Received: 27 November 2019 | Revised: 5 March 2020 | Accepted: 6 March 2020

DOI: 10.1002/ame2.12107

ORIGINAL ARTICLE

Optimization of food deprivation and sucrose preference test in SD rat model undergoing chronic unpredictable mild stress

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Funding information
Chongqing Science and Technology Bureau, Grant/Award Number: cstc2017shms-zdyfX0048 and csts2017shmsA00007

Abstract

Background: The chronic unpredictable mild stress (CUMS) model has long been considered the best model for exploring the pathophysiological mechanisms underlying depression. However, there are no widely recognised standards for strategies for modeling and for behavioral testing. The present study aimed to optimize the protocols for food deprivation and the sucrose preference test (SPT) for the CUMS model.

Methods: We first evaluated the effects of different long periods of food deprivation on the body weight of Sprague Dawley (SD) rats by testing food deprivation for 24 hours (8:00-8:00$^+$), food deprivation for 12 hours during the daytime (8:00-20:00) and food deprivation for 12 hours at night (20:00-8:00$^+$). Next, we established a SD rat CUMS model with 15 different stimulations, and used body weight measurement, SPT, forced swim test (FST), open field test (OFT) and Morris water maze (MWM) test to verify the success of the modeling. In the SPT, consumption of sucrose and pure water within 1 and 12 hours was measured.

Results: Twelve hours of food deprivation during the daytime (8:00-20:00) had no effect on body weight, while 12 hours of food deprivation at night (20:00-8:00$^+$) and 24 hours of food deprivation (8:00-8:00$^+$) significantly reduced the mean body weight of the SD rats. When SPT was used to verify the successful establishment of the CUMS rat model, sucrose consumption measured within 12 hours was less variable than that measured within 1 hour.

Conclusions: Twelve hours of food deprivation in the daytime (8:00-20:00) may be considered a mild stimulus for the establishment of a CUMS rat model. Measuring sucrose consumption over 12 hours is recommended for SPT.

KEYWORDS

chronic unpredictable mild stress, forced swim test, Morris water maze, open field test, sucrose preference test, weight body

1 | INTRODUCTION

Depression is a chronic heterogeneous mental disease associated with high prevalence, recurrence, and mortality, with serious implications for human physical and mental health.[1-4] The World Health Organization has predicted that by 2020 it will become the second leading cause of disability worldwide and by 2030 major depressive disorders (MDDs) will represent the main cost in healthcare spending.[5,6] Although progress has been made in the research and treatment of depression in recent years, the exact pathogenesis of this disease is still not clear, and experimental results from animal models are not in good agreement with those of clinical trials.[7] Therefore, the establishment of appropriate animal models of depression is of great importance.

Current animal models of depression are mainly divided into three categories: stress models, surgical models, and chemical drug-induced models.[8-10] The most commonly used animal model is the chronic unpredictable mild stress (CUMS) model, which is the only model which manifests high surface, structural, and predictive validity.[11,12] However, the CUMS model has been questioned for its poor repeatability, most likely due to variation in stimulus modes, intensity and frequency.[13] Establishment of the CUMS model generally consists of two stages. The first stage is the exposure of the animals to noxious stimuli such as a tilted cage or food/water deprivation for long periods; and the second stage is the use of behavioral tests to screen the animals exhibiting depression-like behavior.[14,15] The use of food deprivation as one of the stimuli for inducing depression has been questioned in previous reports because it results in significant weight loss independently of other stimuli used in the CUMS model.[16,17] One of the behavioral tests, the sucrose preference test (SPT), often differs in its duration, and this can affect the experimental results. Hence, identifying the best time frame for the SPT, that will not impact negatively on the experimental outcome, is very important.

In SPT, the consumption of sucrose and pure water within 1 hour, immediately after 24 hours of food and water deprivation, is calculated. In order to rapidly quench their thirst after 24 hours of food and water deprivation, rats usually consume whatever liquid they come across, regardless of whether it contains sucrose or is pure water. Thus, a 1 hour test may be too short to record any decline in sucrose preference in rats in a depression-like state.

