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The effect of electroconvulsive therapy on the levels of oxidative stress factors in the prefrontal cortex of depressed rats

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Abstract

Background and Objective: Electroconvulsive therapy (ECT) is one of the effective and less complicated methods for treatment of depression in cases of resistance to common treatments. Given the fundamental role of pre-frontal cortex on changing the mood of depression-related behaviors in depressed patients, the effects of electroconvulsive therapy on enzymatic activity of this cortex were taken into account in this study.

Materials and Methods: For this purpose, 42 male Wistar rats were divided into three control, depressed and ECT groups. To create depression, Chronic Unpredictable Mild Stress (CUMS) method was used. Finally, NO, MDA, GSH and SOD in prefrontal portion of the brain in three mentioned groups were measured

Results: Our findings showed a non-significant increase of MDA ($p>0.05$) in both groups of depress and ECT in comparison with control. ECT caused a significant increase in contents of GSH and SOD in prefrontal cortex versus the group of control. Also, ECT significantly increased the level of nitrite as compared with control.

Conclusion: Treatment of depression by ECT could increase the level of antioxidants in the depressed rats' brain and it may be considered as a treatment for moderate depression disorders.

Key words: Depression, Electroconvulsive therapy, Oxidative stress, Rat.

1. Introduction

Major depressive disorder (MDD) is one of the most prevalent forms of mental illness in humans, which its occurrence rate is 16.2% in the United States (1). The disorder is associated with high morbidity and risk of premature mortality (2) and is predicted to be the leading cause of disability in Western countries by 2030 (3). Among patients with major depression, 75–85% has recurrent episodes and 10–30% was incompletely recovered with tenacious residual depressive symptoms (4, 5). Stress-related psychiatric disorders, including major depression, have also been reported to be associated with alternation in hypothalamic–pituitary–adrenal (HPA) axis function. Indeed, the studies show that the abnormality in HPA axis function has a key role in depression incidence (6). Nowadays, the prevailing mechanisms for the development of therapeutic drugs are mostly based on "monoamine hypothesis" which suggests that the decrease in concentration of monoamine neurotransmitters plays the main role in MDD (7). These drugs include selective serotonin reuptake inhibitors (SSRIs), tricyclics (TCAS) and inhibitors of degradation of neurotransmitters such as monoamine oxidase inhibitors (MAOIs) (8). However, a significant population of depressed patients (20% to 30%) does not respond to these medications. This is somewhat due to our limited understanding of the precise neurobiological mechanisms associated with depression(9). Recent evidence suggests that the incidence of depression is caused by alterations in the

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complex signaling networks. These networks included of: monoamine neurotransmitter, neuroendocrine system, neurotropic factors, neurogenesis, immune system deficiency, and epigenetic modifications (10-14). In concomitant, electroconvulsive therapy (ECT) is a highly effective treatment for severe or resistant forms of depression (15). The ECT technique has been considerably advanced in the last 50 years (16). The reports showed that the rehabilitation with electro-convulsion is an effective treatment for bipolar depression, but there are concerns about whether it causes long-term neurocognitive impairment (17). However, despite widespread usage of ECT, the exact neurobiological mechanisms underlying its efficacy are not fully understood. Over the past 3 decades, extensive work in rodents, primates, and humans has begun to delineate the impact of electroconvulsive seizures (ECS) and ECT on neurotransmission systems commonly implicated in depression (18). In the current study, we will focus and investigate the changes of oxidative stress indexes in the prefrontal cortex in depression rats using chronic unpredictable mild stress (CUMS) model.

2. Materials and Methods

2.1. Experimental groups and treatments

Healthy male adult Wistar rats (n=42), weighting 250–300 g, were maintained in a standard environment for one week acclimatization period before experiments. All of the experimental procedures were approved by the Ethical Committee of Shahed Medical University and carried out in accordance with National Institutes of Health Guide for the Care and Use of Laboratory Animals. Rats were randomly divided into three groups: 1- control group of healthy rats without any treatment (group C) and groups 2 and 3 were induced by CUMS to reproduce the rodent model of depression.

2.2. CUMS modeling for induction of depression

Chronic unpredictable mild stress (CUMS) procedure was adopted from a previous study with minor modifications. One randomly selected stressor stimulus among the panel used in this study was applied once daily to the rats in the CUMS-treated groups. The panel of stressor stimuli consisted of 1- swimming in cold water (4°C) for 5 minutes; 2- tail pinching for 1 minute; 3- food deprivation for 24 hours; 4- water deprivation for 24 hours; 5- social crowding (24 rats per cage), with cage being tilted to 30° from the horizontal plane for 24 hours; 6- shaking for 20 minutes (one shake per second); 7-continuous lighting for 24 h; 8- housing in a soiled cage for 24 h; 9- heat stress (45°C) for 5 minutes; 10- undesirable confinement for 2 h. Stressor stimuli were administered three times within the 4 weeks, except for stressors 1 and 2 which were applied two times during 1 month (19). After that, (23^{th} day from start of CUMS), the rats of group 3 was treated with ECT for a period of 7 days. Finally, the brain of each rat was removed and homogenized and the separated supernatant was kept at -70°C for biochemical assay.

