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Effect of electroacupuncture on mice model of permenopausal depressive disorder

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ABSTRACT

Objective: Study the effect of electroacupuncture on permenopausal depressive disorder (PDD) model through the peri-menopausal depression model mice.
Methods: KM female mice were selected. Except for the blank group (BG), the other groups of mice were removed by castration method. The mice of PDD was prepared by combining chronic unpredictable stimulation. Mice in the model group (MG) were not treated and fed normally. The western medicine group (WG) was given the corresponding drug for treatment. The electroacupuncture group (EAG) was given the electroacupuncture for treatment, and consecutive for 28 days. The levels of T, E_2, FSH and LH in serum of mice were measured, and the brain tissue of 5-HT, DA and NE level were measured. Through the HE staining observed the morphological changes of mice hypothalamus.
Results: Compared with MG, EAG could increase the number of spontaneous activities of PDD model mice, the level of T, E_2 in serum and the level of 5-HT, DA, NE in brain tissue was improved, and the level of FSH, LH in serum was reduced, and the hypothalamic lesions was improved.
Conclusion: Electroacupuncture could improve the activity and memory of PDD mice, adjust the disorder of sex hormone, and increased the levels of monoamine transmitters (5-HT, NE, DA), and it could effectively improve the behavior and related biochemical indexes of PDD, and thus play an important therapeutic role.

1. Introduction

Perimenopausal depression disorder (PDD) is an emotional disorder which occurs during menopause for the first time (Gong, 2003; Parry, 2008). Depressive symptoms are the main clinical manifestations, and patients experience decreased happiness, depression, despair, and even suicidal tendencies, it often accompanied by endocrine and autonomic neurological dysfunction. There has study shows that in worldwide, that women have a higher incidence than men (Mitchell et al., 2009), and the patients also had a 50 percent increased risk of cardiovascular disease (Whang et al., 2009). At present, the clinical commonly used antidepressant drugs such as 5-HT reuptake inhibitors (SSRI), tricyclic antidepressants (TCA) and hormone replacement therapy (HRT) alone or combined therapies to treat PDD, there is also assisted by psychological counseling and social support to channel the patient's bad mood, it has been achieved the good curative effect, but also there are some risks, such as HRT also can increase the incidence of cardiovascular and cerebrovascular, breast carcinoma, vaginal bleeding (Wu, 2016), so PDD is becoming more and more social attention from the society.

Traditional Chinese medicine does not have a clear record of PDD, but the description of the symptoms associated with the disease can be found in the records of "depression syndrome", "lily disease", "plum kernel gas" (Li et al., 2013; Yang, 2012; Ma and Yan, 2013). According to traditional Chinese medicine, PDD is the deficiency of kidney essence and liver blood in women, coupled with disorder of liver-qi, causing the disorder of zang-fu organs' function, this leads to the imbalance of Yin and Yang, loss of qi and blood, and inadequate nourishment of heart. In addition, there

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are many factors such as external emotional stimuli and so on, which are jointly triggered. Its main pathological pathogenesis lies in liver and kidney deficiency, and internal impairment by emotional changes, stagnation of qi movement, therefore, Chinese medicine treatment often uses nourishing liver and kidney, and regulating qi to alleviate mental depression, adjustment of mind, pay attention to mental treatment and other methods.

Studies at home and abroad have shown that acupuncture could improve various physical and negative emotions in perimenopausal women (Wu, 2012; Nedstrand et al., 2006), and reduce the Hamilton Rating Scale for Depression (HAM-D) score, the Self-rating Depression Scale (SDS) score, and Kupperman scoring, improve patients with FSH, E_2 and other hormone levels (Wang et al., 2010; Fu et al., 2009; Zhang, 2006), it could better avoid the side effects of oral drugs, so acupuncture treatment of PDD has an important social value.

At present, the main factors related to the pathogenesis of PDD are estrogen withdrawal theory (Schmidt et al., 1994), neurotransmitter factor (Dong and Wang, 2012), neuroendocrine (Min et al., 2012), neurogenesis (Duman, 2004), apoptosis (Magarinos and Mc Ewen, 1995), genetic factors (Feng, 2009), psychological factors and social support (Lorena et al., 2004), etc., but estrogen and neurotransmitters are more recognized in the pathogenesis of PDD, therefore this study explores the effect of electroacupuncture to PDD from the estrogen level and the neurotransmitter.

