different mutations, in which target genes of depression may affect the vulnerability to develop a depressive-like state[21,33].

However, the major drawback of this model is that most of the depression-like symptoms do not persist long enough following cessation of the uncontrollable shock[9]. In addition, the paradigm may be carried out in different ways in varions laboratories[34]. Furthermore, different strains have different susceptibilities to learned helplessness after uncontrollable shock. For example, Kyoto and Charles River Holtzmann lines are the most susceptible to learned helplessness, and Harlan Sprague–Dawley is the intermediate, while Lewis, Brown Norway, Fischer F-344 and Sasco Holtzman are nearly resistant to the effects of inescapable shock[35]. For mice, uncontrollable foot shock induces marked performance deficits only in some strains (e.g., BALB/cByJ and C3H/HeJ), whereas in other strains, the interference is the modest (e.g., C57BL/6J, DBA/2J and CD-1) or entirely absent (e.g., A/J)[36].

2.2 Chronic mild stress (CMS) As is known, repeated presentation of the same stressor usually leads to adaptation which can, however, be excluded by presenting a variety of stressors in an unpredictable sequence. Thus, the chronic stress procedure was developed. CMS paradigms aim to model a chronic depressive-like state that develops gradually over time in response to stress, and they can provide more natural induction. The first CMS paradigm was introduced by Katz and colleagues, which was further developed by Willner[37-40]. It provides the basis for most of the currently used paradigms. Initial protocols included 3 weeks of exposure to electric shocks, immersion in cold water, immobilization, reversal of the light/dark cycle and a variety of other stressors[37]. These series of stressors could cause an increase in plasma corticosteroid level and a reduction in sucrose preference[41], which suggests that chronic stress may cause anhedonia. However, this protocol has been rarely used since the original series of publications[37,38,41-43], mainly due to the raised serious ethical problems. The CMS model is then developed in an attempt to achieve the same endpoints as the chronic stress model, but in an ethically more acceptable manner. This revised procedure involves relatively continuous exposure of rats[39,44] or mice[45] to a variety of mild stressors, such as periods of food and water deprivation, small temperature reductions, changes of cage mates, and other similar individually innocuous, but unpredictable, manipulations. Over a period (usually 3 weeks) of chronic exposure to mild stress, sucrose preference is gradually attenuated (sucrose preference is calculated as the proportion of sucrose consumption out of total consumption of liquid[46]), and the coat state is deteriorated (coat state is calculated as

the sum of the scores of 7 areas of the body: head, neck, back, belly, tail, forepaws, and hindpaws)[47]. According to the studies in our lab and others', these deficits can persist for several weeks following the cessation of stress[34,39,48]. Moreover, CMS causes the appearance of many other symptoms of depression, such as decreases in sexual, aggressive, and investigative behaviors, and a decrease in locomotor activity. In contrast, CMS does not induce the appearance of an 'anxious' profile in 2 behavioral tests of anxiety: the elevated plus maze and the social interaction test, suggesting that the behavioral changes are specific for depression[34,40].

The reduction in sucrose preference, as well as other symptoms induced by CMS, can be gradually reversed by chronic, but not acute treatment with a wide variety of ADs including TCAs, SSRIs, SNRIs, MAOIs, atypical ADs such as mianserin, buspirone and amisulpride, and ECS[34,49]. Importantly, these ADs do not alter rewarded behavior in non-stressed control animals. In addition, the time course of the therapeutic improvement closely mirrors the clinical action of these agents (usually 2-5 weeks). Conversely, a number of non-antidepressants are inactive in the CMS model, as has been predicted.

The advantages of this model are its good predictive validity (behavioral changes are reversed by chronic treatment with a wide variety of ADs), face validity (almost all demonstrable symptoms of depression have been reproduced), and construct validity (CMS causes a generalized decrease in responsiveness to rewards comparable to anhedonia, the core symptom of depression)[40]. Therefore, the currently available CMS model is probably the most valid and the most widely used animal model of depression.

However, the CMS model has 2 major drawbacks. One is the practical difficulty in carrying out CMS experiments, which are labor intensive, demanding of space, and of long duration. The other is that the procedure can be difficult to be established in a new laboratory setting, and data can be hardly replicated across laboratories[40,49].

