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ORIGINAL ARTICLE

Gallic acid activates hippocampal BDNF-Akt-mTOR signaling in chronic mild stress

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Abstract

Gallic acid (3,4,5-trihydroxybenzoic acid) is a naturally occurring polyphenolic compound. Previous study has shown that gallic acid possessed significant antidepressant-like activity in mice, which was partly mediated by increasing serotonin and catecholamine levels. The main aim of the present study is to investigate the possible effects of gallic acid on brain-derived neurotrophic factor (BDNF) signaling activation. Mice were exposed to chronic mild stress (CMS) and orally administrated with gallic acid for four weeks. The behavioral results showed that gallic acid not only reversed the decreased sucrose preference, but also attenuated the increased immobility time. In addition, gallic acid promoted both the BDNF and p-TrkB levels in the hippocampus induced by CMS. Moreover, the results also demonstrated that the inactivated Akt-mTOR signaling pathway, as well as its downstream effectors induced by CMS was activated again by gallic acid. Last, immunofluorescence detection indicated that gallic acid reversed the newborn neurons inhibition in the dentate gyrus by CMS. In conclusion, these results show that the activation of the hippocampal BDNF-Akt-mTOR signaling is involved in the antidepressant-like effects of gallic acid.

Keywords Gallic acid · Brain-derived neurotrophic factor (BDNF) · Chronic mild stress (CMS)

Introduction

Major depression is a chronic mental disease, also known as depressive disorder. Its clinical characters include sustained negative emotions or mental decline, self-doubt or negation, cognitive dysfunction, irritability, loss of appetite, insomnia and other negative emotions (Kessler et al. 2003). With the rapid development of modern society, the pressure for people to face work, study and life has gradually increased, and the incidence of depression has also increased year by year. According to a survey conducted by the World Health Organization, depression is expected to become the second leading cause of human health in 2020, second only to heart disease. Depression brings mental and physical pain and suffering to the patient, and it also puts a huge burden on the patient's family. Therefore, improving the effective treatment of depression will bring great benefits to patients, their families, and society.

Recent studies have found that brain-derived neurotrophic factor (BDNF), one of the most abundant neurotrophic factors in brain, plays an important role in the pathogenesis of depression and the treatment of antidepressant drugs (Warner-Schmidt and Duman 2006). Several clinical investigation also found that the BDNF levels in peripheral blood of depressive patients were less than that in normal people (Drzyzga et al. 2009; Kerling et al. 2017). The long-term use of classical antidepressants or short-term use of rapid antidepressants in patients accompanies with the increase of BDNF content (Rybakowski et al. 2017; Yu et al. 2015). Thus, a 'neurotrophic hypothesis' was proposed for the explanation of depression. It is believed that the depression is intensely correlated to the BDNF expression in the human body (Kishi et al. 2017). This hypothesis also provides an important direction for the research of new antidepressants in recent years.

Gallic acid (3,4,5-trihydroxybenzoic acid) is a naturally occurring polyphenolic compound that is widely found in

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nature. Previous study showed that gallic acid possessed significant antidepressant-like activity in mice (Nagpal et al. 2012). The following study demonstrated that the antidepressant-like effects of gallic acid were mediated by its antioxidant activity and through inhibition of monoamine oxidase-A activity (Chhillar and Dhingra 2013). Consistently, a recent study also showed that increasing both serotonin and catecholamine levels in synaptic clefts of the central nervous system were involved in the antidepressant-like effects of gallic acid (Can et al. 2017). However, there is little information regarding the neurotrophic system or BNDF signaling involved in the antidepressant-like effects of perillaldehyde. Based on the neurotrophic hypothesis of depression, we therefore investigated whether chronic administration of gallic acid could regulate BDNF expression and its downstream signaling pathway in mice exposed to chronic mild stress (CMS).

Materials and methods

Animals

Male ICR mice (26 ± 2 g; 8 weeks old) were purchased from Shanghai Slac Animal Center, PR China. Animals were housed five per cage (320 × 180 × 160 cm) under a normal 12-h/12-h light/dark schedule with the lights on at 07:00 a.m. The animals were allowed 1 week to adapt before the beginning of the experiments. Ambient temperature and relative humidity were maintained at 22 ± 2 °C and at 55 ± 5%. Animals have free access to food and water except during the sucrose preference test. All procedures were approved and performed in accordance with the published guidelines of the China Council on Animal Care.

Reagents

Gallic acid (>98%) was purchased from Aladdin Biotechnology Co. (Shanghai, PR China). DAPI and primary β-actin antibody were purchased from Sigma (St. Louis, USA). The anti-BDNF antibody was purchased from Santa Cruz Biotechnology Inc. (Santa Cruz, USA). The antibodies for TrkB, p-TrkB, Akt, p-Akt, mTOR, p-mTOR, p70s6k, p-p70s6k, 4E-BP-1, p-4E-BP-1 and DCX were purchased from Cell Signaling Technology (Beverly, USA).