2. Experimental materials and methods

2.1. Experimental animals

The mice is a species of KM, the grade is SPF, the sexuality is female, the weight is 18–22 g, it provided by Shandong Lukang Pharmaceutical Co., Ltd., and the animal certificate number is 0021650.

2.2. Experimental drugs and reagents

Clomipramine hydrochloride tablets, 25 mg/tablet (produced by Jiangsu Enhua Pharmaceutical Co., Ltd.); Sodium penicillin for injection, north China pharmaceutical co., LTD., specification: 4 million units, batch number: F4046509; Mice E_2, T, LH, FSH, DA, 5-HT, NE ELISA test kit, R&D company, batch number: 20151001A;

2.3. Experimental instruments

ZZ-6 mice independent activity tester, Shanghai Kangwei Medical Technology Development Co., Ltd.; BA-200 mice darkness tester, Shanghai Kangwei Medical Technology Development Co., Ltd.; TS-200 tail tester, Shanghai Kangwei Medical Technology Development Co., Ltd.; G6805 electro-acupuncture treatment instrument, Qingdao Xinsheng Industrial Co., Ltd.; BX61 electric microscope, Japan OLYMPUS company; X3R high-speed refrigerated centrifuge, American Thermo Fisher Scientific Co., Ltd.

2.4. Animal model preparation

Peri-menopausal model preparation: 50 female KM mice weighing 18–22 g were selected, and randomly taken 10 mice as blank group (BG), and the remaining mice were prepared for peri-menopausal depression model. Mice were given 10% chloral hydrate (0.03 mL/10 g) intraperitoneally for anesthesia. The left and right ovaries were completely removed. After the operation, the penicillin souium was performed to prevent infection by intramuscular injection (200,000 U/kg, 0.02 mL/mice), continuous 3d, 1 time per day. After 5d of operation, the mice were vaginally smeared one by one, once a day for 5d days, and to determine if the ovary is completely removed. Mice with emotive responses to the smear were abandoned and 30 mice with complete emasculation were selected for the experiment.

Preparation of depression model: 30 mice that had a perimenopausal model were housed in single cages and given different stimulation every day. Seven chronic mild unpredictable stress methods were applied in a randomized manner within 21 days: wet pad (1 g pad/1 mL water); ice and cold water swimming (4 °C, 5 min); thermal stimulus (45 °C, 5 min); overnight illumination (24 h); clip tail (1 min); water stop (24 h); fasting (24 h). Each day was given a random stimulus, each of which did not appear continuously for 21 consecutive days.

2.5. Experimental animal group

In addition to BG, 30 mice were divided into model group (MG), western medicine group (WG), and electroacupuncture group (EAG). The mice in BG and MG were not treated and were kept normally; the mice of EAG were treated with electroacupuncture daily, and the mice in the western medicine group were treated with clomipramine hydrochloride daily.

2.6. Electroacupuncture treatment

Electroacupuncture treatment selected "Baihui", "Shenshu" and "Sanyinjiao" points. Acupoint localization reference "experimental acupuncture" and mice acupuncture point mapping, mice acupoint positioning method: Baihui acupoint is located in the middle of the mice parietal bone, and forward oblique acupuncture 2 mm; Shenshu acupoint is located under the second lumbar spinous process of the mice, each point on the left and right sides, and the puncture was 4 mm; Sanyinjiao points is located in the hind limbs of the mice about 5 mm on the tip of the sac, a point on the left and right sides, straight thorn 1.5 mm. After the needle is applied, the electroacupuncture instrument is connected, and the sparse wave is used. The frequency of the thin wave is 2 Hz, while that of the dense wave is 10 Hz, the intensity is slightly twitched by the local skin muscle. At 9o'clock every day, the mice were treated with electroacupuncture in a quiet state, once a day, each time for 20 min, for 28 days.

