

Curcumin relieves CUMS-induced depressive-like behaviors through PGC-1 α /FNDC5/BDNF pathway

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Abstract

Background

Curcumin (CUR), a primary component extracted from the Chinese medicine *Curcuma longa*, has been suggested to be effective in treating symptoms of a variety of neuropsychiatric disorders including depression. However, the underlying mechanism of CUR's antidepressant properties remains largely unknown. In this study, the antidepressant effect and its mechanism of CUR were investigated.

Methods

In this study, the chronic unpredictable mild stress- (CUMS-) induced depression model was employed to investigate the antidepressant effect of CUR. The depressive-like state was evaluated by the behavioral tests. On the day of the sacrifice, blood samples and the hippocampus of Sprague Dawley (SD) rats were collected for the following analysis. The proteins were investigated by Western blotting analysis and immunofluorescence analysis. The mRNA expression was analyzed by quantitative real-time PCR. Cell proliferation and apoptosis was determined with Brdu cell proliferation assay and Nissl staining assay.

Results

After stress exposure for six weeks, the CUMS rats showed depressive-like behaviors, and the administration of CUR successfully attenuated the depressive-like behaviors in CUMS-treated rats. Additionally, CUR effectively increased the expression of peroxisome proliferator-activated receptor γ coactivator 1 α (PGC-1 α), fibronectin type III domain-containing 5 (FNDC5), and brain-derived neurotrophic factor (BDNF). The CUR also stimulated the transcription of PGC-1 α and estrogen-related receptor alpha (ERR α), enhanced PGC-1 α and ERR α translocation from cytoplasm to nucleus, thus activating the PGC-1 α /FNDC5/BDNF pathway. Furthermore, we found the supplementation of CUR effectively promoted neurocyte proliferation and suppressed neural apoptosis induced by CUMS.

Conclusions

Collectively, the study revealed that CUR exerts antidepressant-like effect through the activation of the PGC-1 α /FNDC5/BDNF pathway.

Introduction

Depression is one of the most frequent and severe psychiatric conditions, with more than 264 million people affected worldwide [1]. Depression is often associated with high individual suffering, increased risk of suicide and an enormous economic burden for society. Multiple lines of evidence have illustrated that neuroinflammation, oxidative stress, mitochondrial dysfunction, decreased monoamine

neurotransmitter and neurotrophic factors might be responsible for the development of depression [2]. As a member of the neurotrophin family, BDNF is one of the best-studied neurotrophic factors. It is widely expressed in the central nervous system and serves essential functions in synapse formation, synaptic plasticity and neuronal maturation in the brain. Besides, studies have revealed BDNF's involvement in processes of learning, memory and cognition, as well as mood-related behaviors [3]. In the past two decades, BDNF is widely studied in neuropsychiatric diseases including but not limited to depressive disorders, bipolar disorder, schizophrenia, addiction, and eating disorders [4]. Accumulating evidence indicates that BDNF may function as attractive candidates for the treatment of depression [4, 5]. However, the intracellular signaling pathways necessary for BDNF's antidepressant effects are still a matter of debate.

PGC-1 α was initially discovered as a transcriptional coactivator [6]. It was then known as a metabolic regulator which plays a critical role in the maintenance of glucose, lipid, and energy homeostasis [7]. Subsequent work demonstrated the importance of PGC-1 α in the inhibition of neurodegeneration [8]. Previous studies suggested that PGC-1 α seems to improve learning and memory through regulation of the downstream membrane protein, FNDC5 [8]. FNDC5 was identified as a PGC-1 α -dependent myokine, which is known to be profoundly expressed in the brain in many regions, including the hypothalamus, as well as the hippocampus [12]. A previous study conducted by Wrann, C D [10] showed the strong correlation between PGC-1 α and FNDC5 gene expression and demonstrated that PGC-1 α is a regulator of neuronal FNDC5 gene expression in the brain. More researchers subsequently reported that FNDC5 can modulate BDNF expression and release in the hippocampus [8, 11, 13]. Considering the benefit of BDNF in the inhibition of depression, PGC1 α /FNDC5/BDNF was discerned as a critical pathway for neuroprotection and was expected to be an effective target for therapeutic interventions in depressive disorders [14].

CUR, the major active component extracted from the Chinese medicine *Curcuma longa*, has been reported to possess anti-inflammatory, antioxidant, and neuroprotective effects [15, 16]. CUR's potential antidepressant-like effects have been highlighted in many preclinical trials conducted on rats and mice models of depression [15–18]. Furthermore, several clinical trials have also been conducted on the potential effectiveness of CUR in depression but have yielded conflicting conclusions [19–22]. Despite the contradictory conclusions, a meta-analysis reviewing ten clinical trials concluded that CUR might be effective as adjunctive treatment in depressive disorders, indicating the promising efficacy of CUR in depression [21]. Growing studies have discussed the potential mechanism of CUR's anti-depressive effect, several of which showed CUR seems to increase the levels of BDNF [23–25]. However, how CUR regulates levels of BDNF has not been clearly established.

Therefore, in our present study, we used CUMS model to determine the antidepressant-like effect of CUR. We also examined whether there were changes in hippocampal expression of the PGC-1 α /FNDC5/BDNF pathway. We then investigated whether the possible antidepressant-like effects of CUR are associated with the activation of PGC-1 α /FNDC5/BDNF pathway.

Methods

Animals

SD rats (Male, 180-220g; Beijing Vitonlihua Experimental Animal Technology Co. Ltd, Beijing, China) were initially housed in groups in a temperature-controlled environment under a 12/12 h light/dark cycle. Food and water were freely available in the whole experiment except for rats kept under a deprivation procedure. This study was approved by the Animal Care and Use Committee of the eighth affiliated hospital of Sun Yat-sen University. All experiments were performed in accordance with the Guide for Care and Use of Laboratory Animals (Chinese Council).

