http://jbcp.shahed.ac.ir 10.22070/jbcp.2020.5002.1126

Open Access Research Article

Journal of Basic and Clinical Pathophysiology
Print ISSN: 2322-1895, **Online ISSN:** 2345-4334
Vol.8, No.1, June 2020

A Semiannual Publication of
Shahed University Press

Behavioral function improvement of prefrontal cortex in treated depressed rats by ECT and ketamine

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Abstract

Background and Objective: Depression is one of the most prevalent mental disorders. Electroconvulsive Therapy (ECT) is one of the effective methods for treatment of depression. Regarding the stimulatory effect of glutaminergic system on the progression of depression, the effect of ketamine as one of the most important inhibitors of this system has been investigated on the effectiveness of ECT. Given the fundamental role of pre-frontal cortex on changing the mood of depression-related behaviors in depressed patients, the effects of ketamine with ECT on this cortex were taken into account in this study.

Materials and Methods: For this purpose, 50 male rats were used. Animals were randomly divided into five equal groups, and except the control group, the other ones were depressed by CUMS method. Then, three groups of depressed rats were treated in different ways (ECT, ketamine, and combined ECT and ketamine). Finally, behavioral parameters were measured.

Results: The combination of ketamine and ECT could reduce prefrontal depression like behaviors by testing of: sucrose intake increased, the total immobility rate also decreased and open field behaviors increased.

Conclusion: According to this study, the modification of behavioral parameters in rats treated with ECT and ketamine indicates the specific effect of electroconvulsive and ketamine therapy in modifying the mood and depression behaviors and behavioral test are showing the alleviation of depression signs. Electroconvulsive therapy in depressed rats with ketamine injection is recommended.

Keywords: Depression, Ketamine, Electroconvulsive therapy, Rat

1. Introduction

Depression is a chronic and complex emotional disorder associated with negative persistence of emotions and thoughts that disrupt mood, perception, motivation and behavior (1). Depression and anxiety are the most common mental health disorders in the community and overlap in the community. Recent WHO data, updated in 2017, reported that more than 300 million people worldwide suffer from depression. Increasing evidence suggests that despite efforts by researchers and psychiatrists, there is no way to prevent the spread of the disease in developed countries. The prevalence of depression has increased so much that it is the third most common global disability among non-fatal diseases and is expected to be the most common cause of disability by 2030 (2). Four categories of symptoms are considered for depression disorders. In addition to physical symptoms, physical, motivational, cognitive, or intellectual symptoms must also be added. The main features of depressive disorder are mood reduction, energy loss and loss of interest and enjoyment. Other common symptoms include decreased concentration, decreased self-esteem, guilty thoughts, pessimism, self-harm or suicide. In most patients, periods of depression occur from a combination of family,

Received: 29 Dec 2019, **Accepted:** 28 Mar 2020, **Available online:** 23 June 2020
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biological, psychological, and social factors. Disorders of neurotransmitters, family alcoholism, recent adverse events in life, having a conflicting spouse, lack of close and reassuring communication, lack of appropriate social support, and long-term lack of valuable feeling (3).The most important neurotransmitters associated with depression and anxiety are serotonin, dopamine and noradrenaline.Serotonin is known to be an effective factor in body temperature, sleep regulation and wakefulness, hormone secretion and food intake. Along with mood regulation, serotonin is also involved in external stimuli and impulse control. Patients with major depression show abnormalities in serotonin transmission. The results of neuroendocrine studies suggest that depression is associated with reduced postsynaptic transmission of 5-HT1A receptors. Many antidepressants are designed to exert their therapeutic effect on these receptors. Another neurotransmitter involved in the regulation of mood and anxiety is noradrenaline. Both chronic and acute stresses lead to depression. Adrenaline-secreting cells are highly active in alertness and readiness. Animal studies show that norepinephrine plays an important role in the persistence of depression. Dopamine is a neurotransmitter that plays an important role in sensory motor and mental activity and is also involved in the development of depressive illness. Dopamine regulates mental processes associated with senses and movement. Dopamine dysfunction has been reported in mental illness and bipolar depression; antidepressants can relieve this feeling by increasing the sensitivity of D2 and D3 dopamine receptors. (3).There are various ways to treat depression, including psychotherapy, medication, and physical therapy. Electroconvulsive Therapy (ECT) is a valid treatment for the treatment of major depressive disorder and refractory depression. Because ECT has been used as a non-selective method in the past, the general public has found it to be offensive and punitive. Approximately 80% of patients with major depression respond to ECT. (4). Prefrontal lateral and midbrain areas play an important role in affecting social behaviors. Prefrontal plays a central role in cognitive functions such as working memory, planning, and problem-solving behavior control (5). Prefrontal is an important target of afferents of acetylcholine, serotonin, norepinephrine and dopamine. The D1 and D5 receptors are specifically concentrated in the pre-frontal region and are largely located in the dendritic spines. There is also evidence that the D1 and D2 dopamine receptors are expressed in GABAergic interneurons (6). Although the mechanism for depressive state of consciousness and depression associated with stress-related neurological diseases has not been fully elucidated, it is thought to play a role in the serotonergic or dopaminergic system in the prefrontal cortex. Many neurological diseases, such as depression, Parkinson's, schizophrenia, etc., affect the prefrontal cortex and lead to poor performance in the area, causing working memory deficits (7). The mechanism of action of ketamine is complex, but the main effect is probably due to inhibition of the NMDA receptor complex.

