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ORIGINAL RESEARCH

Intranasal Administration of Brain-Derived Neurotrophic Factor Rescues Depressive-Like Phenotypes in Chronic Unpredictable Mild Stress Mice

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Introduction: Major depression disorder is the most common diagnosed mental illnesses, and it bring a high social and economic burden. However, the current treatment for depression has limitations with side effects. Hence, there is an urgent need to search more effective treatment for major depressive disorder. Brain-derived neurotrophic factor (BDNF) is a neurotrophin that is vital to the survival, growth, and maintenance of neurons.

Methods: We administered BDNF into chronic unpredictable mild stress (CUMS)-induced depression mice and assessed the effects of intranasal delivery of BDNF in depression by the tail suspension test, forced swimming test, novelty suppressed feeding test, and open-field test.

Results: We find that the intranasal administration of BDNF reversed the depressive-like behaviors in CUMS mice as measured Further analyses suggested that BDNF treatment reduced pro-inflammatory cytokine (IL-6, TNF-α, iNOS and IL-1β) expressions in the hippocampus of CUMS mice. In addition, our results showed that BDNF markedly reduced oxidative stress in the hippocampus and blood of CUMS mice. Moreover, our data suggested that BDNF treatment increased neurogenesis in the hippocampus of CUMS mice.

Discussion: Taken together, our results for the first time demonstrated that intranasal delivery of BDNF protein exhibited anti-depressant-like effects in mice, and therefore may represent a new therapeutic strategy for major depressive disorder.

Keywords: depression, BDNF, neurogenesis, inflammatory cytokine, oxidative stress

Introduction

Major depressive disorder (MDD) is a highly prevalent psychiatric disorder characterized by depression mood, loss of interest and cognitive impairment, affecting more than 300 million people worldwide.[1,2] This disorder is easy to be misdiagnosed and with delayed treatment because of overlapping symptoms with other mental disorders.[3,4] It is predicted that MDD will be the leading cause of the global burden of disease by 2030.[5] Despite extensive research into the field and the emergence of a variety of available antidepressants, more than 30% of depressed patients fail to respond to antidepressant drug treatment.[6,7] Therefore, it is necessary to have a deeper understanding of the pathogenesis and molecular mechanism of MDD, which is of great significance for the development of new and effective treatments.

Brain-derived neurotrophic factor (BDNF) is a member of neurotrophin family that includes nerve growth factor (NGF), neurotrophin (NT)-3 and NT-4.[8] Among these neurotrophins, BDNF stands out for its high level of expression in

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the central nervous system (CNS) and its profound effects on development, morphology, and synaptic plasticity and function in the brain.[9,10] It has been widely studied in the past decade because of its association with a number of psychiatric disorders and their treatments, such as schizophrenia, intellectual disabilities, autism, and depression.[9] A growing body of evidence supports the BDNF was involved in the pathophysiology and/or therapeutic progression of MDD. For example, a large number of previous clinical studies have consistently reported significantly decreased serum and plasma BDNF levels in depressed patients and were inversely correlated with disease severity.[11–14] Postmortem studies also support the role of BDNF in MDD, with a study showing reduced expression of BDNF in depressed suicidal patients and increased expression in patients treated with antidepressants.[15] Moreover, Shirayama et al found that injecting BDNF into hippocampus was sufficient to produce an antidepressant-like effect in behavioral models of depression.[16] However, the therapeutic potential of BDNF in MDD is still largely unknown.

Here we used a chronic stress-induced animal model of depression to determine whether intranasal delivery of BDNF can rescue depressive-like phenotypes in mice. The results showed that intranasal administration of BDNF ameliorated stress-induced depressive-like behaviors in mice, normalized peripheral and hippocampal oxidative factors levels, and reduced inflammatory factor levels in the hippocampus of stressed mice.

Materials and Methods

Animals

C57BL/6 mice (male, 6-to 8-week-old) were purchased from Vital River Laboratory (Beijing, China). All mice were provided ad libitum access to a standard diet and drinking water, and raised at the temperature of 24 ± 1°C and humidity of 50 ± 1%) under a 14/10 h light/dark cycle. All animals were housed for 1 week to adapt to the environment. All animal procedures were approved by the Animal Care and Use Committee of the Minzu University of China, and the animal experiments were conducted in accordance with the National Institutes of Health Laboratory Animal Care and Use Guidelines (NIH Publication No. 80–23).