Drug administration

The mice were randomly divided into four groups ($n = 10$): the Control/CMS-vehicle groups (0.9% physiological saline) and Control/CMS-gallic acid groups that received 50 mg/kg gallic acid. Gallic acid was diluted in 0.9% physiological saline and administered by oral gavage once daily at a volume of 10 ml/kg for the last 4 weeks of the experiment (Week 5-Week 8). A previous study have indicated that 60 mg/kg but not 30 mg/kg gallic acid produced the antidepressant-like after acute administration in the tail suspension test (Can et al. 2017). Considering that gallic acid was chronic administrated in the present study, 50 mg/kg gallic acid was used.

CMS

The procedure of CMS was performed as described previously (Yi et al. 2014). In detail, several stressors including water deprivation, soiled cage exposure, light/dark succession (2 h), empty bottle exposure, 45° cage tilt, space reduction, predator sounds and overnight illumination were applied individually and continuously throughout the experiment. The control animals were housed in a separate room and had no contact with the stressed groups. To prevent habituation and ensure the unpredictability of the stressors, all the stressors were randomly applied. The whole CMS was performed during a 8-week period.

Sucrose preference test

Before the experiment, sucrose training was performed to confirm the normal sucrose preference of the animals. The formal test was carried out at the end of 4-week and 8-week CMS exposure (Yi et al. 2015). Briefly, before the test, the mice were trained to adapt to sucrose solution (1%, *w*/*v*): two bottles of sucrose solution were placed in each cage for 24 h, and then one bottle of sucrose solution was replaced with water for 24 h. After the adaptation, the mice were deprived of water for 12 h. During the test, the mice were housed in individual cages and had free access to two bottles containing sucrose solution and water, respectively. After 24 h, the volumes of the consumed sucrose solution and water were recorded and calculated to sucrose preference.

Forced swimming test

The forced swimming test was conducted 24 h after the sucrose preference test (Porsolt et al. 1977). Briefly, a glass cylinder (20 cm in height, 14 cm in diameter) filled with 10-cm of water (25 ± 2 °C) was used for the test. Animals were forced to swim in the cylinder for 6 min. Only the last 4 min of the test was used for immobility time record. Water was replaced every session. The test were recorded and were scored by an blind observer.

Western blot

Mice were sacrificed one day after the behavioral test. Hippocampus samples were homogenized in a lysis buffer and incubated on ice for 30 min. The homogenates were

centrifuged at 15000×*g* for 20 min at 4 °C, and the supernatants were collected. The protein concentration was determined by a BCA assay. The proteins were separated by SDS-PAGE and transferred to a PVDF membrane. Following blocking in 5% BSA/TBST at room temperature for 1 h, the membranes were incubated with the following primary antibodies at 4 °C overnight (anti-BDNF: 1:600, anti-TrkB: 1:1000, anti-pTrkB: 1:1000, anti-Akt: 1:1000, anti-p-Akt: 1:1000, anti-mTOR: 1:1000, anti-p-mTOR: 1:1000, anti-p70s6k: 1:1000, anti-p-p70s6k: 1:1000, anti-4E-BP-1: 1:1000, anti-p-4E-BP-1: 1:1000, anti-β-actin: 1:5000). Then the membranes were incubated with the appropriate secondary antibody (1:2000/1:4000) after washing with TBST for three times. The membranes were subsequently washed again for three times with TBST buffer, and finally the bands were detected using the enhanced chemiluminescence method. The results were normalized to the protein expression level of β-actin.

Immunofluorescence

Mice were anesthetized and then perfusion with PBS and 4% paraformaldehyde, respectively. Whole brains were fixed by using the same 4% paraformaldehyde for 24 h and were subsequently incubated with appropriate sucrose solution, followed by frozen with OCT. Later, 12-μm-thick sections were cut, blocked with a blocking buffer and incubated with anti-DCX (Abcam; 1:250) over night. The sections were washed with PBS and then incubated with a fluorescence antibody for 1 h. Then DAPI (Sigma; 1:5000) was added. Finally, the DCX positive cells in the dentate gyrus were observed under a confocal microscope. The number of positive cells was counted by the average of five slices.

Statistical analyses

All data are expressed as the mean ± S.E.M. The data were analyzed using a two-way ANOVA, followed by a Tukey's post-hoc test. A value of $P < 0.05$ was considered to be statistically significant for analysis.