Ketamine rapidly increases synaptic dentition in the prefrontal cortex. Specific properties of the drug, including profound analgesia, sympathetic nervous system stimulation, bronchial dilatation, and slight respiratory distress, have made ketamine a suitable and important alternative to other intravenous anesthetics, making it in many cases, it is a useful adjunct, despite its psychotomimetic effects. In addition, ketamine can be administered in a variety of ways (intravenous, intramuscular, oral, rectal, epidural), thus making it a suitable pre-drug option in patients with mental illness and patients. Regarding to mentioned reports about of ketamine and ECT, in this study the co-administration of ketamine and ECT was investigated to the prefrontal related- depression like behaviors.

2. Materials and Methods

In this study 50 male rats weighing 300-250 g were used. Rats were housed at atemperature about 21 ° C in a room with 12 h light and 12 h darkness. Mice were fed with standard plates and animals were fed for a maximum of 10 days free to adapt to the environment and food. The water was also given freely to the mice. Animals were randomly divided into 5 groups as follows: 1.Control group, all 10 specimens in this group were in normal condition during the study. 2. Depressed group, animals in this group were depressed according to CUMS model and no treatment was given to them. 3. ECT-treated group, samples of this group were treated with ECT after being depressed. 4. Ketamine-treated group, animals in this group were treated with ketamine after being depressed. 5. The group treated with the combination of ECT and ketamine. At first, each rat was weighted in each group and then exposed to stress for four weeks, except for the control group.

Chronic Unpredictable Mild Stress Procedure (CUMS):

In this model, the animal is exposed to a series of mild and unpredictable stressors on a daily basis, including stress in cold water (4 ° C) for 5 minutes, tail tapping for 5 minutes, food deprivation for 24 hours, water deprivation for 24 hours, Increase in cage rats (24 rats in one cage) with 30 ° inclination for 24 h, shaking for 20 min (one shake per second), lighting conditions for 24 h, placement in dirty cage for 24 h 24 hours, heat stress (45 ° C) for 5 minutes, place in restrainer compartment for 2 hours. Stress stimuli were applied three times in four weeks (8). From the eighteenth day,

the ketamine was injected intra-peritoneally with subcutaneous doses (10 mg / kg) every three days (9).

Anxiety and Depression Tests

Four weeks after induction of depression, rats undergo the anxiety and depression tests within three days. These tests include open box and maze plus elevation for measuring animal anxiety and forced swim tests and sucrose preference for the study of animal depression (10).

Forced swim test

Each animal was exposed to a 60 cm high water cylinder at 25 ° C for 15 min (training phase). Then the animals were tested 24 h later for a periods of 5 min. Total motor or immobility was recorded as an indicator of depressive behaviors. Increase motionlessness indicated the higher rate of depression. However, after swimming test, the animals were removed from the pool and dried (11).