Drug Administration

BDNF was purchased from Novoprotein (Cat. No: C076), and was dissolved in 0.01 M PBS. The mice were subjected to intranasal administration of BDNF at 40 ug/kg (CUMS+BDNF group) or equal volume of 0.01M PBS (control group and CUMS group) every day for 15 days.

CUMS Model Establishment and

The CUMS mouse model of depression was established according to our previously published paper,[17] and sources of stress included restraint stress and tail suspension. After three days of behavioral tests to confirm the establishment of depression model, BDNF or PBS was intranasally injected into the mice in different animal groups for 15 days. Then open-field test (OFT), forced swim test (FST), novelty suppressed feeding test (NSFT) and tail suspension test (TST) were used to measure the effects of BDNF on depressive-like behaviors in mice.

Behavioral Tests

The TST was performed following to previously published literature.[18] The OFT was performed as previously described with some modifications.[19] Briefly, mice were placed in an open-field apparatus (50 × 50×40 cm), and their movements were monitored for 15 min using a chart-couple device (CCD) camera. The image was captured with a computer using SMART V3.0 software. The distance moved and the time spent in the central area were calculated automatically.

The FST was performed according to previous literature with some modifications.[20] Briefly, mice were placed in a Plexiglas cylinder (15 cm diameter and 25 cm in height) containing water at a temperature of 23–24 °C and a depth of 14 cm. The mice were forced to swim for 5 min and recorded with a video recorder.

The NSFT was also performed as described previously with some modifications.[21] Briefly, food-deprived mice were placed in an open field with a small amount of food in the center of the field, and latency to feed was measured under