In this study, we compared the effects of 24 and 12 hours of food deprivation on the body weight of Sprague Dawley (SD) rats. In addition, given the distinctive circadian rhythm of rats, we further analyzed the results of 12 hours of food deprivation during the daytime (8:00-20:00) and at night (20:00-8:00$^+$). For the SPT, consumption of sucrose and pure water within 1 and 12 hours was measured.

2 | MATERIALS AND METHODS

2.1 | Animals and treatment

Twenty adult male SD rats (230-250 g) were used to investigate the effect of food deprivation on body weight. Another thirty adult male SD rats (230-250 g) were used to establish a CUMS rat model and to optimize the SPT method. All rats were purchased from the Laboratory Animal Center of Chongqing Medical University (SCXK (Yu) 2018-0003), housed in a single cage with a 12 hour light/12 hour dark cycle, and fed with food and water ad libitum (SYXK (Yu) 2018-0003). All animals were housed in the laboratory for 1 week prior to experiments to acclimatize to the environment. Experimental manipulations were approved by the Ethics Committee of Chongqing Medical University.

2.2 | CUMS paradigm

The schedule for establishing CUMS was conducted according to previously published methods,[18] but with minor modifications, and is presented in Table 1. The stress stimuli included tilting of the cage, food/water deprivation, a wet cage, crowding, hot water swimming, cold water swimming, no bedding in the cage, restraint, tail clamping, inverted light/dark cycle, hot water in the cage box, strobe lighting, forced swimming, and alternating periods of light and darkness. SD rats in the CUMS group were subjected to stimulation twice a day for 4 weeks. The rats were not exposed to the same stressor for two consecutive days.

2.3 | Scheme of food deprivation

Twenty SD rats were randomly divided into four groups of five rats each, comprising a normal control group, a 24 hour food deprivation group (8:00-8:00$^+$), a 12 hour daytime food deprivation group (8:00-20:00) and 12 hour nighttime food deprivation group (20:00-8:00$^+$). The rats were made to fast every Tuesday for 5 weeks.

2.4 | Body weight measurement

The body weight of each rat was measured with an electronic balance at 9:00 AM every Monday. Weight gain was calculated as the ratio of the weekly weight gain to the initial body weight.

2.5 | Sucrose preference test

Sucrose preference is defined as follows: sucrose preference percentage (%) = sucrose solution consumption (g)/(sucrose solution consumption [g] + water consumption [g]) × 100%. All rats underwent adaptive training from day 1 to day 4, with two bottles of pure water available on days 1 and 2, two bottles of 1% sucrose on day 3, and one bottle of pure water and one bottle of 1% sucrose on day 4. Next, after 12 hours of food and water deprivation, each rat was given 200 mL of pure water and 200 mL of 1% sucrose solution. The quantities of pure water and sucrose consumed were recorded after 1 hour and again after 12 hours. The SPT manipulation procedure is shown in Figure 1.

TABLE 1 Chronic unpredictable mild stress protocols conducted in this study

Stressor	Details
Food deprivation	Rats were subjected to 12 h of food deprivation starting from 8:00 AM
Water deprivation	Rats were subjected to 12 h of water deprivation starting from 8:00 AM
Restraint	Rats were individually restrained for 4 h inside plastic cylinders
Crowding	Rats were placed in a 29 cm × 18 cm × 16 cm cage, five/cage
Strobe light	Rats were subjected to 12 h of strobe light stress starting from 8:00 PM
Wet cage	Rats were immersed in 200 mL water in 100 g sawdust bedding for 24 h
Inversion of light/dark cycle	Rats were subjected to 24 h of reversed light/dark cycle (8:00 AM lights off, 8:00 PM lights on)
No padding	Rats were placed in cages without padding for 24 h
Hot water into the cage box	Rats were exposed to 40°C water at 15 cm depth for 10 min
Tilted cage	Rats were subjected to cage tilting (45°) along the vertical axis for 24 h
Cold water swimming	Rats were placed in a cylindrical clear plastic tank filled with 4°C water for 5 min
Hot water swimming	Rats were placed in a cylindrical clear plastic tank filled with 45°C water for 5 min
Tail clamping	Rats were endured tail pinch 1cm apart from the end of the tail for 1 min
Alternate light and dark	Rats were subjected to light on and off every 1 h for 12 h from 8:00 AM
Forced swimming	Rats were placed in a cylindrical clear plastic tank filled with 20°C water for 5 min

