

The effects of edaravone in ketamine-induced model of mania in rats

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Bipolar disorder is a chronic disease characterized by recurring episodes of mania and depression that can lead to disability. This study investigates the protective effects of edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one), a drug with well-known antioxidant properties, in a model of mania induced by ketamine in rats. Locomotor activity was assessed in the open-field test. Superoxide dismutase (SOD), catalase (CAT) and thiobarbituric acid reactive substances (TBARS) levels were measured in order to evaluate oxidative damage in the rat hippocampus and prefrontal cortex. Increased locomotor activity (hyperlocomotion) was observed at the open-field test with ketamine treatment (25 mg/kg, i.p., 8 days). Edaravone (18 mg/kg) treatment did not prevent hyperlocomotion in the mania model induced with ketamine in rats, but lithium chloride (47.5 mg/kg, i.p., positive control) did prevent hyperlocomotion. Edaravone and lithium chloride treatments were found to reduce the increase in SOD and CAT activity following ketamine administration in a non-significant manner but caused no change in TBARS levels.

Key words: edaravone, bipolar disorder, mania, ketamine, antioxidant, neuroprotective

INTRODUCTION

Bipolar disorder (BD) is a widespread, chronic psychiatric disease that leads to disability and that affects 1–4% of the general population worldwide (Souza et al. 2014). Although the clinical course of BD proceeds with recurring episodes of mania and depression and mixed episodes, the most significant feature of the disease is the acute manic period characterized by euphoria-related rushes of energy, irritable mood, increased psychomotor activation, reduced need for sleep, impulsivity and psychotic symptoms (Andreazza et al. 2008, Brüning et al. 2012, Gazal et al. 2014).

The pathophysiology of BD is difficult to understand due to the complex structure of the condition. There have been increasing evidence in recent years that oxidative stress plays a role in the etiology and progression of neuropsychiatric disorders such as BD (Ozcan et al. 2004, Machado-Vieira et al. 2007, Selek et al. 2008, Brüning et al. 2012, Souza et al. 2014). In the event of increased free oxygen radicals and insufficient antioxidant capacity, oxidative stress contributes to the development of neurodegeneration as a cause of protein, DNA and RNA oxidation and lipid peroxidation in various

cellular layers (Gandhi and Abramov 2012). Clinical studies have shown alterations in major antioxidant enzymes and increased lipid peroxidation in patients with BD (Kuloglu et al. 2002, Ozcan et al. 2004, Machado-Vieira et al. 2007).

Although there have been several studies of drugs with known antimanic effects and the identification of additional treatments in BD, some patients still do not respond well to existing therapies (Brüning et al. 2012). Lithium, the most widely used therapy in BD, fails to provide satisfactory results in approximately 40% of patients due to insufficient response, contraindications and side-effects. Research into different drugs tested on animal models is therefore needed in the treatment of mania (Price and Heninger 1994).

Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one) is a potent free radical scavenger that exhibits antioxidant effects by inhibiting hydroxyl radical-dependent and radical-independent lipid peroxidation (Otomo et al. 2003, Zhou et al. 2013). Edaravone has been shown to have beneficial effects on oxidative stress markers including glutathione, superoxide dismutase, malondialdehyde and glutathione peroxidase (Alhaider 2013). It has been shown to exhibit neuroprotective effects against oxidative stress in patients

with cerebral infarction and acute ischemic stroke (Yoshida et al. 2006). *In vivo* and *in vitro* studies have found that edaravone has a neuroprotective effect in animal models of amyotrophic lateral sclerosis and Parkinson's disease (Kikuchi et al. 2012). We hypothesized that edaravone, a substance with known neuroprotective effects, might have protective effects in mania in an animal model of BD.

This study investigated the behavioral and neurochemical changes caused by edaravone administration in a mania model induced with ketamine in rats.

METHODS

Animals

Forty-eight female Sprague Dawley rats (10–11 weeks old; weighing 180–220 gr) were used. Rats were obtained from the Karadeniz Technical University Experimental Animals Unit. Animals were housed in a quiet room with a relative humidity of 50±10%, and a temperature of 22±1°C in a 12-hour light-dark cycle with free access to food and water. The estrous cycle was evaluated by vaginal smear method (Marcondes et al. 2002). Vaginal secretion was taken with a plastic pipette with 10 µL of normal saline inserted into the rat vagina, but not deeply. The vaginal fluids were dropped on glass slides and examined under light microscope with 10 and 40× objective lenses. Three types of cells were observed: epithelial cells, cornified cells and leukocytes. The proportion among them was used for the determination of estrous cycle phases. The study protocol was approved by Karadeniz Technical University Animal Research Local Ethics Committee (Protocol No: 2014/13).