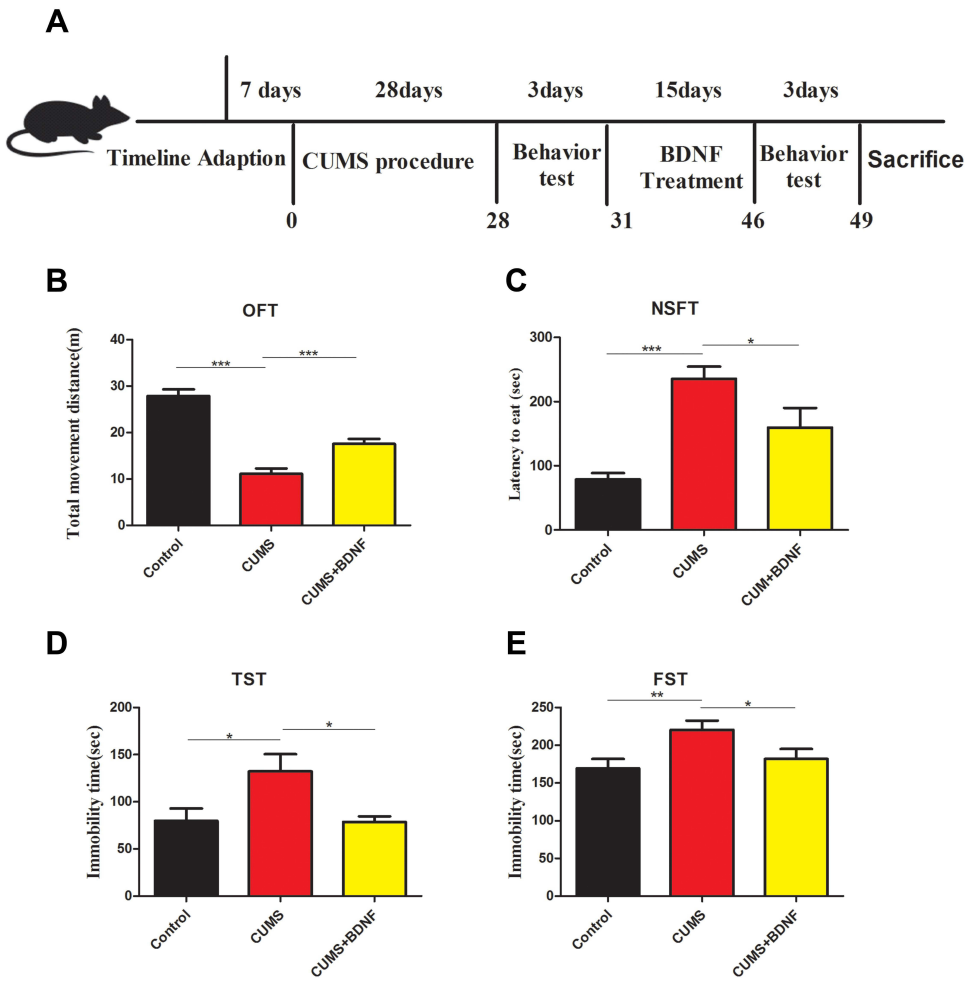

Figure 1 Intranasal BDNF treatment ameliorated CUMS-induced depressive-like behaviors. (**A**) Schematic representation of experimental design for the CUMS-induced depression model. (**B**) BDNF restored the depressive-like behaviors in OFT. (**C**)BDNF restored the depressive-like behaviors in NSFT. (**D**)BDNF treated mice exhibited less depression-like behavior in TST. (**E**) BDNF treated mice showed less depressive-like behavior in FST. Data are presented as mean ± S.E.M, n = 10 for control group, n = 10 for CUMS group, n = 9 for CUMS+BDNF group. *p < 0.05, **p < 0.01 and ***p < 0.001. One way ANOVA statistics: F_a =47.90, F_b = 14.77, F_c =4.991, F_d =4.723.

a time limit of 10 min. The timeline of CUMS model establishment and BDNF treatment was shown in Figure 1A, and the successful establishment of CUMS model was validated by the behavioral tests (Supplementary Figure 1)

Oxidative Stress Marker Level/Activity Measurement

After the behavioral tests, the serum samples and hippocampal tissues from mice under various treatments were extracted with standard protocol. The malondialdehyde (MDA) level and (superoxide dismutase) SOD activity was measured by commercial available kits according to the manufacturer's instructions (Jiancheng Bioengineering Institute, Nanjing, China).

Quantitative Real-Time Polymerase Chain Reaction

Total RNA from hippocampal tissue was extracted with Trizol reagent. A PrimeScript RT reagent kit was used to synthesize first-strand cDNA. Then cDNAs were quantified by real-time polymerase chain reaction on LightCycler 96 (Roche). β-actin was used as a reference gene for analysis. Primers (sequences are shown in Table 1) were synthesized by Sangon Biotech Co., Ltd (Shanghai, China). The relative mRNA expression levels were analyzed using the $2^{-\Delta\Delta Ct}$ method.

Table 1 All Primer Sequences for qRT-PCR

Genes	Primers (5'-3')	
Il-1β	Forward	TGCCACCTTTTGACAGTGAT
	Reverse	CCACAGCCACAATGAGTGAT
INOS	Forward	GGCGCTGTCATCGATTTCT
	Reverse	GCCTTGTAGACACCTTGGTC
IL-6	Forward	CACAGAGGATACCACTCCCA
	Reverse	GAATTGCCATTGCACAACTCT
TNF-α	Forward	GGCTTTCCGAATTCACTGGAG
	Reverse	CCCCGGCCTTCCAAATAAA
β-Actin	Forward	AAGCCCTGGATGAAGAAACAG
	Reverse	TGGGAACCAATCTCGTAGGTC

Western Blotting

Western blotting was performed according to the standard protocol as described previously with modifications.[22] Hippocampal tissues of mice under various treatments were collected, and total proteins were extracted with RIPA buffer. The concentration of total protein was determined using a BCA protein quantification kit and. 30 μg of protein from each sample was separated on SDS-PAGE gel, then transferred to NC membrane. The NC membrane was blocked with blocking solution for 1 h and then incubated with the primary antibody overnight at 4 °C. After washing with TBST three times, the membrane was incubated with the HRP-conjugated secondary antibody for 1 h at room temperature. After washing the membrane, the signal was visualized by a chemiluminescence imager (Beijing Yuan Ping Hao Biotechnology Co. Ltd., Beijing, China). Data were analyzed using Image J software. The primary antibodies used in this study were anti-IL-1β (#254360, Abcam, 1:1000), anti-NLRP3 (AG-20B-0014, Adipogen, 1:1000), anti-TNF-α (#11948S, Cell signaling Technology, 1:1000) and anti- β-Actin (#4967S, Cell signaling Technology, 1:1000).