Drug and treatment

Rats were randomly assigned to four groups (n=7): control, CUMS, CUMS + CUR, CUMS + CUR + SR18292 (PGC-1 α inhibitor). The CUR groups received daily gavage of 100 mg/kg CUR (suspended in 0.5% Tween 80, purchased from Sigma Chemical Co., USA) for 6 weeks at 60 min prior to CUMS. Rats received SR18292 (dissolved in DMSO, purchased from Macklin, Shanghai, China) via intraperitoneal injection at a dose of 40mg/kg every day in the last week for a total of seven injections. The doses of CUR and SR18292 were based on previous studies [15,16].

At the end of six weeks, behavioral tests were carried out, and the rats were sacrificed under anesthesia with an intraperitoneal injection of 1% sodium pentobarbital (50 mg/kg). Blood samples and the hippocampus were collected in our study.

CUMS procedure

Rats in the control group were housed in groups of 3-4 per cage in a separate room while rats in the CUMS groups were housed individually and received random unpredictable stress for 6 consecutive weeks. Stress stimuli included: cage tilting for 24 h; damp bedding for 24 h; fasting for 24 h; water deprivation for 24 h, finally with 1 h an empty bottle; light–dark-cycle reversal (12 h/12 h), behavior restriction for 2 h; 30 min noise, 5 min tail pinch. Rats received one of these stressors per day and same stressor was not applied in 2 consecutive days.

Sucrose preference test (SPT)

The SPT was performed as our previous study [15]. Before the SPT test, all the rats were housed individually and provided two bottles containing 1% sucrose solution for 48h to habituate them to the taste of sucrose. After 14h of water deprivation, two preweighted bottles with one containing 1% sucrose solution and another containing tap water were given to each rat. Then after 1h, the bottles were weighed again, and the weight difference in each bottle was considered the rat intake. The sucrose preference was measured as a percentage of the consumed 1% sucrose solution relative to the total amount of liquid intake.

Open-field test (OFT)

The test was performed in a square arena consisted of a 76×76 cm gray wooden box with 42 cm high boundary walls with the floor divided into 25 equal squares by black lines. Each rat was placed into the center of the open field and allowed to move freely for 5min. The apparatus was cleaned with ethanol and water prior to each test session to remove olfactory cues. The number of crossing and rearing was recorded by the observer blind to the treatment condition of the animal to assess locomotor activity and exploratory behavior.

Forced Swimming Test (FST)

The FST was performed as previously described [15]. Before the FST test, each rat was placed in a plastic drum (45 cm height, 25 cm diameter) containing approximately 35 cm of water (24 ± 1 °C) for a 15-min pretest. After swimming, rats were dried with towels and placed back in their home cage. After 24h, the rats were exposed to the same experimental conditions outlined above for a 5-min FST. Water was changed before each trial. Immobility time was scored by an experienced observer blind to the experiment design and was defined as floating passively and only making slight movements to keep the head above water.

Novelty-Suppressed Feeding Test (NSFT)

The SPT was performed as our previous study [15]. Before NSFT, all the rats were food-deprived for 24 h in their home cages. A small amount of food was placed on a piece of white paper (10 × 10 cm) in the center of an open field (75 × 75 × 40 cm). The rats were allowed to explore the open field for 8 min. The latency time was recorded in our study, defined as the time it took for each rat to approach and take the first bite of the food. Immediately afterwards, the animals were transferred to their home cages and were provided the same amount of food as in the open field. Total food intake for the next 5 min in each cage was weighed to avoid the influence of the animals' appetite.

Western blotting analysis

Total protein was prepared from the hippocampus and the Bradford method was used to determine the protein concentration. Samples were loaded on a precast 12% SDS-PAGE gels with 50 µg of protein in each lane. The proteins in the gels were transferred to a PVDF membrane and then blocked for 1 h in 5% nonfat dry milk in TBS-T (25 mM Tris, 150 mM NaCl, pH 7.5, 0.05% Tween-20). The following antibodies and concentrations were used overnight at a temperature of 4 °C: PGC-1α (ab106814, 1:1000, Abcam), ERRα (#13826, 1:1000, Cell Signaling Technology), FNDC5 (23995-1-AP, 1:1000; Proteintech), BDNF (28205-1-AP 1:1000; Proteintech), β-actin (8046S, 1:1000, Cell Signaling Technology). The membrane was then probed with an HRP conjugated secondary antibody for 40 min. Finally, the film signal was digitally scanned and quantified using Image-Pro Plus 6.0, and values were normalized to β-actin as an internal standard.

Quantitative real-time PCR (qPCR)

Total RNA was isolated from the hippocampal homogenates using Trizol reagent (Invitrogen, USA) according to the manufacturer's instructions. The mRNA expression of PGC-1 α , ERR α , FNDC5, BDNF, Bax, Bcl-xl and Bcl-2 was detected. Quantitative real-time PCR was performed on a Bio-Rad Cx96 Detection System (Biorad, USA) using an SYBR green PCR kit (Applied Biosystems, USA) and gene-specific primers. Oligonucleotide primers specific for rats are listed in Table 1. The 5 ng cDNA samples received 40 cycles of amplification. Each cDNA was tested in triplicate. Relative mRNA expression levels were normalized to β -actin as an internal standard.

Table 1: Primer sequences used for the qPCR analysis.