Results

Effects of gallic acid on sucrose preference and immobility time

CMS induced a significant depressive-like anhedonia in mice, as sucrose preference was decreased [$F(1,36) = 36.41$, $P < 0.01$] according to two-way ANOVA (Fig. 1). In addition, the treatment factor [$F(1,36) = 35.90$, $P < 0.01$] and the interaction [$F(1,36) = 30.97$, $P < 0.01$] between CMS and treatment were also significant. Post hoc test showed that gallic acid significantly reversed the reduction of sucrose preference in CMS mice [$P < 0.01$].

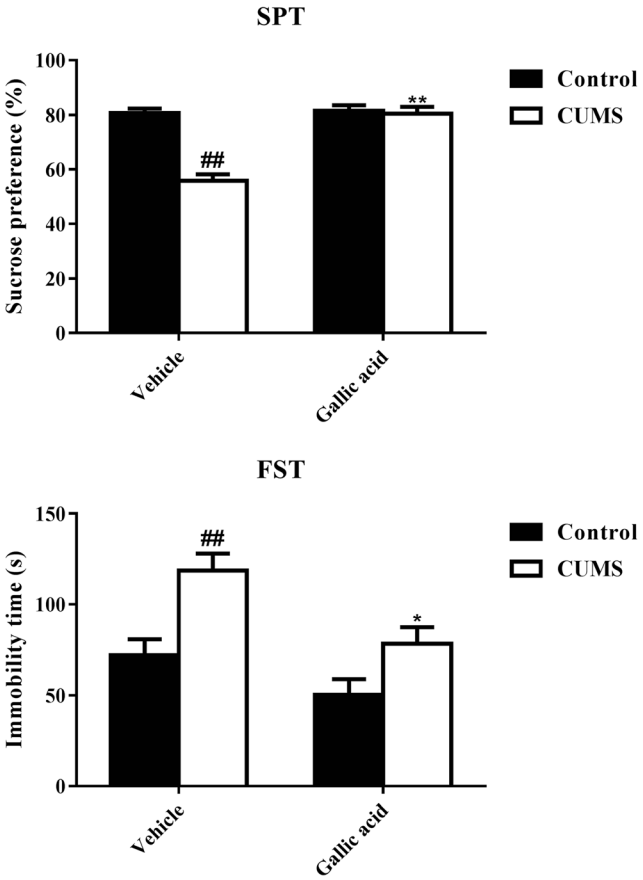

Fig. 1 The effects of gallic acid treatments on the sucrose preference (**a**) and immobility time (**b**) in mice exposed to CUMS. $^{\#\#}P < 0.01$, compared with control-vehicle group; $^{*}P < 0.05$ and $^{**}P < 0.01$,compared with CUMS-vehicle group

In addition, CMS also induced a significant despair symptom in mice, as immobility time was increased [$F(1,36) = 17.19$, $P < 0.01$] according to two-way ANOVA (Fig. 1). In addition, the treatment factor [$F(1,36) = 11.81$, $P < 0.01$] was also significant. Post hoc test showed that gallic acid significantly reversed the reduction of sucrose preference in CMS mice [$P < 0.05$].

Effects of gallic acid on hippocampal BDNF and TrkB expression

According to two-way ANOVA (Fig. 2), CMS induced a significant reduction of BDNF levels in the hippocampus of mice [$F(1,16) = 23.58$, $P < 0.01$]. In addition, the treatment factor [$F(1,16) = 17.62$, $P < 0.01$] and the interaction [$F(1,16) = 10.77$, $P < 0.01$] between CMS and treatment were also significant. Post hoc test showed that gallic acid significantly reversed the reduction of BDNF in the hippocampus [$P < 0.01$].

In addition, CMS induced a significant reduction of p-TrkB levels in the hippocampus of mice [$F(1,16) = 14.38$, $P < 0.01$].

