Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

Research Report

Possible antidepressant effects and mechanism of electroacupuncture in behaviors and hippocampal synaptic plasticity in a depression rat model

Yanling She[a,b,1], *Jian Xu*[a,1], *Yanhong Duan*[c], *Ning Su*[d], *Yanan Sun*[a], *Xiaohua Cao*[d], *Lixing Lao*[e,f], *Ruixin Zhang*[f], *Shifen Xu*[a,*]

[a]*Shanghai Municipal Hospital of Traditional Chinese Medicine Shanghai, Shanghai University of TCM, Shanghai 200071, China*

[b]*Guangdong Traditional Medical and Sports Injury Rehabilitation Research Institute, Guangdong No.2 Provincial People's hospital, Guangzhou 510317, China*

[c]*Key Laboratory of Brain Functional Genomics of Ministry of Education, Shanghai Key Laboratory of Brain Functional Genomics, School of Life Sciences, East China Normal University, Shanghai 200062, China*

[d]*Guangzhou University of Traditional Chinese Medicine, Guangzhou 510405, China*

[e]*School of Chinese Medicine, The University of Hong Kong, 10 Sassoon Road, Pokfulam, Hong Kong*

[f]*University of Maryland, School of Medicine, Center for Integrative Medicine, Baltimore, MD 21201, USA*

ARTICLE INFO

Article history:
Accepted 16 October 2015
Available online 23 October 2015

Keywords:
Electroacupuncture
Depresson
Behavior
Synaptic plasticity

ABSTRACT

Increasing evidences show that hippocampal synaptic plasticity plays a crucial role in the pathogenesis of depression. The objective of this study was to determine whether electroacupuncture (EA) in the Wistar Kyoto (WKY) rat model of depression would exert antidepressant effects and whether this effect would be associated with changes in hippocampal synaptic plasticity. Male WKY rats were randomly divided into three groups (EA, sham EA, and blank control); Wister rats were used as normal control group. Treatment with EA was performed at Baihui (GV20) and Yintang (EX-HN3) once daily for 3 weeks. Forced swimming test (FST), open field test (OFT), and Morris water maze (MWM) were evaluated after 21-day intervention. Long-term potentiation (LTP) was evoked at Schaffer collateral-CA1 synapses in hippocampal slices in vitro. EA treatment significantly reduced immobility time in FST. MWM test showed a significant downward trend in escape latency time from the second to fifth days of experiment, and a higher frequency of crossing the missing quadrant platform in normal control and EA vs other groups. Impaired LTP was detected in Schaffer collateral-CA1 synapses in blank control and sham EA groups. In the western blot, the expression of GluN2B showed significant increase in EA vs sham EA and blank control groups. EA was able to improve depression-like behaviors and reverse the impairment of LTP, which were likely mediated by GluN2B in the hippocampus.

*Corresponding author.
E-mail address: xu_teacher2006@126.com (S. Xu).
[1]These authors made same work for this article.

http://dx.doi.org/10.1016/j.brainres.2015.10.033
0006-8993/

1. Introduction

Depression is a common neuropsychiatric disorder with a lifetime prevalence rate of 16.5% (Aung et al., 2013). It is characterized by low mood, cognitive impairment, low self-worth, loss of interest or appetite, and is accompanied by the feeling of guilt and attempt to suicide. It adversely affects patients' ability to work, lifestyle, quality of sleep, income, and cost (Aung et al., 2013).

Antidepressant drugs present first choice of clinical therapy over the past 50 years,. However, approximately one-third to one-half of patients did not respond to antidepressant treatment (Bschor et al., 2014). In addition, nearly all antidepressants require 4–6 weeks to exert their therapeutic effects and their adverse effects cannot be ignored (Lavergne and Jay, 2010).

Acupuncture is one of the complementary and alternative modalities for the treatment of various psychiatric and emotional disorders including Alzheimer disease, generalized anxiety disorder, posttraumatic stress disorder, sleep disorders, major depression, etc. (Aung et al., 2013; Wang et al., 2012). Experimental studies in humans have supported the idea that acupuncture is a safe and highly effective therapy in treating depression. A recent randomized controlled trial (RCT) used Patient Health Questionnaire to evaluate the effects of acupuncture and counseling on depression in 755 patients in primary care. Results indicated that both acupuncture and counseling significantly reduced depression at 3 months as compared to usual care alone (MacPherson et al., 2013). Another RCT showed that acupuncture combined with selective serotonin reuptake inhibitors (SSRIs) significantly improved the 17-item Hamilton Depression Rating Scale scores as compared to SSRIs alone over the 6-week period (Wang et al., 2014). However, the mechanisms of treatment with electroacupuncture (EA) on depression were not well understood.