2.3 Social defeat stress Although both paradigms mentioned above are capable of inducing long-lasting behavioral, neuroendocrinal and neurobiological effects, they are of non-social nature. Since the majority of stress stimuli in humans that lead to psychopathological changes are of social nature[50], research on the consequences of social stress in experimental animal models is crucial. Social defeat stress paradigm is the most frequently used model in rodents[51-54]. Firstly, experimental male animals are introduced into the territory of aggressive conspecific males. The intruders are rapidly investigated, attacked and defeated by the residents. To ensure the desired outcome of the social conflict, residents usually have a higher body weight and are familiarized with fighting. They usually belong to a strain with a relatively higher level of aggression[55]. After a few minutes of physical interaction, residents and intruders are usually separated by a plastic divider with holes, which allows visual, olfactory and auditory contacts for the remainder of the 24-h period. The experimental rodents are exposed to a different resident aggressor each day for several days[51-54]. According to the studies in our lab and others', this procedure can induce many behavioral changes compared to the control, such as decreased social interaction[51-54] and anhedonia[56], accompanied with physiological, neuroendocrinal and neurobiological consequences of social stress. These changes are interpreted as signs mimicking certain aspects of human depression[55]. Worthy of note, however, is that the long-lasting effects are observed only in single housed but not in socially housed animals[55,56].

Previous studies have proved that behavioral and pharmacological tools in treating human depression are also beneficial for reducing the behavioral, physiological, neuroendocrinal and neurobiological changes following defeat. Sleep deprivation[57], ADs such as clomipramine[58], imipramine and fluoxetine[51-54], as well as social interaction[56] can prevent many of the consequences of social stress. For this aspect, the social defeat stress is generally interpreted as a model of human depression. In addition, this model gives another validity that only chronic but not acute AD administration can reverse the social aversion[59].

However, this model has 2 major disadvantages. One is that a short period paradigm results more likely in the phenotype of anxiety[60], since a previous report has indicated that 20 d of social stress is required to develop depression[61]. The other is that only male rodents can be used for this

model, since female rats or mice do not fight each other in a resident–intruder confrontation[62].

2.4 Other models Apart from the above 3 most widely used models, still many types are being used, such as pharmacological tests and lesion model. Pharmacological screening tests are older models based primarily on mechanistic interactions between ADs and a range of other pharmacological agents. Rarely used nowadays, the predictive validity of these tests for ADs activity is poor[34]. For the lesion model, chemical or surgical lesions of the olfactory bulb could cause behavioral abnormalities, some of which could be reversed by chronic but not acute AD medication. It is not clear, however, how bulbectomy in animals actually relates to depression in humans. It might simply result from a high intensity of chronic stressor caused by chronic sensory deprivation[15].

With the development of genetic approaches, mutant strategies provide a particularly valuable approach to discover the potential targets of depression. Over the past few years, several lines of mice have already been generated to identify the roles of genes involved in depression, according to one of the different theories: the monoamine, the neurotrophin and the hypothalamus-pituitary-adrenal (HPA) axis hypotheses[10,33,63-66]. However, among the generated mutant lines, only a few can be regarded as genetic depression models or as models of predisposition for a depressive syndrome after stress exposure (e.g., α_{2A} adrenergic receptor knockout mice[65], glucocorticoid receptor heterozygous mice[33], and cAMP response element-binding protein overexpressing mice[66]). In addition, a mutant mouse line that presents hyperactivity or altered pain sensitivity may produce artefacts in many subsequent test situations. So the mutant strategies could not be widely used as animal models currently.

Recently, Gourley and colleagues have developed a new animal model with chronic oral exposure to corticosterone (CORT), a stress-associated adrenal hormone, inducing persistent and long-lasting behaviors (including anhedonia and helplessness). These effects can be reversed by chronic AD medication[67-69]. Besides, prior CORT exposure also chronically influences molecular targets that are implicated in negative mood production, such as reduced adult hippocampal neurogenesis[70], decreased expression of brain-derived neurotrophic factor (BDNF) and phosphorylated cAMP response element-binding protein (pCREB) in hippocampus[69]. Therefore, this model may provide a powerful tool for further investigating the neurobiology of complex stress-associated depressive symptoms that persist long after stress exposure itself.

3 Behavioral tests on AD activity

3.1 Forced swimming test (FST) The FST, also known as forced swim test, behavioral despair test or the Porsolt test, was developed in 1977 by Posolt and colleagues in the rat[71] and subsequently in the mouse[72]. The FST has changed the way of drug screening for ADs. Although it works in subacute condition (30 min after drug injection), it does remain highly reliable in predicting the therapeutic potential of the tested compounds[73]. Presently, the FST is the most widely used tool in depression research, more specifically as a screen for ADs[16,73]. The test is based on the observation that animals develop an immobile posture in an inescapable cylinder filled with water. After AD administration, the animals will actively perform escape-directed behaviors with longer duration than animals with vehicle treatment. The apparatus and the typical procedures of FST for mice are totally different from those for rats. For rats, the cylinder is 20 cm in diameter and 46 cm in height, and filled with water at the depth of 30 cm. The water temperature is kept at (24±1) ºC. The original version of FST is unreliable in detecting the effect of AD on SSRI. However, this drawback has been overcome in modified FST, which has been demonstrated to reveal specific behavioral components of active behaviors, namely swimming, which is more sensitive to SSRIs and serotonin antagonists, and claming, which is sensitive to TCAs[74]. In rat FST, a pre-test of 15 min is needed, as rats usually dive in the first exposure and need to be familiarized. For mice, the cylinder in original is 10 cm in diameter and 20 cm in height, with water at the depth of 6-10 cm. The water temperature is kept at (21±1) ºC. For mice FST, one exposure is sufficient to generate a stable immobility readout that can be counteracted by acute pretreatment with ADs[73]. Recently, the modified FST for mice has been introduced. The cylinder size is adjusted to 19 cm in diameter and 45 cm in height, with water