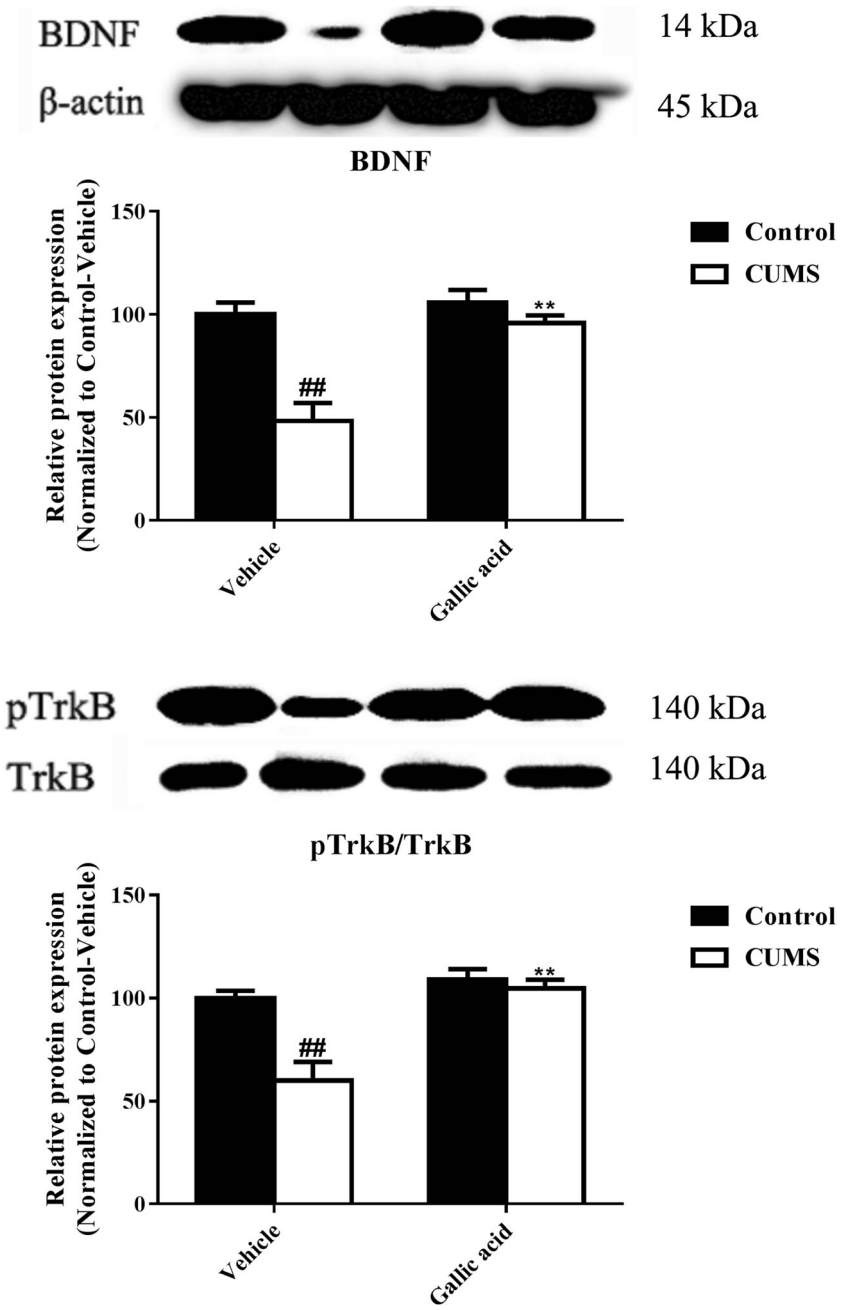

Fig. 2 The effects of gallic acid treatments on hippocampal BDNF and p-TrkB expression in mice exposed to CUMS. **a** Western blot image of BDNF; **b** The statistical results of BDNF expression. **c**Western blot image of p-TrkB; **d** The statistical results of p-TrkB expression. $^{\#\#}P < 0.01$, compared with control-vehicle group; $^{**}P < 0.01$, compared with CUMS-vehicle group

In addition, the treatment factor [$F(1,16) = 21.18$, $P < 0.01$] and the interaction [$F(1,16) = 9.37$, $P < 0.01$] between CMS and treatment were also significant. Post hoc test showed that gallic acid significantly reversed the reduction of p-TrkB in the hippocampus [$P < 0.01$].

Effects of gallic acid on hippocampal Akt and mTOR expression

According to two-way ANOVA (Fig. 3), CMS induced a significant reduction of p-Akt levels in the hippocampus of mice [$F(1,16) = 26.03$, $P < 0.01$]. In addition, the treatment factor [$F(1,16) = 14.79$, $P < 0.01$] and the interaction [$F(1,16) = 19.68$, $P < 0.01$] between CMS and treatment were also significant. Post hoc test showed that gallic acid significantly reversed the reduction of p-Akt in the hippocampus [$P < 0.01$].

In addition, CMS induced a significant reduction of p-mTOR levels in the hippocampus of mice [$F(1,16) = 35.95$, $P < 0.01$]. In addition, the treatment factor [$F(1,16) = 24.26$, $P < 0.01$] and the interaction [$F(1,16) = 15.70$, $P < 0.01$] between CMS and treatment were also significant. Post hoc test showed that gallic acid significantly reversed the reduction of p-mTOR in the hippocampus [$P < 0.01$].

