Review Article

Chronic Unpredictable Mild Stress: An Important Model of Depression to Develop New Anti-Depressants

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ABSTRACT

Chronic unpredictable mild stress (CUMS) model was developed as an animal model of depression more than two decades ago. Important for this model is that after prolonged exposure of tested animals to a series of CUMS stressors, a condition like anhedonia develops, which is noticed in the majority of depressive disorders. CUMS model is used now-a-days in numerous research related to the neurobiological and biochemical changes associated with depressive disorder. Outcomes confirm that CUMS induces various changes in tested animals, which reflect those seen in depressive illness. Because the effects of CUMS can be used in a more accurate diagnosis of the pathophysiology of depressive disorders and expand knowledge of its pharmacology and pharmacotherapy, therefore research in this area has been continued all the time. The animal models of depression like CUMS has contributed to the elucidation of the pathophysiological and hormonal mechanisms of depression includes decreased neurogenesis, HPA axis alterations etc. This model explores the association of depressive-like behavior in mice with changes in peripheral pro-inflammatory cytokines IL-1β, TNFα and IL-6 level such as neuroinflammation by quantifying CD11b expression in brain areas known to be involved in the pathophysiology of depression. The present review focuses on the CUMS procedure, various stressors and behavioral tests. The review also includes neuronal process and mechanisms involved in the CUMS. Search was performed in PubMed, PsycInfo, Web of Science, Scopus and Medline databases. A quality assessment yielded a total of 52 papers to be considered for the review by using strict inclusion and exclusion criteria.

Keywords: Chronic unpredictable mild stress (CUMS), neuroinflammation, cytokines, anhedonia, neurogenesis, HPA axis, hippocampus, infralimbic, psychopathological.

INTRODUCTION

Depression may be a serious illness, generally manifested by symptoms at the psychological, behavioural and physiological levels. Various attempts are created to develop animal models of depression or a minimum of some aspects of the problem. Most of the animal models share the common feature of stress within the sort of varied stress measures or possibly dislike procedures and chronic stress models appear suitable for the experimental investigation of depression than acute stress models.[1,2]

Unipolar depression is one in every of the leading causes of injury. The pathophysiology of depression is inadequately understood. Evidence suggests that inflammation is related to depression. As an example, pro-inflammatory cytokines square measure found to be prominent within the peripheral blood of depressed subjects. Growing evidence has proposed that neuronal loss and cellular atrophy are mediated by neuroinflammation during the pathogenesis of depression. Thus, it is commonly believed that antidepressants exhibit ameliorated effects on depressive-like behavior by suppressing inflammatory mediators and promoting neurotrophic factors. Brain-derived neurotrophic factor (BDNF), a representative member of the neurotrophic factor family, governs the physiological functions of the frontal lobe and hippocampal tissues by regulating neuroplasticity.[3]

CHRONIC UNPREDICTABLE MILD STRESS (CUMS)

The chronic unpredictable mild stress (CUMS) model is broadly used to mimic depressive behavior in rodents. In this model, rats are exposed chronically to a constant bombardment of unpredictable micro-stressors, resulting in the development of a plethora of behavioural changes, including decreased response to rewards, a behavioural correlate of the clinical core symptom of depression, anhedonia. CUMS contributes to endogenous depression that is implicated in neuropsychiatric disorders, including behavioural, biochemical and neurochemical derangements.[4]

CUMS procedure

CUMS has long been used as a model of depression. Most effects of CUMS may be reversed by medicine, illustrating a powerful predictive validity. In rodents, CUMS conjointly has sensible features validity because it will bring out depression-like symptoms. The CUMS model includes the chronic sequent application to rats of a range of very gentle stressors.[5]

