

Strain Differences in the Chronic Mild Stress Animal Model of Depression and Anxiety in Mice

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Abstract

Chronic mild stress (CMS) has been reported to induce an anhedonic-like state in mice that resembles some of the symptoms of human depression. In the present study, we used a chronic mild stress animal model of depression and anxiety to examine the responses of two strains of mice that have different behavioral responsiveness. An outbred ICR and an inbred C57BL/6 strain of mice were selected because they are widely used strains in behavioral tests. The results showed that the inbred C57BL/6 and outbred ICR mice were similarly responsive to CMS treatment in sucrose intake test (SIT) and open field test (OFT). However, the two strains showed quite different responses in forced swimming test (FST) and novelty-suppressed feeding (NSF) test after 3 weeks of CMS treatment. Only C57BL/6 mice displayed the depression- and anxiety-like behavioral effects in response to CMS treatment in FST and NSF test. Our results suggest that there are differences in responsiveness to CMS according to the different types of strain of mice and behavioral tests. Therefore, these results provide useful information for the selection of appropriate behavioral methods to test depression- and anxiety-like behaviors using CMS in ICR and C57BL/6 mice.

Key Words: Chronic mild stress, Depression, Anxiety, Behavior, Mice

INTRODUCTION

Depression is a serious disorder characterized by either a depressed mood or anhedonia, weight changes, sleep disturbances, psychomotor agitation, fatigue, feelings of worthlessness, diminished cognitive functioning, or recurrent thoughts of death. Stressful experiences have been reported to favor the development of depression in humans (Kessler, 1997; Kendler *et al.*, 1999; Kim *et al.*, 2013). Therefore, stress-based animal models were developed to explore depressive phenomena. Depression is thought to result from interactions between the effects of environmental stress and genetic predisposition. In the present study, we used a stress procedure that included most of the commonly used "unpredictable, mild" stressors (Willner *et al.*, 1992; Willner, 1997). The CMS procedure has been shown to decrease rodents' preference for sweet solutions, which is considered to represent anhedonia, a core symptom of major depression (Willner, 2005). Also, the CMS procedure mimics the role of chronic stress in precipitating depression and induces various physical, behavioral, and neurochemical alterations that resemble those observed in

depressed patients.

There has been an increasing number of studies on CMS effects in mice although most studies were previously performed in rats. It has been reported that the CMS paradigm in mice elicits a decrease in responsiveness to rewards, as revealed by decreased palatable sucrose consumption (Pothion *et al.*, 2004), deteriorates their physical state, and induces changes in emotion-related behaviors. In addition, a difference in sensitivity to chronic mild stress has been shown according to the strain of mice. Furthermore, mouse strain differences have been reported in response to antidepressant drugs in depression-related behavior models (Yalcin *et al.*, 2008). These reports suggest that genetic factors, such as strain differences, may contribute to the behavioral effects of mice in models of depression.

Previous studies showed that there are differences between strains of mice in the sucrose consumption test (Pothion *et al.*, 2004) and depression-related behavior models such as the forced swimming test and the tail suspension test (Mineur *et al.*, 2006). For instance, C57BL/6 mice show a decrease in immobility duration in the tail suspension task after

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Table 1. Weekly CMS schedule

	Mon	Tue	Wed	Thu	Fri	Sat	Sun
Morning	Confinement (1 h)	Weekly sucrose intake test (9:00-10:00)	Paired housing (2 h)	White noise (4 h)	Confinement (1 h)	Empty bottle (1 h)	Reversed light/dark cycle
Evening	Food and water deprivation (15 h)	Removal of nesting materials	Overnight illumination	Soiled bedding	Water deprivation	Reversed light/dark cycle	Tilt cage (45°)

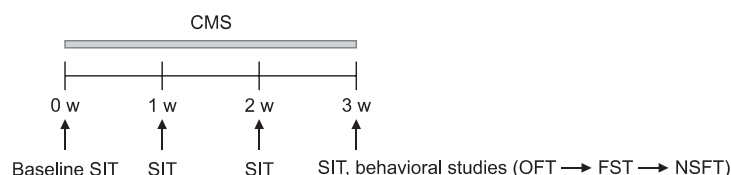


Fig. 1. Experimental schedule. The chronic mild stress (CMS) protocol lasted 3 weeks. Before the CMS procedure, baseline sucrose intake was measured. Once a week, sucrose intake and body weight were measured. After 3 weeks of CMS, behavioral tests were carried out in order as follows.