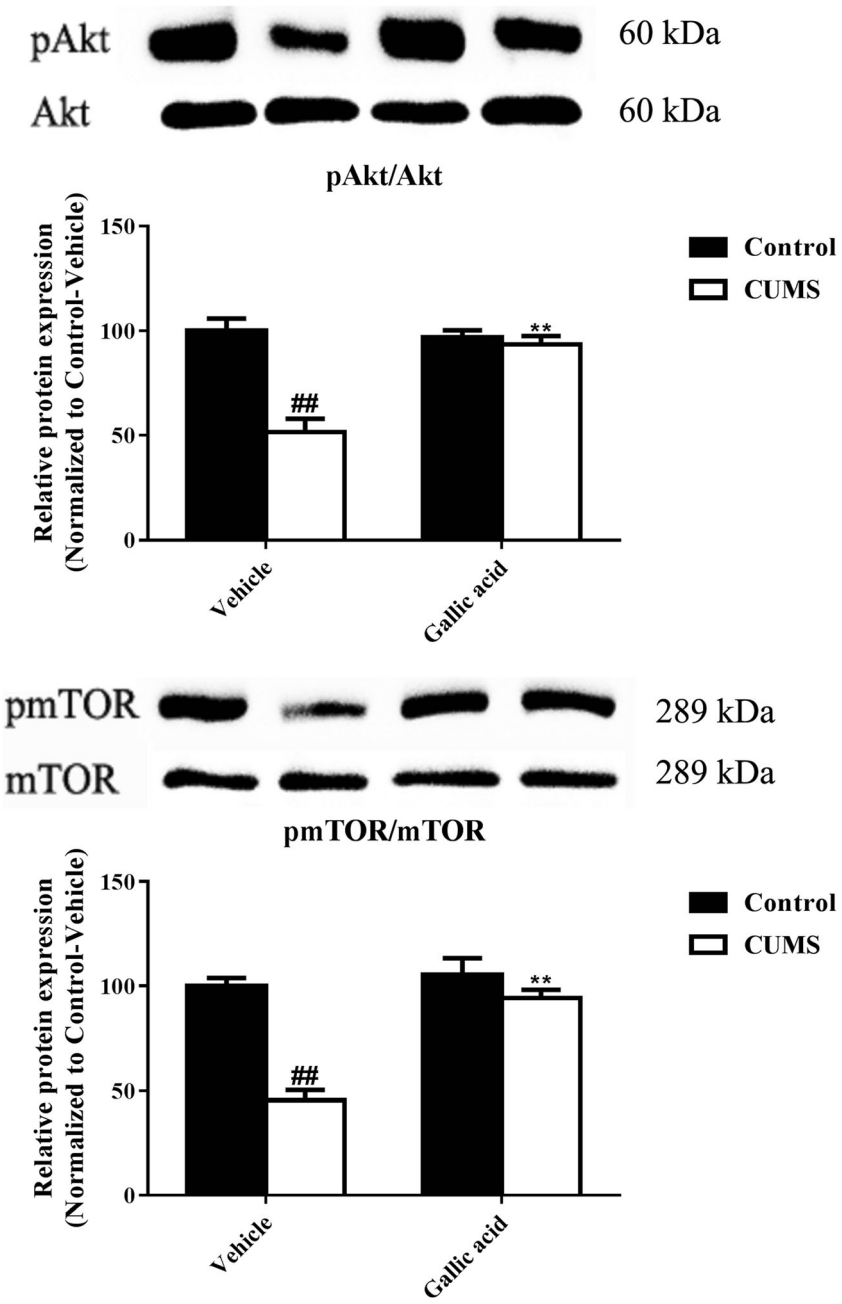

Fig. 3 The effects of gallic acid treatments on hippocampal p-Akt and p-mTOR expression in mice exposed to CUMS. **a** Western blot images; **b** The statistical results of p-Akt expression. **c** Western blot image of p-mTOR; **d** The statistical results of p-mTOR expression. $^{\#\#}P < 0.01$, compared with control-vehicle group; $^{**}P < 0.01$, compared with CUMS-vehicle group

Effects of gallic acid on hippocampal mTOR downstream signaling

According to two-way ANOVA (Fig. 4), CMS induced a significant reduction of p-p70s6k levels in the hippocampus of mice [$F(1,16) = 14.81$, $P < 0.01$]. In addition, the treatment factor [$F(1,16) = 14.23$, $P < 0.01$] and the interaction [$F(1,16) = 6.24$, $P < 0.05$] between CMS and treatment were also significant. Post hoc test showed that gallic acid significantly reversed the reduction of p-p70s6k in the hippocampus [$P < 0.01$].

In addition, CMS induced a significant reduction of p-4E-BP-1 levels in the hippocampus of mice [$F(1,16) = 7.24$, $P < 0.05$]. In addition, the interaction [$F(1,16) = 5.80$, $P < 0.05$] between CMS and treatment were also significant. Post hoc test showed that gallic acid significantly reversed the reduction of p-4E-BP-1 in the hippocampus [$P < 0.05$].