2.7. Drug treatment

The western medicine group was treated with clomipramine hydrochloride tablets, and the clomipramine hydrochloride tablets were crushed and dissolved in 0.9% physiological saline, and by a dosage of 62.5 mg/(kg·d) (administered volume 0.1 mL/10 g) to administration, once times for one day, continuous administration for 28 days.

2.8. Forced swimming experiment

The forced swimming experiment is test whether the mice were in a state of "behavioural despair". The mice initially appears to be struggling vigorously and swim in the water. When it feels impossible to escape, the mice no longer struggles and swims, while the limbs float and remain motionless. The state of this state is called "behaviour despair". On the 23rd day of treatment, the immobility time of each group of mice was measured for 2–6 min in 6 min. Each group of mice was placed in a 2000 mL beaker. The water temperature was 25 °C. In addition to the minimum movement required to keep the animals floating, the limbs stopped moving and were recorded as stationary. The total time of the 2–6 min of immobility within 6 min was recorded.

2.9. Independent activity test

On the 24th day of treatment, the number of spontaneous activities in each group of mice was measured within 5 min. The mice were placed in a reaction box (330 mm × 100 mm × 110 mm), and 36 high-resolution infrared array detection points were adopted, and measure the activity and standing of the mice.

2.10. Avoiding dark experiment

On the 25th day of treatment, the mice were put into the bright room, when the mice went into the dark room, the door which connecting the two room was closed, and at the same time the electric stimulator was activated, and the animal's foot was subjected to electric shock for training. After 24 h, the mice were placed in the bright room again, and re-measured to record the latency of the first time of the mice entering the dark room and the number of errors entering the dark room within 5 min.

2.11. Tail suspension experiment

On the 27th day of treatment, the immobility time of each group of mice was measured for 2–6 min in 6 min. The posterior 1/3 of the tail of the mice was fixed with tape, suspended on the support, and the head was 15 cm away from the table. The camera background was contrasted with the mice coat color, and the white mice were black background. The time was stopped after 6 min, and the immobility time of the mice for four minutes (2–6 min) was counted using the small animal behavior analysis software.

2.12. Determination of E2, T, LH and FSH levels in serum

After 2 h of the last treatment of each group of mice (fasting for 12 h), the mice were weighed and then the eyes were taken for blood. Separation of serum and plasma (4 °C, 3500 rpm, 10 min), stored in the refrigerator at −80 °C, and the level of T, E_2, LH and FSH were determined by ELISA.

2.13. Determination of 5-HT, DA and NE levels in brain homogenate

After the blood was taken, the mice were killed, and the brain tissue was taken to prepare a tissue homogenate. The homogenization method was as follows: the ratio of brain tissue mass to normal saline was 1:9, and fully grind, make the tisse homogenate, centrifuge (the centrifuge temperature is 4 °C, the centrifuge speed is 3500 rpm, the centrifuge time is 10 min), and stored in refrigerator at −80 °C.

The level of 5-HT, DA, NE in brain tissue homogenate was determined by ELISA. The specific operation method was followed according to the instructions.

2.14. Morphological observation of the hypothalamus

Pathological sections of hypothalamus were made by HE method, and the morphological changes were observed under microscope.

2.15. Statistical methods

SPSS21.0 was used for data analysis, mean plus or minus standard deviation was used for measurement data, univariate analysis of variance was used for comparison between groups, when the homogeneity test of variances is equal variance the method of LSD was used, when the homogeneity test of variances is not equal variance the method of games-howell was used, the ordinal data was used Ridit test.

3. Experimental results

3.1. Effect of forced swimming time on peri-menopausal depression model mice

From Fig. 1 to be seen, the forced swimming time between the MG mice and BG was significantly prolonged ($P < 0.01$), it reflected the escape behavior of the model mice in the desperate state was reduced. Compared with MG, WG and EAG could significantly shorten the fixed time of forced swimming ($P < 0.01$), and it could improve the survival desire of mice in harsh environments.

