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## Utility of the chronic unpredictable mild stress model in research on new antidepressants

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Unpredictable chronic mild stress model was developed as an animal model of depression more than 20 years ago. Essential for this model is that after prolonged exposure of tested animals to a series of unpredictable mild stressors, a condition similar to anhedonia develops, which is observed in the majority of depressive disorders. Unpredictable chronic mild stress model is used nowadays in numerous studies related to the neurobiological and biochemical changes associated with depressive illness. Their results confirm that chronic unpredictable mild stress induces in tested animals a number of changes, which reflect those seen in depressive disorders. Because the effects of unpredictable chronic mild stress can be used in a more accurate diagnosis of the pathophysiology of depressive illness and expand knowledge of its pharmacotherapy, therefore research in this area has been continued all the time.

**INTRODUCTION**

Depression is a severe disorder, which is often manifested by many psychological, behavioral and physiological disturbances. Clinical symptoms characteristic for depression include low self-esteem, fatigue, feelings of worthlessness, loss of interest or pleasure. Nowadays, depression affects 17-20% of the world population. The World Health Organization (WHO) predicts that depression will be the second leading cause of the global burden of disability in 2020. The etiology of depression is very complicated, and involves a large number of factors [32] including:

- genetic predisposition, which is determined by varying expression of genes related to the specific neurotransmitters,
- recurrent life events and chronic stress,
- specific type of personality development, formed as a result of adverse life experiences, which composes the basis for the internal stress,
- biologically conditioned sensitivity to sunlight deficit (seasonally) [9].

So far, numerous attempts have been made to develop animal models of depression, which allowed focusing on at least some aspects of the disease. These paradigms are

conducted in order to mimic the similarities of clinical symptoms of depression, in laboratory condition. These models make testing many factors involved in the pathogenesis, etiology, symptomatology, and the pharmacological treatment of depression possible [2].

The incidence of depression and its negative consequences still have been intensely studied. The “ideal” animal model of depression should have as many criteria specific to depression in humans as possible, should be sensitive to antidepressants, and should identify similarities in the pathophysiology and etiology of different kind of depressive states [31]. It should be noted that animal models of depression do not always reflect all the irregularities of depression in humans. However, patients do not always reveal all possible symptoms of this disease, either. We may mention here anhedonia, one of the primary symptoms of depression in humans, whereas most of the current animal models of depression only mimic it [9].

**MODELS OF DEPRESSION**

Currently, many various models of depression have been used to mimic depressive state in humans. Each model has advantages and disadvantages. The most commonly used paradigms are as follows:

**Learned helplessness.** In this paradigm the depressive state is induced by uncontrolled and unpredictable electric shock in rodents. Model of learned helplessness was firstly used at the early 60's. In these experiments, animals are

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repeatedly exposed to aversive stimuli without possibility of escape. The animals discontinue attempts to avoid stimuli. As a consequence, when finally possibility to escape becomes available, they do not perform any action [17].

**Social defeat stress.** This model shows that the majority of stressful stimuli leading to psychopathological changes have a social nature. In this paradigm, it is possible to study the social stress that consequently leads to depressive-like state in rodents [29].

**Chronic unpredictable mild stress (CUMS).** This model intends to use chronic stress, which leads to the depressive state. The mentioned paradigm was firstly used by Katz and colleagues, and next it was developed by Willner [25]. CUMS is now the most useful model of depression. It is widely adapted rodent paradigm, used to induce depressive and anxiety-like behaviors. It imitates stressful situations of peoples' everyday life. Impulses that initiate the stress response in laboratory animals, so-called stressors, act usually from two to four weeks, and are potentially harmless to the body. Stressors used in the CUMS model include, among others, food and water reduction, swimming in hot and cold water, wet litter, squeezing the tail, temperature changes, sounds of predators, cage tilt of 45°, changes in light-dark cycle, the presence of rat droppings in the mouse cages etc. [5] (see also: Table 1).

