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Resident intruder paradigm-induced aggression relieves depressive-like behaviors in male rats subjected to chronic mild stress

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Background: Accumulating epidemiological evidence shows that life event stressors are major vulnerability factors for psychiatric diseases such as major depression. It is also well known that the resident intruder paradigm (RIP) results in aggressive behavior in male rats. However, it is not known how resident intruder paradigm-induced aggression affects depressive-like behavior in isolated male rats subjected to chronic mild stress (CMS), which is an animal model of depression.

Material/Methods: Male Wistar rats were divided into 3 groups: non-stressed controls, isolated rats subjected to the CMS protocol, and resident intruder paradigm-exposed rats subjected to the CMS protocol.

Results: In the sucrose intake test, ingestion of a 1% sucrose solution by rats in the CMS group was significantly lower than in control and CMS+RIP rats after 3 weeks of stress. In the open-field test, CMS rats had significantly lower open-field scores compared to control rats. Furthermore, the total scores given the CMS group were significantly lower than in the CMS+RIP rats. In the forced swimming test (FST), the immobility times of CMS rats were significantly longer than those of the control or CMS+RIP rats. However, no differences were observed between controls and CMS+RIP rats.

Conclusions: Our data show that aggressive behavior evoked by the resident intruder paradigm could relieve broad-spectrum depressive-like behaviors in isolated adult male rats subjected to CMS.

Keywords: resident intruder paradigm • aggression • depressive-like behaviors • chronic mild stress

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Background

Depression is a severe disorder characterized by behavioral, neurochemical and other physiological abnormalities that affect 15–20% of people at some point in life [1,2]. Yet, despite intensive research on the pathophysiology of depression, the factors causing depression disorders remain poorly identified. One experimental method to explore the mechanisms and functional consequences of depression is the use of animal models based on exposure to repeated stress. The chronic mild stress (CMS) paradigm is the most popular animal depression model; it can induce various behavioral, neuro-immune, and neuroendocrine changes that resemble those observed in patients with depression, where symptoms can be reversed with some antidepressants [3–8].

Conversely, resident intruder stress is based on the nature of rats observed in different situations that can influence behavioral and biological responses. These procedures minimize injury while emphasizing the psychosocial component of the stress [9,10]. There is a large body of evidence that indicates that resident intruder stress leads to aggressive behavior in rats [11–14]. Some studies also revealed that there was no difference between aggressive and non-aggressive female rats in anxiety, locomotor activity, and sensitivity to restraint stress and sucrose consumption [15]; indicating that aggressive behavior induced by the resident-intruder paradigm differed from depression in rats. Additionally, Mitchell and Fletcher [16], Mitchell and Redfern [17] and Mitchell et al. [18] showed that acute treatment with antidepressant drugs decreased aggressive behavior of resident animals, but that aggressive behavior increased after chronic treatment, as it was proved that antidepressants are effective in treating the depression rat model if administered long-term [19]. Collectively, it is of great interest to investigate the likely effects of resident intruder paradigm-induced aggression on the depressive-like behavior in male rats subjected to CMS.

Therefore, in the present study, we investigated the effects of resident intruder paradigm-induced aggression on depressive-like behaviors induced by the CMS procedure in socially isolated male rats. The experimental protocol and behavioral evaluations for this study are shown in Figure 1.

Material and Methods

Animals

A total of 54 male, specific pathogen-free Wistar rats, weighing 180–220 g, were provided by the Center for Laboratory Animals, Shandong University of Traditional Chinese Medicine (SCXK LU 2011-0019). The rats were housed separately in Type III Macrolon cages and were allowed *ad-libitum* access to food and water. Room temperature was controlled at 21±1°C with a 12-h light/12-h dark cycle (lights on at 22:00 h). The animals were allowed to acclimate to the environment for 2 weeks (control phase). All experiments were performed during the dark phase of the light/dark cycle under a dark red light (<2 lux).

In addition, 34 male, specific pathogen-free Wistar rats, weighing 120–150 g, were provided by the Center for Laboratory Animals, Shandong University of Traditional Chinese Medicine (SCXK 2005-0015), and were selected as intruders. The rats were housed in another room (4–5 rats per cage), but subjected to conditions identical to those described above.

Animal experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals, formulated by the National Institutes of Health, USA, and were approved by the Institutional Committee for Animal Care and Use of Shandong University of Traditional Chinese Medicine (Approval ID: DWSY201004183).