2.3. Measurement of oxidant and anti-oxidant metabolites

Malondialdehyde (MDA)

The concentration of malondialdehyde (MDA) as a lipid peroxidation marker was calculated by measuring thiobarbituric acid reactive substances (TBARS) in the supernatant as described by Roghani et al. (20). Briefly, trichloroacetic acid and TBARS reagent were added to aliquots of the supernatant, which were subsequently mixed and incubated at 100°C for 80 min. After cooling on ice, the samples were centrifuged at 1000×g for 10 min, and the absorbance of the supernatant was read at 532 nm. The results of TBARS measurements were expressed as MDA equivalents, using tetraethoxypropane as standard.

Nitrite as NO metabolite

Supernatant NO content was assayed by the Griess method. Since NO is a compound with a short half-life and is rapidly converted to the stable end products of nitrate (NO_3^-) and nitrite (NO_2^-), the principle of the assay is the conversion of nitrate into nitrite by cadmium and followed by color development with Griess reagent (sulfanilamide and *n*-naphthyl ethylenediamine) in acidic medium (21). The total nitrite was measured by Griess reaction. The absorbance was determined at 540 nm with a spectrophotometer (22).

Superoxide dismutase (SOD)

SOD activity measurement was according to our previous work (23). Briefly, supernatant was incubated with xanthine and xanthine oxidase in potassium phosphate buffer (pH 7.8, 37ºC) for 40 min and NBT was added. Blue formazan was then monitored spectrophotometrically at 550 nm. The amount of protein that inhibited NBT reduction to 50% maximum was defined as 1 nitrite unit (NU) of SOD activity.

Glutathione (GSH)

Glutathione level in homogenized supernatant was measured with Ellman reagent at 412 nm.

2.4. Data analysis

Data were expressed as the mean ± standard error. Statistical analysis was performed using SPSS software program (version 13; SPSS, Chicago, IL, USA). The results were compared using an analysis of

variance (ANOVA). P-values <0.05 were considered significant.

3. Results

3.1. Prefrontal cortex MDA concentration

As shown in figure 1, MDA was slightly and non-significantly increased in depressed and ECT treatment animal groups as compared to control rats.

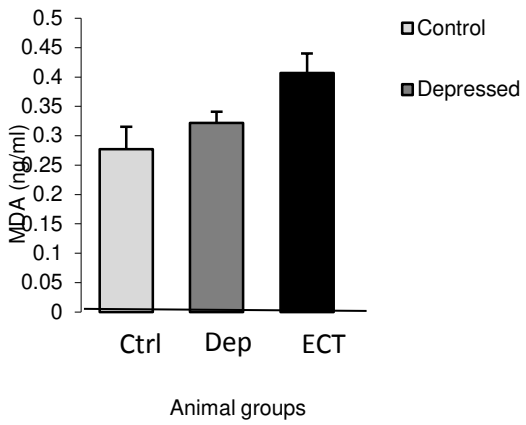

Fig. 1. Prefrontal malondialdehyde (MDA) concentration in control and treatment animals. Bars show Mean±SEM. n = 14/group.

3.2. Nitrite concentration of prefrontal cortex

There was no significant differences in nitrite (NO) concentration between control and depression groups (Fig. 2), but in depression animals which treated with ECT, we found a marked elevation (1.75±0.21) in nitrite versus control (1.02±0.15) p < 0.05.

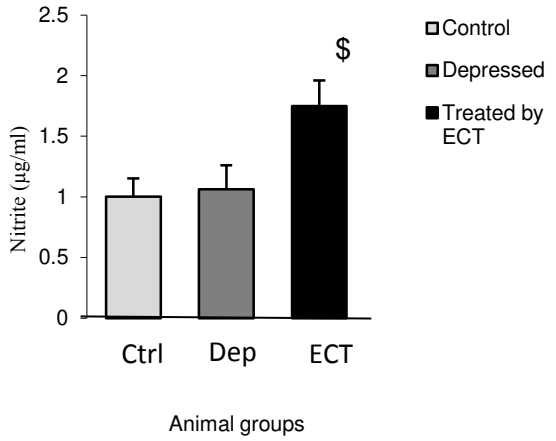

Fig. 2. Prefrontal nitrite concentration in control and treatment animals. Bars show Mean±SEM of nitrite concentration. n = 14/group.

