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Ameliorative activity of co-administration of ketamine and ECT on depression like behaviors in depressed rats

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ABSTRACT

Background and Objective: Electroconvulsive therapy (ECT) is the end choice treatment for patients with major depressive disorder (MDD). Regarding researches that show NMDA receptor inactivation could yield the same results as anti-depressant drugs, however, the present study examined co-administration of ECT and ketamine (as NMDA antagonist) on depressed rat behaviors.

Materials and Methods: Fifty healthy adult male Wistar rats were divided into control (normal, no treatment) and CUMS induced depressed rats. The depressed animals were subdivided into 1- ECT, 2-ketamine, and 3- ECT + ketamine and 4- no treatment. We used sucrose preference, forced swimming, open field and elevated plus maze tests for evaluation of depression-related behavioral function.

Results: Data analysis in CUMS depressed rats that treated with ketamine + ECT showed higher sucrose consumption in sucrose preference test, more immobility in forced swimming, and the vast activity in open field and plus maze tests.

Conclusion: The behavioral analysis tests show that combination therapy with ketamine and electroconvulsive could markedly reduce depression and anxiolytic behaviors than ketamine or ECT treatment alone.

1. Introduction

Major depression is commonly a chronic, recurring and debilitating disorder, which brings about much impairment to the functioning and quality of life of patients (1,2). The high rates of major depression, affecting an estimated 350 million people worldwide (3), and the only moderate success rates of available antidepressant treatments underscore the importance of unraveling the biological bases of therapeutic response (4). Despite insufficiency of drug medicine therapy for depressed patients, approximately one third of them are resisted to such treatment. However, for these one the end option treatment is electroconvulsive therapy (ECT). It was shown that ECT is a highly effective and rapidly acting treatment for severe depression ill (5). ECT is also recommended for mania and Parkinson disease (6). However, similar to drug-medicine, the success of ECT therapy is variable and the mechanisms underlying the symptoms improvement remain unclear (3).

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ECT therapy is a procedure which consists of confined electrical current application throughout the brain for therapeutic purposes. Nevertheless, besides someone depressed resist to ECT treatment (7, 8), in ECT treated ones, a series of undesirable symptoms may be left. Moreover, recent reports have focused on the rapid antidepressant effects that are observed in treatment resistant patients produced by the NMDA receptor antagonist (9). Yet, the antidepressant mechanism(s) activity of NMDA receptors is not fully understood, but it has shown that the drugs like ketamine could yield an effective anti-depressant effect (10). In addition, regarding the complexity and heterogeneity of response to ECT therapy and with respect to the studies that show NMDA receptor inactivation could yield the same results as anti-depressant drugs, however, the present study examined the effect of co-administration of ECT and ketamine (as NMDA antagonist) on depressed rat behaviors.

2. Materials and Methods

2.1. Experimental groups and treatments

Fifty healthy adult male Wistar rats, weighing 250-300 g, were maintained in a standard environment for one week acclimatization period before experiments. All the experimental procedures were approved by the Ethical Committee of Shahed University and carried out in accordance to National Institutes of Health Guidelines for the Care and Use of Laboratory Animals.

Rats were randomly divided into five groups: one control group of healthy rats without any treatment (group C) and four groups induced by CUMS to reproduce the rodent model of depression (groups D, E, K, and B). The rats in groups D, E, K, and B were subjected to the CUMS procedure for 28 days. On the day following completion of the CUMS procedure (i.e, day 29 after the start of the experiment), the baseline measurements of behavioral tests were conducted in all the rats: sucrose preference test (SPT), open field test (OFT), force swimming test (FST), and elevated plus maze test (EPMT). From day 18, rats in groups K and B received sub-anesthetic doses of ketamine (10 mg/kg, i.p.) daily until the end of treatment by ECT (day 38). It must be mentioned that from days 32 to 38, rats in group E and B received ECT and subsequently, the behavioral tests were repeated on all animals.

