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The Anti-Depressant Effect of Praeruptorin C on the Chronic Unpredictable Mild Stress Mouse Modely

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Abstract

Praeruptorin C (Pra-C), a widely used antioxidant and a calcium antagoinsts is the principal bioactive components derived from the Peucedanum praeruptorum Dunn, root. In this study, we investigated the anti-depression effects of Pra-C on chronic unpredictable mild stress (CUMS) mice model and identify the possible mechanisms. After CUMS procedure, mice exhibited the decreased locomotor and exploratory activity in open field test (OFT), increased immobility time in forced swimming test (FST) and tail suspension test (TST). Both 0.5 mg/kg and 2 mg/kg Pra-C alleviated the depression-like behaviors in CUMS mice. In addition, the decreased levels of GluA1 receptors and BDNF in amygdala of CUMS mice were upregulated by 2 mg/kg Pra-C. Therefore, we suggested Pra-C may act as an anti-depressant by restoring the AMPA receptors and neurotrophic factors.

Keywords: Chronic unpredicted mild stress; Depression; Praeruptorin C; AMPA receptors

Abbreviations: MDD: Major depressive disorder; CUMS: Chronic unpredicted mild stress; OFT: Open field test; FST: Forced swimming test; TST: Tail suspension test

Introduction

Depression is one of the most common psychiatric illnesses. Patients often experience sadness, distrustfulness, low self-esteem and lose motivation to do activities they would have otherwise enjoyed. When these feelings become pervasive, persistent, and interfere with everyday activities it is called major depressive disorder (MDD). MDD is a complex condition that results from the disrupted interactions between genetic, physiological, psychological, and environmental factors. Its clinical manifestations include affective, cognitive, somatic and behavioral symptoms [1]. Recent data from the National Comorbidity Survey Replication (NCS-R) indicates the lifetime prevalence of MDD at 16.6% and the 1-year prevalence at 6.7% [2,3].

Currently prescribed drugs to treat or manage MDD include monoamine oxidase (MAO) inhibitors, and 5-HT and norepinephrine (NE) reuptake inhibitors [4-6]. Other antidepressants, such as fluoxetine, are widely prescribed. However, their mechanisms of action are not known. Neurotrophic factors such as brain-derived neurotrophic factor (BDNF), can contribute to the therapeutic effects of antidepressant treatments as well [7-9]. Recently, modulation of the glutamatergic system has become an attractive strategy for discovering new-generation antidepressants [10]. Some studies have revealed that α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptors activation were required for eliciting the antidepressant-like effects in both acute and chronic stress models of depression [11].

In the CNS, the amygdala coordinates emotional responses. The amygdala consists of several anatomically and functionally distinct nuclei; the lateral (LA), basolateral (BLA), and the central nucleus

[12,13]. Amygdala is the main site for negative affective states such as fear anxiety, dysphoria, and irritability [14]. Studies on amygdala function have focused mostly on the plasticity at the sensory inputs from the thalamus and cortex to the LA and BLA [15,16].

First-line antidepressants, including MAOI and TCA, at current dosage commonly prescribed for MDD are not very efficacious. Therefore, there is an increasing need to explore novel drugs to treat depression [17]. Chronic unpredictable mild stress (CUMS) is a well-established and accepted animal model to study depression. In this model, animals are exposed to a series of unpredictable mild stressors that simulate events that are stressful for humans [18]. Several ethological symptoms and neurobiological abnormalities found in CUMS-induced animals are similar to those exhibited by depression patients thus making it a reliable model to apply series of behavioral test to screen for new antidepressants [19].

Praeruptorin C (Pra-C), one of the principal bioactive components derived from the root of Peucedanum praeruptorum Dunn, a traditional Chinese medicine, has been widely used as an antioxidant and a calcium antagonist to treat diseases. We recently showed a protective effect of Pra-C against glutamate-induced injury in cultured cortical neurons [20]. To understand the effects of Pra-C on MDD, we studied the expression of GluA1, GluA2 and BDNF in CUMS only mice and CUMS mice treated with Pra-C.