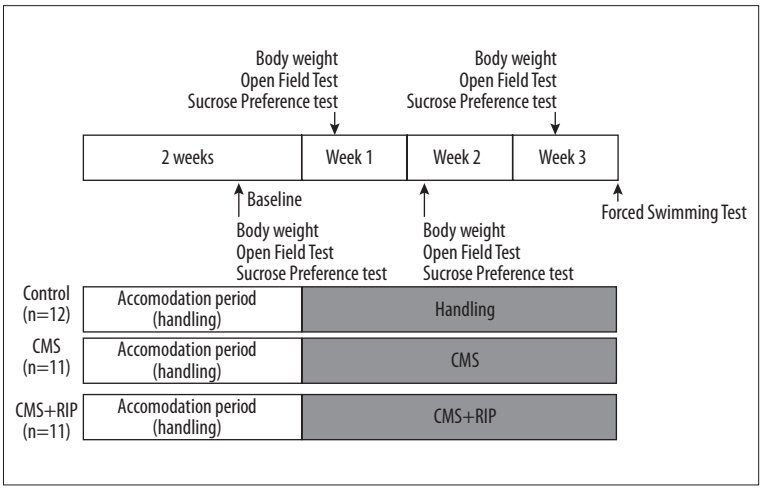

Figure 1. Experimental protocol. CMS procedures were performed on CMS and CMS+RIP animals for 3 weeks. The sucrose preference test (SPT) was performed at 12, 16, 23, and 30 days. The open-field test (OFT) was performed at 12, 16, 23, and 30 days. The forced swimming test (FST) was performed at day 35. The body weights were measured at 12, 16, 23, and 30 days.

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Table 1. Schedule of chronic mild stress (CMS) procedure.

	Stroboscope	Rotation	Food deprivation	Water deprivation	Wet bedding	White noise	Continuous light	Empty water bottle	Foreign object	Tilt 45°	Nip tail	Restricted access to food	Odor
Monday	10:00 12:00	15:00 15:30	15:00	15:00	17:00								
Tuesday			14:00	14:00 15:00	10:00	18:00 21:30	18:00						
Wednesday	10:00 17:00		17:00	11:00 17:00			10:00	10:00 11:00	17:00				
Thursday		10:00 10:30	10:00	10:00					10:00	10:30 17:00	17:00 17:01		
Friday						12:00 17:00						10:00 12:00	17:00
Saturday			10:00	10:00			17:00						10:00
Sunday			12:00	12:00			12:00						17:00
Monday													10:00

Throughout the entire experiment, control animals (n=18) were grasped, held, and transferred each day to the experimental room, but then returned to the home cage.

CMS paradigm

Animals were housed singly for 2 weeks to achieve better acclimatization to conditions. They were trained to consume 1% (w/v) water sucrose solution before the start of the CMS protocol. After rats were food- and water-deprived for 23 h, training consisted of three 1-h tests (Monday, Wednesday and Friday) in which animals could select between 2 pre-weighed bottles, 1 with 1% (w/v) sucrose solution and 1 with tap water. On the basis of sucrose preference and open-field test (see below), on the last training test (Friday, baseline test), the animals with varying sucrose preference and open-field scores were approximately equally distributed into 3 groups.

Two days after the sucrose training, the animals received daily CMS treatment during weeks 1 to 3 (Figure 1). The control rats remained undisturbed in their room under the aforementioned maintenance conditions, while the stress group was moved to a separate room and the CMS protocol started according to the methods described by Willner et al. [3–5]. This condition lasted for 3 weeks and consisted of 2 to 5 different stressors per day. The stressors were food or water deprivation, cage tilt, continuous lighting, soiled cage (100 mL of water spilled onto the bedding), stroboscopic lighting (100 flashes/min), intermittent white noise (85 dB), odor, foreign object in cage, restricted access to food (3 pellets); and/or empty water bottles (Table 1).

Every Tuesday between 14:00 and 15:00 h from weeks 1 to 3, the sucrose preference and open-field tests were carried out in both groups. Body weight measurements were recorded on the same day, 4 h before the sucrose preference test. As was previously mentioned, the sucrose preference test was performed after 23 h of food and water deprivation in all 3 rat groups.