2.2. CUMS procedure

The CUMS (chronic unpredictable mild stress procedure) 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 (11).

2.3. Electroconvulsive therapy

After making depression and pretreatment with ketamine (in group B) according to the group assignments, ECT was delivered via ear clip electrodes, with bidirectional square wave pulses, 60 mA in amplitude, 0.5 ms in width, 100 pulses per second, a duration of 1.1 seconds, once daily for 7 days (12).

2.4. Behavioral tests

2.4.1. Sucrose Preference test

The animals were individually housed in a cage and given two bottles of 1% w/v sucrose solution 72 h before the actual test. After 24 h, one bottle containing 1% sucrose solution was replaced with a bottle containing tap water for next 24 hr for the animals to adapt to sucrose solution. After adaptation period, the animals were deprived of food and water for 24 hr. Sucrose preference test was conducted by placing two pre-weighted bottles to each cage, one containing tap water and the other one containing 1% w/v sucrose solution. The animals had free choice to drink from either bottle. The animals were allowed to drink for 1 hr. The weight of both bottles was recorded and

the difference in their respective initial and final weights was calculated(13). The percentage of sucrose preference was calculated based on the following formula:

$$\%\ \text{Sucrose preference} = \frac{\text{Sucrose consumption}}{\text{Sucrose + Water consumption}} \times 100$$

2.4.2. Forced swimming test

Briefly, rats were forced to swim in a cylinder (diameter 25 cm, height 60 cm) containing fresh water maintained at 25°C ± 1°C. At this height of water, rats were not able to support themselves by touching the bottom or the side walls of the cylinder with their paws or tail. Water in the cylinder was changed after each animal to prevent the behavioral alteration among animals due to used water. Each animal showed vigorous movement during initial 5 min period of the test. The duration of immobility was manually recorded. Rats were considered to be immobile when they floated in an upright position, making only small movements to keep their head above the water. Following swimming session, animal were dried using room heater or towel and returned to their home cages. A decrease in the duration of immobility is indicative of an antidepressant-like effect, whereas an increase of immobility time, when compared with the control group, is associated with depressive-like effect (14).

2.4.3. Open field test

OFT is a useful tool to assess the effect of restraint stress on motor and behavioral changes in the rat. Wooden box (60 cm × 60 cm × 30 cm) with its floor divided into 16 equal sized squares (15 cm × 15 cm) was used. Four squares were considered as the center and the 12 squares along the walls were considered the periphery. Each rat was placed in the very center of the open field and (a) number of central crossing, and (b) line crossing were observed during a 5 min exposure period for all groups(15).

2.4.4. Elevated Plus Maze test

The adult elevated plus-maze (EPM) consisted of two open arms, 48.3×12.7 cm, and two closed arms, 48.26×12.7×29.2 cm. After testing each animal, the apparatus was cleaned with alcohol and dried before the next animal was placed on the apparatus. At the start of the EPM session, each subject was placed on the center platform facing a closed arm and its behavior on the maze videotaped for 5 min. Measures assessed included time spent on the open (OAT) arms and number of entries into the open (OAE), and also number of entries into the both open and closed arms (mobility). An arm entry was defined by all four paws being placed in the arm, whereas an exit was considered to have taken place when at least the two front paws were placed outside of the arm. Percentage of time spent on the open arms and percentage of open arm entries have repeatedly been shown to be reliable measures of anxiety on the EPM. Additionally, closed and open arms entries are generally considered as indices of activity (16-18).

2.5. 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

Table 1 shows the mean and standard deviation of the results of behavioral function in control and depressed groups animals (contain D, E, K and B groups) after 4 weeks of CUMS procedure. As shown (Fig.1), there is a significant difference in both groups in terms of the percentage of sucrose preference ($p<0.05$).