Method and Materials

Animals

We used adult male BALB/c mice aged 6-8 weeks. All procedures involving animals were approved by the Animal Care and Use Committee of the Fourth Military Medical University. The animals were housed randomly five per cage with ad libitum access to food and water. All mice were fed standard rodent chow. Mice were maintained

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at a temperature of 24 ± 2°C, humidity (50-60 %), with a 12 h light-dark cycle with lighting on at 7 am.

CUMS Procedure

After acclimatization for 3 days, mice were semi-randomly exposed to following stressors; restraint in plastic tube, cage tilting, white noises, lights on during the dark phase, placed in an empty cage with no nesting, placed in crowded cage; and cage shaking. The duration and frequency of exposure were based on the procedure and shown in previous study [21]. Time and length of stressors used in one week of the chronic mild stress procedure: on Monday, we put the mice in the crowded cage from 10:00 to 13:00 and restraining them in plastic tube from 15:00 to 17:00; On Tuesday, we put them in a dark chamber with the white noise from 10:00 to 14:00 and we shook the cages from 12:00 to 22:00; On Wednesday, we restrained them in plastic tube from 12:00 to 14:00 and shaking the cages from 16:00 to 18:00;On Thursday, we placed them in an empty cage with no nesting from 12:00 to 20:00 and made an illumination in dark phase from 19:00 to 21:00; On Friday, we put them in a dark chamber with the white noise from 10:00 to 14:00 and made an illumination in dark phase from 19:00 to the next day 07:00; On Saturday, we restrained them in plastic tube from 09:00 to 11:00, put them in the crowded cage from 16:00 to 19:00 and made the cage tile 45° from 19:00 to the next day 07:00 meanwhile made an illumination in dark phase; On Sunday, we placed them in an empty cage with no nesting from 12:00 to 20:00 and shook the cages from 18:00 to 20:00. On average, two or three of these stressors were applied daily at different time. The stress procedure lasted for 6 weeks followed by behavioral testing period.

Drug administration

Pra-C was purchased from the Shanghai PureOne Biotechnology (Shanghai, China; purity: 98 % by HPLC). Pra-C was dissolved in saline and administered intraperitoneally at a dose 0.5 mg/kg and 2 mg/kg according to our previous study [20]. Mice were housed four per cage, which had a control group (V). For intraperitonal injections, the vehicle for Pra-C was sterile saline solution (0.9 % W/V). Pra-C or vehicle was injected for three days, once a day after the CUMS procedure. Animals are divided into four groups: 1) control or naïve, 2) CUMS only or vehicle, 3) 0.5 mg/kg Pra-C, 4) 2.0 mg/kg Pra-C.

Behavioral test schedule

Mice were tested for open field test (OFT), forced swim test (FST), tail suspension test (TST), and nesting behavior. All test were conducted between 9:00 am to 5:00 pm. Scorers were blind to treatment.

Behavioral Tests

Open field test

After CUMS procedure, all mice were tested in an open field arena that consisted of a 40 cm × 40 cm× 40 cm square box. Testing was carried out without light. The mice were placed in the center of the arena and their behavior was recorded for 15 minutes by using a video camera and analyzed by using the motion tracking system (MedAssociates). The frequency and duration of the following behavioral parameters were recorded during the test: the total time spent in the center square, the total distance traveled and the number the mice went through the center arena [22].

Forced swimming test

Mice were placed in a big plastic basin (100 cm × 50 cm × 30 cm, filled with 23-25°C water). The mice were placed in the water for 5 min. The duration of immobility behavior (floating in water without active movements of forepaws) was measured manually. After the test, mice were covered by a dry towel and then placed in a warm cage until they were dry [23].