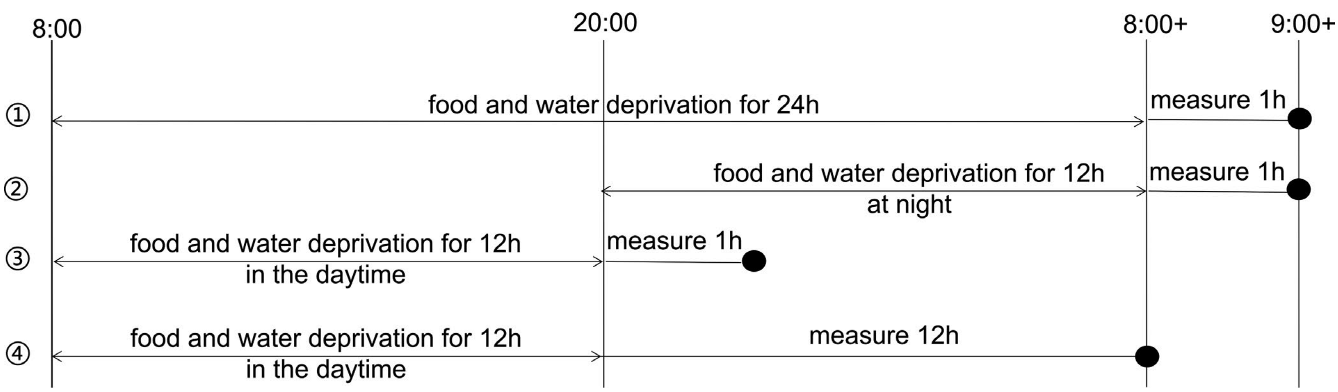

FIGURE 1 Time schedule for sucrose preference test. ①, ②, ③, and ④ represent different durations of food and water deprivation and time points at which sucrose preference was performed

2.6 | Behavioral experiments

2.6.1 | Forced swim test

Rats were put individually in a transparent plexiglass cylinder (20 cm diameter × 50 cm high) filled with water (23-25°C) to a depth of 30 cm. Immobility time was measured over a period of 5 minutes after 1 minute of adaptable swimming. Rats that floated without swimming to keep their heads above the water were judged to be immobile.

2.6.2 | Open field test

After being placed in the center of a 100 cm × 100 cm × 40 cm black square cage, the rats freely explored the environment for 5.5 minutes, with the first 30 seconds used to adapt to the environment. Between each test, the inner wall and the bottom surface of the square box were cleaned with 75% alcohol to eliminate the odor from the previous rat. The movements of the rats were recorded by a camera mounted above the center of the field. Smart 2.0 software was used to analyze the time spent in the center of the open field box and the total distance moved during the 5.5 minute test. Open field test (OFT) was performed on days 0 and 28 to assess the impact of CUMS on locomotor activity.

2.6.3 | Morris water maze test

A Morris water maze (MWM) is a black open circular pool with a diameter of 180 cm and a height of 60 cm. The pool was filled with 24 ± 1°C water, and an escape platform was placed 1.5 cm below the surface of the water during training. Black ink was then added to the water and stirred in order to obscure the platform. The pool was divided into four quadrants with the platform being placed in the center of the third quadrant.