depth modulated to 23 cm, which could facilitate the stable immobility performance[51,73]. In the FST, subacute AD (including SSRIs) administration decreases immobility, with a corresponding increase in climbing or swimming behavior[75] without altering locomotor activity in an open field test[16,76]. However, the psychostimulants, such as caffeine and amphetamine which increase the general activity, can also decrease immobility[77], suggesting that the spontaneous locomotor activity can influence the immobility in the FST. Therefore, an open field test is usually needed to control the effects of drugs on locomotion.

Moreover, in this test, different strains of mice or rats often show different basal responses[78,79]. DBA/2 mice, for example, do not have an appropriate response and should not be employed in FST. On the contrary, the immobility time of ddY mice in 4-min testing is 200 s on average, which is the highest among the reported[73]. In addition, outbred strains of mice are more responsive to ADs in the FST than the inbred ones, but the inbred strains of mice can generally reduce the variability of performance[73]. Anyway, background strain is a crucial factor in drug discovery studies, because it might influence the detection of ADs with varying pharmacological selectivity and mechanism(s)[80]. For example, among various strains, Swiss mice are the most sensitive to the effect of serotonin (5-HT) and/or noradrenalin (NA), but the use of DBA/2 inbred mice is limited, due to the absence of antidepressant-like response in FST[81].

The advantages of FST are that it is low-costing and is a fast and reliable tool to test potential AD activities with a strong predictive validity. Besides, it is readily automated, allowing rapid screening of large numbers of compounds[73]. The disadvantages of FST are that it has poor face and construct validities. Besides, acute treatment with ADs is effective for FST, which, however, does not correspond to the clinical time course of their action. On the other hand, the poor construct validity is due to the acute and non-ecologically relevant stressor that produces immobility behavior[6]. Nonetheless, the FST is still one of the most used testing methods for screening ADs.

3.2 Tail suspension test (TST) The TST, which was first introduced in 1985 to measure the potential effectiveness of ADs[82], shares a common theoretical basis and behavioral measure with the FST. In this procedure, tails of rodents (mainly mice, although gerbils and rats are also used) are suspended using adhesive tape to a horizontal bar for 6 min, and the time of immobility is recorded. Typically, the suspended rodents are immediately engaged in several agitation- or escape-like behaviors, followed temporally by developing an immobile posture[83]. If ADs at doses are given prior to the test (usually 30-60 min prior to testing), the subjects will be actively engaged in escape-directed behaviors for longer periods of time than after vehicle treatment, exhibiting a decrease in duration of immobility.

Like the FST, the advantages of this test are that it can detect a broad spectrum of ADs irrespective of their underlying mechanisms[83], that its conduction is inexpensive, and that it is methodologically unsophisticated and easily amenable to automation. Thus, the use of TST has been substantially increased in recent years to assess AD-relevant behaviors. Although TST and FST share a common theoretical basis, there are many differences between them, therefore they could complement each other in some situations. For example, TST avoids problems of hypothermia or motor dysfunction that could interfere with the performance in swimming test, while FST could overcome the tail-climbing problem in TST[80,82]. In addition, the sensitivity and the pattern of dose-response to drugs are different between the 2 tests. For instance, imipramine had a U-shaped dose-response function in FST while in TST, it has a linear pattern of activity over the same dose range[84]. Moreover, baseline immobility can vary substantially between the 2 tests. For example, Swiss mice exhibit 7 times less immobility in TST than in FST, while C57BL/6 mice do not have such difference[84]. By using the 2 classic behavioral models, we can get more convincing data to show whether the tested compounds have the predicted effects. The other advantage of TST, compared to FST, is that mice behave worse in water-based tasks, while they perform as well as rats on a large scale of dry-land tests[85].

Similar to FST, one of the shortcomings of TST is that AD takes effect quickly, which is in contrast with chronic treatment with the same drugs in patients[83]. Another disadvantage is that some commonly used inbred mouse strains,

such as the C57BL/6, might be unsuitable for TST due to their tendency to grasp with front paws and climb up to the horizontal[80].