Tail suspension test

Mice were suspended by the tails from a lever so that their body dangled in the air, facing downward. Each mouse was suspended for 5 min approximately 30 cm above the surface. Mice initially struggle to face upward and climb to a solid surface. When the animal stops struggling and hangs immobile it is considered to have "given up". Longer periods of immobility are characteristic of a depressive-like state. The duration of immobility was manually recorded. Immobility was defined when the animals hung passively without limb movement [24].

Nesting

Mice were individually housed for at least 24 h in clean plastic cages with approximately 1 cm of corn cob bedding before nesting. On the evening of the test, all cages were provided with pressed cotton square of about 5 cm. The next morning (16 h later) cages were inspected for nest construction. To document, pictures were taken before and after evaluation [25,26].

Western blot analysis

After the day following behavioral testing, all mice were anesthetized with an overdose of sodium pentobarbital, and then decapitated. The amygdala tissue was chopped into small pieces and homogenized in ice-cold RIPA lysis buffer containing 1x protease inhibitor cocktail. Equivalent amounts of protein were resolved using 9 % SDS-PAGE gel and transferred to a nitrocellulose membrane. After incubation with the secondary antibodies, the proteins were observed using enhanced chemiluminescence (ECL, GE Healthcare Pharmacia, Uppsala, Sweden). The following primary antibodies were used: anti-BDNF (1:200; Abcam, ab6201), anti-GluA1 (1:1000; Abcam, ab31232), anti-GluA2 (1:1000; Abcam, ab20673), β-actin (1:10000; Sigma, A5316). The secondary antibody was horseradish peroxidase conjugated goat antibody to rabbit immunoglobulin (1:10000; Santa Cruz, sc-2004). The densitometric analysis of Western blots was conducted using a ChemiDoc XRS (Bio-Rad, Hercules, CA) and quantified using Quantity One version 4.1.0 (Bio-Rad).

Results

Behavior Tests

Open field test: As seen in Figure 1, both 0.5 mg/kg and 2 mg/kg Pra-C treated animals spent significantly longer time in the center, and only 2 mg/kg Pra-C treatment extended the total distance travelled. However, Pra-C treatment had no effect on the frequency of visits to the center and the total distance walked in a given time.

Forced swim test: Figure 2 shows the swimming behavior of control, CUMS only mice, and Pra-C treated CUMS mice. We found that CUMS mice spent more immobility time than control group. Both 0.5 mg/kg and 2 mg/kg Pra-C treatments lowered the immobility time during the 5 min test session in all experimental groups.

Tail suspension test: The results show the tail suspension behavior of model and control mice (Figure 3). The Pra-C treatment significantly decreased the immobility time during the 5 min test session in all model groups. Both 0.5 mg/kg and 2 mg/kg Pra-C treated mice spent more exploratory time than the CUMS only mice group.