3.2. Effects of independent activities on mice with perimenopausal depression

From Fig. 2. (A, B) to be seen, the number of spontaneous activities and standing times between the MG and BG were decreased significantly ($P < 0.01$), and it reflected the decrease of curiosity degree of the peri-menopausal depression mice to the fresh environment. Compared with MG, WG and EAG could significantly improve the activity and standing times of perimenopausal depression mice ($P < 0.01$), and improved the curiosity of the perimenopausal depression mice to the fresh environment.

3.3. Effects of incubation period and frequency of electric shocks in the method of avoiding darkness in perimenopausal depression model mice

From Fig. 3. (A, B) to be seen, the incubation period of the mice between MG and BG was reduced significantly, and the frequency of electric shocks were significantly increased ($P < 0.01$), it reflected the learning and memory ability of mice with perimenopausal depression was decreased. Compared with MG, WG and EAG could increase the incubation period of perimenopausal depression mice significantly, and reduced the number of electric shocks ($P < 0.01$), and improved the ability of learning and memory.

3.4. Effect of the time of suspension of the peri-menopausal depression model mice

From Fig. 4. to be seen, the time of suspension between MG and BG mice was significantly prolonged ($P < 0.01$), it reflected the prolongation of immobility in perimenopausal depressed mice in a desperate environment. Compared with MG, WG and EAG could significantly reduce the time of suspension of peri-menopausal depression mice, and reduced the number of electric shocks in perimenopausal depression mice ($P < 0.01$), and improved the survival desire.

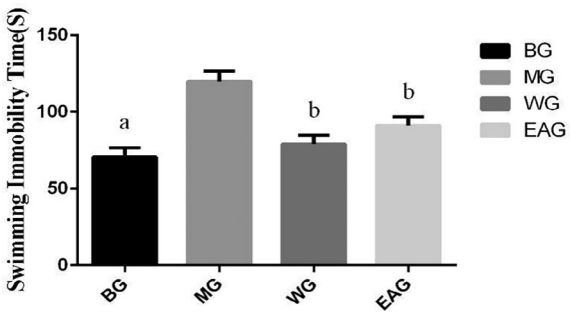

Fig. 1. Effect of forced swimming time on peri-menopausal depression model mice. In the figure, "a" indicates the significant variation between BG with MG ($P < 0.01$), "b" indicates the significant variation between the treatment group with MG ($P < 0.01$), n = 10 mice/group.

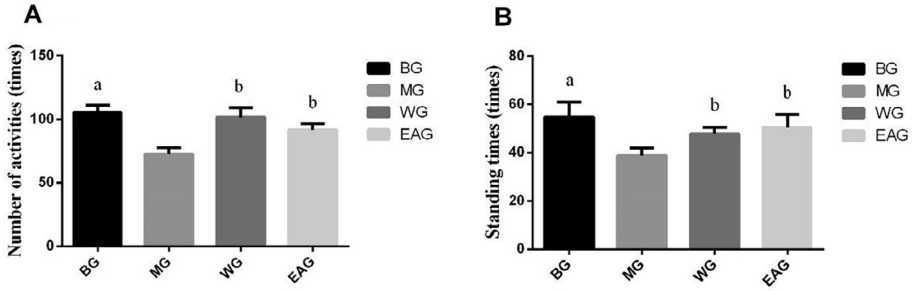

Fig. 2. Effect of forced autonomic activity on mice with perimenopausal depression. In the figure, "a" indicates the significant variation between BG with MG ($P < 0.01$), "b" indicates the significant variation between the treatment group with MG ($P < 0.01$), n = 10 mice/group.

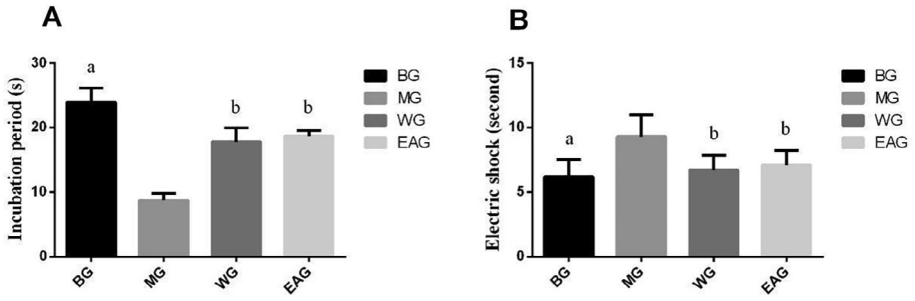

Fig. 3. Effect of incubation and the frequency of shocks in perimenopausal depression mice. In the figure, "a" indicates the significant variation between BG with MG ($P < 0.01$), "b" indicates the significant variation between the treatment group with MG ($P < 0.01$), n = 10 mice/group.