Statistical Analysis

All data are presented as means ± SEM (standard error of the mean). Statistical significance was analyzed by one-way ANOVA followed by multiple comparison tests with GraphPad Prism 8, $p < 0.05$ was considered statistically significant.

Results

Intranasal BDNF Administration Ameliorates Depression-Like Behaviors in CUMS Model Mice

To investigate the effects of BDNF on CUMS-induced depressive-like behaviors in mice, we performed several behavioral test including OFT, NSFT, FST and TST. The OFT showed that the total distance traveled in CUMS model mice was significantly reduced comparted to non-stressed controls (Figure 1B, $p < 0.001$). However, treatment with BDNF significantly increased the traveled distance (Figure 1B, $p < 0.001$), which reflected BDNF markedly improved the CUMS-induced reduction of locomotor activity in mice. Moreover, the NSFT demonstrated that compared with the control mice, the latency to feed was significantly increased in the CUMS mice (Figure 1C, $p < 0.001$), while intranasal delivery of BDNF significantly reversed this effect (Figure 1C, $p < 0.05$). Additionally, the desperate behaviors in mice were assessed by the immobility time in the TST and FST. The results showed that durations of immobility were significantly longer in the CUMS mice than in controls, whereas BDNF administration remarkably reduced the immobility time in the stressed mice (Figure 1D and E). Taken together, these results shown that intranasal administration of BDNF ameliorates CUMS-induced depressive-like behaviors in mice.

Intranasal Delivery of BDNF Reduced Oxidative Stress in CUMS Mice

Next, we analyzed oxidative stress marker level or activity in each group of mice to assess the effects of BDNF on CUMS-induced oxidative stress damage in mice. The result indicated that, compared to the control group, CUMS model