Sucrose preference test

The animals were housed in separate cages and were drunk by two bottle of sucrose solution 72 h before the main test. After 24 hours these bottles was replaced with the water bottle for the next 24 hours .This is done for mouse adaptation. After the animal adaptation period, water and food are deprived for 24 hours. The sucrose test is calculated by placing two weighted bottles for each cage, one containing water and the other containing sucrose. The animals could access to both kind of bottles freely during 1 h. The drunk volume of each bottle was measured at the end of experiment, and the ratio of sweet/absolute water consumption was documented (12).

Open box Test

This test is used to evaluate the effect of stress on behavioral and motor changes in mice. The container is 60 x 60 x 60 cm. The floor of the compartment is divided into 16 squares 15 × 15. Among the four squares in the middle one square is centered and the surrounding 12 square as peripheral squares. Each rat is placed in the center of an open field and the actions of mice are evaluated (number of crossings, number of crossings peripheral squares). These cases are calculated within 5 minutes (13).

Elevated plus maze test

Animal anxiety indices were investigated in the elevated plus maze, which is an unconditional model for producing and measuring anxiety and determining the anxiogenic and anxiolytic effects of the drugs. The elevated plus maze consists of two opposite open arms and two opposite closed arms (40 cm long and 10 cm wide), with the arms closed on both sides by a 40 cm wall. In the center of the maze is a square measuring 10 x 10 cm. A 40-watt bulb is located one meter above the maze surface and 50 m above the ground. In this test, each animal is used once and then the animal is removed from the test. Anxiety indices include length of stay in open arms and closed arms and number of animals moving between arms, based on the percentage of number of open arms entering the total openings (OAE%), length of stay in the total open arm. Time elapsed in the arms (OAT%) and total number of arms and motor activity were determined. Thus, increasing the number of open arms entry and increasing residence in these arms is considered to reduce animal anxiety, and decreasing the number of open arms entry and decreasing residence in these arms indicates an increase in anxiety. Be it. The total number of arms entering represents the locomotor activity of the animal and the higher the number of arms indicates the higher motor activity (14). On day 32, mice were given daily ECT for seven days. ECT was applied in bitemporal, 60 mA current, 1.1 s period, pulses 100 s / s, and 0.5 ms pulse duration. After ECT,on day 39 for 3 days anxiety and depression behavioral tests were again performed.

3. Results

Sucrose preference test

The results of the sucrose preference behavioral test are shown in Figure 1, as shown there was a significant difference in sucrose intake between the control and depressed groups. In depressed group, a reduction in sucrose intake was observed. Among the treated groups, the group receiving the combination of ketamine and ECT showed a significant increase ($P<0.05$) in sucrose intake compared to the two depressed groups.

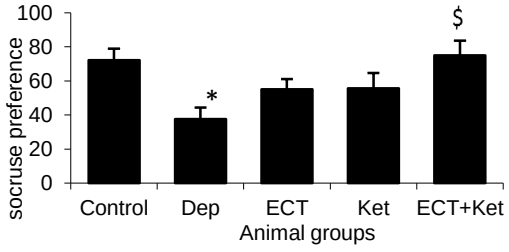

Figure 1: The results of behavioral survey on Sucrose Preference Test between Groups after Treatment. Columns represent Mean ± SEM and denote sucrose intake in ml (n = 10). * And $ P <0.05, respectively for depressed and control groupsAcknowledgements

Forced swimming test:

The results of behavioral assessment in the forced swimming test between the studied groups after completing the treatment steps are presented in figure 2, in this test, total immobility was significantly increased in the depressed group compared to the control group. This parameter decreased significantly in the group receiving ECT as a treatment compared to the depressed group. Also, the total immobilization in the ketamine-receiving groups, and the combination of ketamine and ECT significantly decreased at the P <0.01 level compared to the depressed group.

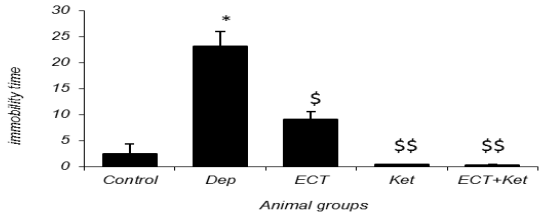

Fig. 2. Results of Behavioral Assessment in Post-Obligatory Swimming Test. The columns represent Mean ± SEM and denote the duration of inactivity in seconds (n = 10). * And $ P <0.05, respectively for depressed and control groups $$ show P <0.01 compared to depressed group after treatment

Open field test

The results of the open field behavioral test after completing the treatment steps are shown in figure 3 and 4, two parameters were considered in this test and each was examined separately among all groups. The first parameter was counting the number of animals passing through the perimeter squares of the open field compartment floor. In the study, shown in Figure 3, there was no significant difference in the number of crossing lanes between the control and depressed groups, but this parameter was higher in the treatment receiving groups (each The three groups (ECT, ketamine and ketamine + ECT) showed a significant increase compared to the control group.