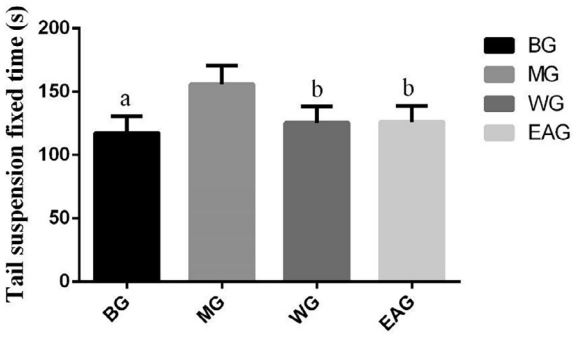

Fig. 4. Effect of the time of suspension of the peri-menopausal depression model mice. In the figure, "a" indicates the significant variation between BG with MG ($P < 0.01$), "b" indicates the significant variation between the treatment group with MG ($P < 0.01$), n = 10 mice/group.

3.5. Effect of T, E2, LH, FSH level in perimenopausal depression model mice

From Fig. 5. (A, B, C, D) to be seen, the level of T and E_2 in the serum between MG and BG were significantly reduced ($P < 0.01$), LH and FSH level were significantly increased ($P < 0.01$), it indicated the serum sex hormone level was disturbed in the model of perimenopausal depression mice. Compared with MG, EAG could increase T and E_2 level and reduced FSH and LH level in serum significantly ($P < 0.01$), while WG only had a tendency to reduce the disorder of sex hormones caused by castration, but there was no statistics significance.

3.6. Effect of 5-HT, DA and NE level in brain tissue of mice with perimenopausal depression

From Fig. 6. (A, B, C) to be seen, the level of 5-HT, DA, and NE in the brain tissue between MG and BG were reduced significantly than BG ($P < 0.01$), it indicated that the levels of monoamine transmitters in peri-menopausal depression model mice brain tissue was reduced. Compared with MG, WG could significantly increase 5-HT, DA and NE level in brain homogenate ($P < 0.01$). EAG could increase 5-HT and DA level in brain tissue homogenate significantly ($P < 0.01$), increased NE level in brain tissue significantly ($P < 0.05$).

3.7. Effects of the histopathologic morphology of hypothalamic tissue in perimenopausal depression model mice

From Fig. 7. and Table 1, It can be seen that, the hypothalamus of BG has a large body of nerve cells, the patina was rich, and the multi-level synapses were clear. The number of neurons in the hypothalamus of MG was reduced, most of the nerve cells are pyknosis, and the synapses were significantly reduced, and most of the neurokeratin cells also showed pyknosis. In the WG, most of the neurons in the hypothalamus were large, the patina was rich, and the multi-level synapses were clear. In the EAG, the hypothalamus has a large body of nerve cells, the patina was reduced, and the multiple synapses of the nerve are reduced.

4. Discussion

In this experiment, the PDD mice model was prepared by using the castration method combined with chronic unpredictable stimulation. At present, the methods for preparing peri-menopausal animal models include natural aging and castration methods. However, it has been reported in the literature that the natural aging model has a long modeling period, large individual differences, and unstable results, which cannot meet the experimental demands (Liu et al., 2014). And the peri-menopausal animal model caused by the castration method has obvious disorder of sex hormones, and the modeling time is short, the model has high success rate, stable and reliable. Therefore, the animal model prepared by the castration method can better simulate with the peri-