CMS, whereas BALB/c mice show increased immobility. On the other hand, C57BL/6 mice show increased immobility in the forced swimming test after CMS. However, reports are still controversial, making it difficult to establish a clear behavioral profile of genetically/phenotypically different mouse strains after stress.

Generally, high comorbidity rates of depression and anxiety are observed in depressed patients, and the margins between depression and anxiety become blurred, which suggests that these disorders may not be entirely distinct conditions in humans or animals (Kaufman and Charney, 2000). Increases in anxiety-related behavior and locomotor disturbances were found to be induced by the stress procedure (Strekalova *et al.*, 2004; Schweizer *et al.*, 2009). These behavioral changes were considered to reflect additional depression-related symptoms (Willner, 2005). However, very little is known about how strain differences in mice impact stress-induced behavioral changes in behavior models including the open field test and novelty-suppressed feeding test.

In the present study, we examined the impact of differences in responsiveness to CMS on “anhedonia” (sucrose consumption) and depression- and anxiety-like behaviors in different strains of mice. We investigated the effects of CMS on different tests measuring anxiety- and depression-like behaviors using the sucrose intake test, forced swimming test, open field test, and novelty-suppressed feeding test. C57BL/6 and ICR strains of mice were selected because they are representative of inbred and outbred strains, respectively. Also, they are the most widely used strains in various behavioral tests. The purpose of this study was to identify potential behavioral differences in depression and anxiety between C57BL/6 and ICR strains after CMS treatment.

MATERIALS AND METHODS

Animals

Male C57BL/6 (J) and ICR mice weighing 22-30 g were purchased from Dae Han Biolink, Co., Ltd (Eumseong, Korea).

The animals were housed 4-5 mice per cage in a temperature- and humidity-controlled room ($23 \pm 1^\circ\text{C}$, $55 \pm 5\%$) under a 12-h light/dark cycle (light on 07:00-19:00) and allowed access to food and water *ad libitum*. After arrival, mice were acclimatized for 1 week prior to use in experimental procedures. Mice were introduced to the experiment room at least 1 h before the behavioral tests. All animal care procedures were conducted in accordance with the U.S. National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of Sungkyunkwan University.

Chronic mild stress schedule

The CMS procedure was performed as described (Elizalde *et al.*, 2010; Briones *et al.*, 2012) with slight modifications. The mice in the experiment were subjected to CMS for 3 weeks. The stressors were applied twice per day, in the morning (9:00) and the evening (19:00). The CMS procedure consists of a variety of unpredictable mild stressors including two periods of confinement (1 h), one period of paired housing (2 h), one period of white noise (85 dB, 4 h), one period of tilted cage (45°, overnight), one period of nesting materials removal (overnight), one period of water deprivation (overnight), one period of exposure to an empty bottle (1 h), one period of soiled bedding (overnight), one period of overnight illumination, and one period of reversed light/dark cycle (24 h). The weekly CMS schedules are listed in Table 1. The stressors were randomly scheduled over a 1-week period and repeated throughout the 3 weeks. The non-stressed control mice were housed in groups (4-5 per cage), and the stressed mice were singly housed. After 3 weeks of CMS, behavioral tests were carried out in the order presented in Fig. 1. The sucrose intake tests were performed at baseline, 7, 14, and 21 days along with body weight measurement. The open field test, forced swimming test, and novelty-suppressed feeding test were performed at 22, 23, and 25 days, respectively. All behavioral tests were conducted between 9 h and 13 h.

Sucrose intake test

The SIT was conducted as described (Gronli *et al.*, 2005; Schweizer *et al.*, 2009; Ma *et al.*, 2011; Lee *et al.*, 2013) with slight modifications. Following acclimation, mice were first trained to consume a 1% (w/v) sucrose solution for 48 h. After consumption stabilization, mice were divided into two groups and matched for sucrose intake baseline and body weight baseline. Once a week, sucrose intake (1% sucrose solution) and body weight of all animals were measured during a 1 h window (Tuesday 9:00-10:00) after 15 h of food and water deprivation in both the CMS and control groups. The food and water deprivation period preceding sucrose intake measurement may be considered to be a further stress applied on top of the CMS protocol. However, control mice were also exposed to food and water deprivation as a part of the test (Stedenfeld *et al.*, 2011; Zhang *et al.*, 2013). Consumption was measured by weighing the pre-weighed bottle at the end of the test. The relative sucrose intake was expressed as absolute intake (g) per mouse body weight (g).