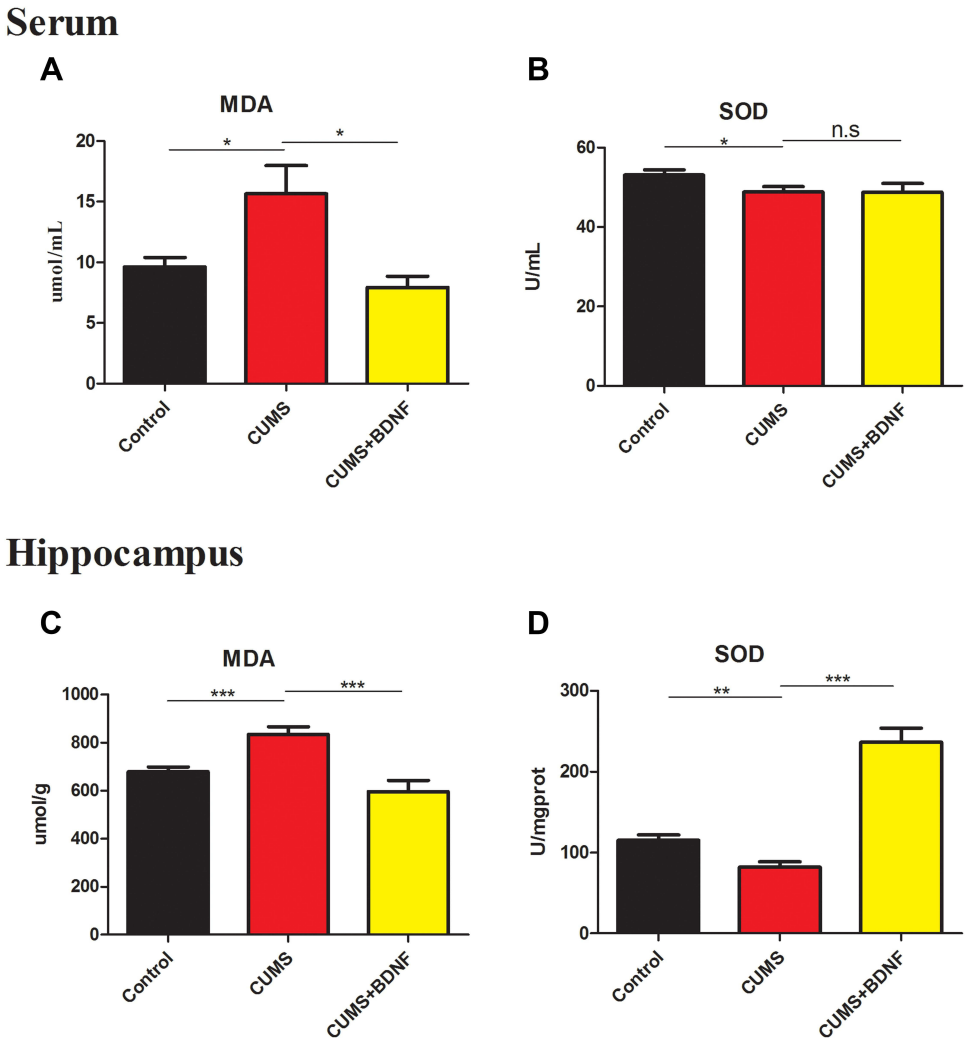

Figure 2 Intranasal BDNF treatment reduced oxidative stress in CUMS model mic. The serum MDA levels (**A**) and SOD activities (**B**) in mice under various treatments. The hippocampal MDA levels (**C**) and SOD (**D**) activities in mice under various treatments. Values are expressed as the mean ± SEM, n = 8 for control group, n = 8 for CUMS group, n = 7 for CUMS+BDNF group. *p < 0.05, **p < 0.01 and ***p < 0.001. One way ANOVA statistics: F_a =6.943, F_b = 2.401, F_c =13.36, F_d =54.60.

mice had significantly increased serum MDA level (Figure 2A, $p < 0.05$) and reduced SOD activity (Figure 2B, $p < 0.05$). However, BDNF treatment markedly reduced MDA level in CUMS mice, but did not have significant effect on SOD activity, as shown in Figure 2A and B. We also found that CUMS mice had significantly increased MAD level (Figure 2C, $p < 0.001$) and decreased SOD activity (Figure 2D, $p < 0.001$) in the hippocampus when compared with controls, and these effects were abolished by intranasal administration of BDNF in the CUMS mice (Figure 2C and D).

Intranasal Delivery of BDNF Inhibited Inflammatory Response in the Hippocampus of CUMS Mice

To further explore potential mechanism underlying the anti-depressant effects of BDNF, we next examined several of pro-inflammatory cytokine mRNA expression in the hippocampus. As demonstrated in Figure 3, the results revealed that the mRNA levels of interleukin (IL)-1β, IL-6, iNOS, and tumor necrosis factor (TNF)-α were significantly increased in the CUMS mice when compared with control mice. However, BDNF treatment significantly reduced TNF-α, IL-1β, and IL-6 mRNA levels in the hippocampus of CUSM mice (Figure 3).