3.3. SOD activity in prefrontal cortex

In depression animal group, SOD reduced from 9.08±0.99 (in control rats) to 6.26±1.87, which was not significant. However, there was a significant elevation of SOD in ECT treated animals (18.18±1.97) with respect to control (6.26±1.87) rats (p < 0.05).

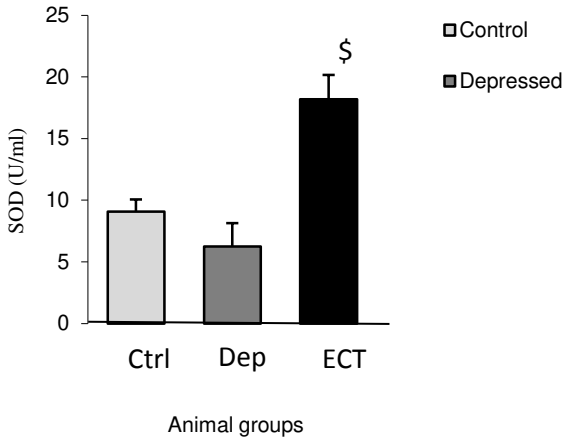

Fig. 3. Prefrontal SOD activity in control and treatment animals. Bars show Mean±SEM of SOD activity. n = 14/group.

3.4. Glutathione (GSH) concentration of prefrontal cortex

Evaluation of the prefrontal cortex GSH showed that there is a significant reduction in depression group GSH concentration (33.56±8.64) as compared to the control (63.54±7.26) animals. (p < 0.05). Though, treatment of the animals with ECT could antagonize the reduction effect of depression on GSH concentration to 118.22±10.32 value (p < 0.05).

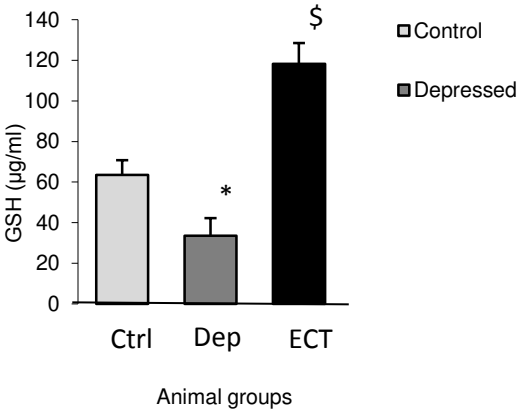

Fig. 4. Prefrontal GSH concentration in control and treatment animals. Bars show Mean±SEM of GSH concentration. n = 14/group.

4. Discussion

It is well established that neuroinflammation, oxidative stress and neuroendocrine disturbance have the main role in the pathogenesis of major depression (24). Reports show that excessive production of reactive oxidative stress (ROS) and decrement of antioxidants levels lead to cellular's protein, lipid, and DNA injury and subsequent cellular apoptosis. Many studies have indicated that GSH depletion leads to oxidative stress induction, mitochondrial complex I inhibition, ubiquitin–proteasome dysfunction and ultimately neuronal cell death (25, 26). In the study by Filho et al., it was reported that CUMS could decrease the level of non-protein thiol (NPSH) and increase reactive oxygen species (ROS). In response to these changes, glutathione reductase (GR), glutathione peroxidase (GPx) and catalase (CAT) activities were increased in mice exposed to CUMS (27). Other studies like JieCheng reports showed that the levels of prefrontal cortex pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-1 (TNF-1) increases by CUMS. Moreover, many investigations illustrated an increase in lipid peroxidations such as malonaldehyde (MDA) and also a decrement level for antioxidant defense enzymes including superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) following CUMS (24). However, Thakare finding revealed that the mice subjected to CUMS exhibited low levels of IL-6 and TNF-α which is concomitant with oxidant-antioxidant imbalance in the hippocampus and cerebral cortex (28). In another study by Lopresti, it was shown that in the depressed patients, MDA concentrations would be significantly increased as compared to healthy control persons (29). The nitric oxidative production disturbance i.e, high level of nitric oxide synthase activity was shown following depression (30). However, our investigation results are related to other mentioned reports. Chronic inflammation is conducted by several molecules which signaled by JAK/STAT transduction or microbial sensors such as Toll Like Receptor and absent in melanoma 2, and also (NLR) Node-like receptor. It seems that these molecules are involved in inflammatory cytokines production in patients with depression. Oxidative lipid damage was evident only in the frontal cortex than hippocampus, cerebellum and the pons/medulla region (31). We can guess the benefit protective anti-oxidant effects of ECT in frontal region could help to depressed patients to recover and reach to better border line for living.

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