Open field test

Locomotor activity was assessed by OFT after 3 weeks of CMS exposure. The open field consisted of an opaque plastic box (30×30×30 cm) divided into 16 (4×4) identical sectors (7.5×7.5 cm). The field was subdivided into peripheral and central sectors, where the central sector included 4 central squares (2×2) and the peripheral sector was the remaining squares (Li *et al.*, 2008; Sakata *et al.*, 2010). The animals were placed into the center of an open field and allowed to explore for 10 min under dim light. The open field arena was thoroughly cleaned with 70% ethanol between each test. A video tracking system (NeuroVision, Pusan, Korea) was used to record the distance traveled as a measure of locomotor activity. The time spent in and entries into the center were measured as an anxiolytic indicator (Prut and Belzung, 2003; Grivas *et al.*, 2013).

Forced swimming test

The FST was carried out on mice according to the method of Porsolt (Porsolt *et al.*, 1977). Briefly, mice were individually placed into a glass cylinder (20 cm in height, 14 cm in diameter) filled 16 cm high with water (25 ± 1°C). A styrofoam divider separated the cylinders so that the mice could not see each other during the trials. After a 6-min swim test session, the immobility time during the final 4-min interval of the test was measured using the video tracking system (EthoVision, Noldus, Wageningen, Netherlands). Immobility time was considered to be a mouse floating passively, making only small movements to keep its nose above the surface.

Novelty-suppressed feeding test

The NSF test was performed according to a modified procedure, as described previously (Jang *et al.*, 2013). Twenty-four hours after food deprivation, mice were placed in a plastic box, where they were subjected to the NSF test for 5 min. At the beginning of the test, a single food pellet was placed in the center of the box, and mice were placed in one corner. Latencies to approach and to begin eating were recorded. Scoring for the measure of interest did not begin until the mouse reached for the food with its forepaws and began eating. Immediately after the test, the mouse was transferred to its home cage and the amount of food consumed in the next 5 min was measured

(home-cage food consumption).

Statistical analysis

Data are expressed as the means ± SEMs. The data were analyzed by two-way ANOVA followed by the Bonferroni post hoc test using Prism 5.0 (GraphPad Software, Inc., USA). Significant differences were set at the $p < 0.05$ level.

RESULTS

Sucrose intake test

Before the onset of CMS, sucrose intake was similar in both the control group and in the group of mice that were to undergo stress. In ICR mice, there was a significant interaction between stress and time ($F_{1,80} = 3.897$, $p < 0.05$) (two-way ANOVA). The post hoc test revealed that exposure to CMS produced a significant decrease in the sucrose intake (absolute intake per body weight) in the third week, compared to the control mice ($t = 3.327$, $p < 0.01$, Fig. 2A). In C57BL/6 mice, a significant interaction between stress and time was found in the group exposed to CMS ($F_{1,72} = 3.026$; $p < 0.05$) (two-way ANOVA). The post hoc test revealed that exposure to CMS produced a significant decrease in sucrose intake after 3 weeks, compared to the control mice ($t = 4.190$, $p < 0.001$, Fig. 2C). Moreover, the stressed mice showed significant decreases of body weight compared to the control groups in ICR and C57BL/6 mice ($p < 0.001$, $p < 0.05$, Fig. 2B, 2D).

Open field test

After 3 weeks of CMS exposure, the open field test was performed to evaluate locomotion and anxiety-like behaviors. The stressed mice showed increased movement without significant changes compared to the control mice in both strains (Fig. 3A). In addition, the two strains of ICR and C57BL/6 mice caused significant central activities in the open field test. Both strains, ICR and C57BL/6 mice, showed significant decreases in time spent in the center after CMS (ICR: $t = 2.438$, $p < 0.05$; C57BL/6: $t = 3.672$, $p < 0.01$, Fig. 3B). Furthermore, entries into the center decreased significantly in stressed mice of both strains (ICR: $t = 3.996$, $p < 0.001$; C57BL/6: $t = 2.923$, $p < 0.05$, Fig. 3C).