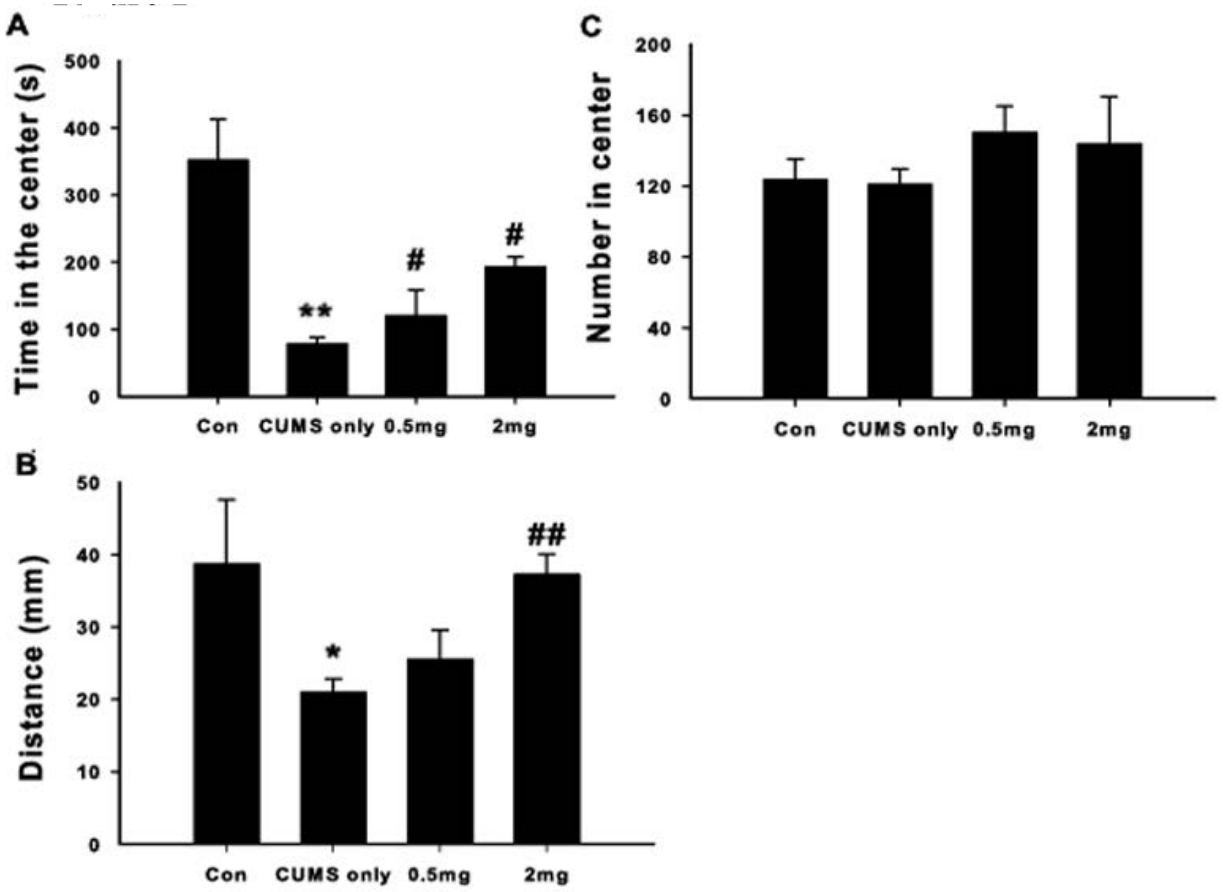

Figure 1: *Depression-like parameters during open field test.*

Mice were divided into control (n=6), CUMS only (n=4), 0.5 mg/kg (n=4) and 2 mg/kg (n=4), four groups. The black columns present the mean ± SEM for all groups. A) Time spent in the center. B) The frequency at which mice from various groups visited the center of the box is expressed as means + S.E.M. No significant difference was detected. ˚ P < 0.05, ˚˚ p < 0.01 compared to control and # P < 0.05, ## p < 0.01 compared to CUMS only. C) The total distance moved by mice during the testing period. Again no significant differences were observed across the groups.

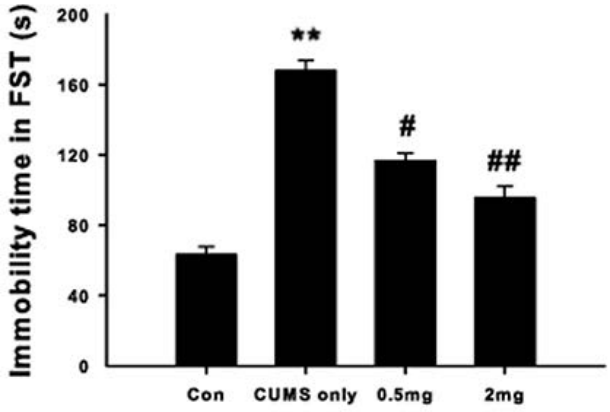

Figure 2: *Depression-like parameters during forced swim test.*

Mice were divided into four groups: control (n=6), CUMS only (n=4), 0.5 mg/kg (n=4) and 2 mg/kg (n=4). The black columns present the mean ± SEM for all groups. Data of immobility time in forced swim test are expressed as means + S.E.M. Significant difference was detected between CUMS only mice group and 0.5 mg/kg and 2 mg/kg group. ˚ p < 0.01 compared to control and # P < 0.05, ## p < 0.01 compared to CUMS only.

