Original Article

The effect of electroacupuncture on regulating pain and depression-like behaviors induced by chronic neuropathic pain

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Background: Recently, the role of electroacupuncture (EA) in chronic neuropathic pain has been widely reported. However, its specific mechanisms and ability to mitigate depression-like behaviors induced by chronic pain remains unclear. This study aims to determine the analgesic and antidepressant effect of EA.

Methods: The mechanical threshold sensory and hot plate tests were employed to measure mechanical hyperalgesia and thermal allodynia. The open filed test (OFT) and tail suspension test (TST) were used to observe depressive behavior in chronic constrictive injury (CCI) mice. In addition, the 5-hydroxytryptamine (5-HT) and brain-derived neuropathic factor (BDNF) levels in the anterior cingulate cortex (ACC) and spinal cord were assessed using enzyme-linked immunosorbent assay (ELISA). The protein levels of cAMP-response element-binding protein (CREB) and BDNF in the ACC were analyzed by western blotting.

Results: Our results demonstrated that EA treatment could increase the mechanical withdrawal threshold (MWT) and thermal withdrawal latency (TWL) values. Also, EA improved the CCI-induced depression-like behaviors, and significantly reversed the down-regulation of BDNF and 5-HT expression in the ACC and spinal cord after CCI. Furthermore, EA regulated the level of CREB in the ACCs and spinal cords of mice.

Conclusions: These results suggested that the analgesic and antidepressant effect of EA is achieved through regulating CREB-5-HT/BDNF signaling pathway in the ACCs and spinal cords of mice.

Keywords: Electroacupuncture (EA); chronic pain; depression-like behaviors; 5-hydroxytryptamine (5-HT); brain-derived neuropathic factor (BDNF); anterior cingulate cortex (ACC); spinal cord; neuropathic pain

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Introduction

Pain and depression are serious disorders that often coexist and interact. However, the underlying basis for this comorbidity and the dynamic interactions between pain and depression remain unclear. Chronic pain is prevalent in depression patients (1), and patients with chronic inflammatory diseases and pain also typically present with depressive symptoms (2,3). However, there is currently no effective treatment regimen for the pain-depression comorbidity.

Electroacupuncture (EA) is universally used as a therapeutic intervention for the treatment of pain (4). However, the biological basis and underlying mechanism of the analgesic effect of EA remains unclear. Studies have shown that EA has an exact analgesic effect on neuropathic

pain in mice, which is related to the mouse hippocampal cholinergic system and extracellular signal-regulated kinase (ERK) signaling pathway (5,6). EA can also alleviate chronic constrictive injury (CCI)-induced neuropathic pain in mice, which is reportedly caused by interference with the functional activity of the NR1 protein and messenger ribonucleic acid (mRNA) in the spinal cord (6). Several studies have also indicated that EA can regulate the levels of the neurotrophic factors, brain-derived neuropathic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF), and suggested that they may be related to the role of EA in pain treatment. However, the ability of EA to relieve depressive behaviors induced by CCI is not clear at present.

Previous articles indicated that pain and depression behavior is related to the coordination of multiple brain areas and several neurochemical pathways (7,8). The anterior cingulate cortex (ACC) is located in the medial subfield of the frontal lobe, and it is primarily involved in motivating behavior and hierarchical reinforcement learning (9). Numerous studies have shown that some neural markers may be expressed in the thalamus and the ACC for the detection of depression. Structural analysis of neuroimaging shows that the volume of gray matter in the ACC brain area of depression patients is smaller compared with healthy controls (10). The structural and functional alterations in the ACC may be associated with the depression process. Mature BDNF belongs to the neurotrophin family and is produced by glial cells and neurons (11,12). In humans or animals with depression, the mature BDNF level is always reduced (13,14). BDNF and 5-HT play a key role in most depression, which may depend on their influence on neuronal plasticity and depression susceptibility (15,16). These results suggest that the ACC, BDNF, and 5-HT may play an important role in the pain-depression comorbidity. Treatment with EA may provide new avenues to treat this comorbidity.

Therefore, our study aims to explore the effect and the possible mechanisms of EA in regulating allodynia and depression-like behaviors associated with chronic neuropathic pain in mice. Our data showed that EA treatment can relieve CCI-induced mechanical allodynia and thermal hyperalgesia in mice. EA treatment also improved the CCI-induced depression-like behaviors, and significantly increased the levels of BDNF and 5-HT in the ACC and spinal cord after CCI, probably via regulating the expression level of CREB. Our findings suggest that the analgesic and antidepressant effects of EA may be achieved by regulating CREB-5-HT/BDNF signaling pathway in the ACC.