Gene	Sense primer (5'–3')	Antisense primer (5–3')	Amplicon length (bp)
PGC-1 α	5'-GAACCATGCAAACCACACCC-3'	5'-GGAGGGTCATCGTTTGTGGT-3'	162
ERR α	5'-AACCTGAGAAGCTGTACGCC-3'	5'-CCATCCACACACTCTGCAGT-3'	186
FNDC5	5'-TATATCGTCCACGTGCAGGC-3'	5'-ACGACGATGATCAGCACCTC-3'	179
BDNF	5'-TACCTGGATGCCGCAAACAT-3'	5'-CGACATGTCCACTGCAGTCT-3'	135
Bax	5'-GAACCATCATGGGCTGGACA-3'	5'-GTGAGTGAGGCAGTGAGGAC-3'	157
Bcl-xl	5'-AGGCTGGCGATGAGTTTGAA-3'	5'-AGAAGAAGGCCACAATGCCA-3'	159
Bcl-2	5'-GAACTGGGGGAGGATTGTGG-3'	5'-CATCCCAGCCTCCGTTATCC-3'	164
β -Actin	5'-CCACCATGTACCCAGGCATT-3'	5'-CGGACTCATCGTACTCCTGC-3'	189

Nissl staining

The Nissl staining was performed as previously described [26]. Formaldehyde-fixed specimens were embedded in paraffin and cut into 4- μ m-thick sections that were deparaffinized with xylene and rehydrated in a graded series of alcohol. Samples were treated with Nissl staining solution for 5 min. Damaged neurons were shrunken or contained vacuoles. Normal neurons had a relatively large, full soma, and round, large nuclei. We calculate the average intensities or cell counts from the same sections in seven rats per group with Image-Pro Plus 7.0. Investigators were blinded to the experimental groups.

Immunofluorescence analysis

The Immunofluorescence analysis was performed according to the previous study [9]. Formaldehyde-fixed specimens were embedded in an optimal cutting temperature compound (SAKURA, USA), and cut in sections using a microtome. After washing three times using PBS, the tissues were blocked with 10% goat serum (Solarbio, China) and 0.3% Triton X-100 (Solarbio, China) in PBS at 37°C for 2 h. Then the tissue were incubated with primary antibodies (PGC-1 α , ab106814, 1:300, Abcam) overnight at 4°C. After washing with PBS, the tissues were incubated with secondary antibodies (4412, 1:1000, Cell Signaling Technology) for 1 h and with 4',6-diamidino-2-phenylindole (Solarbio, China) for 5 min. Fluorescence was observed using a fluorescence microscope. The results were analyzed using Image-Pro Plus software. Investigators were blinded to the experimental groups.

Bromodeoxyuridine treatment

BrdU (100 mg/kg) was injected intraperitoneally once daily for 3 consecutive days before the brain slice collection. After washing in 0.1M borate buffer (pH=8.5) for 30 min, the thirty- μ m-thick coronal sections containing dentate gyrus (DG) were collected and pretreated with HCl at 37 °C for 30 min, and then incubated with 3% BSA for 1 h. Then the sections were incubated with the antibody for BrdU, followed by Alexa Fluor secondary antibody. Photomicrographs were obtained with a FluoView FV1000 microscope.

Statistical Analysis

All statistical procedures were performed using Statistical Package for the Social Science (SPSS) 24.0. Data were expressed as mean \pm SD. All the data were analyzed statistically by one-way analysis of variance (ANOVA) with Tukey post hoc multiple comparisons. $P < 0.05$ was considered as statistically significant.

Results

Effects of CUR on behavioral tests

After stress exposure for six weeks, the CUMS rats represented depressive-like state with reduced sucrose preference in SPT (Fig. 1a), prolonged immobility (Fig. 1b) in FST, and increased latency time (Fig. 1c) in NSFT compared to the rats in the control group. In addition, the CUMS rats displayed a reduction of the number of crossing (Fig. 1e) and rearing (Fig. 1f) in OPT.

In comparison with the CUMS group, the supplementation of CUR significantly increased the sucrose preference (Fig. 1a), decreased immobility time (Fig. 1b) and latency time (Fig. 1c), and increased the number of crossing (Fig. 1e) and rearing (Fig. 1f) in the CUMS+CUR group.

When compared to CUMS+CUR group, the administration of PGC-1 inhibitor SR18289 successfully decreased sucrose preference (Fig. 1a), increased immobility time (Fig. 1b) and latency time (Fig. 1c), and decreased the number of crossing (Fig. 1e) and rearing (Fig. 1f) in the CUMS +CUR+ SR18292 group.

In addition, no significant difference in food intake was observed in NSFT (Fig. 1d), which is consistent with the results of the previous studies.

Effects of CUR on PGC-1 and ERR α expression

As shown in Fig. 2a-b, the mRNA levels of PGC-1 and ERR α were markedly decreased in the CUMS group compared to the control group, and CUR treatment significantly decreased the mRNA expression of PGC-1 and ERR α in the CUMS + CUR group compared to the CUMS group. The CUMS + CUR + SR18292 group showed a significant decrease in the mRNA levels of PGC-1 and a slight but not significant decrease in the mRNA levels of ERR α when compared to the CUMS + CUR group.

The rats in the four groups represented no significant changes in the cytoplasmic protein expression of PGC-1 and ERR α (Fig. 2d-e), except that the cytoplasmic PGC-1 protein expression in the CUMS group was significantly decreased (Fig. 2d) when compared to the control group. However, the protein expression of PGC-1 and ERR α in nuclear varied significantly in different groups. As shown in Fig. 2f-g, the CUMS group showed a marked decrease in the protein expression of nuclear PGC-1 and ERR α when compared to the rats in the control group, while daily administration of CUR prevented these changes with a significant increase in the protein expression of nuclear PGC-1 and ERR α in the CUMS + CUR group. In addition, administration of SR18292 significantly decreased the protein expression of nuclear PGC-1 and ERR α in the CUMS + CUR + SR18292 group compared to the CUMS + CUR group.