Effects of gallic acid on the newborn neurons in the dentate gyrus

According to two-way ANOVA (Fig. 5), CMS induced a significant reduction of DCX positive cells in the hippocampus of mice [$F(1,8) = 14.13$, $P < 0.01$]. In addition, the interaction [$F(1,8) = 7.57$, $P < 0.05$] between CMS and

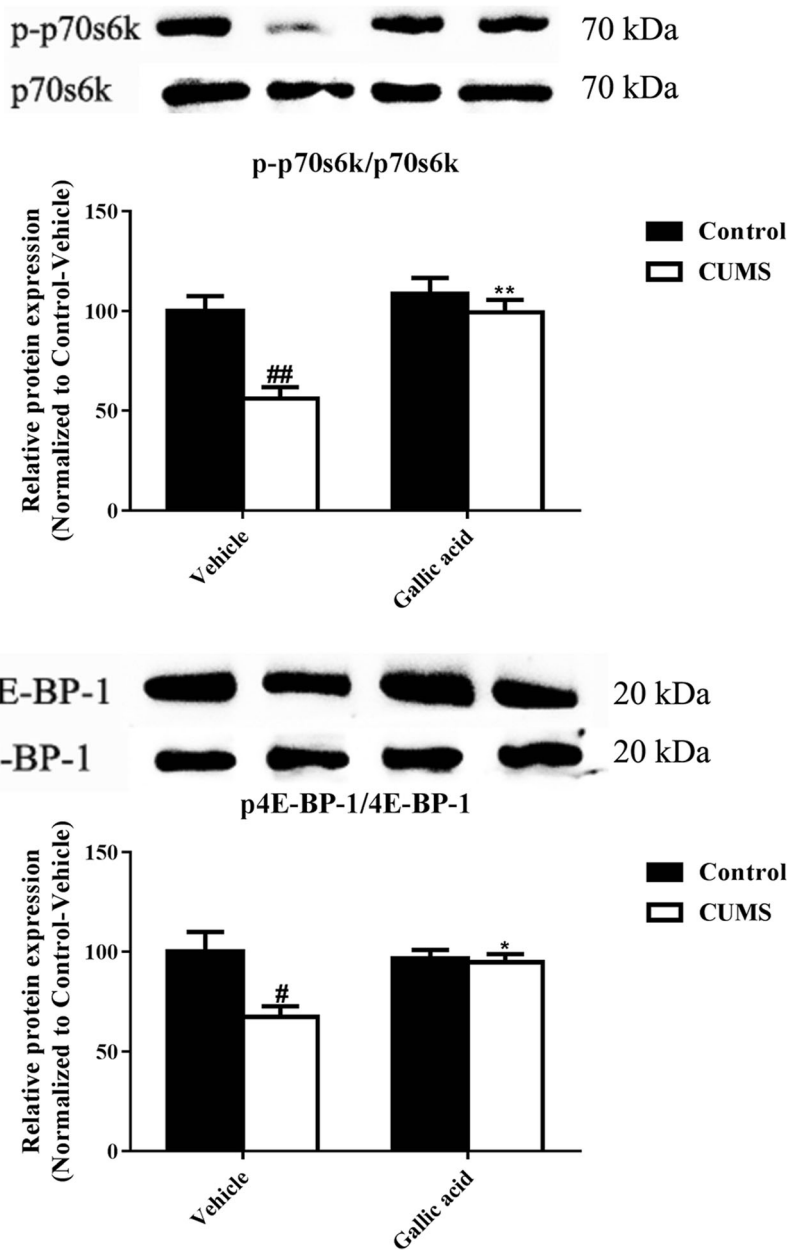

Fig. 4 The effects of gallic acid treatments on hippocampal p-p70s6k and p-4E-BP-1 expression in mice exposed to CUMS. **a** Western blot image of p-p70s6k; **b** The statistical results of p-p70s6k expression; **c** Western blot image of p-4E-BP-1; **d** The statistical results of p-4E-BP-1 expression. $^{\#}P < 0.05$ and $^{\#\#}P < 0.01$, compared with control-vehicle group; $^{*}P < 0.05$ and $^{**}P < 0.01$, compared with CUMS-vehicle group

treatment were also significant. Post hoc test showed that gallic acid significantly reversed the reduction of DCX positive cells in the hippocampus [$P < 0.05$].