Table 1. Behavioral test results after CUMS

Test		Control group	Depressed group
SPT		82.41±1.4	57.03±3.4*
FST		6.21±2.40	8.26±1.41
OFT	Central entry	0.5±0.19	0.2±0.14
	Line crossing	51.3±7.5	34.5±4.0 *
EPMT	OAT	16.82±4.8	14.93±3.5
	OAE	29.03±6.9	32.22±3.6
	Mobility	7.02±1.06	4.55±0.67*

* $p<0.05$ relative to control group

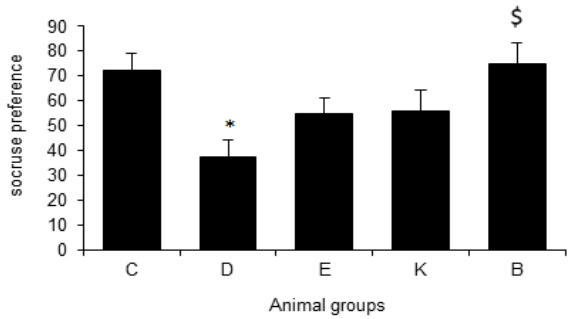

Fig 1. Behavioral alternation in different groups in sucrose preference test. (C: control, D: Depressed, E: ECT, K: ketamine, B: Ketamine+ECT). * p<0.05, (as compared to control). $ p<0.05, (as compared to depressed group)

In forced swimming test (Table 1, Fig. 2), a marked significant increment of immobility time were indicated in depressed animals. In all of the treated animals, immobility reduced the same significantly.

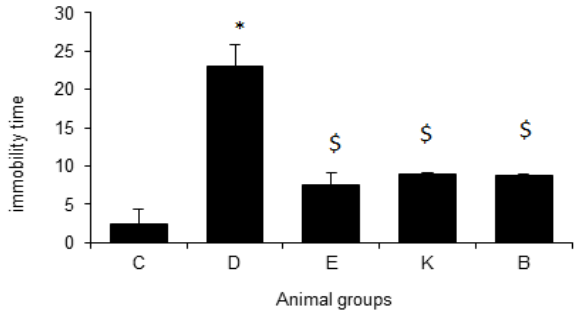

Fig 2. Behavioral alternation in different groups in Forced swimming test. (C: control, D: Depressed, E: ECT, K: ketamine, B: Ketamine+ECT). * p<0.05, (as compared to control). $ p<0.05, (as compared to depressed group).

In figure 3, there was more and marked line crossing in treatment groups in open filed test as compared with depressed animals (p <0.05).

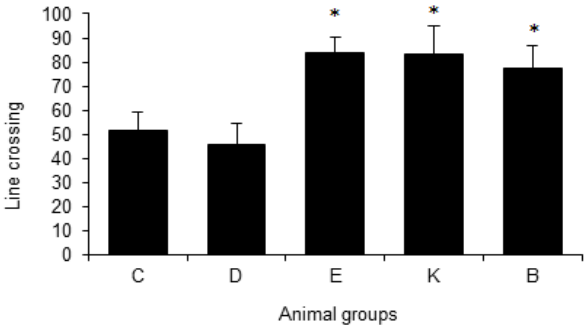

Fig 3. Alternation in different groups in line crossing of open field test. (C: control, D: Depressed, E: ECT, K: ketamine, B: Ketamine+ECT). $ p<0.05, (as compared to depressed group).

In EPM test, three parameters (Fig. 4), %OAE and %OAT and mobility were measured. As shown, nearly none of the parameters were affected by treatments.