SL. NO.	DAY	PROCEDURE
1	Monday	9:00 Closed light 11:00 Remove food and water, 20 h cold–wet cage (200 ml water (4 °C)/cage)
2	Tuesday	9:00 Change dry cage, restore food and water, and 40 min of case shaking (200 rpm) 9:40 Stop case shaking, continuous light for 24 h
3	Wednesday	9:00 Closed light, record animal weight 10:00 24 h of tilted cage (45°), and remove water
4	Thursday	9:00 Stop tilted cage(45°), restore water, and change to 5 mice/cage 15:00 Change to single cage, remove food
5	Friday	9:00 Restore food, 40 min of case shaking (200 rpm) 9:40 Stop case shaking, 20 h hot–wet cage (200 mL water (45 °C)/cage)
6	Saturday	9:00 Change dry cage 10:00 24 h of tilted cage (45°), and remove water
7	Sunday	9:00 Stop tilted cage (45°), restore water, and change to 5 mice/cage 15:00 Change to single cage, continuous light for 20 h

Stressors

SL.NO.	STRESSORS
1.	Forced swimming in cold water (4° C)
2.	Swimming in 45° C hot water
3.	Deprivation of water and food for 24 h
4.	Noise
5.	Intermittent white noise
6.	Tail squeezing (2 min)
7.	Inversion of the light/dark cycle
8.	Cage shaking (30 min)
9.	Cage tilting (12 or 15 h)
10.	Damp sawdust (12 or 15 h)
11.	Confinement in a tube (3 h) 20
12.	Testing the dark phase and reversed light– dark cycle
13.	Predator sounds
14.	Placement in an empty cage
15.	Placement in an empty cage with water on the bottom
16.	Switching cages
17.	Without sawdust + cat feces
18.	Without sawdust + cage tilting
19.	Wet bedding
20.	Soiled bedding
21.	Rat droppings to mouse cages
22.	Overnight illumination
23.	Physical restraint
24.	Soiled cage
25.	Fasting for 48 h
26.	Empty water bottles
27.	Grouped housing
28.	Stroboscope lighting
29.	Restricted access to food
30.	Exposure to a foreign object (e.g., a piece of plastic)
31.	Small temperature reductions
32.	24 h social isolation
33.	24 h social crowding
34.	Hot stress in oven at 42° C

BEHAVIORAL TESTS

Sucrose Preference Test (Spt)

The SPT is generally used to estimate rodent behavior associated with a human clinical depressive symptom by assessing the ability to search for pleasure. This test was conducted as described earlier. After the removal of water for 12 hour, each mouse was simultaneously presented with 2 premeasured bottles filled with water or 1% sucrose solution (w/v) for 6 hour. Then the fluid ingestion was recorded and the bottles were exchanged their place for an extra 6 hour. The sucrose preference was defined as follows: [6]

Tail Suspension Test

The tail suspension test is frequently used to study depressive-like behaviors in mouse and it was performed according to previous methods with small modification in procedure. Briefly, mice tail were suspended in a hook by adhesive tape. The hook was located approximately 1 cm from the tip of the tail and which was 50 cm above the floor. Each animal was isolated to avoid hindrance during the experiment. The immobility was defined as the absence of movement during the last 4 min of the 6 min test. [6]

Forced Swim Test

Individual rats were placed in a clear plastic cylinder. The diameter of cylinder was 23cm. The peak of the cylinder was 65cm that was filled with 40cm of clear water at 25°C. The duration of the test was 5min and a trained investigator scored the behavior of the animals. Immobility was outlined because the absence of all movement except minor movement that's commonly needed for the mouse to settle its head higher than the surface. Consequently, the rat was towel dried

and came to its home cage. The water used in the test was replaced between each animal testing cycle. [6]

METHODOLOGICAL ISSUES IN CUMS MODEL

In the standard version of the CUMS protocol, as described by Willner and colleagues, male Lister hooded rats are first trained to consume a weak sucrose solution, which was available for 60 min in the home cage, following 20-h food and water deprivation. The concentration of sucrose used was 0.7070 (w:v) in the early experiments, and was slightly higher in more recent studies. The choice of sucrose concentration is dictated by the fact that the sucrose concentration intake function is bell-shaped. At low concentrations, on the ascending limb of the concentration-intake function, sucrose intake rises monotonically with concentration, and intake is monotonically related to reward value, as assessed by preference measures in choice tests.[7]However, at high concentrations, on the descending limb of the concentration-intake function, intake is no longer related in a simple way to reward value. For CUMS studies, sucrose concentration was set midway up the ascending limb of the concentration-intake function (1%), so that changes in responsiveness to reward, in either direction, would be reflected in corresponding changes in sucrose intake. The training phase of the procedure typically lasts for 2-3 weeks. Subsequently, half of the animals are subjected to CUMS, and sucrose intake tests are conducted once weekly. The standard CUMS protocol consists of the sequential application of a variety of mild stressors, each for a period of between 2 and 20 h, in a schedule that lasts for a full week, and is repeated thereafter. [8]