The results of the immunofluorescence staining was shown in Fig. 2h. Consistent with the western blot results, CUMS rats showed a decreased PGC-1 expression when compared to the control group. And the expression of PGC-1 in the CUMS + CUR group was obviously increased when compared to the CUMS group. Moreover, SR18292 significantly decreased the expression of PGC-1 in the CUMS + CUR + SR18292 group when compared to the CUMS + CUR group.

Effects of CUR on FNDC5 and BDNF expression

As shown in Fig. 3a, the mRNA levels of FNDC5 and BDNF was significantly decreased in the CUMS group compared to the control group, while the supplementation of CUR markedly increased the mRNA expression of FNDC5 and BDNF. Furthermore, administration of SR18292 reversed the effects of CUR and significantly reduced the mRNA expression of FNDC5 and BDNF.

As shown in Fig. 3c-d, the western blot results represented that the protein expression of FNDC5 and BDNF was significantly decreased in the CUMS group compared to the control group, while the supplementation of CUR markedly increased the protein expression of FNDC5 and BDNF. In addition, administration of SR18292 reversed the effects of CUR and significantly reduced the protein expression of FNDC5 and BDNF.

Effects of CUR on the neural proliferation and apoptosis

The immunofluorescence staining of BrdU was used to determine the neural proliferation in hippocampus tissue. As shown in Fig. 4b, the quantitative results of the immunofluorescence staining showed that CUMS significantly decreased the number of BrdU+ cells in the hippocampus in comparison with the control group. Administration of CUR significantly increased the number of BrdU+ cells when compared to the CUMS group. Additionally, SR18292 reversed the effects of CUR and significantly decreased the number of BrdU+ cells.

Nissl staining was used to identify apoptotic neurons in hippocampus tissue. As shown in Fig. 4d, the quantitative results of the Nissl staining showed that the number of viable neurons in the CUMS group was significantly reduced to that in the control group. Administration of CUR significantly increased the number of viable neurons when compared to the CUMS group. Moreover, SR18292 reversed the effects of CUR and significantly decreased the number of viable neurons.

As shown in Fig. 4e-g, the CUMS group significantly increased the mRNA expression of Bax, and decreased the mRNA levels of Bcl-2 and Bcl-xl, while the CUMS + CUR group significantly decreased the mRNA expression of Bax, and increased the mRNA levels of Bcl-2. Furthermore, administration of SR18292 reversed the effects of CUR and dramatically induced the mRNA expression of Bax, and reduced the mRNA levels of Bcl-2.

Discussion

The present study provides novel evidence supporting the link between the antidepressant-like activities of CUR and the PGC-1 α /FNDC5/BDNF pathway. In this study, we observed that the chronic administration of CUR normalized behavioral changes in rats exposed to CUMS, showing the antidepressant activity of CUR. We also found that CUR could effectively prevent CUMS-induced reduction of PGC-1 α , ERR α , FNDC5, and BDNF expression. Besides, CUR could promote cell proliferation and suppress neural apoptosis induced by CUMS. Additionally, we found the PGC-1 α inhibitor, SR1829, markedly reversed the antidepressant-like effects of CUR in the behavioral test, as well as the effects of CUR in the expression of PGC-1 α , ERR α , FNDC5 and BDNF. These findings demonstrated the potential benefits of CUR to reverse the development of depression and indicated that the antidepressant mechanism of CUR might be mediated by the activation of the PGC-1 α /FNDC5/BDNF pathway.

CUMS, a valid model of depression for rodents [27], was established in the present study. Consistent with previous reports [28, 29], we showed that 6 weeks of CUMS induced the rats to a depressive state. Moreover, the results of behavioral tests indicated that administration of CUR was able to attenuate the behavioral abnormalities induced by CUMS, reflecting the antidepressant-like properties of CUR [15, 16, 30]. However, the administration of PGC-1 inhibitor SR18292 reversed the beneficial effects of CUR and induced abnormal behaviors, which indicated that PGC-1 might play an important role in the antidepressant-like effects of CUR.

Numerous studies have demonstrated that the expression levels of BDNF mRNA and protein were decreased in the brain of depressive rats [4, 5]. Animal studies reported that CUR seem to have the ability

to reverse CUMS-induced decrease in brain BDNF level [15, 31]. Our results were consistent with the previous study. The expression of BDNF in the CUMS + CUR rats was significantly higher compared with the CUMS rats, confirming the capacity of CUR to increase the expression of BDNF in hippocampal neurons. To our best knowledge, it has been demonstrated that PGC-1 α is closely related to the regulation of BDNF expression in the hippocampus through an FNDC5-dependent mechanism [14, 32]. Wrann et al. (2013) [10] reported that endurance exercise can induce increased expression of BDNF through activating the PGC-1 α / FNDC5/BDNF pathway in the hippocampus. In their study, it was proved that neuronal FNDC5 gene expression is regulated by PGC-1 α , and then FNDC5 regulates BDNF gene expression in a cell-autonomous manner. In our present study, we also examined the effects of CUR on the expression of PGC-1 α and FNDC5. Our results showed that the levels of PGC-1 α and FNDC5 were highly increased in the CUMS + CUR rats compared with the CUMS rats. Combined with the results of behavioral tests and the increased expression of PGC-1 α , FNDC5, and BDNF in the CUMS + CUR rats, we concluded that the antidepressant-like effects of CUR might be closely linked to the positive regulation of the PGC-1 α /FNDC5/BDNF pathway.