We present the following article in accordance with the ARRIVE reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1900).

Methods

Animals

Bagg albino (BALB/c) mice (male, 4–5 weeks, 18–22 g) were housed in a room with alternating 12 hours of light and 12 hours of dark for a week, and a constant temperature of 23±1 ℃. Food and water were freely available. Experiments were performed under a project license (No. 17-2020113) granted by Animal Care and Use Committee of Wenzhou Medical University, in compliance with China guidelines for the care and use of animals. The animals were randomly divided into four groups: Sham group, CCI group, sham + EA group (sham mice with EA treatment), and CCI + EA group (CCI mice with EA treatment).

EA stimulation

EA treatment was implemented on Day 8 after CCI surgery, and was performed between 09:00 and 11:00 am successively for 7 days. The mice were restrained in a fixed apparatus, and a stainless steel acupuncture needle (Gauge 28) with a diameter of 0.20 mm was used to puncture the Zusanli (ST36) and Yanglingquan (GB34) points (both sides) to a depth of 4 mm, respectively. Studies have shown that alternating the stimulation between low (2 Hz) and high frequency (100 Hz) (called 2/100 EA) can elicit a synergistic analgesic effect (17). By observing the slight contraction of the muscle, we determined the strength of the EA, which was about 1.5 mA. So, in our experiment, we used an electrical stimulation apparatus (HANS-200E; Jisheng Medical Instruments, Nanjing, China) to provide stimulation with a current of 2/100 Hz and 1.5 mA for 30 minutes each day.

Animal model

Based on the previously described method with some modifications, we established a mouse chronic contractile injury (CCI) pain model. In short, we used 4% chloral hydrate (10 mL/kg, intraperitoneal injection) to anesthetize mice, and the right sciatic nerve was exposed at the mid-thigh level and approached to the sciatic trifurcation. Four

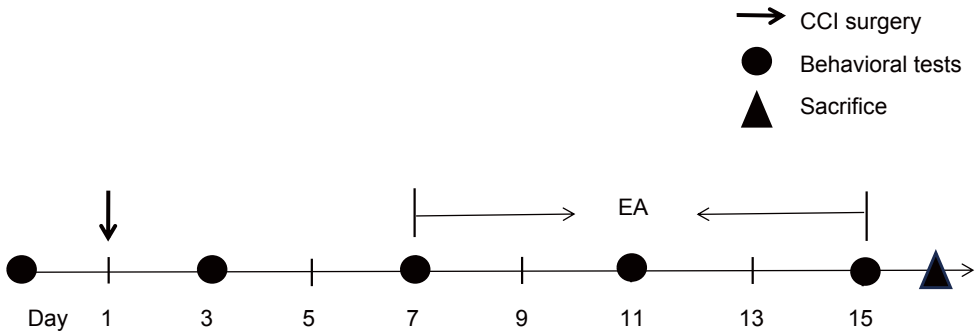

Figure 1 A schematic diagram of the experimental arrangement. CCI, chronic constrictive injury; EA, electroacupuncture.

constrictive ligatures (4-0 surgical suture) were tied around the nerve at the distal end close to the bifid site at intervals of about 1.0 mm. The mild contraction of the local muscle of the leg signified the completion of the ligation operation. In order to reduce experimental differences, all operations were performed by the same operator. For mice in the sham CCI group, we only performed surgery to expose the sciatic nerve for 2–3 minutes without ligation. The mechanical withdrawal threshold (MWT) and thermal withdrawal latency (TWL) of the mice were measured as nociceptive evaluations prior to CCI surgery and at 3, 7, 11, and 15 days after CCI surgery, and depression-like behaviors were tested both before and after CCI surgery (on days 7 and 15) (*Figure 1*). The behavioral testing was conducted by an experimenter that was blinded to the experimental design.