Resident intruder paradigm

The resident intruder test was performed according to previously described methods [20,21]. The aggression test was performed using a dark red light (<2 lux, during the dark period). The cage was moved to an observation table and after approximately 15 min of adaptation, a male intruder (of smaller size than the resident rat) was transferred from his home cage and introduced into the resident's cage for a period of 10 min. The intruder was typically attacked and defeated by the resident, as exemplified by his exhibition of freezing behavior and assumption of a submissive posture. The rats were considered to be aggressive when they displayed at least 1 of the following behaviors: bite, lateral attack, or piloerection. Subsequently, intruders were returned to their home cages. The rats from the CMS+RIP group (n=18) were subjected to daily resident-intruder tests for 3 weeks. To avoid individual differences in defeat intensity, residents were confronted each day with a different intruder in a Latin square design.

Behavioral tests

Behavioral tests were performed in the following order: open-field and sucrose preference test on the 12th, 16th, 23rd, and

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30th day; and the forced swimming test (FST) on the 35th day (Figure 1). Rats were placed into the test room 30 min before the test. All tests were performed in a quiet room. After each test, rats were replaced in their individual cages and returned to the breeding room.

Sucrose preference test

The sucrose preference test was based upon previously published methods [22]. During testing, rats were for 1 h allowed a free choice between 2 bottles – one bottle contained 1% sucrose solution and the other contained tap water. To prevent the possible effects of side preference in drinking, bottle positions were switched after 1/2 h. Sucrose preference was calculated from the amount of sucrose solution consumed, which was expressed as a percentage of the total amount of liquid consumed.

Open-field test

Automatic recording of open-field activity was performed using the Opto-Varimex-3 Activity Meter (Columbus Instruments, Columbus, OH, USA), which was equipped with a standard, open, Plexiglas arena (100×100×50 cm). Animal movement was recorded with infrared sensors positioned 3 cm above the floor, according to previously described methods [23]. Each animal was placed in the center of the experimental apparatus immediately prior to testing and was allowed to explore it for 3 min. During this period, open-field activity was automatically recorded, and elements of exploratory activity (rearing and sniffing) were carefully observed and quantified. The 2 parameters were defined as follows: rearing as standing on hind legs with paws pressed against arena wall; and sniffing as continuous sniffing for at least 2 seconds [24]. Open-field activity scores represented the sum of sniffing and rearing scores.

Forced swimming test

Six rats were randomly selected from each group for the forced swimming test. The forced swimming test followed the method described by Porsolt [25–27]. The animals were individually placed into glass cylinders (40 cm in height; 18 cm in diameter) containing 18 cm of water at 23°C. After 15 min, rats were transferred to a 30°C drying environment for 30 min (the pre-test). The animals were then returned to the cylinder 24 h later for 5 min (the test), and this session was recorded with a video camera. Fresh water was used for each rat and the cylinder was cleaned after each use. Experiments were performed between 12:00 h and 16:00 h. An experimenter observed the videotapes blinded as to the treatment received by the animals, and the immobility time was measured. A rat was considered immobile when floating and only making movements necessary to keep its nostrils above the water surface.

Body mass measurements

Body mass was measured on the 12th, 16th, 23rd, and 30th day (Figure 1). All measurements were performed at 12:00 h. Body mass gain was calculated as a percentage of individual, baseline body mass at the beginning of the experiment. Initial (baseline) values were transformed to percentages of the mean value from baseline.

Statistical analysis

Data were analyzed using Graph Pad Prism version 5.0. All results are expressed as mean ± standard error of mean. The data were tested for normality (Kolmogorov-Smirnov test) and homoscedasticity (Levene test) before being analyzed by either parametric ANOVA or parametric repeated measures ANOVA among all 3 groups tested. The criterion for statistical significance was set at $p<0.05$. The sucrose preference test and body mass gain were analyzed using two-way (stress *vs.* control) × (baseline, week 1, week 2, week 3) analysis of variance for repeated measurements. The open-field test was analyzed using 2 factorial (stress *vs.* control) × (baseline, week 1, week 2) repeated-measures analysis of variance. Bonferroni *post hoc* tests were used to detect differences between groups. The forced swimming test was analyzed using one-way ANOVA.