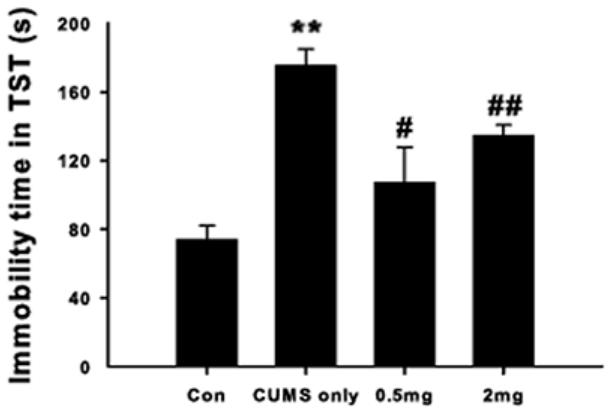

Figure 3: *Depression-like parameters during tail suspension test.*

Mice were divided into control (n=6), CUMS (n=4), 0.5 mg/kg (n=4) and 2 mg/kg (n=4). The black columns present the mean ± SEM for all groups. Data of immobility time in tail suspension test are expressed as means + S.E.M. Significant difference was detected between CUMS only mice group and the 0.5 mg/kg and 2 mg/kg group. ˚p < 0.01 compared to control and # P<0.05, ## p < 0.01 compared to CUMS only.

Nesting: To precisely score nest construction by hand, we adapted the Robert MJ Deacon's method and followed the Deacon 5 point scaling system. We found that there is a strong association between Pra-C treatment and nesting habits of CUMS mice (Figure 4). Both 0.5 mg/kg and 2 mg/kg Pra-C treated scored higher than CUMS only mice nesting score.

Western blotting: The effect of Pra-C on BDNF, GluA1 and GluA2 expression level in the amygdala in CUMS mice are shown in Figure 5. CUMS significantly reduced BDNF and GluA1 expression in the amygdala compared with that in control mice. Administration of 2 mg/kg Pra-C was able to reverse the effects of CUMS on these receptors. However, there is no significant difference on GluA2 receptors expression in the amygdala compared with the control group.

Discussion

Studies have shown that Pra-C has protective effects against H2O2-induced damage in myocardial cells [27], and calcium antagonistic action [20,28]. Here we report that Pra-C produced anti-depressant-like effects on the CUMS-induced depressed mice. We previously reported the possible neuroprotective properties of Pra-C against excitatory neurotoxicity mediated by NMDA in primary cortical neurons and suggested its possible mechanisms [20]. In our present study, we report for the first time that Pra-C can alleviate depression-like behavior in CUMS mice.

Long-term (6 weeks) CUMS-induced depressed mice showed decreased locomotor and exploratory activity in OFT, increased immobility time in FST and TST. These behaviors are reversed by injection of Pra-C (2 mg/kg) for 3 consecutive days at the end of the CUMS procedure. In CUMS procedure, animals are exposed to chronic and continuous low-grade stressors analogous to those associated with human depression. It has been shown that CUMS-induced animals present a lot of ethological symptoms and neurobiological