MWT

Based on previous studies, we used an electronic von Frey anesthesiometer (Model 1601; IITC Life Science, Woodland Hills, CA) to measure mechanical allodynia. The mechanical stimulation intensity of the plantar surface corresponding to the withdrawal of the hind paw in each mouse was considered as the pain threshold. In short, animals were individually placed in bottomless cages (20 cm × 15 cm × 15 cm) with several compartments, and all of them were placed on a 40 cm high wire mesh shelf. Below the wire mesh floor, a punctuate stimulus was transmitted through the uniform tip of the von Frey fiber to the middle part of each rats' hind paw for 2 seconds, and applied 0 to 30 grams of pressure (with an accuracy of 0.2 grams). The von Frey instrument would then automatically read the withdrawal threshold. A total of five tests at intervals of 5 min were conducted on each hind paw, and the average value was used.

TWL

Thermal hyperalgesia was evaluated using a hot plantar test apparatus (BIO-CHP, Bioseb, France). Mice were placed individually on a hot plate with a constant temperature of 52.5±1 ℃. After 15 min of acclimation, an electronic timer was used to record the time required for reactions, such as jumping or hind paw licking. To prevent scalding of the paws, we set the maximum heating time at 30 seconds. Each mouse repeated the measurement three times, with an interval between each measurement ≥10 minutes. We took the average value of each measurement as the final result. Normal foot lifting motions were not counted.

Tail suspension test (TST)

Briefly, we fixed the rear of the tail (1–1.5 cm) with tape and suspended it on a flat metal surface 40 cm above the floor inside the test equipment (Bioseb, USA), with the head 15 cm away from the floor. Each mouse was suspended for a total of 6 min for escape movements recording. The duration of immobility within the 2–6 min interval was considered an indicator of depression-like behavior (18).

Force swim test (FST)

Briefly, mice were placed individually in a clear cylinder (diameter 10 cm, height 25 cm), containing 15 cm of water at 25 ℃. Mice were forced to swim for 6 min, and the immobility time during the last 4 min was manually measured by a blinded observer. Mice were considered immobile when they ceased struggling, remained floating motionless, and only made those movements necessary to keep their head above the water.

Open-field test (OFT)

The OFT was used for locomotor activity measurement, which was performed as previously reported (19). Briefly, motor activity was quantified in a square cage with a 50×50 cm^2 floor and a 30-cm high wall. There were 25 equal squares on the floor of the apparatus. We placed each animal in the center of the cage and recorded manually for 4 min for the immobility time. A video camera was located 100–120 cm above the floor for behavior recording. Following the completion of a test, 75% alcohol solution was used to clean the arena.

Enzyme-linked immunosorbent assays (ELISAs)

We took out the ACC and spinal cord samples, and immediately put them on dry ice, and then stored them at −80 ℃ for ELISA experiments to measure 5-HT and BDNF levels. The experiment used an ELISA kit (Thermo Fisher Scientific, USA) to measure the 5-HT and BDNF levels in the supernatant according to the protocol.

Western blot

Mice were killed by anesthesia with 2% sodium pentobarbital, and the ACC and spinal cord tissue were harvested on ice and lysed in ice-cold radioimmunoprecipitation assay (RIPA) lysis buffer (Applygen Technologies Inc., Beijing, China), which contains protease inhibitors. Homogenates was centrifuged at 13,000 rpm for 15 min at 4 ℃ and the protein concentrations were determined using the bicinchoninic acid (BCA) method. 10% sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) was applied to separate protein samples (25 ned was, which were then transferred to a polyvinylidene difluoride (PVDF) membrane with 120 mA current for 2 h. Next, the membranes were blocked using 5% non-fat milk for 1 h at room temperature and incubated with specific primary antibodies, including cAMP-response element-binding protein (CREB) (1:200, ab32515, Abcam, UK) and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) (1:2,000, ab9485, Abcam, UK) at 4 ℃ overnight. After being washed three times, the membranes were incubated in a goat anti-rabbit immunoglobulin G (IgG) horseradish peroxidase (HRP)-linked antibody (1:2,000, ab6721, Abcam, UK) for 1 h at room temperature. We used the Western Blotting Imaging System (Clinx Science Instruments Co., Ltd, China) to obtain the imaging results, and Image J software (Wayne Rasband, National Institutes of Health, USA) to measure the optical density of the bands from the Western blot. The protein density of GAPDH was used as an internal control.

Statistical analysis

All data in our study were presented as the mean f GAPDH was used as an inte, and were analyzed using Prism 7.0 software (Graghpad, LaJolla, CA, USA). Behavioral experiment data were analyzed by repeated-measured one-way analysis of variance (ANOVA), followed by Dunnett's test. Comparisons were performed using one-way ANOVA, followed by Dunnett's test. A P value of <0.05 was considered indicative of a statistically significant difference.