Discussion

In the present study, we used CMS procedure to mimic common stress in people's daily life (Willner et al. 1987). Then we measured sucrose preference at the end of drug asministration as sucrose preference could be pointed to the anhedonia, one core symptom of human major depression (Stepanichev et al. 2016). The results indicated sucrose preference was decreased by CMS but reversed by a 4-week administration of gallic acid. In addition to sucrose preference, we also performed forced swimming test to double check the effects of gallic acid, as the immobility time of forced swimming test could reflect a despair, which is also related to depression. The results from forced swimming test demonstrated that gallic acid reversed the increase of immobility time induce by CMS. Consistent with the three previous studies which indicated that administration of gallic acid increased sucrose preference in CMS mice, decreased immobility time in the forced swimming test and tail suspension test (Can et al. 2017; Chhillar and Dhingra 2013; Nagpal et al. 2012), these behavioral results in the present study confirmed the antidepressant-like effects of gallic acid.

BDNF is synthesized and widely distributed in the central nervous system. The expression of BDNF is highest in the

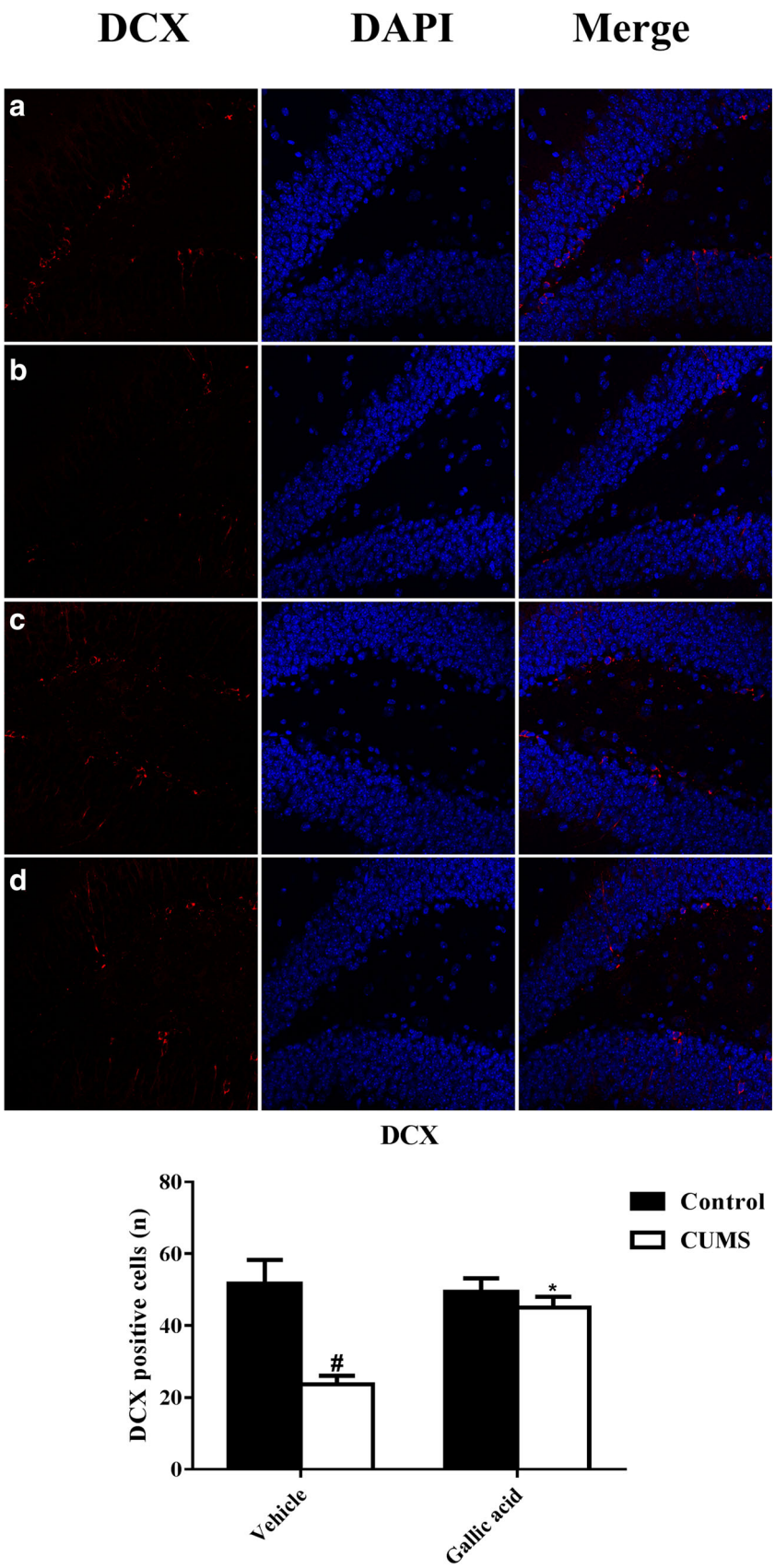

Fig. 5 The effects of gallic acid treatments on hippocampal newborn neurons in mice exposed to CUMS. **a** Immunofluorescence image of DCX positive cells; **b** The statistical results of DCX positive cells. $^{\#}P < 0.05$, compared with control-vehicle group; $^{*}P < 0.05$, compared with CUMS-vehicle group