Learning trials to test the rats' ability to navigate the maze were conducted over 7 days. On the first day (day 1), rats were dropped

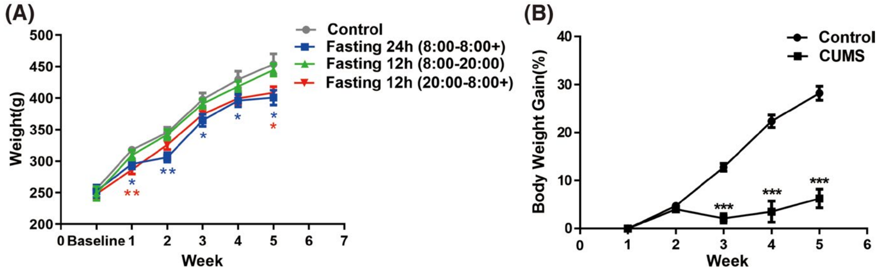

FIGURE 2 Effects of food deprivation and chronic unpredictable mild stress (CUMS) on rat body weight. A, Effects of 12 and 24 h of food deprivation on body weight in rats. 12 h of food deprivation in the daytime (8:00-20:00) had no effect on body weight ($P > .05$), while 24 and 12 h of food deprivation at night (20:00-8:00$^+$) for 5 wk significantly decreased body weight ($P < .05$). B, Effects of CUMS on body weight in rats. Results are presented as the mean ± SEM (n = 8), *$P < .05$, **$P < .01$, ***$P < .001$, CUMS group compared with the control group

from any quadrant into a platformless pool for 60 seconds to adapt to the environment. From days 2 to 6, each rat was placed into the water and expected to find the platform within 60 seconds. When a rat failed to find the hidden platform within 60 seconds, it was guided gently onto the platform and made to stay on it for 15 seconds. Each rat was trained 4 times daily with 30 minute intervals between successive training sessions. On day 7, the platform was removed and each rat was put into the water on the side opposite the original platform quadrant for a free 60 second probe. The escape latency, ie the time taken for the rat to find the platform (days 2-6), was recorded by a tracking-system as a measure of spatial learning and memory ability.

2.7 | Statistical analysis

Statistical analysis was performed with SPSS18.0 software. Data are presented as mean ± SE. Differences between the control and CUMS groups in body weight, and SPT and MWM data were assessed using repeated measures ANOVA; for other parameters, differences were assessed using a two-sample Student's *t* test or a non-parametric Mann-Whitney test. All tests were two-tailed. A *P*-value of less than .05 was considered statistically significant. All analyses and graph generation were performed with GraphPad Prism 8.0 software.

3 | RESULTS

3.1 | The effects of food deprivation and CUMS on body weight in SD rats

As shown in Figure 2A, after 5 weeks, the mean body weight of the 12 hour daytime food deprivation (8:00-20:00) group of rats was not significantly different from that of the control group ($F(1,8) = 0.372$, $P = .559$). However, the body weights of the 12 hour nighttime food deprivation (20:00-8:00$^+$) group and of the 24 hour food deprivation (8:00-8:00$^+$) group were significantly lower than the control group ($F(1,8) = 6.322$, $P = .036$; $F(1,8) = 5.373$, $P = .049$). Therefore, the 12 hour daytime food deprivation (8:00-20:00) group was selected to establish the CUMS rat model. As shown in Figure 2B, after being exposed to stressors for 4 weeks, the results of repeated measures ANOVA showed that body weight gain in the CUMS group was persistently significantly lower than in the control group ($F(1,14) = 70.490$, $P < .0005$). This first became evident by the end of week 2.

3.2 | Behaviorial tests

After conducting sucrose preference and OFTs at the baseline stage, two rats with low activity and intolerance to sucrose were eliminated, and the remaining 28 normal rats were randomly divided into two groups: a control group (n = 8) and a CUMS group (n = 20) for the subsequent experiments. After 4 weeks of stress, 8 out of 20 rats with depression-like tendencies were selected for the final behavioral comparison with the control group (n = 8). The corresponding results are summarized below.