**Table 1.** Stressor used during the CUMS model

Forced swimming in cold water (4° C)	1, 6, 12, 13, 14, 22, 26, 30
Swimming in 45° C hot water	26, 30
Deprivation of water and food for 24 h	3, 6, 12, 13, 14, 20, 21, 22, 26, 29, 30
Noise	6, 12, 20
Intermittent white noise	8, 22
Tail squeezing (2 min)	6, 13, 14, 30
Inversion of the light/dark cycle	3, 6, 7, 15, 26, 30
Cage shaking (30 min)	26, 30
Cage tilting (12 or 15 h)	5, 7, 12, 13, 20, 22, 26
Damp sawdust (12 or 15 h)	3, 7, 15, 20
Confinement in a tube (3 h)	20
Testing the dark phase and reversed light-dark cycle	7, 20
Predator sounds	15
Placement in an empty cage	15
Placement in an empty cage with water on the bottom	15
Switching cages	15
Without sawdust + cat feces	7
Without sawdust + cage tilting	7
Wet bedding	7, 26, 31
Soiled bedding	8
Rat droppings to mouse cages	7, 29
Overnight illumination	8, 12, 13, 14, 22
Physical restraint	6, 13, 14, 22
Soiled cage	12, 22
Fasting for 48 h	31
Empty water bottles	22
Grouped housing	22
Stroboscope lighting	22
Restricted access to food	22
Exposure to a foreign object (e.g., a piece of plastic)	14
Small temperature reductions	29
24 h social isolation	26
24 h social crowding	26
Hot stress in oven at 42° C	26

Furthermore, long-term exposure (of experimental animals) to various mild stressors is associated with significant changes in the behaviors. Three or four-weeks-exposure to stressors cause an increased level of corticosteroids in plasma, and anhedonia evaluated as reduction of saccharose preference in tested animals. A very important issue in this model is that all behavioral changes induced by stress can be reversed by giving antidepressants [20].

Besides above-mentioned animal models of depression, one of the most widely used screening tests for antidepressants is **the forced swimming test (FST)**. Rodents are placed individually in glass cylinders and are allowed to swim for 6 min. Total duration of immobility is recorded during the last 4 minutes of the test. The duration of immobility is defined as the time when an animal remained floating passively, made no attempts to escape and showed only slow movements to keep its head above the water.

Another widely used behavioral test used to study the effect of antidepressants is **the tail suspension test (TST)**. In this paradigm, the rodents are suspended on the rod by tail for 6 minutes, and the duration of their immobility is recorded [7]. However, in these tests, a depression state is not induced, in contrary to CUMS model when exposure to various chronic stressors induces numerous changes leading consequently to depression state of the animals [28].

### CUMS procedure: animals, modifications, type of stressors

CUMS stress procedure is currently the subject of numerous scientific research studies and still undergoes many modifications. The possible modification involves chronic exposure of laboratory animals (mice, rats) to different, randomly scheduled social and environmental stressors. The duration of each stressor action usually ranges up to several weeks (about 3-4 weeks) [6]. The use of the CUMS model allows explaining the pathophysiological mechanisms of depression, such as loss of neurogenesis and changes in the hypothalamic-pituitary-adrenal axis (HPA). This model is currently used in order to investigate

**Table 2.** Animals used in the CUMS model

<b>Gender</b>	
Rats	1, 2, 3, 6, 8, 12, 13, 14, 22, 29, 30
Mice	5, 7, 10, 15, 20, 21, 23, 27, 29
<b>Sex</b>	
Males	1, 2, 3, 5, 6, 7, 8, 10, 12, 13, 14, 20, 21, 28, 29, 30, 32
Females	26
Both males and females	15, 23
<b>Age</b>	
Immature, i.e., 20–23 days (weanling), 29–40 days (juvenile), days (young adulthood) old and more than 50 days	1, 8, 14
Animals 2–4 months old	7, 10, 15, 20, 27, 31
Aged, i.e., 7–9 months and 24–25 months old	2
<b>Housing</b>	
Individual cage	1, 20, 21, 30
In groups (2-9/cage)	2, 3, 5, 6, 7, 8, 10, 14, 15, 17, 23, 26, 30
<b>Feeding</b>	
Access restricted (25–30 g/day)	1, 8
Ad libitum	2, 3, 5, 6, 7, 8, 10, 12, 13, 15, 20, 21, 22, 23, 27, 31

the influence of environmental stressors, on the prodepressive behavior of tested laboratory animals, rats or mice [15].

Chronic stress procedure was initially developed in rats by Willner [25], and at present both rats and mice are commonly used (see also Table 2). All conditions, under which the research is performed, must be adapted to the species, sex, age, and physical state of the tested laboratory animals. These conditions should be especially important in the tests and models when a state of depression or anhedonia is provoked and can be manifested by behavioral disturbances [21].

### Neuronal processes and brain structures involved in the CUMS model

Until recently, many of undertaken studies have indicated that depression occurs due to the numerous changes in the body, which may result from the reduction of structural plasticity of neurons [27]. CUMS performed on rodents is often used to explain the pathophysiology of nerve inflammation in depression and to assess disorders associated with an increased risk of neurodegenerative diseases [5]. Clinical and pre-clinical data show that depression is associated with activation of the immune system, which is manifested as the inflammation state. In particular, this disease is characterized by an increase in pro-inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-6. Depression may also be caused by an increase in peripheral cytokine. The drug therapy involves administration of their antagonists or antidepressants, also supporting the anti-inflammatory properties of cytokines [18].