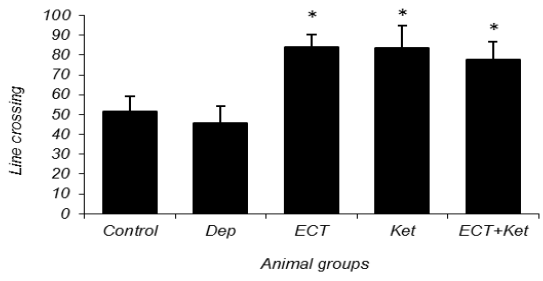

Fig. 3. Results of checking the number of lines crossing in open Field test after treatment. The columns represent Mean ± SEM and indicate the number of crossing peripheral lines (n = 10). * P <0.05 compared to control group

Number of central box entrance

Another parameter examined in the open-field test was the number of rats entering each center square. The results of this test are illustrated in Figure 4. It was shown that the rate of entry into the center square in the open-field compartment increased in the rats treated with ketamine and ECT compared to the ketamine and ECT groups, but this increase is not significant at P <0.05 level.

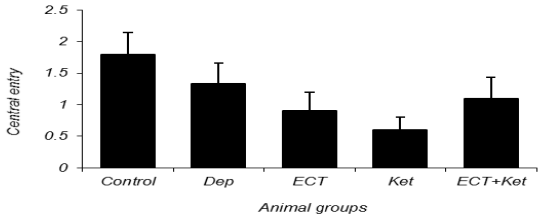

Fig. 4. Results of checking the number of center square entry in open field test after treatment. . The columns represent Mean ± SEM and indicate the number of centripetal entrances (n = 10)

4. Discussion

Depression is one of the most common mental health disorders and one of the most important causes of disability worldwide. Antidepressant treatment has been available for decades, but the study of anxiety and depression has also devoted much of its research to mental health. Despite various investigations into the effects of ECT on major depressive disorder, no research has been conducted or at least reported, the effect of subconscious ketamine doses on ECT efficacy in the prefrontal cortex. Therefore, in the current research plan, we attempted to examine these potential effects for the first time and report the achievements, being a good guide for future research on this pathway and treating depression more effectively. One of the aims of this study was to evaluate the effect of subconscious anesthetic doses of ketamine on the efficacy of ECT in the treatment of depression. In various studies, rats treated with CUMS have shown some degrees of depression and anxiety in various behavioral tests, including forced swimming and sucrose preference (15). In the present study, as observed in numerous other studies, after the CUMS model, animals in the forced swimming behavioral tests, sucrose preference, open field and maze plus

elevated depression. One of the aims of this study was to evaluate the effect of electroconvulsive therapy on the prefrontal cortex in depressed rats. Reduced immobility time in forced swim test, increased sucrose intake in sucrose preference test, increased number of peripheral crossings in open field compartment in ECT-treated group compared with depressed group, indicating improved behavioral performance in depressed animals after get an ECT. It is possible that electrical stimulation of the brain from the skull through electrical current leads to the alteration of the activity and resting potential of the neuronal cell membrane, which in turn reduces the resting potential of the neuronal cell membrane and thus increases Depolarization. This stimulation enhances facilitation and increases the stimulation of the stimulated cortex. So it can improve moods. Concerning the effect of ketamine on behavioral characteristics in animal studies, it can be concluded that in a study in rats receiving ketamine, immobility time in the forced swim test. It had decreased significantly higher than in the control group (16). The effect of ketamine on open-field test behaviors has also been reported to be increasing (17). In the present study, all three treatments (ketamine injection, ECT treatment, and ketamine and ECT combination group) had positive effects on open-field behavior, forced swimming, and sucrose.

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