Neural plasticity, especially hippocampal synaptic plasticity, is thought to contribute to learning and memory (Foy, 2011). Impaired plasticity leads to cognitive deficits and memory loss. It is well known that learning ability decreased in depressive subjects. Pharmacological intervention that manipulates synaptic plasticity promotes the formation of memory. Zhang et al. (2012) reported that in corticosterone-stressed rats, hippocampal cell proliferation significantly decreased, and treatment with *Lycium barbarum* increased immobility time in forced swimming test (FST), restored the reduced spine density and the decreased levels of (postsynaptic density-95) PSD-95 in the hippocampus. It has also been reported (Luo et al., 2014) that chronic unpredictable mild stress model rats resulted in damaging the memory, impairing long-term potentiation (LTP), and downregulating PSD-95. The treatment with electroconvulsive shock under anesthesia improved memory possibly through reversing the excessive changes in hippocampal synaptic plasticity. LTP is considered as a cellular mechanism of memory formation and its induction required increased numbers of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) and the activation of N-methyl-D-aspartate receptors (NMDARs) (Foy, 2011).

In this study, a well-established model of depression, the putative genetic Wistar Kyoto (WKY) rat model of co-morbid depression and anxiety, was used (López-Rubalcava and Lucki, 2000; Rittenhouse et al., 2002), to investigate the effect and mechanism of EA on depression. Behavioral studies including FST, OFT, and Morris water maze (MWM) test were used to evaluate depression-like behavior. Electrophysiological study was used to record LTP evoked at Schaffer collateral-CA1 synapses in the hippocampus, and western blot was used to measure the expression of hippocampal AMPAR and NMDAR subunits. It was hypothesized that treatment with EA will modulate the expression of hippocampus AMPAR and NMDAR, and LTP to improve depression-like behavior.

2. Results

2.1. FST

The results of FST are shown in Fig. 1. Duration of immobility was significantly ($P<0.01$) longer in the blank controls (WKY rats, column 2) than in the normal controls (Wistar rats, column 1), indicating that WKY rats showed depression-like behavior. Interestingly, the duration of immobility was significantly ($P<0.05$) shorter in the EA group (95.11±10.28 s) than in the blank control and sham EA groups (119.49±9.12 s and 114.63±7.07 s, respectively), suggesting that treatment with EA improves the depression-like behavior.

2.2. OFT

The results of the OFT are shown in Fig. 2. The total distance (Fig. 2A), mean speed (Fig. 2B), and distance traveled within the central area (Fig. 2C) were significantly ($P<0.01$) shorter in the blank control (WKY rats) than in the normal control (Wistar rats). Duration of time spent by the rats in the central area was significantly ($P<0.05$) shorter in the blank control and sham EA than in the normal control (Fig. 2D). The number of rearing and grooming incidents is significantly ($P<0.01$) smaller in the blank control than in the normal control (Fig. 2E). These data indicate that WKY rats showed depression-like behavior. Although statistically significant differences were not found among the EA, blank control, and sham EA groups in any of these parameters, EA showed

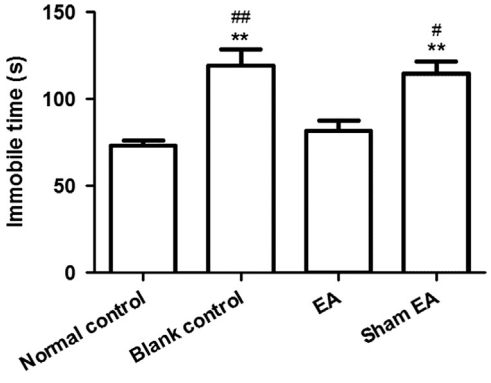

Fig. 1 – Forced swimming test in rats after 3-week intervention. Data were expressed as mean±SEM. $^{**}P<0.01$ compared to normal control; $^{\#}P<0.05$ compared to treatment with EA; $^{\#\#}P<0.01$ compared to treatment with EA. EA, electroacupuncture; SEM, standard error of mean.