Forced swimming test

Depression-like behavior of the different strains in the FST is shown in Fig. 4. The stressed C57BL/6 mice significantly showed depressive behavior by displaying increased immobility compared to the non-stressed mice after CMS ($t = 2.548$, $p < 0.05$). On the other hand, ICR mice did not show a significant change after the stress exposure ($t = 1.002$, $p > 0.05$). With regard to significant effect across strains, we have performed further statistical analysis. When CMS group was compared between ICR and C57BL/6 mice, the results showed a significant effect ($p < 0.05$, Fig. 4).

Novelty-suppressed feeding test

The NSF test measures food consumption in a novel environment under food deprivation, where reduction is interpreted as anxiety-like behavior as well as depression-related behavior (Bodnoff *et al.*, 1988). Depression- and anxiety-like behavior of the different strains during the NSF test is illustrated in Fig. 5. In ICR mice, the latency of eating in the NSF test

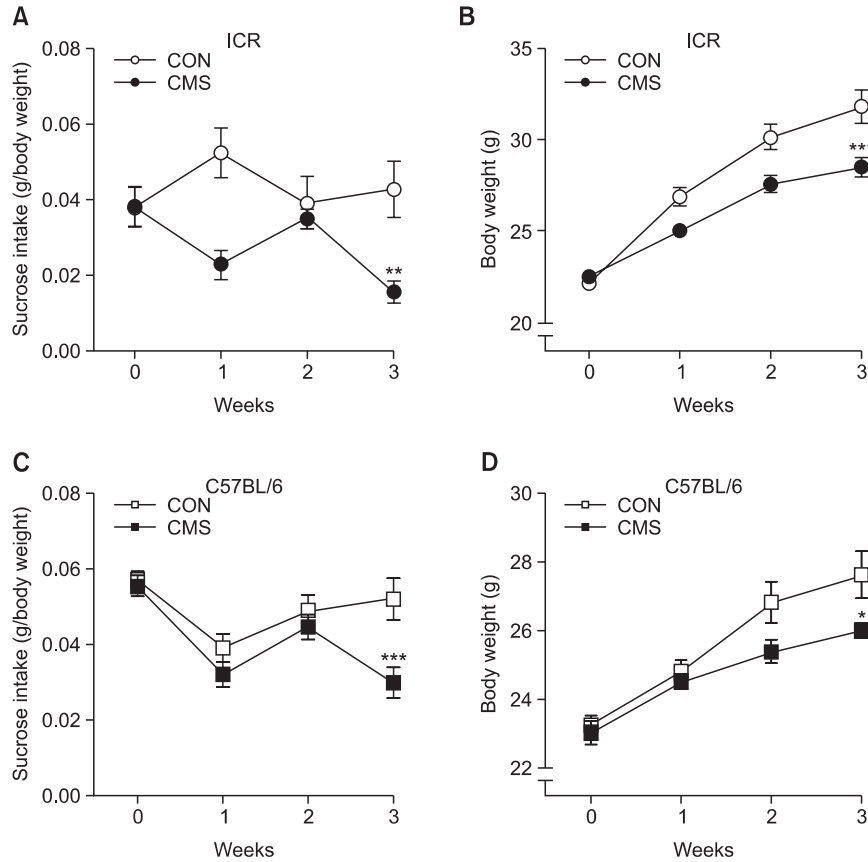


Fig. 2. Effects of CMS on sucrose intake test and body weight in ICR (A and B) and C57BL/6 (C and D) mice. Once a week, sucrose intake and body weight of all animals were measured during a 1-h window after 15 h food and water deprivation in both control and CMS group. The relative sucrose intake was expressed as absolute intake (g) per mouse body weight (g). Data are presented as means \pm SEMs (n=10-12/group). * p <0.05, ** p <0.01, *** p <0.001 compared to the corresponding control (two-way ANOVA, Bonferroni post-test).