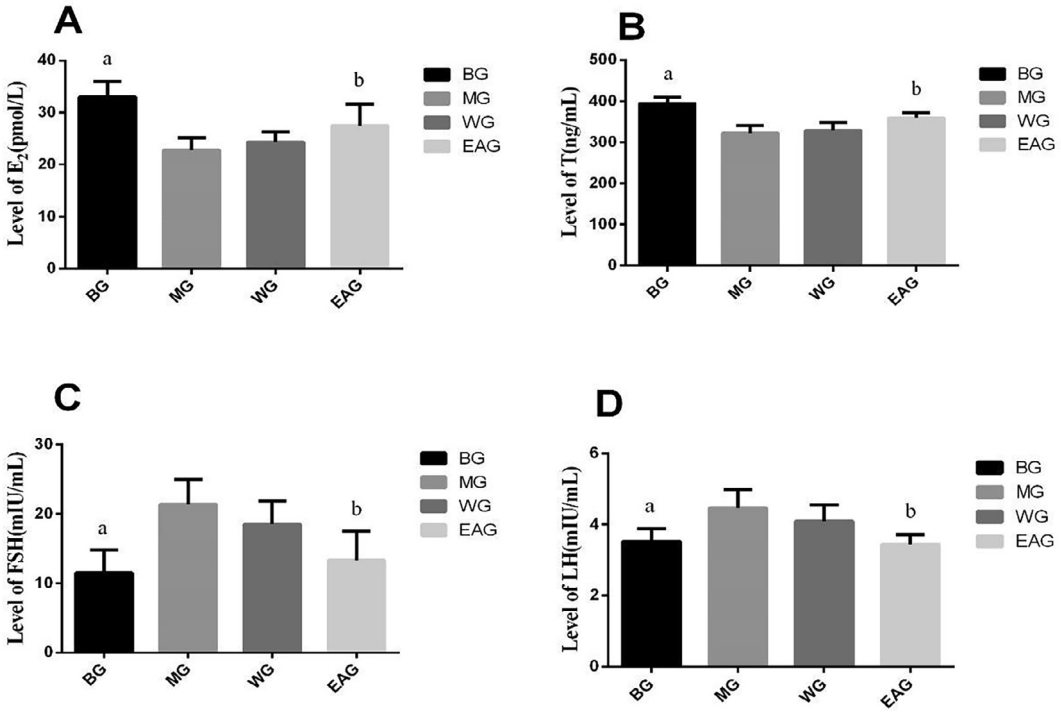

Fig. 5. Effect of E_2, T, LH and FSH level in serum of peri-menopausal depression model mice. In the figure, "a" indicates the significant variation between BG with MG ($P < 0.01$), "b" indicates the significant variation between the treatment group with MG ($P < 0.01$), n = 10 mice/group.

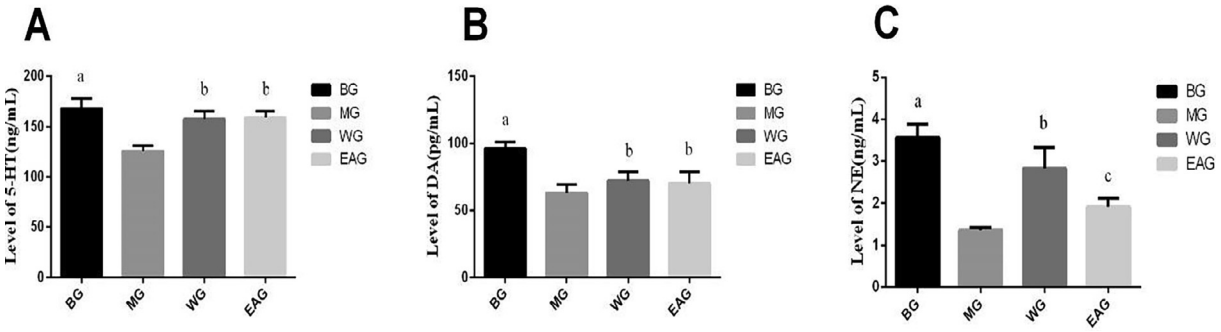

Fig. 6. Effect of homogenate 5-HT, DA and NE on brain tissue of mice with perimenopausal depression. In the figure, "a" indicates the significant variation between BG with MG ($P < 0.01$), "b" indicates the significant variation between the treatment group with MG ($P < 0.01$), "c" indicates the significant variation between the treatment group with MG ($P < 0.05$), n = 10 mice/group.