The schedule typically consists of: two 20-h periods of food and water deprivation, one immediately prior to the sucrose intake test, the other followed by 2 h of restricted access to food (scattering of a few 45 mg precision pellets in the cage); [9]one additional 16-h period of water deprivation; two periods of continuous overnight illumination; two periods (7 and 17 h) of 45 degree cage tilt; one 17-h period of paired housing; one 17-h period in a soiled cage (100 ml water in sawdust bedding); two periods (3 and 5 h) of intermittent white noise (85 dB); three periods (7, 9, and 17 h)[10]of low intensity stroboscopic illumination (60 flashes/minute). In the paired housing condition, animals are always housed in the same pairs, but the location alternates between the home cages of each member of the pair.[11]CUMS reliably causes a decreased intake of sucrose, relative to non-stressed control animals, which, once established, can be maintained by continued application of CUMS for 3 months or more, and persists for 2-3 weeks following the termination of CUMS.[12]Although the majority of studies in this model have used Lister hooded rats, sucrose intake is also suppressed by CUMS in Long Evans rats. Strain differences have been reported in other animal models of depression, and it was recently reported that sucrose intake was more suppressed by CUMS in an inbred Sprague-Dawley-derived hypercholinergic strain (FSL) than in the corresponding hypocholinergic strain (FRL). Although control animals are described as "non-stressed," they are, in fact, subjected to two stressors, which could potentially confound the results: all animals are housed singly and sucrose consumption tests are routinely carried out following 20-h food and water deprivation, applied equally to "stressed" animals and "controls." [13,14]

However, neither of these factors is responsible for the difference in sucrose intake between CUMS-exposed and control animals: Sucrose intake was decreased by CUMS to a similar extent in singly-housed and paired-housed animals, and also similar proportional decreases were seen in deprived and non-deprived as in animals. However, relative to testing with deprivation, intakes in non-deprived animals were both smaller and more variable, greatly reducing the statistical power of the experiment. Testing is therefore carried out following deprivation in order to reduce the number of animals needed to obtain statistically significant effects. Studies have been carried out to examine whether any of the elements of the CUMS protocol are either necessary or sufficient to cause anhedonia. In these experiments the CUMS timetable was first simplified by simply presenting stressors overnight, rather than at all times of day and night. Using this simplified procedure, the effects of subsets of stress elements were examined. This revealed particularly potent effects of a subset of three elements, each presented twice weekly: paired housing, exposure to wet bedding, and 45 ° cage tilt. [15]

The effects of each of these elements individually were therefore examined on single and repeated presentation. Of the various elements used, the only one that by itself reduced sucrose intake was paired housing. However, the effects of a single weekly pairing showed rapid habituation, and the effects of 6 weekly pairings (i.e., almost every night) also showed habituation, though more slowly. Although paired housing (in animals normally housed singly) appears to be the single most potent element in the CUMS protocol, it is not a necessary element. Experiments have also been conducted in which pairing was simply removed from the standard protocol. In three successive replications, the remaining elements, in combination, were found to decrease sucrose intake, despite the fact that none of them did so individually. Furthermore, while the effect of 6 weekly pairings habituated after 4-5 weeks, the effects of 2 weekly pairings, in combination with four other elements that in themselves were ineffective, were large and persistent. Thus, no one element of the CUMS protocol is either necessary or sufficient to maintain a persistent decrease in sucrose intake, but variety does appear to be essential.