Results

EA treatment reduced mechanical allodynia and thermal hyperalgesia in CCI mice

Firstly, we tested the possible effects of EA treatment in the CCI mouse model. To understand the change schedule of MWT and TWL, we tested the baseline MWT and TWL prior to surgery. The baseline measures of the MWT V (*Figure 2A*; n=8, per group; P<0.05, repeated ANOVA) and TWL (*Figure 2B*; n=8, per group; P<0.05, repeated ANOVA) on mice hind paws exhibited no differences among all groups. The MWT and TWL were reduced markedly after CCI, compared with the sham and sham + EA groups. On the 15th postoperative day, the MWT and TWL values of the CCI + EA group increased significantly compared with the CCI group. These results indicated that EA treatment can relieve mechanical and thermal allodynia in CCI mice with neuropathic pain.

Repeated EA treatments reversed depression-like behaviors induced by chronic pain

We also studied the effects of EA on depression induced by chronic pain. We performed OFT and TST and FST behavioral tests, which were indicative of depressive phenotypes. In the OFT, we can seen time spend in central zone of the CCI group was significantly decreased compared with the sham group, which can be can be

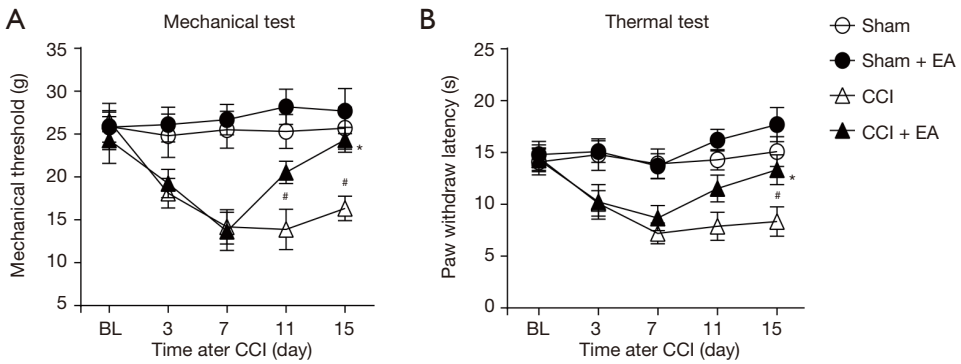

Figure 2 Mechanical threshold and paw withdrawal latency in mice from different groups. (A,B) Mechanical threshold (A) and paw withdraw latency (B) were assessed using von Frey filaments and hot plate test. Tests were performed prior to CCI and on day 3, 7, 11, and 15. The data were presented as the mean ± SEM. Compared with sham group, #P<0.05; compared with CCI group, *P<0.05. Analysis was performed by repeated-measured ANOVA followed by Dunnett's test (n=8 in each group). CCI, chronic constrictive injury; EA, electroacupuncture; BL, base line.

reversed by EA treatment (*Figure 3A*; n=8, per group; P<0.05, repeated ANOVA).In the FST/TST, the CCI group showed an obvious increase in immobility time compared to the sham group on day 7 and day 15 (*Figure 3B* and *C*; n=8, per group; P<0.05, repeated ANOVA). Meanwhile, the CCI+EA group showed a decreased immobility time when compared to the CCI group on day 15 after CCI surgery (*Figure 3B* and *C*; n=8, per group; P<0.01, repeated ANOVA). We did not find a significant difference between the sham and sham + EA groups in the FST and TST tests. Our data demonstrates that EA treatment ameliorates depression-like behaviors induced by neuropathic pain.

EA treatment reversed the decrease in the levels of serotonin (5-HT) and BDNF in the ACCs and spinal cords of CCI mice

It has previously been shown that 5-HT and BDNF play an important role in the development of depression. We examined the expression levels of 5-HT and BDNF in the ACC and spinal cord. Our data indicated that the 5-HT level was significantly reduced in the ACCs and spinal cords of CCI mice (*Figure 4A* and *B*; n=6, per group; P<0.05, one-way ANOVA) compared to the sham group. However, we found that EA treatment reversed the decrease of 5-HT in the ACC and spinal cord induced by neuropathic pain. Moreover, the BDNF expression level was also significantly decreased in the ACC and spinal cord in CCI group (*Figure 4C* and *D*; n=6, per group; P<0.01, one-way ANOVA). However, this was dramatically reversed by EA treatment in CCI mice.