menopausal period of human beings, it has a high degree of clinical consistency. There are many modeling methods for animal models of depression. Among them, chronic unpredictable stimulation is the animal model preparation method which is the closest to the cause of perimenopausal depression (Katz et al., 1981), it is also a recognized depression model. Therefore, the combination of two animal models and the synthesis of perimenopausal depression model by compound factors is consistent with the characteristics of clinical diseases and the pathogenesis.

In this experiment, the "Baihui", "Shenshu" and "Sanyinjiao" points were selected. Baihui is located at the top of the head scorpion. It has the function of waking up the mind, installing the five organs, setting the mind. It is the most commonly used acupuncture point for clinical treatment of emotional diseases, and Baihui is the key point of the governor vessel, which can transport and communicate the brain and kidney, balance yin and yang; Shenshu is the place where the gas of kidney are ventilated, it is the place where the essence of the kidney gathers, and it is the first point to nourish the kidney yin, it also can nourish the kidney essence, egulating thoroughfare and conception vessels, adjust yin and yang, and improve the immunity of perimenopausal women (Wang et al., 2012); Sanyinjiao is the place where the liver, spleen and kidneys meet, it has the functions of strengthening the spleen, soothe liver, replenishing the kidney, and coordinating qi and blood. Acupuncture the Sanyinjiao can regulate the functions of liver, spleen and kidney, the yin and yang are balanced, the patient's symptoms have also improved (Zhou et al., 2006). The acupoints are combined to play the role of nourish the kidney and replenishing the brain, relieving depression to tranquilize mind. PDD is an emotional disorder which occurring in the perimenopausal period, its onset time coincides with the physiological perimenopausal period of women, which determines the need for both the treatment of the mentality, and also from the perimenopause of women of this special period of physiological change treatment.

The most obvious change in depression is the change in behavior. Therefore, this study responds to depression and treatment by measuring a variety of behavioral changes such as forced swim-