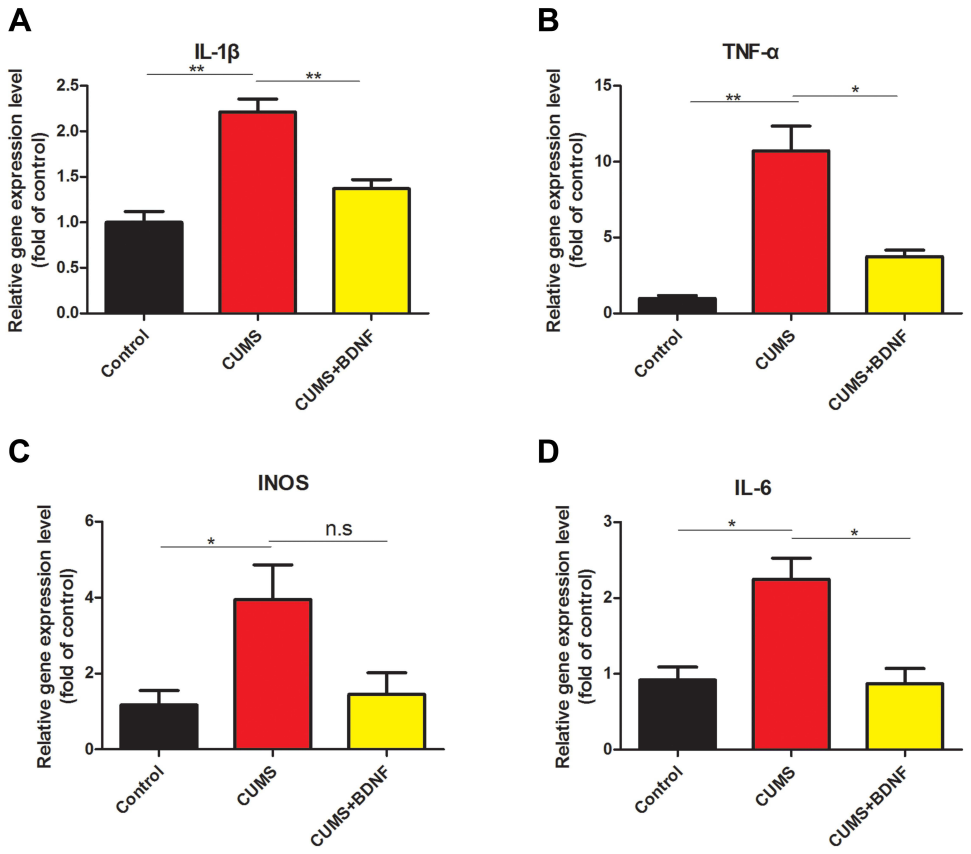

Figure 3 Intranasal BDNF treatment reduced inflammatory-associated gene expressions in the hippocampus of CUMS model mice. The hippocampal mRNA expression levels of IL-1β (**A**), TNF-α (**B**), iNOS (**C**) and IL-6 (**D**) in mice under various treatments. Data are presented as mean ± S.E.M, n = 3, *$p < 0.05$ and **$p < 0.01$. One way ANOVA statistics: F_a =25.20, F_b = 25.93, F_c =5.338, F_d =12.56.

Additionally, the Western blot results showed that IL-1β and TNF-α protein were significantly up-regulated in the hippocampus of CUMS model mice relative to the control mice, whereas BDNF treatment significantly reduced IL-1β and TNF-α protein expression in the hippocampus of the model mice, as shown in the Figure 4. Interestingly, our results also showed that BDNF significantly inhibited stress-induced up-regulation of NLRP3 protein expression in the hippocampus (Figure 4). These results therefore suggested the involvement of anti-inflammatory response on the intranasal BDNF induced-antidepressant-like effects.

BDNF Restored Hippocampus Neurogenesis in the CUMS Mice

We then used the immunofluorescence analysis to evaluate the effect of BDNF on hippocampal neurogenesis, and this protocol was followed by our previously published literature.[21] We found that CUMS exposure markedly reduced doublecortin (a marker of neurogenesis) positive cells in the dentate gyrus of hippocampus, and the reduction was recovered after intranasal BDNF treatment (Figure 5), suggesting that intranasal administration of BDNF may exert antidepressant effect by increasing neurogenesis.

Discussion

In the present study, we found that intranasal BDNF administration produces antidepressant-like behavioral responses in stress-induced depression in mice. These effects were similar to the actions of subcutaneous BDNF administration in an animal model of depression,[23] as well as centrally administered BDNF which included the midbrain,[16] hippocampus[21] and lateral ventricles.[24] Preclinical studies have also suggested reduced BDNF levels in animal models of depression, both in central and peripheral.[25,26] Although the molecular mechanisms underlying the link between stress and depression is still largely unknown, these preclinical studies have shown that chronic stress induced