Drugs and experimental design

The ketamine, edaravone and lithium chloride used in the study were obtained from Sigma Chemical

Company, USA. Lithium chloride was dissolved in saline solution (0.9% NaCl) and administered twice a day by the intraperitoneal route (i.p.). Edaravone was dissolved in 1N NaOH, diluted with distilled water, and pH-adjusted to 7.4 with 1 N HCL according to the manufacturer's instructions. Edaravone was administered twice a day i.p. The doses of lithium, ketamine and edaravone employed were selected on the basis of the literature (Ghedim et al. 2012, Zhou et al. 2013).

The study groups were designed as follow. Rats were administered saline solution, lithium chloride 47.5 mg/kg and edaravone 18 mg/kg twice a day i.p. Saline or ketamine (25 mg/kg) were administered once a day i.p. from the 8th day to the 14th day. Locomotor activities were evaluated using the open-field test 30 min after a single injection of saline or ketamine on the 15th day (Fig. 1).

Open-field test

The open field procedure is a test used for assessment of general activity level, locomotor activity, and exploratory behavior. The test apparatus is a rectangular structure with a size of 100×100×30 cm³ (width×length×height). This apparatus is made of a white wooden hypethral material evenly divided into 16 squares. Rats were placed to a predetermined corner of the apparatus and observed for 5 min. The whole experiment was recorded digitally with the help of a camera placed above the test apparatus and the recorded images were used for scoring. Within 5 minutes interval, the total number of squares crossed with all paws was counted and the total distance travelled was measured to evaluate their exploratory behavior. The time spent in the center of the open field was also measured. In addition, the number of central crossings was counted to assess the anxiety level of the animals. The apparatus was cleaned up with a 10% alcohol solution and dried after each individual mouse session.

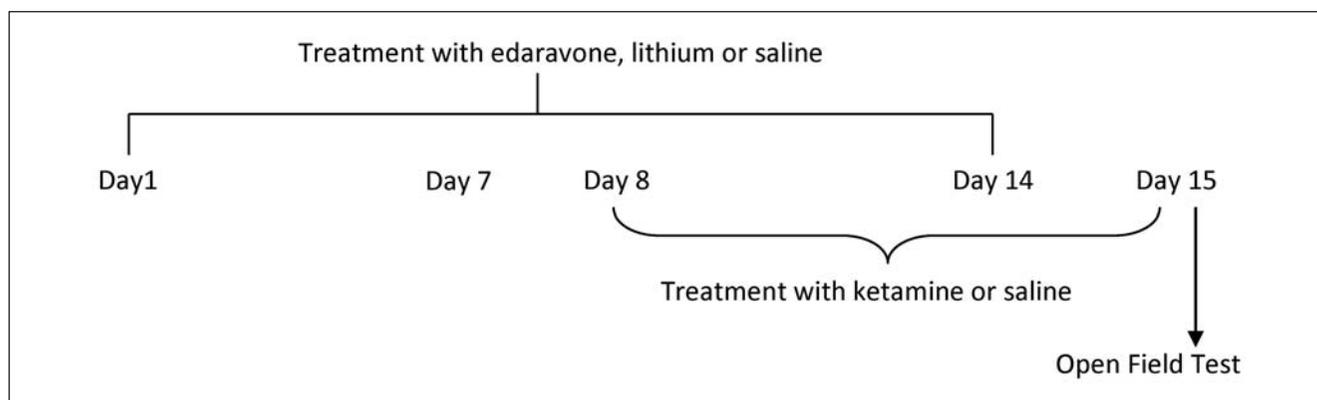


Fig. 1. Schematic representation of the experimental design.