Chronic exposure to the stress in the CUMS model has a large influence on the function of the brain regions involved in memory and learning process in rodents. Observed dysfunctions are accompanied by disturbances in the hormonal system of HPA and numerous changes in the complex cascades of intracellular processes involving G proteins, protein kinases, second messengers, and transcription factors. Many studies have shown a link between disorders caused by various long-term acting stress factors and depression.

Chronic stress causes a series of physiological changes in a body. One of the most important is the activation of the HPA, which is associated with excessive release of cortisol (called "stress hormone") in the blood. Moreover, increased glucocorticosteroids (GKS) level, induces damage to the dopaminergic, serotonergic or glutamatergic neurons. GKS also cause the reduction in dendrites branching and reduction in the number of dendritic spines. Increased GKS blood levels also lead to inhibition of neurogenesis process. The consequence of all these changes is reduction in size of the hippocampus and the frontal cortex, which is characteristic for patients with severe depression [3].

Disorder of the HPA is one of the most important mechanisms of depression. Moreover, increased release of corticotropin (CRH), caused by adrenocorticotrophic hormone (ACTH) releasing factor (CRF) is observed. CRF plays a very important role in the body's response to various stress stimuli, by enhancement of CRH and cortisol secretion. Moreover, CRH has its own very strong psychotropic effects (anxiety- or depressive-like reaction, sleeping and

eating disorders). Chronic stress causes the enhanced CRH secretion as a result of the protein kinases phosphorylation and of CREB-transcription factor activation. CRH acts on receptors in the anterior pituitary and causes stimulation of ACTH release. Furthermore, ACTH increases the synthesis and release of adrenal GKS (e.g., cortisol). In chronic depression, two opposing processes occur simultaneously, i.e., stimulation of ACTH secretion by excessively secreted CRH and ACTH-induced strong inhibition due to increased release of cortisol [19]. The results of a recent study clearly show that adding an additional gene coding CRH to the mouse genome, significantly increases anxiety reactions, and also enhances responses to stress. The influence of CRH on anxiety processes runs through the cell receptor CRHR1 in the pituitary and other brain structures, such as the limbic pathway and the frontal cortex.

Direct mechanism of corticotropin action is not fully understood, because of interaction with multiple neurohormonal and neurotransmitter systems. Many studies confirmed the link between CRH and monoaminergic neurotransmitter, i.e., 5-hydroxy tryptamine (5-HT, serotonin) and noradrenaline (NA). This fact is confirmed by a significant influence of CRH on the tyrosine kinase activity participating in the NA synthesis. Appetite is associated with the CRH interactions with some endogenous substances that regulate appetite, like leptin.

The hippocampus and frontal cortex i.e., structures responsible for emotional responses, are particularly susceptible to this factor. Studies conducted on laboratory animals in CUMS model have shown that long-acting stressors cause atrophy of hippocampal pyramidal cells of CA3 and lower the resistance to other damaging agents (e.g., hypoglycemia and hypoxia). Chronic stress also impairs the neurogenesis that occurs in the hippocampus and the associative cortex. Thus, the neurogenesis is inhibited and in consequence hippocampus (structure responsible for emotional responses) size undergoes reduction [4].

### Drugs evaluated in the CUMS model

CUMS has been used to assess the mechanism of action of some antidepressants and their effect on the HPA system. Particularly, from pharmacological point of view they have a significant effect on the nervous system, which protects neurons against a variety of stressful stimuli and against all kinds of interference of internal processes in the body. The goal of research studies carried out in this area is to prove neuroprotective properties of the psychotropic drugs [16]. Recently, a similar effect has been observed using four **antidepressants** in the mice CUMS model. The effect of imipramine (20 mg/kg), desipramine (10 mg/kg), maprotiline (20 mg/kg) and fluoxetine (10 mg/kg) in 6-week schedule of administration was measured [28]. Results confirm the antidepressant and neuroprotective effects of above-mentioned drugs in anhedonia-related state in rodents.

A recent study on **resveratrol**, a natural polyphenol, aims at determining whether its chronic administration (80 mg/kg, for 5 weeks) can affect cognitive deficits induced by chronic stress in laboratory animals and finding the possible mechanism of this phenomenon. The results of these studies show that administration of resveratrol causes a significant

reduction in behavioral and biochemical changes in the brain caused by stress. These studies may indicate that resveratrol can have some neuroprotective properties and may be an effective therapeutic agent in the treatment of depression. This compound also participates in regulating the cortisol level in the blood, a neurotrophic factor BDNF in the prefrontal cortex as well as hippocampus and is responsible for the decrease in phosphorylation of cellular signal-regulated kinase [12].