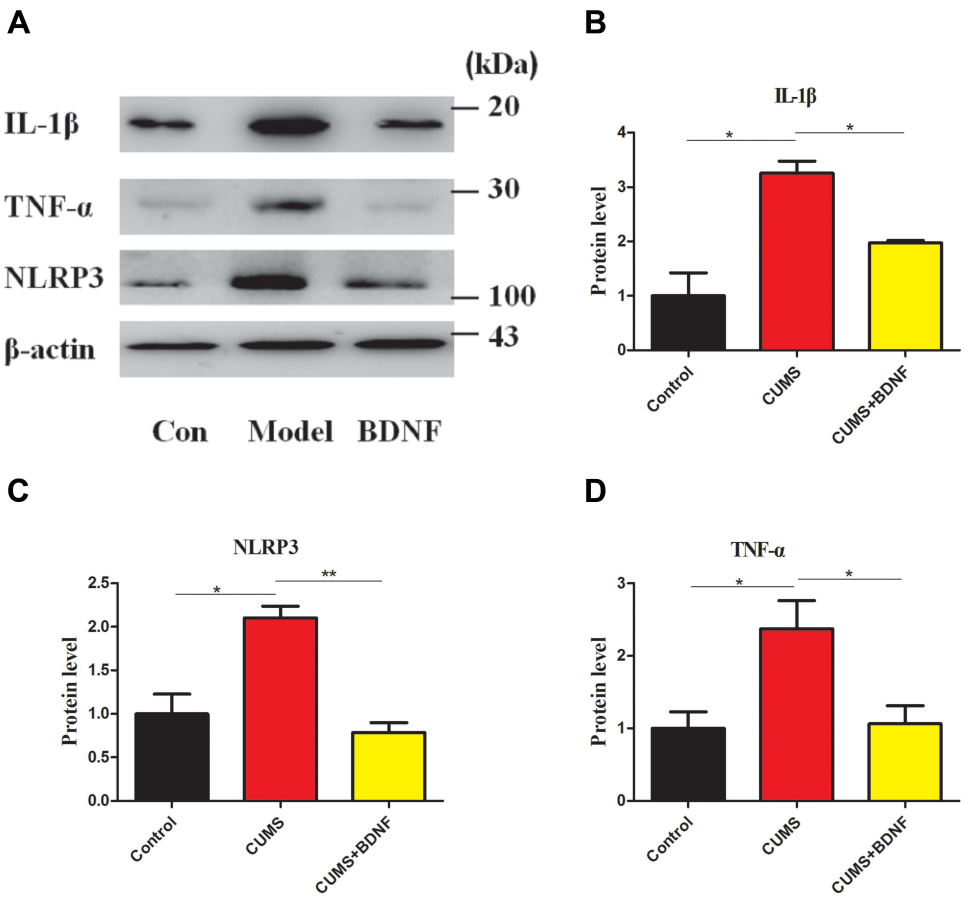

Figure 4 Intranasal BDNF treatment reduced inflammatory-associated protein levels in the hippocampus of CUMS model mice. (**A**) Representative images showing BDNF reduced NLRP3, IL-1β and TNF-α protein levels in the hippocampus of CUMS mice as measured by Western blot.Quantifications of the relative band densities of IL-1β (**B**), NLRP3 (**C**), and TNF-α (**D**) in the hippocampus of mice under various treatments. Data are presented as mean ± S.E.M, n = 3. *$p < 0.05$ and **$p < 0.01$. One way ANOVA statistics: F_b =16.74, F_c = 18.12, F_d = 6.832.

depression-like symptoms are associated with decreased levels of BDNF. Additionally, neurotrophic factors have been demonstrated to control depressive-like behaviors in rodents through hippocampus, these include BDNF[27] and neurotrophic factor-α1.[28] Furthermore, there is a well-established body of clinical evidence demonstrated that the levels of BDNF in serum and plasma were reduced in MDD patients.[29,30] Interestingly, antidepressants have been shown to increase BDNF levels in the peripheral blood of MDD patients.[31] Therefore, our results presented in this study together with previous findings provide strong evidence to support the hypothesis that BDNF is involved in the pathogenesis of depression, and intranasal delivery of BNDF may represent a novel strategy for treatment of depression.

Although the down-stream signaling pathway alterations caused by BDNF deficiency are not fully understood, the abnormal BDNF level-induced pathological conditions may be due to the chronic inflammatory state of the brain in certain diseases, as evidence from recent studies reporting that peripheral immune challenge caused BDNF deficiency resulted in an abnormal neuroinflammation response, which then lead to the development of inflammation-induced anhedonia in mice.[32,33] In addition, Gibney et al have also found increased expression of IL-1β, IL-6, and TNF-α and reduced expression of BDNF genes in depressive-like rats 6 h after an inflammatory challenge.[34] Consistently, our results showed that the expressions of pro-inflammatory cytokines including IL-1β, IL-6, and TNF-α levels were significantly elevated in the hippocampal tissues of CUMS-induced depressed mice, whereas intranasal delivery of BDNF significantly improved CUMS-induced depression-like behaviors and reduced these pro-inflammatory cytokine expressions in the hippocampus. Based on these findings, it is reasonable to speculate that long-term exposure to stress caused decreased levels of BDNF and neuroinflammation in the body and ultimately contributes to the pathophysiology of MDD.[35,36]