Biochemical assay

Homogenization stage

Rats were sacrificed by decapitation. Hippocampus (HP) and cortex tissues extracted after decapitation were homogenized in 50 mM 1.5 mL Tris-HCl (0.5 mL/L Triton X-100) cold buffer solution with a pH of 7.4. Homogenates were centrifuged at 3000 rpm at +4°C; 0.5 ml homogenate was then mixed with 0.25 mL ethanol-chloroform (in a ratio of 2:3) and centrifuged at +4°C at 14,000 g for 60 min. SOD measurement was performed in the supernatant obtained. CAT and MDA measurement and protein screening were performed in supernatant not precipitated with ethanol-chloroform.

Tissue malondialdehyde level measurement

MDA measurement was performed following the method described by Mihara and Uchiyama (Mihara and Uchiyama 1978). This method involves measurement of the color formed by MDA with thiobarbituric acid (TBARS) in an acidic environment at an absorbance of 532 nm.

Superoxide dismutase activity assay

Superoxide dismutase activity was measured following the method described by Sun and Oberley (Sun et al. 1988). This is based on spectrophotometric measurement of the absorbance of the color resulting from the reduction of nitroblue tetrazolium by superoxide radicals produced by the xanthine-xanthine oxidase system at 560. Percentage inhibition of the reaction catalyzed by SOD was calculated based on the decrease occurring in optical density as a result of removal of superoxide radicals in the SOD environment. The amount of SOD responding to 50% inhibition was regarded as one unit.

Catalase assay

Catalase activity was measured using the spectrophotometric Goth (Goth et al. 1991) method. Measurement is based on measuring the absorbance of the stable yellow complex formed by hydrogen peroxide and ammonium molybdate at 405 nm.

Statistical analysis

The recorded behavioral patterns of the animals were viewed offline and scored after the experiment. The distance travelled within 5 minutes was measured

by Tracker 4.92 software program. The normality of the data was tested with Shapiro-Wilk test. The non-normally distributed data were analyzed using Kruskal-Wallis test followed by Mann-Whitney U test. Biochemical data were analyzed by one-way analysis of variance (ANOVA) followed by Bonferroni or Tamhane *post hoc* tests when appropriate. The study data were expressed as mean \pm standard error. Statistical significance was accepted when $p < 0.05$. A power analysis was performed using G.POWER 3.0.10 software program. When the effect size is 0.6, α -error is 0.05, total sample size is 48 and number of groups is 6, the power was evaluated as 87% for one-way ANOVA test.

RESULTS

Locomotor activity

The study was designed to evaluate the effects of edaravone on ketamine induced mania in rats. The chronological order of injections and tests is shown in a flow diagram (Fig. 1). As presented in Figs 2A and 2C, the experimental mania model was successfully established with ketamine treatment which induced hyperlocomotion in rats evidenced by the significant increase in the number of crossings and total distance travelled in the open-field test ($p < 0.05$). Edaravone pretreatment (18 mg/kg) did not prevent the hyperlocomotion induced by ketamine in the open-field test. Lithium chloride pretreatment (47.5 mg/kg) significantly reduced the number of crossings and total distance travelled in the open-field test ($p < 0.05$). The anxiety behaviour measured as the percentage of central crossings did not significantly change in ketamine, edaravone and lithium treatment groups in comparison to control group (Fig. 2B). There was no statistically significant difference between groups according to the duration of central crossings (Fig. 2D).

Measurement of oxidative stress parameters in the prefrontal cortex

The oxidative stress parameters in the prefrontal cortex (PFC) of rats were measured to evaluate the neuroprotective effects of edaravone in a ketamine-induced mania model (Table 1). Ketamine therapy did not result in a significant change in TBARS in the PFC compared to the control group ($p > 0.05$). Edaravone therapy did not significantly alter TBARS levels in the PFC in a ketamine-induced mania model (edaravone pretreatment $p > 0.05$).

The effect of edaravone therapy on the activities of the antioxidant enzymes of SOD and CAT in the PFC was

investigated. Although ketamine increased SOD and CAT enzyme activities in the PFC, this increase was not statistically significant ($p>0.05$). Although edaravone reduced the increased activities of CAT and SOD, the difference did not reach to a statistically significant level (edaravone pretreatment $p>0.05$).

The effect of lithium chloride, used as a positive control, on oxidative stress parameters in the PFC was also investigated. The application of lithium in a ketamine-induced manic model reduced the increase in CAT and SOD activities in a non-significant manner but caused no change in TBARS levels ($p>0.05$).