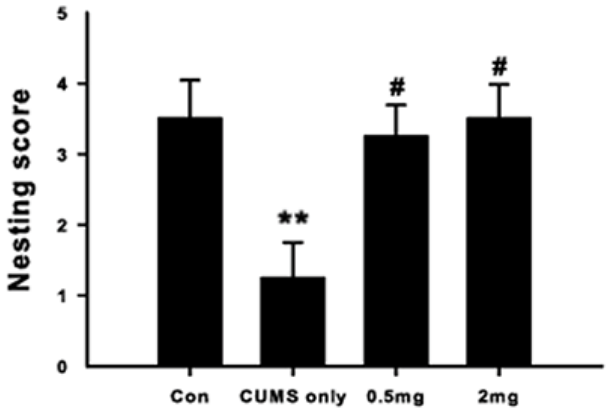

Figure 4: *Effect of Pra-C on nest construction.*

Mice were divided into four groups; control (n=6), CUMS only (n=4), 0.5 mg/kg (n=4) and 2 mg/kg (n=4). (A) Representative pictures of nest construction: control, CUMS only, 0.5 mg and 2 mg groups. The mice that received Pra-C tore the pressed cotton squares and constructed well-defined nests with them. Whereas the mice that did not receive Pra-C left the pressed cotton square mostly undisturbed. (B) The graph showing the results from nest construction experiments. Black columns represent the mean ± SEM for all groups. Data of nesting score are expressed as means + S.E.M. Significant difference was detected. ¨ p < 0.01 compared to control and # P < 0.05 compared to CUMS only.

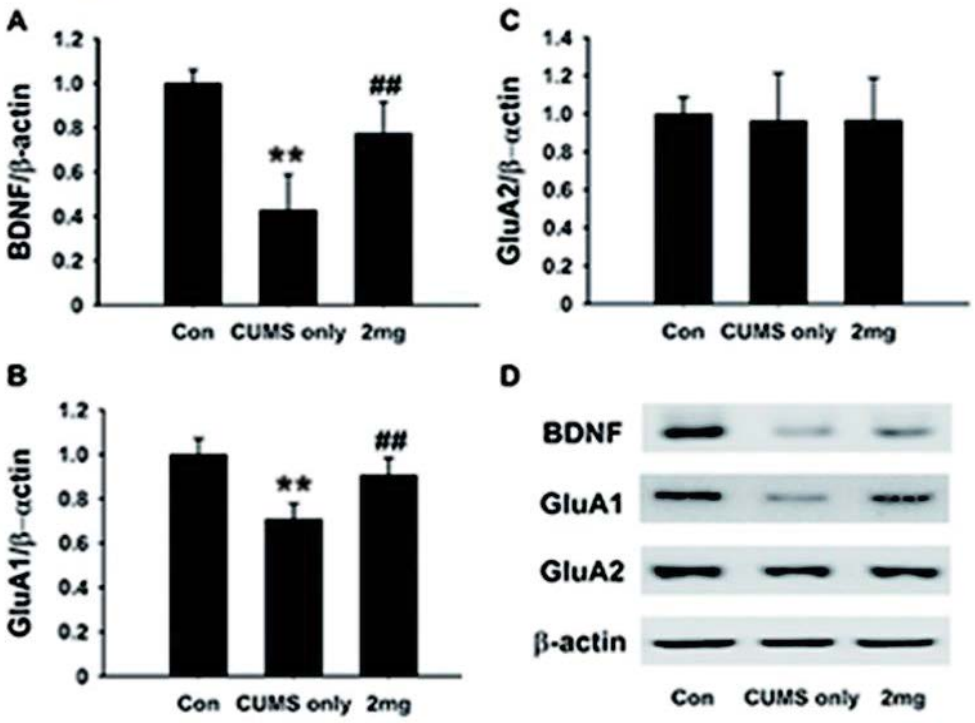

Figure 5: *Effect of Pra-C on protein expression in the amygdala in CUMS mice*.