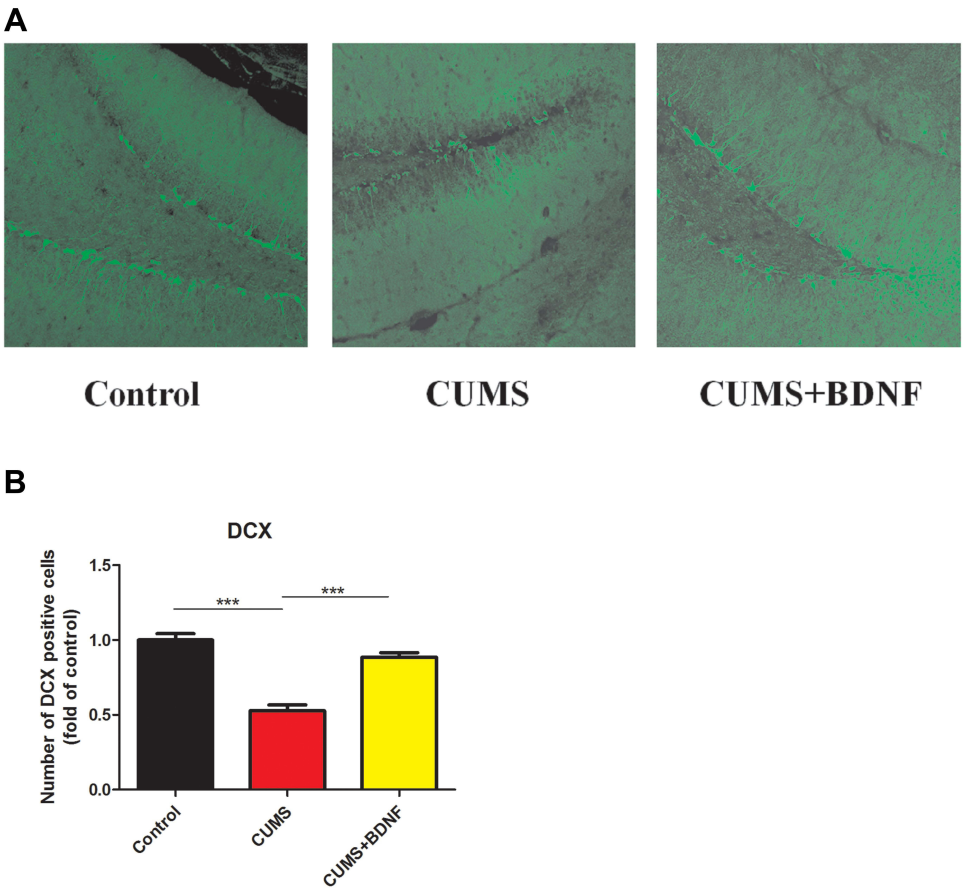

Figure 5 Effect of BDNF treatment on neurogenesis in the hippocampus. (**A**) Confocal photomicrographs of doublecortin-immunostained immature neurons in the dentate gyrus of mice under various treatments. (**B**) Quantification of doublecortin-positive cells in the dentate gyrus of mice under various treatments. Data are presented as mean ± S.E.M, n = 4. ***$p < 0.001$. One way ANOVA statistics: $F_a = 42.39$.

However, further research is needed to further understand the role interactions between neurotrophic factors and neuroinflammation in the pathogenesis of depression.

In conclusion, we demonstrated that intranasal administration of BDNF rescued depressive-like behaviors in a CUMS-induced mice model of depression. The therapeutic effects of BDNF were accompanied by restorations of neuroinflammation, oxidative stress and hippocampal neurogenesis in CUMS model mice. Therefore, future studies are warranted to explore the potential of intranasal BDNF delivery as a therapeutic target to treat MDD.

Data Sharing Statement

All data are contained within the manuscript.

Acknowledgments

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that there are no conflicts of interest.

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