3.3 Other behavioral tests Besides FST and TST, there are many other tests. Novelty-suppressed feeding (NSF) test is a hyponeophagia-based behavioral test and provides an anxiety-related measure that is sensitive to the effects of chronic treatment with AD. The NSF also exhibits considerable potential as animal models for studying the neurobiology of the AD response[86]. The NSF elicits competing motivations: the drive to eat and the fear of venturing into the center of a brightly lit arena. Chronic, but not acute treatment with AD could significantly decrease the animal's latency to eat, while it does not affect the food intake of animals in their home cage[87]. Furthermore, in the CMS paradigm, the latency can be elevated by stress, while chronic treatment with AD can reverse this effect. More interestingly, for NSF test, the latency is causally related to the adult hippocampal neurogenesis. Studies have shown that the localized X-ray irradiation that would disrupt the hippocampal neurogenesis can block the effect of ADs on the latency in NSF test[48,87]. The physical state of coat assay and the sucrose preference test are usually used for analyzing the effect of drugs on depressive animals. Coat state assay has been indicated as a good index of rat response to CMS[88, 89], as the coat state can be rapidly observed and the assay is reproducible. Usually, the total coat score is calculated as the sum of the scores of 7 different body parts: head, neck, dorsal coat, ventral coat, tail, forepaws and the hind-paws. For each body area, a score of 1 is assigned to animals whose coat is well-groomed and 0 for an unkempt coat[47]. Chronically stressed animals exhibit a marked degradation of the physical state of the coat, and this can be tentatively explained by a decrease in grooming activity. On the contrary, treatment with ADs such as fluoxetine, can reverse the coat state in depressive rats or mice. Reduced preference for sweet solution in sucrose preference test represents a loss of interest, fatigue and a loss of energy during depressive episodes, while this reduction can be reversed by treatment with ADs. The reduced sucrose preference has been used as a measure of anhedonia in the animal models of CMS and learned helplessness[27,39].

4 Future directions

Despite the difficulties in translating human affective disorders into relevant tests in rodents, attempts have been made to establish animal models of depression, or at least the models with some core symptoms. The present review listed the most widely used animal models of depression and behavioral tests for screening AD activity. Also, the advantages and major drawbacks of them were discussed individually. As mentioned above, all these models or tests can induce anhedonia or identify the effect of ADs in rodents, but the main limitation is that the pathophysiological changes observed in these models might be the results of our manipulation (e.g., stress or pharmacological treatment), rather than the true manifestation of the depressive state of animals[10].

Current progress in biology offers corporation of new findings into animal models of depression. For example, the development of transgenic and knockout strategies has increased interest in murine depression models[74]. Since depression is a multi-genetic disease and the number of genes potentially involved is large, it is not surprising that the inactivation of one certain gene in mice cannot reflect all the features of the human disorder. Strategies for improving genetic modeling of depression-like syndromes in animals possibly require a simultaneous targeted dysregulation of several genes involved in the pathogenesis of depression[10]. In the past few years, there has been considerable interest in epigenetic modifications in the pathophysiology of depression and AD action. In this point, gene-environment interactions should be taken into account when modeling depression in animals. Indeed, studies have shown that although some mutant lines (e.g., glucocorticoid receptor heterozygous mice[33] and cAMP response element binding protein overexpressing mice[66]) do not present depression-like symptoms under baseline conditions, they are more 'depressed' following environmental stress, like the learned helplessness procedure or CMS. Additionally, more attention should be paid to the sexual difference in behavior in future studies, since depression is twice as common in women as in men, although the vast majority of preclinical studies have been conducted

in male animals[16].

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抑郁症动物模型的研究进展

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摘要：抑郁症是一种慢性的、具有高复发率的精神性疾病，往往会危及到病人的生命。尽管其全球发病率高达20%，但人们对其病理生理机制了解甚少，这主要归因于缺乏有效可靠的动物模型。此外，抑郁症的核心症状，例如抑郁心境、无价值感和反复出现自杀念头等，均无法在实验动物上得以模拟。目前，大部分动物模型的建立主要参照以下两个原则之一：对于已知抗抑郁药的作用或者是对应激的反应。本综述主要介绍目前最常用的几个抑郁症动物模型，包括获得性无助、慢性温和应激和社会失败应激，以及一些用于筛选有抗抑郁活性药物的行为学检测方法（如强迫游泳实验和悬尾实验），并对它们的优点与不足进行讨论。最后，对动物模型和行为学检测方法的发展方向进行展望。

关键词：抑郁症；动物模型；获得性无助；慢性温和应激；社会失败应激；强迫游泳实验；悬尾实验