Results

Behavioral tests

Open-field test

In the open-field test, repeated-measures ANOVA analysis revealed that the total scores over 3 min were significantly different among the 3 groups after 3 weeks of the experiment. Subsequent Bonferroni *post hoc* testing showed that CMS rats had significantly lower ($p<0.001$) open-field scores compared to control rats (Figure 2), suggesting reduced locomotor and exploratory activity in CMS animals. Furthermore, the total scores achieved by the CMS group were significantly less ($p<0.01$) than by the CMS+RIP rats (Figure 2). However, there were no statistical differences between controls and CMS+RIP rats (Figure 2). Two-way ANOVA revealed significant effects of stress [$F(2, 128)=14.32$, $p<0.001$], time [$F(3, 128)=18.07$, $p<0.001$] and significant stress × time interaction [$F(6, 128)=2.70$, $p<0.05$].

Sucrose preference test

Following the control phase (baseline) and after 1 week of stress, both groups of animals (stress and control) had a similar preference for the sucrose solution (Figure 3). Two weeks

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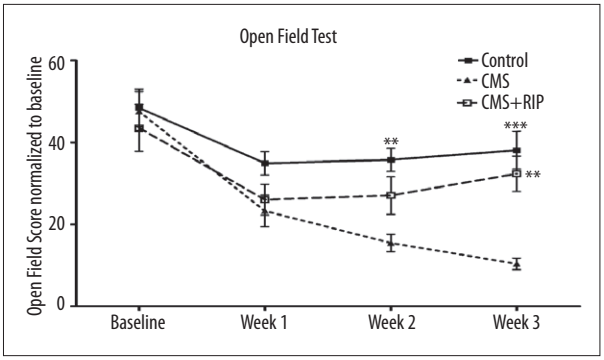

Figure 2. Open-field test. The open-field test (OFT) was performed at 12 (baseline), 16 (week 1), 23 (week 2), and 30 (week 3) days after the start of CMS as shown in Figure 1. CMS rats had significantly lower open-field scores compared to control rats at 28 or 35 days. The total scores assigned the CMS group were significantly less than in the CMS+RIP rats at 35 days. There were no differences between controls and CMS+RIP rats. Values represent the mean ±SEM (n=12 for controls, n=11 for the CMS group, n=11 for the CMS+RIP group). * p<0.05, ** p<0.01, *** p<0.001.

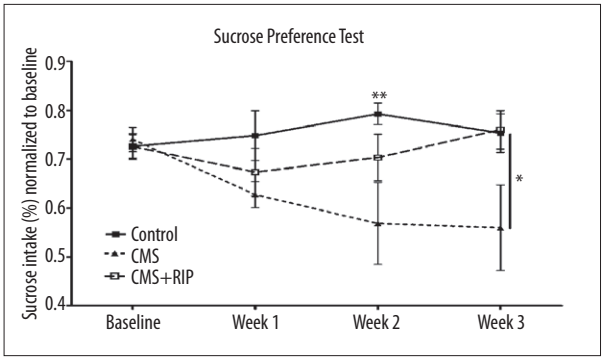

Figure 3. Sucrose preference test. A sucrose intake test was performed at 12 (baseline), 16 (week 1), 23 (week 2), and 30 (week 3) days after the start of CMS as shown in Figure 1. The intake of 1% sucrose solution in CMS rats was significantly lower than in controls (at 28 and 35 days) or CMS+RIP rats (at 35 days) after the start of CMS. Values represent the mean ±SEM (n=12 for controls, n=11 for the CMS group, n=11 for the CMS+RIP group). * p<0.05, ** p<0.01, *** p<0.001.

of stress reduced this preference in CMS and CMS+RIP animals, which reached statistical significance after 3 weeks of stress (Figure 3). Furthermore, subsequent Bonferroni *post hoc* tests showed that the intake of 1% sucrose solution in the CMS group was significantly ($p<0.05$) lower than in controls or CMS+RIP rats (Figure 3). These findings suggest that aggressive behavior induced by the resident intruder paradigm relieves the severity of potential anhedonia evoked by CMS. Two-way ANOVA revealed significant effects of stress [$F(2, 126)=9.14$, $p<0.001$].

Forced swimming test

As shown in Figure 4, CMS rats spent a significantly longer time immobile (101.92±22.608 s) than did the controls (76.3±10.858) ($p<0.01$); or the CMS+RIP rats (84.92±9.059 s) ($p<0.05$). However, no differences were observed between controls and CMS+RIP rats [$F(2, 31)=8.99$, $p<0.001$] (Figure 2).