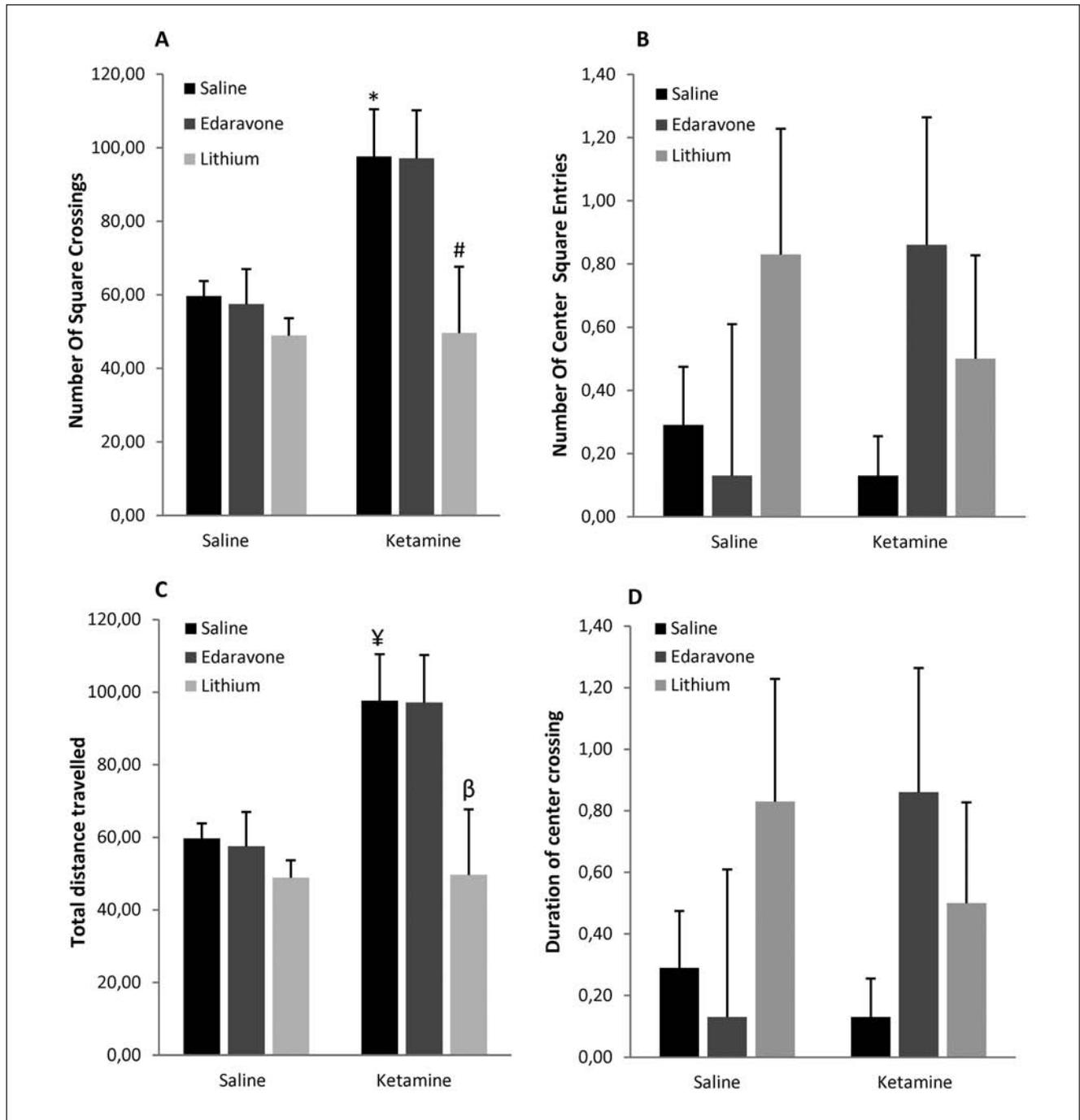


Fig. 2. The effect of lithium chloride (47.5 mg/kg i.p) on ketamine-induced hyperlocomotion represented by (A) number of square crossings; (B) number of center square entries; (C) total distance travelled; (D) duration of center crossing. * denotes $p<0.05$ as compared to saline/saline group. # denotes $p<0.05$ as compared to saline/ketamine group. ¥ denotes $p<0.05$ as compared to saline/saline group. β denotes $p<0.05$ as compared to saline/ketamine group.