Furthermore, to explore whether PGC-1 α is required for CUR's regulation of BDNF expression, SR1829 was used to inhibit the expression of PGC-1 α . After administration of SR1829, we examined the expression of PGC-1 α in the hippocampus. SR1829 effectively decreased PGC-1 α expression in this area. The expression levels of FNDC5 and BDNF was also significantly decreased. The abnormal behaviors induced by SR1829 in the behavior tests and the effects of SR1829 on the expression of PGC-1 α , FNDC5, and BDNF implied the essential role of PGC-1 α in the induction of BDNF by CUR. As a transcriptional coactivator, PGC-1 α does not bind to the DNA itself but interacts with transcription factors to execute its effects on gene expression. The orphan nuclear receptor ERR α is a central metabolic regulator and is known to be a very important interactor with PGC-1 α . The interaction of the PGC-1 α with ERR α has been proved to be crucial for FNDC5 gene expression [10]. In our hypothesis, CUR could activate the transcription of PGC-1 α and ERR α , thus leading to increased FNDC5 and BDNF levels [10, 11]. Our results were consistent with these findings. we found that CUR effectively restored the decreased gene expression of PGC-1 α and ERR α induced by CUMS. Remarkably, the results of western blot showed significantly increased nuclear protein expression of PGC-1 α and ERR α in CUMS + CUR rats compared with the CUMS rats, while the cytoplasmic protein expression of PGC-1 α and ERR α showed no significant difference in different groups. Together these data suggest that CUR administration not only elevated the expression of PGC-1 α and ERR α , but also promoted PGC-1 α and ERR α nuclear translocation. In summary, the above results indicated that the PGC-1 α /FNDC5/BDNF pathway was inhibited under CUMS, and chronic administration of CUR stimulated the transcription of PGC-1 α and ERR α , enhanced PGC-1 α and ERR α translocation from cytoplasm to nucleus, and thus activating the PGC-1 α /FNDC5/BDNF pathway.

We also investigated the effects of CUR on the proliferation and survival of neuronal cells [33]. Previous studies showed decreased neural proliferation and increased cell apoptosis in depressive rats [34, 35]. We observed the same results in CUMS model rats. Our results also represented the neuroprotective capacity of CUR. The immunofluorescence staining showed that CUR led to a significant increase in the average number of BrdU positive cells in the hippocampus, suggesting the potential roles of CUR in promoting

neural proliferation in rats. In addition, CUR significantly increased the numbers of viable neurons in the DG area of the hippocampus, markedly inhibited the gene expression of pro-apoptotic Bax and enhanced the gene expression of anti-apoptotic factor Bcl-xl, which suggested that CUR could effectively suppress the apoptosis induced by CUMS. As the most abundant neurotrophic factor in the brain, BDNF has been suggested to play a crucial role in the regulation of neural proliferation and survival [36]. Given the neurotrophic actions of BDNF and CUR's effects on the BDNF level, we speculated that the neuroprotective capacity of CUR might be attributed to the elevated expression of BDNF.

Conclusions

Collectively, our present study suggests that the administration of CUR could ameliorate depressive-like behaviors in CUMS rats. Furthermore, our study linked the activation of a metabolic regulator, PGC-1 α , via FNDC5 to the increased BDNF levels induced by CUR. Our study provides novel evidence to the hypothesis that the antidepressant-like effects of CUR might be mediated by restoring changes in the PGC-1 α /FNDC5/BDNF signaling pathway in the hippocampus of CUMS rats, which might ultimately contribute to the neuroprotective effect of CUR.

Abbreviations

CUR: curcumin; CUMS: chronic unpredictable mild stress; PGC-1 α : Peroxisome proliferator-activated receptor γ coactivator 1 α ; FNDC5: fibronectin type III domain-containing 5; BDNF: brain-derived neurotrophic factor; ER α : estrogen-related receptor alpha.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

PJ and RD designed the research. YW and FS conducted the experiments. YW wrote the manuscript. PJ, RD, FS, YG revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

The study was established according to the ethical guidelines and approved by the Ethics Committee on Laboratory Animal Management of the eighth affiliated hospital of Sun Yat-sen University.

Consent for publication

We declare that the Publisher has the Author's permission to publish the relevant contribution.

Competing interests

The authors declare no competing conflict of interests.