NEURONAL PROCESS INVOLVED IN CUMS MODEL

Until recently, several researches have indicated that depression happens recognition to the various changes within the body, which can result from the reduction of structural flexibility of neurons. CUMS performed on rodents is generally wont to make a case for the

pathophysiology of nerve inflammation in depression associated to assess disorders related to an enlarged risk of neurodegenerative disorders. Clinical and pre-clinical information prove that depression is related to activation of the immune system that is manifested as the inflammation state. Particularly,[16] this problem is characterized by a rise in pro-inflammatory cytokines like TNF and interleukin-6. Depression can also be caused by increase in peripheral protein. The drug medical care involves administration of their antagonists or antidepressants and supporting the medicine properties of cytokines. Chronic exposure to the stress within the CUMS model features a massive influence on the brain regions concerned in memory and learning method in rodents. Discovered dysfunctions are in the middle of disturbances within the secretion system of HPA and various changes within the advanced cascades of living thing processes involving G proteins, super molecule kinases, second messengers, and transcription factors. Several studies have shown a link between disorders caused by varied semi-permanent acting stress factors and depression.[17]

Chronic stress causes a series of physiological changes in human body. One in all the foremost vital is that the activation of the HPA, that is related to excessive release of adrenal cortical steroid (called "stress hormone") within the blood. Moreover, enlarged glucoco-rticosteroids (GKS) level, induces harm to the dopaminergic, serotoninergic or glutamatergic neurons. GKS additionally cause the reduction in dendrites branching and reduction within the variety of nerve fibre spines. Enlarged GKS blood levels moreover result in inhibition of growing method. The importance of these changes is reduction in size of the hippocampus and therefore the frontal area that is characteristic for patients with severe depression. Disorder of the HPA is one in all the primary vital mechanism of depression. Moreover, enlarged release of adrenocorticotropin (CRH), caused by adrenocorticotropin (ACTH) emotional issue (CRF) is discovered. CRF plays a really vital role within the body's response to varied stress stimuli, by sweetening of CRH and adrenal cortical steroid secretion. Moreover, CRH has its own terribly robust psychedelic effects (anxiety- or depressive-like reaction, sleeping and ingestion disorders). Chronic stress causes the enhanced CRH secretion as a result of the super molecule kinases phosphorylation and of CREB-transcription issue activation. CRH acts on receptors within the adenohypophysis and causes stimulation of corticotropin release. Moreover, corticotropin will increase the synthesis and release of adrenal GKS (e.g., cortisol). In chronic depression, 2 opposing processes occur at the same time, i.e., stimulation of corticotrophin secretion by too secreted CRH and ACTH-induced robust inhibition to enlarged release of adrenal cortical steroid. The results of a recent study clearly show that adding a factor secret CRH to the mouse order, considerably will increase anxiety reactions, and additionally enhances responses to worry. [18]

The influence of CRH on anxiety processes runs through the cell receptor CRHR1 within the pituitary and alternative brain structures, like the body structure pathway and therefore the frontal area. Direct mechanism of adrenocorticotropin action is not totally understood, attributable to interaction with multiple neurohormonal and neurochemical systems. Several studies confirmed the link between CRH and monoaminergic neurochemical, i.e., 5-hydroxy tryptamine (5-HT, serotonin) and catecholamine (NA). This truth is confirmed by a big influence of CRH on the aminoalkanoic acid enzyme activity taking part within the Na synthesis. Desire is related to the CRH interactions with some endogenous substances that regulate desire like leptin.

The hippocampus and frontal area i.e.,[19] structures answerable for emotional responses, are notably liable to this concern. Studies conducted on laboratory animals in CUMS model have shown that long stressors cause atrophy of hippocampal pyramidic cells of CA3 and lower the resistance to alternative damaging agents (e.g., symptom and hypoxia). Chronic stress additionally impairs the growing that happens within the hippocampus and therefore the associative cortex. Thus, the growing is restricted and in consequence hippocampus (structure answerable for emotional responses) size undergoes reduction.[20]

Microglia are brain equivalent of peripheral immune cells i.e., lymphocytes. It was found throughout the brain and represent the prime cluster of cells that are activated in response to immune challenge. Microglia's activation alters the subject's response to worry. [21]It is useful within the starting, as for long run synergism and growing in hippocampus, mediate through neurotransmitters and inflammatory cytokines like glucocorticoids and IL-1. [22] However, it continues for long, it will progress towards vegetative cell injury and degeneration. Any kind of stress like traumatic brain injury, neural structure accidents, neurodegenerative diseases and infections will result in microglial activation. Moreover, microglial activation and therefore the ensuing neuroinflammation is also concerned within the pathophysiology of neurodegenerative disorders and depressive illness.23Increasing epidemiologic information counsel a relationship among inflammation, depression and neurodegeneration. Epidemiologic studies have shown that depressed subjects are a lot of apparently to develop chronic disease like Alzheimer's disease (AD) or Parkinson disease (PD) in older ages. Any diagnosis studies counsel that neuroinflammation can be one in all the mechanisms concerned during this association. [24,25]