The aim of another research was to investigate the mechanisms underlying the antidepressant effect of **curcumin** in the rat CUMS model. This study provides new information concerning the basic mechanisms leading to neuronal dysfunction in depression and the discovery of the therapeutic potential for the use of curcumin in clinical trials [33].

Results of many research studies have shown that the level of pro-inflammatory cytokines and oxidative stress (i.e., lipid peroxidation growth, reduced glutathione, and endogenous levels of oxidative enzymes) are increased in patients with depression. Therefore, the effect of **sesamol**, a strong antioxidant and inhibitor of cytokine production, was examined on biochemical and behavioral changes induced by chronic stress in mice. The chronic administration of sesamol (21-day) reverses the behavior caused by chronic stress (i.e., increased duration of immobility, reduced preference for glucose) and biochemical changes (i.e., decreased levels of glutathione, superoxide dismutase and catalase activity, increased levels of lipid peroxidation) [10].

Additionally, behavioral and biochemical effects of **piperine** were studied in rats exposed to the CUMS. Significant changes in rats' behaviors, including decrease in saccharose intake and increased duration of immobility in the FST were observed. The results also revealed that piperine could change the concentration of 5-HT and BDNF in the hippocampus and frontal cortex of rats, which may indicate its potential antidepressant activity also suggesting that piperine administration to rats significantly suppressed both biochemical and behavioral changes induced by the CUMS [14].

A recent study examined antidepressant effects of **magnolol** from the bark of *Magnolia*, used in China in treatment of psychiatric disorders, including depression. In this study, the antidepressant action of magnolol was studied in rats. These data have revealed that this compound has the ability to increase the expression of BDNF and enhances the activity of the serotonergic system. These effects confirm antidepressant activity of magnolol [11].

Research studies describing the influence of **agmatine** on the CUMS in mice as well as its biochemical and behavioral changes have also been performed. This compound has been shown to exert modulatory action at multiple molecular targets, notably neurotransmitter systems, key ion channels, nitric oxide (NO) synthesis and polyamine metabolism. The results reveal that the chronic administration of agmatine reduces CUMS parameters characteristic for depression behavior in tested animals, i.e., increase in saccharose preference or reduction of immobility time in the FST. It has been proved that the administration of agmatine normalizes

the elevated level of corticosterone and prevents the changes in body weight of animals subjected to the CUMS model. The pharmacological effects of agmatine were compared to the action of the selective serotonin reuptake inhibitor (SSRI) - fluoxetine. Results of this study clearly showed the antidepressant action of agmatine [23].

Recent studies using the CUMS model have also confirmed the action of **Xiaochaihutang** (XCHT), a substance used in China for thousands years for treatment of symptoms similar to depression. The results have confirmed that XCHT significantly increases food intake and saccharose preference in rats, and reduces all depression-like behavior. Moreover, XCHT significantly increases 5-HT and dopamine levels and improves cerebral expression of all factors (including BDNF), which were reduced in rats expressing symptoms of anhedonia. Therefore, these studies suggest that XCHT may have therapeutic effect in the treatment of depression and any related symptoms [22].

Another study aimed at demonstrating the antidepressant action of **Fuzi polysaccharide-1** (FSP), a new water-soluble polysaccharide used for centuries in traditional Chinese medicine in the treatment of mood disorders. Research has shown that FSP increases the number of new cells in the dentate gyrus of adult mice, where the majority of the cells are differentiated into new neurons. It has been proved that the FSP reduces the duration of immobility in the FST and reverses the inhibition of neurogenesis process, characteristic for depression. Results of this study have revealed that acute treatment with FSP do not directly affect the level of monoamines in the brain, but considerably increases the level of BDNF in the hippocampus. The described study was designed to determine the utility of FSP as an antidepressant with a very fast onset of action, in contrast to many currently used anti-depressant drugs the therapeutic effect of which appears after several weeks of administration [29].

## CONCLUSION

CUMS animal model is now a valuable tool to investigate the neurobiological, behavioral and hormonal changes underlying the psychopathology associated with stress. It plays a very important role in understanding the pathophysiological mechanisms of depression and efficacy of antidepressant therapy [15].

So far, many studies have confirmed that CUMS contributed to the exploration of many pathophysiological mechanisms of depression, such as inhibition of neurogenesis in the hippocampus, a disorder of the HPA axis, peripheral changes in the level of pro-inflammatory cytokines, increased lipid peroxidation, reduced glutathione level, increased levels of endogenous oxidative enzymes, and numerous nerve inflammations [13].

The purpose of CUMS animal model is therefore to determine the relation between the behavioral changes caused by stressful situations which tested animals are subjected to, and the identification of the clinical symptoms of depression [5].

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