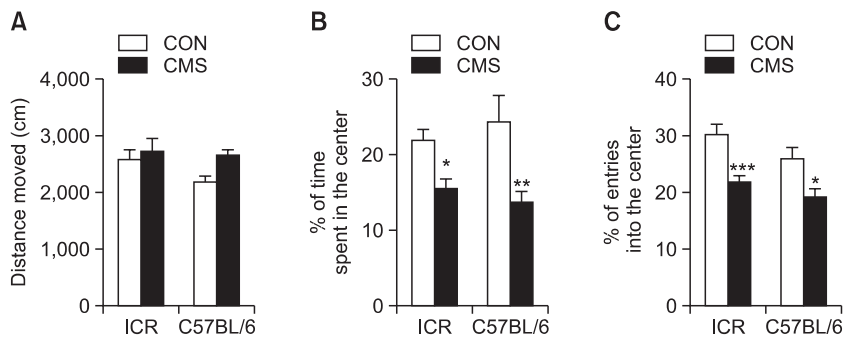


Fig. 3. Effects of CMS on locomotion and central activity in the open field test. The animals were allowed to explore the open field arena for 10 min. (A) Total distance moved (cm), (B) % of time spent in the center, (C) % of entries into the center in ICR and C57BL/6 mice. Data are presented as means \pm SEMs (n=10-12/group). * p <0.05, ** p <0.01 and *** p <0.001 compared to the corresponding control (two-way ANOVA, Bonferroni post-test).

was not affected by 3 weeks of CMS experience (Fig. 5A). On the other hand, C57BL/6 mice showed a significant increase in latency of eating after CMS ($t=4.200$, $p<0.001$, Fig. 5A). We also tested home-cage food consumption to assess whether the increased feeding latency of stressed C57BL/6 mice could be attributed to a change in appetite. However, there were no differences in home-cage food consumption among groups in

either the ICR and C57BL/6 strains (Fig. 5B).

DISCUSSION

In the present study, we assessed potential differences between one outbred (ICR) and one inbred (C57BL/6) mouse

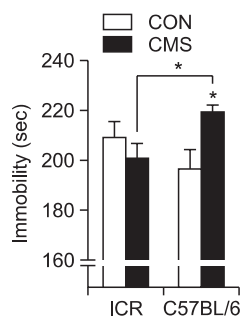


Fig. 4. Effects of CMS on immobility in the forced swimming test. Immobility was analyzed by final 4 min of total 6 min test. Data are presented as means \pm SEMs ($n=10-12$ /group). * $p<0.05$ compared to the corresponding control (two-way ANOVA, Bonferroni post-test).

strain in response to different types of behavioral tests in the CMS model. The present data showed marked differences between the two mouse strains in their responsiveness to the CMS procedure. The C57BL/6 mice showed depression- and anxiety-like behavioral effects in the SIT, OFT, FST, and NSF tests after 3 weeks of CMS treatment. However, ICR mice failed to display depression-like behaviors in the FST and NSF tests.

CMS is generally thought to be the most promising and valuable rodent model for studying depression in animals because it mimics several human depressive symptoms. Moreover, genetic factors, such as strain differences, may contribute to the behavioral performance of mice in models of depression. Previous studies reported that there were differences between strains of mice in sucrose intake (Pothion *et al.*, 2004) or in some of the CMS-induced behavioral alterations (Mineur *et al.*, 2003, 2006).

Reduced consumption of sucrose solutions induced by CMS has been used as a measure of anhedonia, a major symptom of depression (Willner *et al.*, 1992). As weight loss following CMS may influence sucrose intake and could be a confounding variable, we measured relative sucrose intake as absolute intake (g) per mouse body weight (g), which is considered to be an index for anhedonia (Matthews *et al.*, 1995). In our experiment, a variety of mild stressors induced similar significant effects in sucrose intake in both strains. Stressed ICR mice showed a 63.3% decrease in sucrose intake compared to the non-stressed control group, whereas stressed C57BL/6 mice displayed a 42.6% decrease in the 3rd week of CMS. In this study, we applied a food and water deprivation schedule for sucrose intake measurement. The food and water deprivation period preceding sucrose intake measurement may be considered to be a stressor for the CMS group but as a part of the test for the control group. However, we cannot exclude the possibility that an overnight food and water deprivation period influences other behaviors besides depressive behaviors. Moreover, we observed fluctuations in the consummatory data in both strains. These might be a consequence of the short measurement interval and the consequential low intake during test time.

When testing anxiety-related behaviors in the open field, similar effects on CMS were obtained in both strains. When the mice were placed in a novel environment, increased tendencies of locomotor activity in the stressed mice were observed.