(A-C) Western blot analysis of GluA1, GluA2 and BDNF in total homogenates of amygdala in CUMS mice. Infusion with 2 mg/kg Pra-C reversed the decreased BDNF (A) and GluA1 (B) expression in CUMS mice. The columns present the mean ± SEM for all groups. However, the GluA2 (C) did not change significantly as compared with control. Data of western blot are expressed as means + S.E.M. Significant difference was detected. ¨p < 0.01 compared to control and ## p<0.01 compared to CUMS only. (D) Representative bands of BDNF, GluA1 and GluA2 after vehicle or Pra-C treatment in CUMS mice.

abnormalities, which are similar to those exhibited in depressed patients [19]. Several studies have used CUMS-induced depression animal models to search and design potential antidepressants using classic behavioral tests such as OFT, FST and TST. Herein, mice with 6 consecutive weeks of CUMS exhibited the behavioral deficits including reduced time in the center and length of travel in OFT, prolonged immobility time in FST and TST, which are similar to that of common depressive states in patients.

The OFT is well accepted to assess locomotor and exploratory behaviors in experimental animals, which in turn are indications of fear and anxiety [29]. The CUMS only mice spent less time in the center and covered shorter distances in OFT, indicating decreased exploratory behavior and spontaneous locomotion in these animals. This suggests an increased anxiety level in CUMS only mice. Figure 1 indicates that Pra-C administered CUMS animals spent more time in the center and covered longer distances exploring the cage environment as compared to the CUMS only mice animals. This indicates that Pra-C administration has a positive effect on locomotor and exploratory behavior in CUMS mice and might help in reducing fear and anxiety in depressed animals.

The FST, is a classical behavioral model in rodents for assessing pharmacological antidepressant activity by measuring the time spent being immobile, swimming, or struggling [30]. More time spent swimming or struggling is an indication of persistent motivation. On the other hand, more time spent being immobile indicates loss of motivation and hopelessness, a symptom of depression observed both in animal models of depression and depression patients. The main indication of the antidepressant-like effect is the marked reduction in time spent being immobile [31]. In our present study, CUMS mice exhibited prolonged immobility time during FST and Pra-C administration significantly reduced this immobility time.

The TST is also an established behavioral test to assay mood and motivation in rodents [32]. The longer the immobility the mice show during TST, the more depressed is the mice. Our current data indicates that, CUMS mice show more immobility time during TST compared with control mice. With Pra-C administration mice exposed to CUMS spent less time being immobile and helpless and struggled more to get free. This suggests that Pra-C administration alleviates anxiety and hopelessness.

Increasing evidence shows that a reduction in BDNF is a significant factor in the depression pathogenesis. Studies have demonstrated that the alteration in BDNF expression is closely associated with chronic stress-induced depression [33]. Infusion of BDNF into the brains produces antidepressant-like behavioral effects in rats [34]. BDNF dysfunction in amygdala is related with depression in patients [35]. In lines with this, in our present study we found that Pra-C treatment increased the CUMS-associated reduction in BDNF levels. Most importantly, these findings suggests the possibility that Pra-C treatment may protect against CUMS-induced depression by influencing BDNF expression.

AMPA receptor (AMPAR) activation is currently considered as one of the most promising new approaches for new antidepressant therapies as the balance between glutamate and GABA in general is becoming increasingly relevant in the field of depression. AMPA receptor potentiation has an antidepressant effect in mice with chronic mild stress [36]. Down regulation of AMPA receptor subunit 1 (GluA1) protein levels at the plasma membrane induced by lipopolysaccharide injection results in a decrease in the strengthening of excitatory synapses, which might contribute to the pathogenesis of depression [37]. Additional preclinical support comes from the finding that GluA1 knockout mice show increased learned helplessness [38]. The amygdala is critical for processing various kinds of emotions, including fear, anxiety and depression [39]. In our study, we found that the GluA1 protein level in the amygdala of CUMS mice was significantly lower than that in control mice. Pra-C administration reversed the reduction of GluA1 in CUMS mice. It shows that the effect of Pra-C on depression-associated behaviors may be through upregulation of GluA1 receptors and BDNF in the amygdala. This suggested that Pra-C might play an anti-depression role through restoring the AMPA receptor levels, especially GluA1. However, the specific regulatory mechanism is not clear, and other supportive experiments need to be performed for further investigation.

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