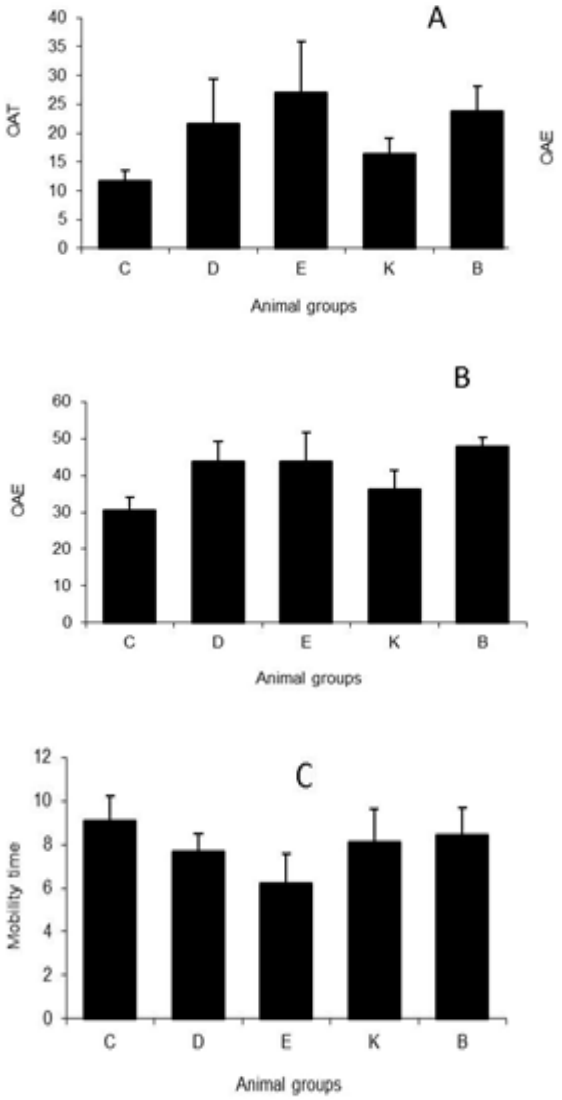

Fig 4. Alternation in different groups in activities of elevated plus maze test. (C: control, D: Depressed, E: ECT, K: ketamine, B: Ketamine+ECT).

4. Discussion

In this study, like other researchers, we showed the anxiety and depression-like behaviors in depression rats which were depressed by CUMS method. Mentioned results indicated that CUMS is an efficient model for induction of depression (19-21). The results of SPT showed that co-administration of ketamine and ECT in depressed rats could markedly increase the interest of the animals to sweet water and so this kind of

treatment might alleviate anhedonia as the core symptom of depression (22). Also, spontaneous exploratory behaviors of the rats in aversive environments that reduced prominently in depression ones (20, 23), were improved in the rats which treated by ketamine+ECT. However, data obtained from OFT parameters which index the activity, excitation and exploratory abilities in unskilled environment, has been mentioned previously. In consistent with our reports on FST and OPT, we can point to the previous studies of electroconvulsive therapy which improved the behavioral characteristics of rats i.e, anxiety and depression-like behaviors in FST and OPT tests (12). The FST is used to monitor depressive-like behavior and is based on the assumption that immobility reflects a measure of behavioral despair the main advantages of this procedure lie in its relatively easy operation and fast results (24). In the complementary experiment which were done by EPM, we showed that the animals which treated by ketamine and ECT application have lower fear with respect to other group tests, because their number and duration entrance to open arms were markedly increased. Though, precise mechanisms for ECT is not found, but likely the trans-cranial direct current stimulation induces a relatively weak constant current which increases spontaneous neuronal activity within the cortex (25).

Furthermore, regarding anti-depression activity of calcium current through the glutamate reports, it was unexpectedly shown that ketamine as an glutamate receptor antagonist by a burst increase in BDNF release and activation of downstream signaling pathways can stimulate the new synapses formation (26). However, the marked anti-depression activity of co-ketamine and ECT which was obtained from our results, support the idea that ECT and ketamine in combination could effectively decrease depressive behaviors in rats. Perhaps, combination effect of ketamine and ECT potentiate activity of each kind of treatment on the other one and or other mechanism (s) are involved which must be studied in future researches.

In summary, behavioral analysis tests showed that combination therapy with ketamine and electroconvulsive could markedly reduce depression and anxiolytic behaviors than ketamine or ECT treatment alone.

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