Body weights

CMS rats gained less body weight than did the controls or CMS+RIP rats (Figure 5). Statistical analyses revealed a significant effect of stress [$F(2, 124)=16.39$, $p<0.001$] and a significant stress × time interaction [$F(6, 124)=3.18$, $p<0.01$]. Subsequent Bonferroni *post hoc* tests confirmed a significant ($p<0.01$) reduction in body weight gain in CMS animals after 2 and 3 weeks of experimentation, compared with the controls or the CMS+RIP groups. However, there was no statistical difference between the controls and CMS+RIP rats during the entire experimental period.

Discussion

To examine whether resident intruder paradigm-induced aggression affected the depressive-like behavior evoked via the CMS model, we subjected male Wistar rats to 3 weeks of daily exposure to resident intruder paradigm and chronic mild stress. The major findings of this study were that the CMS procedure induced depressive-like behavior in male adult rats, and that aggression from the resident intruder paradigm in rats could relieve depressive-like behavior. To our knowledge, this is the first study showing that resident intruder paradigm-induced aggressive behavior might relieve depressive-like behavior caused by the CMS procedure.

The forced swimming test (Porsolt's test) is considered to be highly specific for the detection of antidepressant drugs [19,28–31]. The shortened immobility time we observed with this test indicated anti-depressive activity that countered the behavioral expression of depressive-like symptoms in rats. This finding appears to suggest that CMS stress affects an animal's motivation and may lead to the development of behavioral despair. Similar observations have been reported before [32,33]. In addition, we also found that resident intruder paradigm-induced aggressive behavior might diminish the effects caused by the CMS procedure in a manner similar to that with antidepressants [30,34,35] (Figure 4). These correlated effects are unlikely to be accidental, and the proposed protocol (Figure 1) allowed the elimination of possible variations in the intensity of the aggression experience. Although the reasons underlying this difference are currently unclear, it is likely that the neurobiological pathways mediated by these 2 models are different [36]; this highlights the genetic contribution to the behavioral performances in these 2 paradigms. Nonetheless, it

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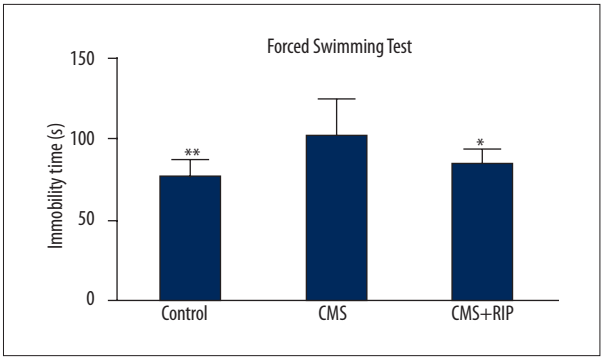

Figure 4. Forced swimming test. CMS rats spent a significantly longer time immobile than did the control and CMS+RIP rats. No differences were observed between controls and the CMS+RIP rats. Values represent the mean ±SEM (n=6 for controls, n=6 for the CMS group, n=6 for the CMS+RIP group). * p<0.05, ** p<0.01, *** p<0.001, by one-way ANOVA.

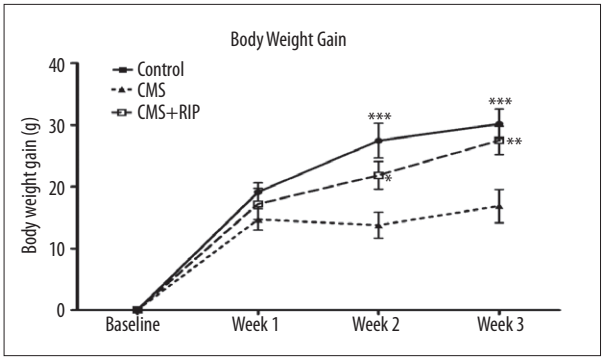

Figure 5. Body weight gain. Body weight gain was measured at 12 (baseline), 16 (week 1), 23 (week 2), and 30 (week 3) days after the start of CMS as shown in Figure 1. There was a significant reduction in body weight gain in CMS animals after 2 and 3 weeks compared with control and CMS+RIP groups. There was no statistical difference between the controls and CMS+RIP rats during the entire experimental period. Values represent the mean ±SEM (n=12 for controls, n=11 for the CMS group, n=11 for the CMS+RIP group). * p<0.05, ** p<0.01, *** p<0.001, by two-way ANOVA, split-plot for time.

should be noted that resident intruder paradigm-induced aggressive behavior could attenuate the depressive-like behavior of animals subjected to CMS.