Vaso-constrictive has been shown to suppress noble metal-induced protein and chemokine production and to extend microglial migration and therefore the bodily process, whereas antidepressants like impramine hydrochloride are shown to limit amyloid brain deposition within the mouse.[26] This later impact is mediate by a decrease in TNFα expression. Brain imaging studies in

humans have shown that depression or depressive-like states are associated to morphological (e.g., reduced volume of the hippocampus and enlarged basal ganglion volume) moreover as functional/molecular brain alterations (such as reduced activation of the temporal cortex and insula;[27] enlarged activity within the neural structure, ventromedial anterior and anterior cingulate cortices; enlarged activation of the amygdala; reduced hippocampal neurogenesis;[28] and altered BDNF levels within the nucleus accumbens). It will be hypothesized that a number of these brain changes can be associated with neuroinflammatory method and notably microglial activation.[29] However, at now, only a few studies have tried to look at the impact of stress-induced microglial activation within the varied brain areas proverbial to be concerned within the pathophysiology of depression. Consequently, the target of this study was to assess the power of the unpredictable chronic gentle stress (CUMS) model, a valid gnawer model of depression, to elucidate the role of neuroinflammation within the pathophysiology of depression and any connected increase within the risk of neurodegenerative disorders. Therefore it had been wanted to exist microglial activation in mice exposed to the CUMS procedure during a set of brain regions, namely, the cortex (infralimbic, prelimbic, medial orbital, cingulate), nucleus accumbens (core, shell), caudate basal ganglion, amygdala, bed nucleus of the stria terminalis and hippocampus (Cornu Ammonis one & three, rough complex body part, polymorphous layer and molecular layer of the rough gyrus). It tends additionally compared these results to the consequences of microorganism lipopolysaccharide, a well known substance of neuroglia.[30] Moreover, to check the stress-induced neuroinflammation with the peripheral immune alterations, we tend to measured bodily fluid levels of pro-inflammatory cytokines. [31]

Neuronal mechanism

In recent years, a strong consensus has emerged that the mesolimbic dopamine (DA) projection from the ventral tegmental area (VTA) to the nucleus accumbens plays a crucial role in mediating the behavioural effects of rewards, [32,33] one of the most important lines of evidence being the suppression of rewarded behaviour by DA receptor antagonists. There are striking parallels between the effects of DA receptor antagonists and those of CUMS. [34,35]

Effects of DA antagonists comparable to those described above for CUMS include:

1. Selective suppression of the intake of, and preference for, dilute sucrose solutions while sparing consumption of more concentrated solutions. This effect of neuroleptics has been shown to be localized within the nucleus accumbens.[36]

2. Attenuation of the intake-reducing and rate-enhancing effects of high sucrose content on the consumption of wet mash. [37]

3. Attenuation of food-induced place preference conditioning. [38]

4. Attenuation of amphetamine- and morphine-induced place preference conditioning; again, an effect localized to the accumbens. [39]

5. An increase in electrical threshold for ICSS through electrodes implanted in the VTA. [40]

In view of the extent of behavioural similarities between DA antagonist- and CUMS-treated animals, the mesolimbic DA system has formed a natural focus for studies of the neural mechanisms underlying CUMS-induced anhedonia and its reversal by antidepressant drugs.