3.2.1 | The effect of CUMS on anhedonia in the SD rats

As shown in Figure 3A, when the sucrose preference percentages of normal rats tested after 1 hour or after 12 hours were compared, greater data deviation was seen after 1 hour. This suggested that the accuracy and reproducibility of the sucrose preference percentage value was higher after 12 hours than that after 1 hour. In further tests with the CUMS rat model (Figure 3B), tested weekly from week 0 to week 4, repeated measures ANOVA showed that rats in the CUMS group had significantly lower sucrose preference percentages than the rats in the control group ($F(1,14) = 7.583$, $P = .016$).

3.2.2 | The effect of CUMS on the despair state of SD rats

As shown in Figure 4A, after 4 weeks of stimulation, the immobility time of the CUMS group in the forced swim test (FST) significantly increased compared with the control group ($t = 2.151$, $P = .0494$).

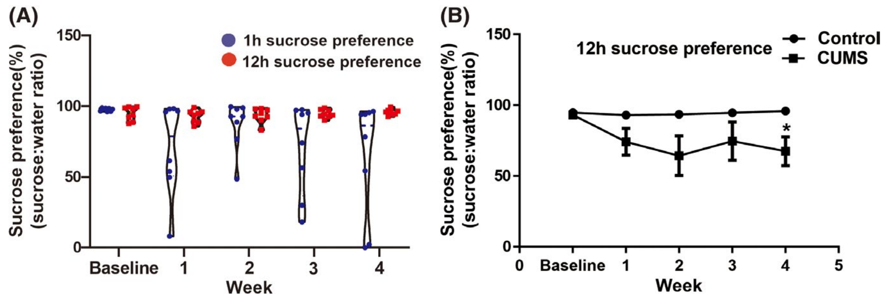

FIGURE 3 Effect of chronic unpredictable mild stress (CUMS) on the sucrose preference percentage in rats. A, Sucrose preference measured within 1 h (blue) and within 12 h (red). B, Sucrose consumption within 12 h was examined in rats after 4 wk of treatment with CUMS. CUMS exposure decreased the sucrose preference in rats. Results are presented as the mean ± SEM (n = 8), **P* < .05, CUMS group compared with the control group