EA treatment regulated the protein expression of CREB in the ACC and spinal cord

To clarify the possible mechanisms involved in the analgesic role of EA treatment, a western blot experiment was carried out to examine the protein expression of CREB in the ACC and spinal cord. Our data revealed that CREB expression level was decreased dramatically in the ACC (*Figure 5A,B*; n=6, per group; P<0.05, one-way ANOVA) and spinal cord (*Figure 5C,D*; n=6, per group; P<0.05, one-way ANOVA) of CCI mice compared with the sham group. However, treatment with EA markedly reversed the protein expression level of CREB in the ACCs and spinal cords of CCI mice.

Discussion

Acupuncture is generally utilized to alleviate pain in humans and experimental animals, and has been used as a safe and effective method for more than 3,000 years in China (20,21). Presently, EA treatments are widely practiced globally. Acupuncture needles are used to apply different levels of stimulation current to acupoints. However, the underlying mechanisms of EA for the treatment of neuropathic pain remain unclear. Many studies have suggested that various neurotransmitters and neuromodulators in peripheral and

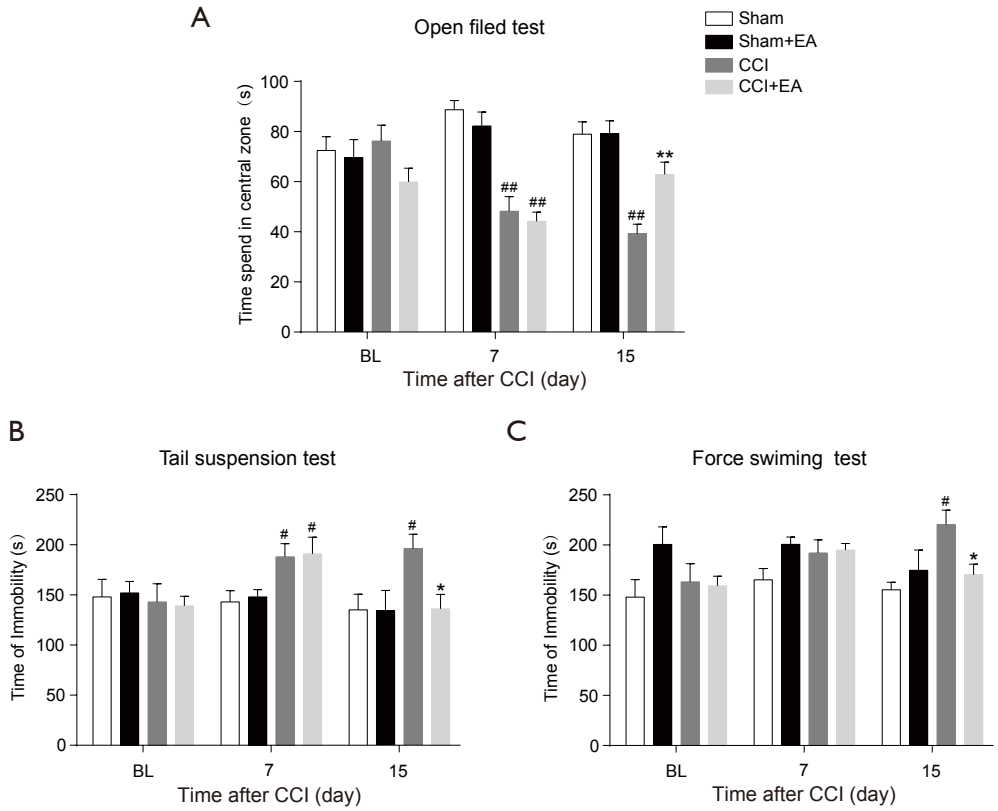

Figure 3 The effects of EA on CCI-induced mouse depression-like behaviors. The time spend in the central zone in OFT (A). (B,C) The depression-like behaviors in mice were examined and exhibited by immobility time in TST (B) and FST (C). The data were presented as the mean ± SEM. Compared with sham group, $^{\#}P<0.05$, and $^{\#\#}P<0.01$; compared with CCI group, $^{*}P<0.05$, and $^{**}P<0.01$. Analysis was performed by repeated-measured ANOVA followed by Dunnett's test (n=8 in each group). EA, electroacupuncture; CCI, chronic constrictive injury; OFT, open filed test; FST, force swimming test; TST, tail suspension test.

central nervous systems are involved in the pain treated by EA, including glutamate, norepinephrine, opioid peptides, g-amino-butyric acid (GABA), adenosine, and serotonin (22). Some emotional syndromes, such as depression and anxiety, are also typically associated with long-term neuropathic pain (23,24).