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Figures

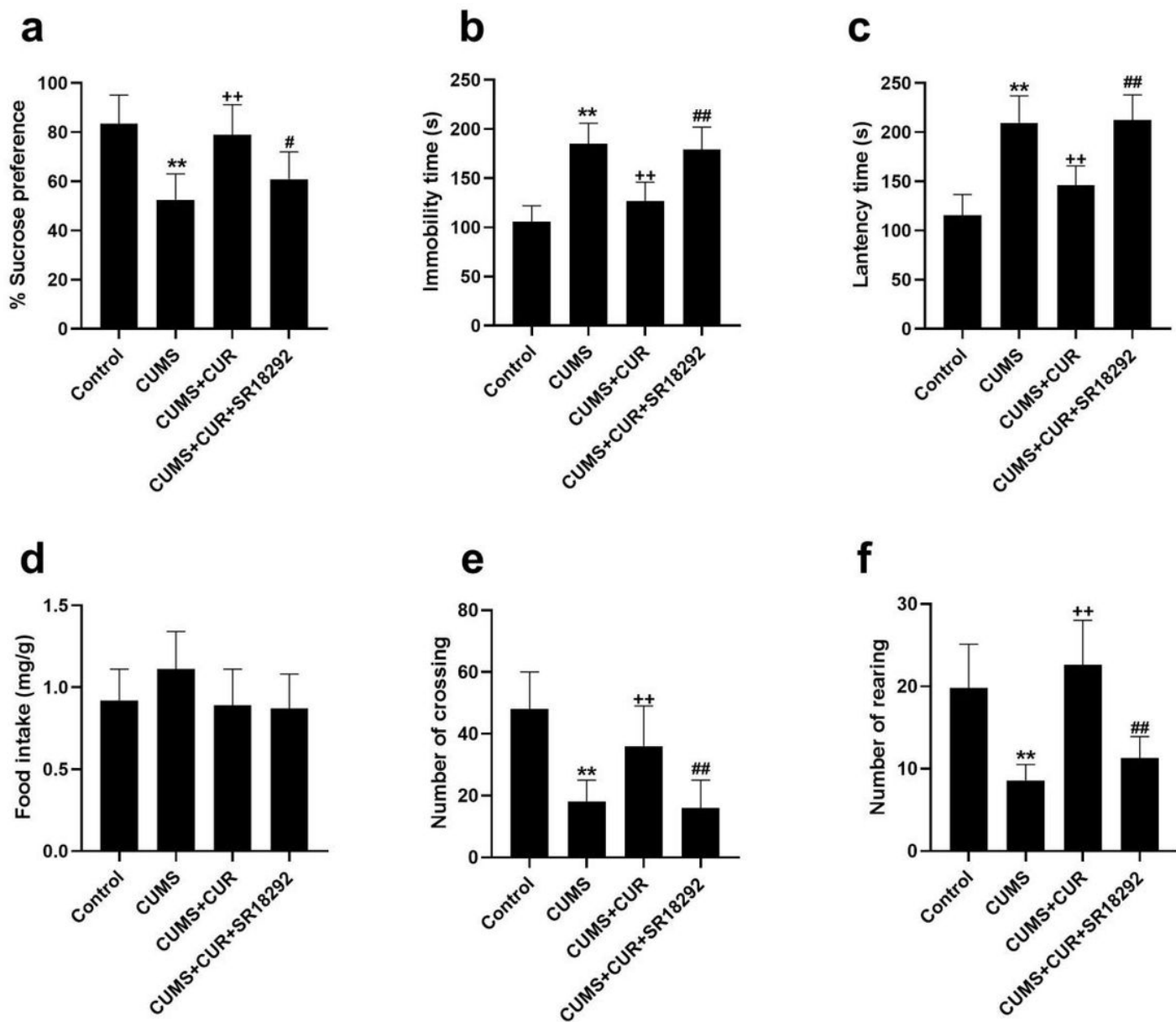


Figure 1

Effect of CUR on CUMS-induced behavior changes. (a) Sucrose preference in SPT. (b) Immobility time in FST. (c) Latency time in NSFT. (d) Food intake in NSFT. (e) Number of crossing and (f) number of rearing in OPT. Data are expressed as means \pm SD ($n = 7$). * $p < 0.05$ and ** $p < 0.01$ compared to the control group. + $p < 0.05$ and ++ $p < 0.01$ compared to the CUMS group. # $p < 0.05$ and ## $p < 0.01$ compared to the CUMS+CUR group.