cerebral cortex and hippocampus. BDNF not only plays an important role in the generation, differentiation and maturation of neurons, but also maintains the normal morphology and physiological functions of neurons, prevents neurons from being damaged, and enhances neuronal plasticity (Huang and Reichardt 2001; Mattson et al. 2004). BDNF can regulate the levels of synaptic neurotransmitters, promote the release of neurotransmitters from the presynaptic membrane, and enhance the response of the postsynaptic membrane, thereby enhancing synaptic signal transmission (Li and Keifer 2012). Therefore, it is well accepted that BDNF is involved in the pathophysiology of depression. In the present study, the results showed that not only the expression of BDNF but the phosphorylation of TrkB was inhibited by CMS, which was in accordance with plenty of previous studies (Ren et al. 2017; Thakare et al. 2018). In contrast, gallic acid significantly abolished this inhibition to increase BDNF expression and TrkB phosphorylation in the hippocampus, which was partly in line with a recent study showing that gallic acid reverted 6-Hydroxydopamine -induced BDNF down-regulation in human dopaminergic cells (Chandrasekhar et al. 2018). These results suggested that gallic acid reversed depressive-like bahaviors through BDNF-TrkB signaling.

The specific binding of BDNF to its receptor TrkB will further activate the three downstream signaling pathways of MEK-ERK, PLCγ-Ca^{2+} and PI3K-Akt, of which the MEK-ERK and PI3K-Akt signaling pathways are the most widely studied (Duman and Voleti 2012; Jourdi et al. 2009). A previous study suggested that smaller phenolics such as gallic acid were capable of exerting improvements in spatial memory via the modulation in hippocampal mTOR signaling (Corona et al. 2013). In this way, the present study focused on the improvement of Akt regulation by gallic acid in mice exposed to CMS. Generally, phosphorylated TrkB activates the downstream protein Akt, followed by the activation of mTOR by p-Akt. Then mTOR activates two downstream signaling proteins p70s6k and 4E-BP-1 and controls the expression of proteins correlation to neuronal proliferation or survival (Liu et al. 2015; Park et al. 2014). In the current study, the results from western blot indicated that CMS caused a reduction of p-Akt, p-mTOR, p-p70s6k and p-4E-BP-1, suggesting the inhibition of Akt-mTOR signaling pathway in the hippocampus. However, the reduction was totally attenuated by administration with gallic acid, indicating that Akt-mTOR signaling pathway was involved in the antidepressant-like effects of gallic acid.

Generally, the process and maintenance of memory, learning and other cognitive functions require neurogenesis in the brain (Seib and Martin-Villalba 2015). In addition to embryonic development, neurogenesis continues throughout adult life. However, the adult neurogenesis occurs at low levels as compared with embryonic development and mainly occurs in the dentate gyrus of the hippocampus (Lim and Alvarez-Buylla 2016). A clinical meta analysis found that the volume of hippocampus was reduced after disease onset in patients with major depression (McKinnon et al. 2009). Therefore, the authors suggested the potential clinical interventions aimed at reducing the harmful impact on brain volume or neurons. Moreover, another clinical investigation also demonstrated that available antidepressants increased neural progenitor in the in the dentate gyrus of patient with major depressive disorder (Boldrini et al. 2009). On the other hand, accumulating evidence showed that chronic stress impaired the proliferation of neurons, and this abnormality was reversed by effective antidepressants or treatment (David et al. 2009; Mu et al. 2016; Olesen et al. 2017; Santarelli et al. 2003). Therefore, some clinical doctors predicted the treatment response to electroconvulsive therapy by using volumetric information of hippocampus in the patient with depression (Cao et al. 2018). In the present study, we found that newborn neurons were significantly inhibited by CMS. On the contrary, gallic acid restored the proliferation of neurons. These results further verifies that BDNF-related neurogenesis is required for the effects of gallic acid and provides a possibility for the clinical application of gallic acid.

In summary, our results provided the direct evidence that chronic administration with gallic acid produced antidepressant-like effects in CMS, and these effects were mediated, at last partly through activation of the hippocampal BDNF-Akt-mTOR signaling pathway. Our study provides a further insight into the possible mechanism of gallic acid and its therapeutic use for treating major depression.

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Compliance with ethical standards

Competing interests The authors declare that they have no conflicts of interest.

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