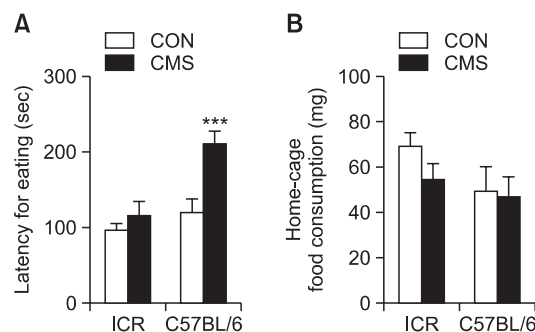


Fig. 5. Effects of CMS on depression- and anxiety-like behavior in the novelty suppressed feeding test. (A) Latency for eating (sec), (B) Home-cage food consumption (mg). Twenty-four hours after food deprivation, mice were subjected to the NSF test for 5 min. Immediately after the test, the mouse was transferred to its home cage and the amount of food consumed in the next 5 min was measured. Data are presented as means \pm SEMs ($n=10-12$ /group). *** $p<0.001$ compared to the corresponding control (two-way ANOVA, Bonferroni post-test).

A previous study reported that CMS-treated mice showed more activity than control mice in the open field (Mineur *et al.*, 2006). Moreover, Strelakova and colleagues (2009) showed that chronic stress caused hyperactivity in mice, when tested under a light of modest brightness. These results are in accordance with our data that show increased tendency of movement after chronic stress. In this study, the CMS procedure significantly decreased preference for the central area in both strains. A decrease in these parameters could be indicative of anxiogenic behaviors (Prut and Belzung, 2003). These results suggest that anxiety-related behaviors in the OFT may be relatively unaffected by genetic susceptibility to CMS.

Some strain differences have been described previously for the tail suspension test (Liu *et al.*, 2001) and forced swimming test in mice (Lucki *et al.*, 2001). However, we chose only the FST because C57BL/6 mice have a strong tendency to climb up their tails, which would have defeated the purpose of the TST (Mayorga and Lucki, 2001). In our experiment, C57BL/6 mice showed increased immobility after CMS, whereas ICR mice did not show a significant change in the FST (Fig. 4). These results suggest that ICR mice are inappropriate for evaluating stress-induced depressive behavior in the FST. These results also underscore the strong influence of genetic background on susceptibility to CMS. Similarly, Lucki *et al.* (2001) reported that the C57BL/6 mice with the highest immobility values may be more vulnerable to stress-evoked depressive behavior.

The NSF test is often used as an additional measurement of depressive behavior and is also used to assess chronic antidepressant efficacy in rodents (Santarelli *et al.*, 2003; Bessa *et al.*, 2009; Zhu *et al.*, 2010). The NSF test is more sensitive to chronic depression-like responses that are correlated to anxiety, whereas the FST evaluates severe depression-like responses in desperate situations. In this study, C57BL/6 mice showed significantly increased latency in eating compared to the control group. Our results also support the idea that mice exposed to chronic stress respond more sensitively to the NSF test ($p<0.001$) than to the FST ($p<0.05$). On the other hand, ICR mice failed to display depression-like behavior in the NSF test.

In this study, we found that the C57BL/6 and ICR strains of mice displayed different responsiveness to CMS through depression- and anxiety-like behaviors. It should be mentioned that there might be relevant neurochemical differences between two strains that could influence behavioral responsiveness. Previously, it has been reported that a specific and regionally differentiated serotonin-dopamine interaction is directly related to the observed stress-induced anhedonia in different rat strains (Bekris *et al.*, 2005). Moreover, Wu and Wang (2010) reported that there were differences in HPA axis responsiveness between inbred and outbred strains of rats, thereby affecting the manifestation of depressive behavior. The evaluation of neurochemical alterations following behavioral changes may help to elucidate clear differences of responsiveness in different mouse strains.

In summary, this study showed that different strains of mice exhibited different behavioral patterns in various animal models including the SIT, OFT, FST, and NSF tests. The inbred C57BL/6 and outbred ICR mice were similarly responsive to CMS treatment in SIT and OFT. However, two strains showed quite different responses in FST and NSF test. Only C57BL/6 mice displayed depression- and anxiety-like behavioral effects to CMS treatment in FST and NSF test. Our results suggest that there are differences in responsiveness to CMS according to the different types of strain of mice and behavioral tests. Therefore, these results provide useful information for the selection of appropriate behavioral methods to test depression- and anxiety-like behaviors using CMS in ICR and C57BL/6 mice.

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