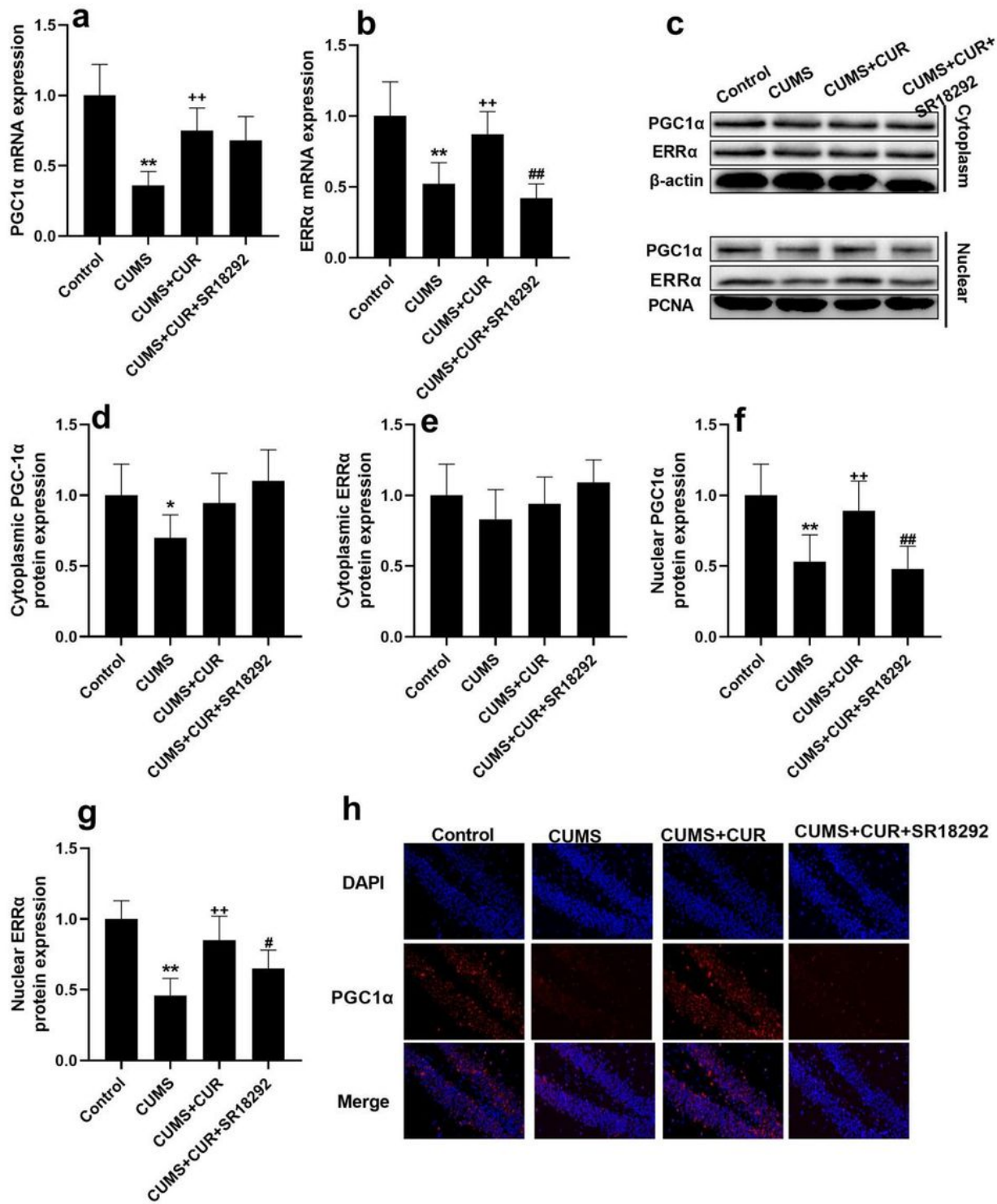


Figure 2

Effect of CUR on PGC-1 and ERRα expression in the hippocampus. (a, b) Relative mRNA expression of PGC-1 and ERRα. (c) Western blot bands indicating the protein expression of PGC-1α and ERRα in the hippocampus. (d-g) Protein expression of PGC-1α and ERRα normalized to that of the β-actin internal control. (h) Representative images of immunofluorescence staining for PGC-1α in brain slices of the hippocampus. Data are expressed as means ± SD (n = 7). *p < 0.05 and **p < 0.01 compared to the

control group. +p < 0.05 and ++p < 0.01 compared to the CUMS group. #p < 0.05 and ##p < 0.01 compared to the CUMS+CUR group.

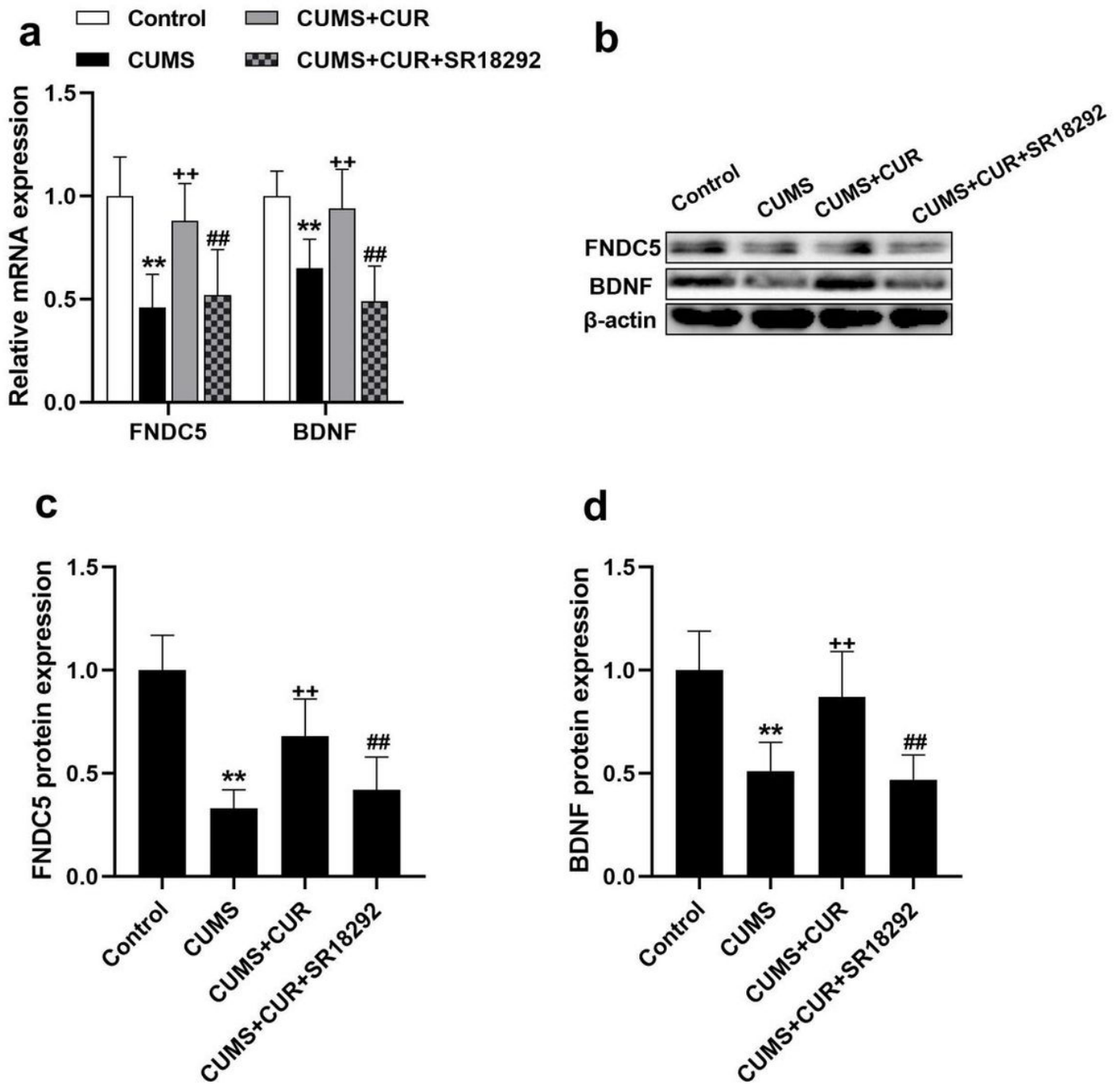


Figure 3

Effect of CUR on FNDC5 and BDNF expression in the hippocampus. (a) Relative mRNA expression of FNDC5 and BDNF. (b) Western blot bands indicating the protein expression of FNDC5 and BDNF. (c, d) Protein expression of FNDC5 and BDNF normalized to that of the β -actin internal control. Data are