Presynaptic Mechanisms

Three or seven weeks exposure to CUMS increased the concentration of DA and 5HT and their metabolites in limbic areas, but not in the caudate nucleus; concentrations of NA were unaltered by CUMS. [41]In subsequent experiments, DA release was measured in vivo, in anaesthetized animals, using fast cyclic voltammetry. In these studies, CUMS increased the electrically-stimulated release of DA, and again, these effects were observed in the nucleus accumhens only, not in the caudate nucleus. [42] A related observation was that CUMS also decreased the sensitivity of inhibitory DA autoreceptors, again, in the nucleus accumbens only, consistent with earlier behavioural observations that CUMS decreased sensitivity to a low (autoreceptor-selective) dose of apomorphine. [43]

These studies point to the nucleus accumbens as a region significantly involved in mediating the effects of CUMS.[44] However, these presynaptic changes cannot in themselves explain the alterations in sensitivity to reward. [45] One immediate problem is that CUMS apparently increases DA release in the accumbens, as observed also with acute stressors, which is difficult to reconcile with a neuroleptic-like behavioural profile. [46] A second problem is that the effects of chronic imipramine were very similar to those of CUMS.[47] Thus, chronic treatment (5 weeks) with imipramine (5 mg/kg/day) normalized sucrose intake, but also increased electrically-stimulated DA release to an extent similar to that seen following CUMS. Furthermore, imipramine did not reverse the increased DA release in CUMS-exposed animals.[48]

Postsynaptic Mechanisms

The similarity in the presynaptic effects of imipramine and CUMS suggests that changes in sensitivity to reward in this model are more likely to be mediated postsynaptically. Consistent with this hypothesis, a significant decrease in the number of D2 receptors in the nucleus accumbens was observed following prolonged (7 weeks) exposure to CUMS. Functional evidence of postsynaptic receptor subsensitivity was provided by a series of experiments assessing rewarding and locomotor stimulant effects of the D2/D3 agonist, quinpirole, administered at postsynaptically active doses (100-400 µg/kg).[49]

Locomotor activity was assessed by the distance traversed in a 45-min session in a runway; rewarding effects were assessed using the place conditioning paradigm, with administration of quinpirole on either the initially nonpreferred (white) or the initially preferred (black) side. In a further place preference experiment, quinpirole was administered directly within the nucleus accumbens (0.75 µg/side). In all experiments, responses to quinpirole were attenuated or abolished following CUMS. It therefore appears that anhedonia in CUMS-exposed animals results from subsensitivity of reward-related D2 receptors in the nucleus accumbens. [50] Our working hypothesis is that this effect is secondary to a prolonged and persistent overexposure to DA, resulting from an increase in DA release. Interestingly, subsensitivity to DA agonists has also been reported in the hypocholinergic FSL strain, which show increased susceptibility to the anhedonic effect of CUMS. [51]

A small decrease in the number of D2 receptors has also been observed in FSL animals, though this effect was not replicated in a later study. Antidepressant drugs have traditionally been assumed to exert their clinical effects through an interaction with NA or 5HT systems. [52] However, after chronic administration, antidepressants have also been found to potentiate the psychomotor stimulant effects of DA agonists, administered systemically or by direct injection into the nucleus accumbens. [53,54] Strong evidence that antidepressants reverse CUMS-induced anhedonia by potentiating DA transmission was provided by a series of studies in which the therapeutic response to tricyclic antidepressants was reversed by DA receptor antagonists. In these experiments, which were carried out following successful chronic treatment of CUMS-exposed animals with antidepressants, DA receptor antagonists were administered acutely immediately prior to sucrose intake tests, at low doses that are without effect in untreated animals or in non-stressed animals. [55]

The effects of D_1 (SCH-23390) and D_2 (pimozide, sulpiride, raclopride) antagonists were similar: all decreased sucrose intake in antidepressant-treated stressed animals, but not, at low doses, in any other group. By contrast, the 5HT receptor antagonist metergoline, which reverses certain other actions of antidepressants, was without effect in stressed animals successfully treated with imipramine. [56]The most striking finding from this series of experiments was that the therapeutic effects of fluoxetine and maprotiline in the CUMS model, which act primarily as 5HT and NA reuptake inhibitors, respectively, were also reversed by acute administration of raclopride (100 µg/kg).[57] This suggests that sensitization of D2 receptors within the nucleus accumbens may represent a final common pathway for the anti-anhedonic actions of antidepressant drugs and could well explain why it is that so little progress has been made in identifying groups of depressed patients who respond preferentially to 5HT or NE uptake inhibitors.[58,59,60]

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. 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. 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.

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