In this study, we used a CCI (mild sciatic nerve injury) model to induce depression-like behavior and explore the effects of EA on pain and depression (25). Mechanical and thermal hypersensitivity are indications of chronic neuropathic pain, and behavioral despair (OFT) and mobility time (FST and TST) serve as indices for mood disorders and depression (26). In our study, CCI induced significant mechanical allodynia, thermal hypersensitivity, and depressive-like behaviors. The increase in immobility time of CCI mice suggested that CCI can induce both chronic pain and depression. Moreover, we observed that treatment with EA significantly reduced the symptoms of pain and depression-like behaviors in CCI mice (*Figures 2,3*). These results suggest that repeated EA treatment significantly ameliorates neuropathic pain and depression-like behaviors.

Recently, the role of CREB and BDNF in central sensitization has been assessed in numerous chronic pain and depression studies. BDNF and protein kinase C (PKC) were shown to exhibit feedback interactions and participate in the regulation of emotional functions (27). Chronic pain with depression is now considered to be a sensory dysfunction involving the thalamus, spinal dorsal horn, and limbic system, especially in the ACC (28,29). The ACC is a critical brain region; imaging studies have shown that the dorsal function of the ACC is low and the volume of

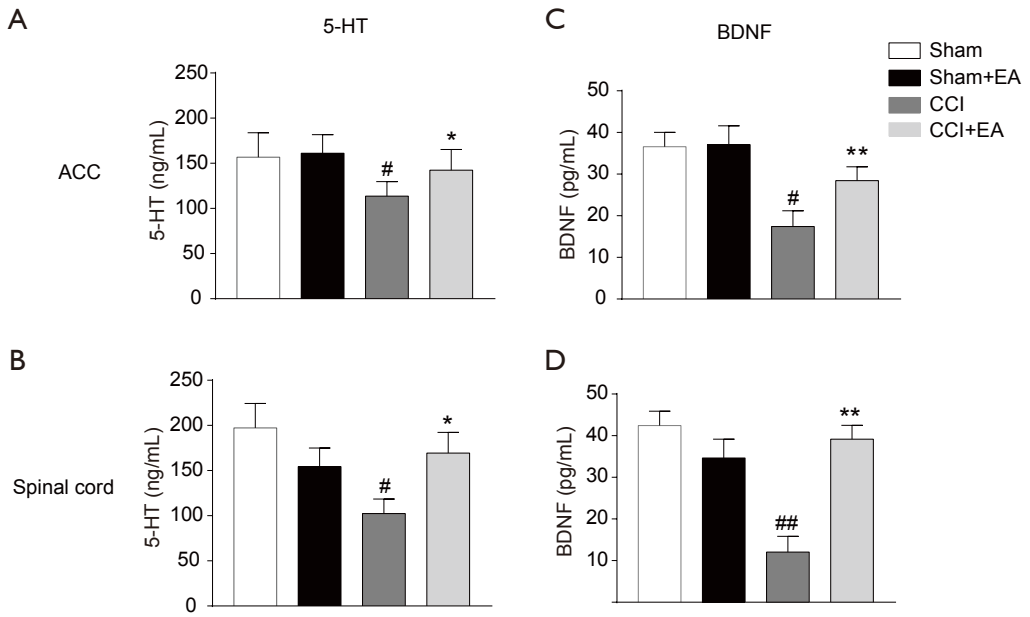

Figure 4 The regulation of EA treatment on 5-HT and BDNF in the ACCs and spinal cords of mice from different groups. The levels of 5-HT (A and B) and BDNF (C and D) were measured by ELISA. The data were presented as the mean ± SEM. Compared with sham group, $^{\#}P<0.05$, and $^{\#\#}P<0.01$; compared with CCI group, $^{*}P<0.05$, and $^{**}P<0.01$. Analysis was performed by one-way ANOVA followed by Dunnett's test (n=6 in each group). EA, electroacupuncture; BDNF, brain-derived neuropathic factor; ACC, anterior cingulate cortex; CCI, chronic constrictive injury.