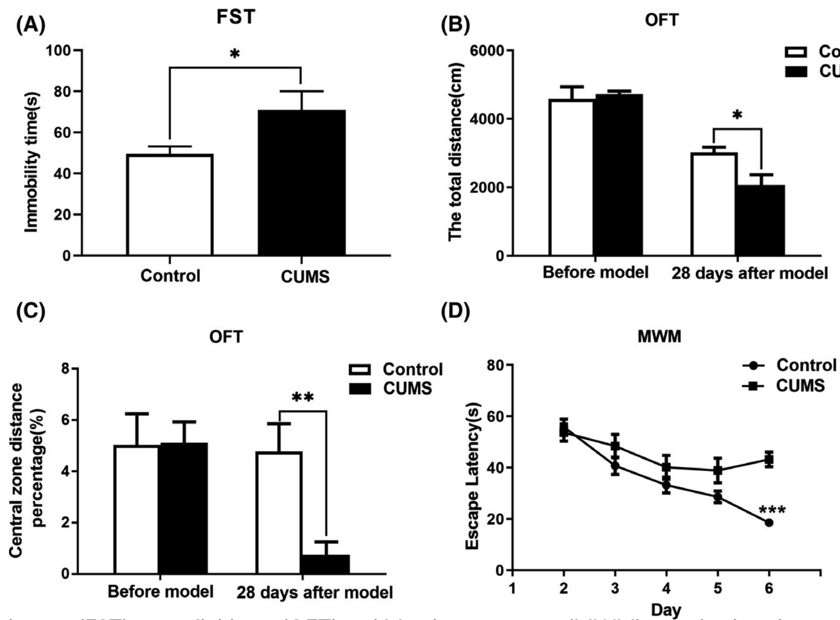

FIGURE 4 Forced swim test (FST), open field test (OFT) and Morris water maze (MWM) tests in chronic unpredictable mild stress (CUMS)-induced rat. A, The immobility time in FST. B, The total distance moved in OFT. C, The central distance percentage in OFT. D, The time to find the platform (indicated as escape latency time) in the MWM test probe trial. CUMS exposure decreased the total distance moved and central zone distance percentage in OFT and increased immobility and escape latency times in FST and MWM, respectively. Results are presented as the mean ± SEM (n = 8), **P* < .05, ***P* < .01, ****P* < .001, CUMS group compared with the control group

3.2.3 | The effect of CUMS on the locomotor activity of SD rats

After 4 weeks of stimulation, the total distance moved and the central distance percentage in OFT was significantly reduced in the CUMS group compared with the control group ($z = -2.209$, $P = .027$; Figure 4B) ($t = -3.385$, $P = .0044$; Figure 4C).

3.2.4 | The effect of CUMS on learning and memory in SD rats

Figure 4D shows that the escape latency of both groups declined gradually over 5 consecutive days of the MWM test. The CUMS rats seemed to spend slightly more time finding the hidden platform than the control rats, and repeated measures ANOVA confirmed that the rats in the CUMS group had a longer escape latency than the control group ($F(1,14) = 6.733$, $P = .021$).

4 | DISCUSSION

Research into dynamic changes during depression in human beings is constrained by methodological and ethical issues. Hence, establishing relevant animal models has become a common investigation strategy.[19] The most appropriate depression model of CUMS, first proposed by Willner et al in 1987, is a stress rat/mouse model in which the reward reflex activity is damaged.[20] Obvious anxiety, motility agitation, slow response, decreased learning and memory ability are clinically observed in patients with depression, with each episode lasting for at least two weeks. These symptoms also manifest in the CUMS animal models.

Decreased appetite is one of common symptoms of depressed animals so that weight loss is often used as one of the auxiliary indicators of depression. However, many reports have argued that it may not be a wholly satisfactory indicator, because weight loss could be the consequence of food deprivation alone rather than the combined effect of various stimuli during the CUMS modeling process. Any one of a variety of chronic mild stimuli may contribute, more or less, to weight loss in depressed animals. Out of 91 related reports in the literature (Table 2), 70 employed 24 hours of food deprivation.

TABLE 2 Durations of food deprivation from 91 published reports in the past 3 y

Duration (h)	No. reports	Percentage (%)
24	70[19,26-94]	76.9
48	4[95-98]	4.4
40	1[99]	1.1
23	1[100]	1.1
20	1[101]	1.1
17	1[102]	1.1
15	1[103]	1.1
16	1[104]	1.1
12	11[105-115]	12.1

TABLE 3 Variation in SPT protocols from 74 reports published in the past 3 y (the default concentration of sucrose is 1%)

Duration of food and water deprivation (h)	Duration of exposure to sucrose and pure water after deprivation (h)	No. reports
24	1[50-64,110,116-118]	19
	24[65-67,119]	4
	3[22,68,120-122]	5
	2[69,104]	2
	12[70]	1
23	1[71-81,100,123,124]	14
20	2[111]	1
	1[82,83]	2
	24[99]	1
18	1[6,125-127]	4
15	2[103]	1
12	1[84-85,112,128,129]	5
	3[19,86,87]	3
	12[88,113,114]	3
	2[89]	1
	24[90]	1
	4[91-92,115]	3
	6[93,94]	2
4	1[130,131]	2

Abbreviation: SPT, sucrose preference test.