expressed as means \pm SD (n = 7). *p < 0.05 and **p < 0.01 compared to the control group. +p < 0.05 and ++p < 0.01 compared to the CUMS group. #p < 0.05 and ##p < 0.01 compared to the CUMS+CUR group.

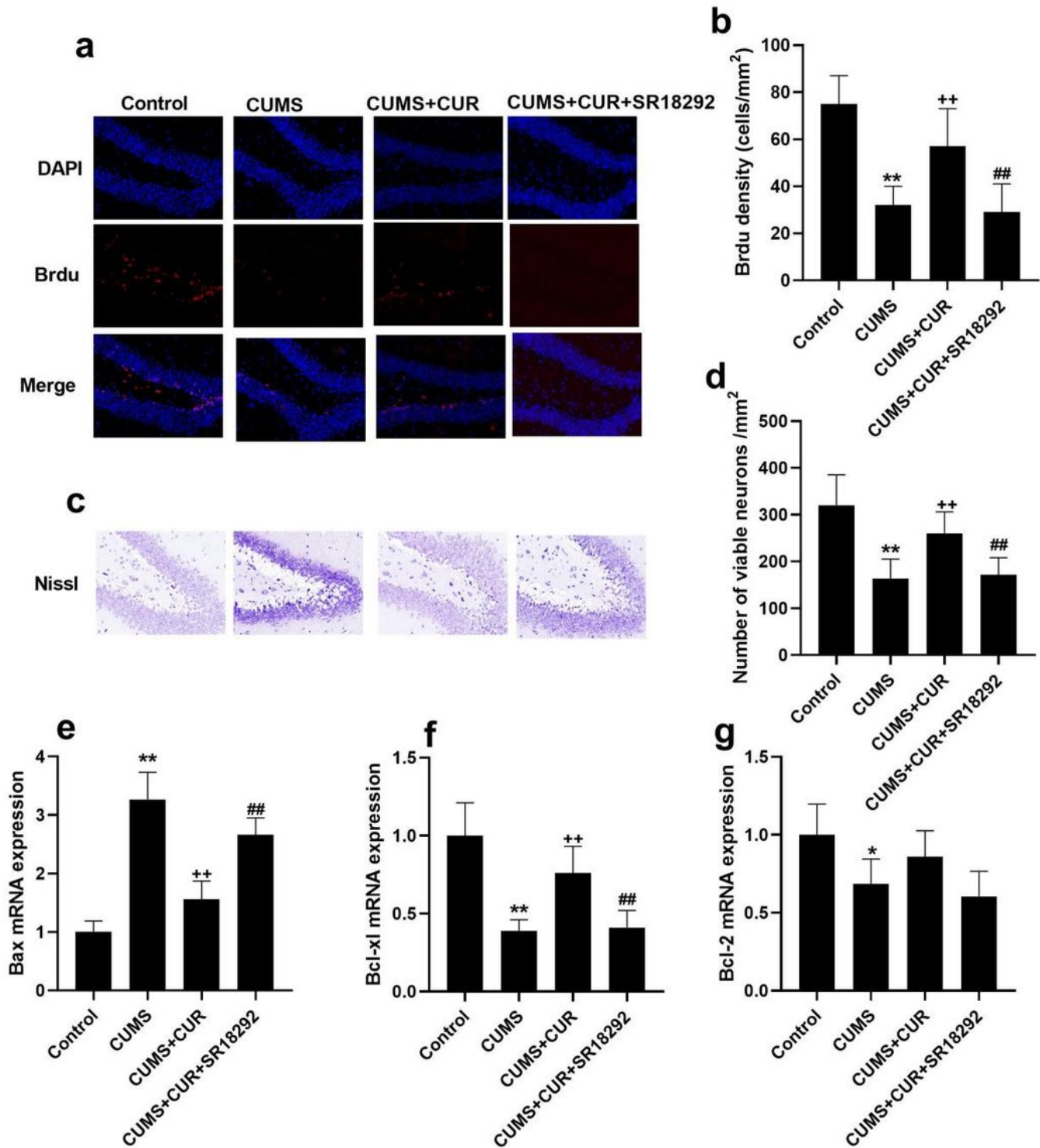


Figure 4

Effect of CUR on cell proliferation and apoptosis in the hippocampus. (a) Representative images of immunofluorescence staining for BrdU positive cells. (b) Quantification of BrdU fluorescence in the DG area of the hippocampus. (c) Representative images of Nissl-stained neurons. (d) Quantification of viable

neurons in the DG area of the hippocampus. (e-g) Relative mRNA expression of Bax, Bcl-xl, Bcl-2. Data are expressed as means \pm SD (n = 7). *p < 0.05 and **p < 0.01 compared to the control group. +p < 0.05 and ++p < 0.01 compared to the CUMS group. #p < 0.05 and ##p < 0.01 compared to the CUMS+CUR group.