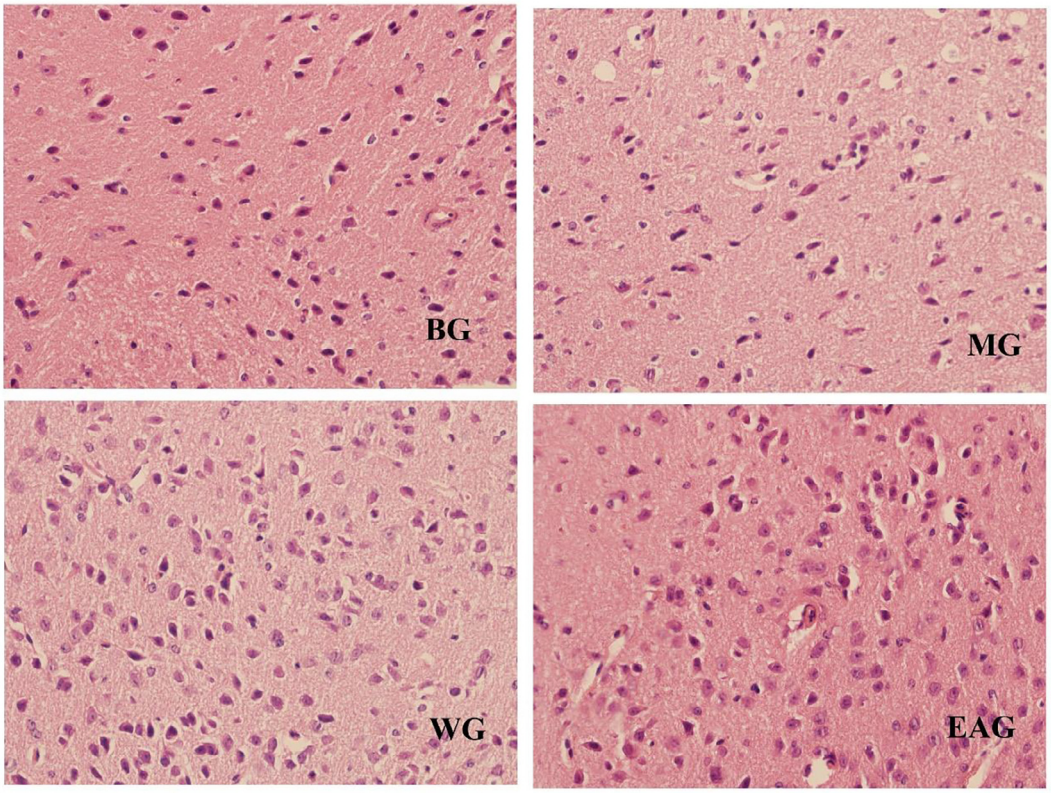

Fig. 7. Effect of hypothalamic tissue pathology on mice with perimenopausal depression.

Table 1
Histopathologic morphological grading of hypothalamus in perimenopausal depression model mice.

Group	N	–	+	++	+++
BG	10	10	0	0	0
MG	10	0	0	1	9
WG	10	6	7	3	0
EAG	10	0	3	3	4

Note: "–" the hypothalamic nerve cells are large, the patina is rich, and the multi-level synapses are clear; "+" the hypothalamic nerve cells are large, the patina is reduced, and the multi-level synapses are reduced; "++" the hypothalamic nerve cells are reduced, the patina is pyknosis, and the multi-level synapses are reduced; "+++" the hypothalamic nerve cells are significantly reduced, the patina is pyknosis, the synapses are reduced, and the glial cells are pyknosis.

ming, spontaneous activity, avoidance of darkness, and tail suspension. Forced swimming (FST) is a "behavioral desperation" model, it observes the response of mice to the threat of drowning. The results of the experiment are used to assess the sensitivity of animals to negative emotions and are often used to measure the effectiveness of antidepressant treatment. Autonomic activity is an important indicator of the functional state of the central nervous system, the number of activities during excitement increases, and the number of activities during suppression decreases. The light/-dark box (LDB) is mainly used to evaluate rodent anxiety through the number of shuttles, which can reflect the animal's anxiolytic state (Sun et al., 2014). The tail suspension test (TST) belongs to another model of acute behavioral despair, most antidepressant treatments can significantly shorten their immobility time and are the classic method for evaluating antidepressant drugs. Among them, FST and TST are common models for evaluating depression. LDB is more inclined to evaluate exercise exploration behavior (Sun et al., 2012; Shimada et al, 1995), detect changes in related behaviors, and intuitively respond to treatment effects.

The monoamine hypothesis suggests that sustained stress or brain dysfunction causes a decrease in the concentration and activity of monoamine neurotransmitters, leading to depression (Zhang and Li, 2010). Monoamine transmitters include dopamine (DA) and norepinephrine (NA), and serotonin (5-HT). PDD is mainly due to the significant decrease in estrogen expression level in women enter the menopause, the physiological activity of monoamine oxidase is significantly enhanced, and the degradation process of monoamine transmitters is significantly accelerated, which makes the expression levels of substances of 5-HT, DA and NE are significantly decreased, leading to depressive symptoms (Li et al., 2009, 2010) So, this study mainly detects levels of E2, T and other sex hormones in serum and the monoamine neurotransmitters level in brain tissue such as 5-HT, DA and NE could reflect the effect of electroacupuncture treatment.

5. Conclusion

Studies have shown that electroacupuncture can significantly reduce the time of forced swimming and tail suspension in mice, reduce the number of shocks to mice, improve memory, and increase the number of spontaneous activities of mice, and increase 5-HT, DA, and NE level in the brain tissue homogenate, increased T and E_2, FSH level and decreased LH level, and regulate hormone levels disorder, and improve pathological changes in the hypothalamus. It can be seen from the above that electroacupuncture has a certain therapeutic effect on perimenopausal depression, which provides a basis for clinical treatment of the disease. However, there are still some problems, which need to be further studied on its mechanism, and clarify the mechanism of action, it will better serve for the clinical.

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