Our results show that 24 hours (8:00-8:00$^+$) of food deprivation significantly reduced the body weight of the rats. Furthermore, 11 out of the 91 reports listed in Table 2 recommended 12 hours of food deprivation. However, no specific circadian period (daytime or night) for the 12 hour deprivation period was clearly indicated. In this study, we observed that 12 hours of food deprivation during the daytime (8:00-20:00) did not affect the weight of the rats, but food deprivation for 12 hours at night (20:00-8:00$^+$) and for 24 hours significantly decreased their body weight. This is probably due to the distinctive circadian rhythm of the rats which makes them more active, and therefore more likely to eat, at night.

In this study, 15 types of mild stressors were selected to induce depression in the SD rats. A classic test for anhedonia (the core symptom of depression) is the SPT.[21] Of the 74 reports in the literature that described methodologies involving SPT, most of the researchers measured sucrose and pure water consumption within 1 hour immediately after 24 hours of food and water deprivation (Table 3). Under normal physiological conditions, the water intake of rats is 10-12 mL/100 g/d, which means that the quantity water drunk in each hour is small. Rats experiencing 24 hours of food and water deprivation would be in a state of desperate thirst, and so would drink whichever of sucrose solution or pure water they found first. Since rats eat and drink more at night, as mentioned above, measuring the consumption of sucrose and pure water ad libitum between 20:00 and 8:00$^+$ could more accurately reveal the mood of rats. In the CUMS verification protocol, SPT is usually performed immediately after food and water deprivation. In this study, 12 hours of food and water deprivation (8:00-20:00) were followed by SPT measured over 12 hours from 20:00 to 8:00$^+$.

The immobility time in the FST is thought to reflect the behavioral despair state of rats, so it is often used to determine whether the rats are depressed. OFT is used to assess locomotor activity and spontaneous exploration in a novel environment.[22] The MWM test, an experiment in which rats or mice are forced to swim and learn to seek hidden platforms in the water, is mainly used to test the learning and memory ability of experimental animals for spatial location and sense of direction.[23-25] In this study, the immobility time of the CUMS group was longer than that of the control group, indicating that CUMS induced a depression-like state in the rats. Moreover, on OFT, the total distance moved and the percentage of distance moved in the central area were decreased in the CUMS group, indicating that the curiosity and preference for spontaneous activities of the rats were decreased. In addition, the time spent by the CUMS group in finding the platform in the MWM test was longer than the time spent by the control group, indicating that exposure to stressful stimuli damaged the cognitive ability of the rats. Overall, the 15 mild stimuli in the present study induced a behavioral despair state (immobility) as well as a significant reduction in body weight, exploration ability, learning and memory ability and the sucrose preference rate of the rats, which collectively are similar to the anhedonia in clinical patients with MDD. Our results indicate that a rat model of depression was successfully established in the current study.

There are about 20 stressors that are used in the CUMS model. However, this study only focused on food deprivation and SPT since they are frequently questioned or challenged in the literature. Future research will test other CUMS stressors, such as a safe and effective intensity of tail clamping.

5 | CONCLUSION

In summary, we suggest that 12 hours of food deprivation during the daytime (8:00-20:00) is a mild stimulus for the establishment of CUMS rat model, because it did not directly affect body weight, which is considered to be an indicator of the success of the depression animal model. Sucrose consumption over 12 hours is recommended for SPT.

ACKNOWLEDGMENTS

This work was supported by Social livelihood projects of Chongqing Science and Technology Bureau (cstc2017shms-zdyfX0048, csts2017shmsA00007).

CONFLICTS OF INTEREST

None.

AUTHOR CONTRIBUTIONS

YT and QZ conceived the idea and designed the experiments. LWH, LZ, YL participated in the main experiments. LWH and DMT co-wrote the main manuscript. NT and QZ analyzed data. TH took care of animals. YT revised the manuscript. All authors read and approved the manuscript.

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How to cite this article: He LW, Zeng L, Tian N, et al. Optimization of food deprivation and sucrose preference test in SD rat model undergoing chronic unpredictable mild stress. *Animal Model Exp Med*. 2020;3:69–78. https://doi.org/10.1002/ame2.12107