the ventral area of the ACC is reduced and hyperactive in patients with depression (30). Preclinical studies have shown that social failure paradigms resulted in an increase in cingulate activity, which also supported the role of the ACC in pain and depression processes (31). These studies have also shown that in chronic pain models, social failure paradigms could also induce functional changes, such as reduction in long-term depression (32). They could also trigger synaptic enhancement, glutamate release, and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor-mediated responses in the ACC, suggesting both presynaptic enhancement and postsynaptic potentiation, respectively (33).

Many studies have reported there will be a downregulation of BDNF in the forebrain regions like mPFC and ACC, in both rats and mice neuropathic pain model (27). Moreover, BDNF levels in BLA and RVM were also reported to be downregulated in neuropathic pain model. The present data accords with similar rodent depression models (34). Our data demonstrated that repeated EA treatment reverses CCI-induced down-regulation of 5-HT and BDNF in the ACC and spinal cord (*Figure 4*), suggesting that the analgesic and anti-depression effects of EA may be achieved by regulating 5-HT and BDNF protein levels in the ACC and spinal cord.

Further exploration was conducted to examine how the 5-HT and BDNF are regulated. The data we obtained in *Figure 5* demonstrated that CREB, an important transcriptional factor, may be involved in the regulation of 5-HT and BDNF protein levels in the ACC and spinal cord because the expression level of CREB was also reversed by repeated EA treatment. Although we could not exclude other possible EA mechanisms that might be involved in the regulation of 5-HT and BDNF in the ACC and spinal cord, CREB could be a possible mechanism according to our findings.

In conclusion, the present study demonstrated that the analgesic and anti-depression effects of EA may be achieved by preventing the down-regulation of CREB-5-HT/BDNF signaling pathway in the ACC and spinal cord.

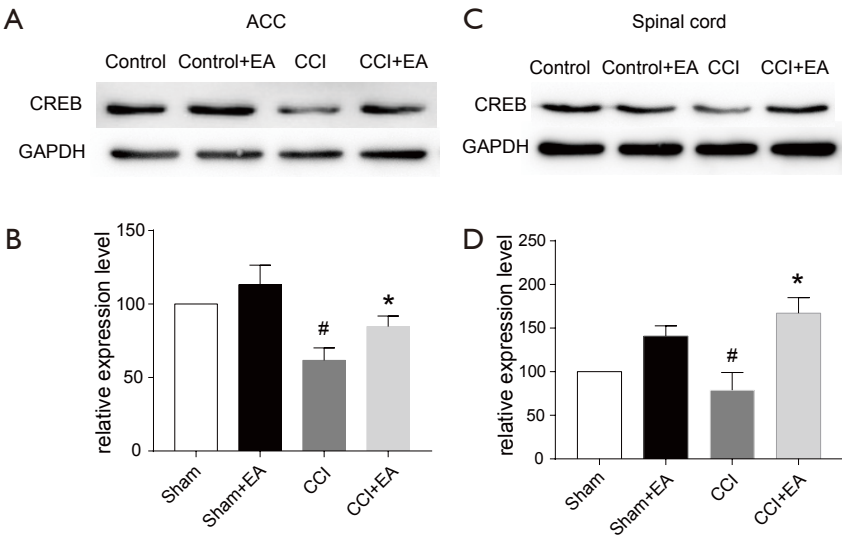

Figure 5 Effect of repeated EA treatment on CREB protein expression levels in mice ACCs and spinal cords. The expression of CREB proteins in the ACC (A) and spinal cord (B). Quantitative analysis of the expression of CREB proteins in the ACC (C) and spinal cord (D). GAPDH was used as an internal reference protein to quantify the expression of the CREB protein. Data were presented as the mean ± SEM. Compared with sham group, #P<0.05; compared with CCI group, *P<0.05. Analysis was performed by one-way ANOVA followed by Dunnett's test (n=6 in each group). EA, electroacupuncture; ACC, anterior cingulate cortex; CCI, chronic constrictive injury.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-1900). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Experiments were performed under a project license (No. 17-2020113) granted by Animal Care and Use Committee of Wenzhou Medical University, in compliance with China guidelines for the care and use of animals.

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