Rats subjected to chronic mild stress showed a decrease in sucrose preference in a time-dependent manner. Reduced preference for the sucrose solution in rats indicates a decreased sensitivity to reward, and may be analogous to anhedonia [37–40]. In the present study, the CMS paradigm produced a decrease of 1% in sucrose intake, consistent with previous reports [37,41]. Herein, we found that aggression due to the resident intruder paradigm potentiated the increase of 1% sucrose consumption in isolated rats in the CMS model, showing that resident intruder-induced aggressive behavior may decrease the severity of anhedonia in isolated male rats.

The initial activity of a rat placed in novel surroundings (*e.g.*, an open field) can be taken as an indicator of its emotional and motivational state [42–46]. It is assumed that an inescapable open-field situation reflects both the stress and the reward components of novelty. In rats, decreased locomotor and exploratory activity in a novel environment reflects decreased motivation or drive, a behavior that represents "refractory loss of interest" [47]; and may also be related to hedonic deficit, since novelty is rewarding. In the open-field test, the locomotor and exploratory activities of CMS rats were significantly diminished compared with control animals. Furthermore, locomotor and exploratory activities of CMS rats were significantly lower than in the CMS+RIP group, suggesting that aggression in isolated rats exposed to the resident intruder paradigm might increase locomotor and exploratory activity of rats within the CMS paradigm. A slight reduction in locomotor activity of control animals observed at the end of our experiment can be explained by habituation learning, which is typical after repeated open-field exposure [48]. The decreased exploration of a novel environment may also be related to elevated levels of anxiety in stressed animals. We did not test whether the observed changes in motility were related to altered anxiety level. However, behavioral despair observed in the forced swimming test as well as the decrease in preference for sucrose solutions suggest motivational deficits. Furthermore, the open-field paradigm (darkness) was minimally anxiogenic. The unidirectional effects of social stress on locomotion, rearing, and sniffing suggest that the chosen parameters of exploratory activity were dependent on overall activity of the animals.

It is well known that the resident intruder paradigm induces aggressive behavior in male rats [49]; and many researchers are inclined to believe that resident intruder paradigm-induced aggression should be regarded as a model of depression since the aggressive behavior can be relieved by antidepressants. However, this is not the case, as more and more researchers in fact have revealed that aggressive animals are different from depressive ones in many aspects, including locomotor activity, sensitivity to restraint stress, anxiety levels, *etc.* [15]. We also have the similar results in this experiment that there is no difference between RIP and control groups in locomotor activity, sucrose consumption, and immobility time (data not shown). Moreover, acute treatment with antidepressant drugs decreases aggressive behavior of resident animals but aggressive behavior increases after chronic treatment, since it has been demonstrated that antidepressants were effective in treating the depressive rat model only if administered long-term. Ho [20] showed that although the behavior displayed by animals in this paradigm is usually referred to as 'aggression'

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rather than 'irritability' or 'anger', the neuroendocrine mechanisms underlying this behavior in rats relate to those underlying irritability and anger. Therefore, there is ample reason to believe that aggression induced by the resident-intruder paradigm and depression induced by chronic mild stress are 2 opposite states of mood [50]. This opinion is supported by our results in which aggression relieved depressive behavior. In addition, we must emphasize that we selected the aggressive rats according to a standard in which the aggressors must defeat the intruders completely. We also excluded intruder rats if the aggressors encountered retaliation by the intruder rats. This may be the primary reason why there is discrepancy between our results and results reported previously showing that social isolation-induced aggression potentiated anxiety and depressive-like behavior in male mice [36].

Several factors could affect results in the present study. For example, the various effects of social isolation, resident intruder stress, and social isolation plus resident intruder stress need to be compared; although adverse effects of resident intruder stress have been shown to be reversed by social housing [20]. Moreover, daily exposure to a novel environment could affect results, *e.g.*, by enhancing the effects of habituation in the open-field test.

Conclusions

In conclusion, our data show that aggressive behavior evoked by the resident intruder paradigm in isolated rats could relieve broad-spectrum depressive-like behaviors in adult male rats subjected to CMS. Since our CMS model is a reliable animal model for depressive-like symptoms in humans, we conclude that resident intruder paradigm-induced aggressive behavior in rats may play a significant anti-depressant role. However, the underlying mechanism(s) at work need further exploration.

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