Table I. Effect of pretreatment with edaravone or LiCl on oxidative stress parameters in the prefrontal cortex and hippocampus of rats

Groups	TBARS (nmol/mg protein)	SOD (units/mg protein)	CAT (units/mg protein)
prefrontal cortex			
saline/saline	3059.14±51.67	0.56±0.08	1.17±0.13
ketamin/saline	3180.98±208.28	0.57±0.05	1.40±0.21
edaravone/saline	2894.47±117.30	0.37±0.03	1.20±0.14
edaravone/ketamine	3015.94±192.80	0.38±0.08	0.94±0.13
lithium/saline	3474.60±204.92	0.34±0.02	1.11±0.09
lithium/ketamine	3202.24±223.65	0.46±0.10	0.92±0.08
hippocampus			
saline/saline	2718.21±226.54	0.55±0.08	0.56±0.09
ketamin/saline	2743.1±200.11	1.9±0.74	0.77±0.25
edaravone/saline	2880.81±281.57	1.79±0.19	0.65±0.07
edaravone/ketamine	3050.03±236.50	1.67±0.17	0.47±0.09
lithium/saline	3027.24±148.33	1.53±0.62	0.53±0.10
lithium/ketamine	2982.40±134.44	1.06±0.16	0.55±0.05

TBARS: thiobarbituric acid reactive species formation; CAT: catalase; SOD: superoxide dismutase. Data was expressed as mean ±S.E.M (n=6–8 animal per group).

Measurement of oxidative stress parameters in the hippocampus

The effect of edaravone therapy on oxidative stress parameters in the HP was investigated (Table I). Ketamine therapy caused no change in TBARS activity ($p>0.05$). Edaravone pretreatment did not alter TBARS activity in the HP in a ketamine-induced manic model ($p>0.05$). Although ketamine caused an increase in CAT and SOD enzyme levels, the rise was not statistically significant ($p>0.05$). Edaravone pretreatment did not cause a significant change in CAT and SOD levels when compared to saline-ketamine group. The effect of lithium chloride pretreatment on oxidative stress parameters was assessed in the HP. Lithium chloride pretreatment caused no significant change in TBARS levels.

DISCUSSION

Our study shows that the administration of edaravone in a ketamine-induced mania model in rats does not prevent an increase in locomotor activity, while the application of lithium in the positive control group prevents such an increase.

Animal models are used to research pharmacological and intracellular mechanisms in psychiatric disorders. It is difficult to establish an experimental animal model reflecting the complex clinical characteristics of BD (Gazal et al. 2014). The principal behavioral model that can be

assessed in the manic period of BD in experimental studies is hyperlocomotion. Ghedim and others (2012) showed that hyperlocomotion can be induced with ketamine at subanesthetic doses. Ketamine at these doses has also been reported to alter oxidative stress parameters in the rat brain (Ghedim et al. 2012). Preclinical studies have reported that ketamine has an antidepressant effect at low doses (5–10 mg/kg). Ketamine at subanesthetic doses (10–50 mg/kg) has been shown to lead to hyperlocomotion and cellular dysfunction and higher doses have been shown to have an anesthetic and dissociative effect (Kato et al. 2007). An experimental mania model can also be induced with substances other than ketamine. Some studies have shown that d-amphetamine and ouabain induce a hyperlocomotion model specific to mania (Gould et al. 2001, Wang et al. 2013).

In our study ketamine administered i.p. for 1 week at a dose of 25 mg/kg statistically significantly increased the total number of squares crossed and the total distance travelled in the open-field test. This finding shows that an experimental model of hyperlocomotion, a behavioral template and marker of the manic period of BD, can be induced with ketamine. In addition, the significant decrease in hyperlocomotion observed with lithium chloride in the positive control group strengthens the validity of this model. Edaravone, a potent antioxidant drug, was expected to be able to reduce hyperlocomotion in the ketamine-induced mania model in the present study. However, in contrast to similar studies with antioxidants

such as curcumin and melatonin (Gazal et al. 2014, Sauza et al. 2014), no significant decrease in hyperlocomotion was observed with edaravone.

Oxidative stress has been shown to play a significant role in the pathophysiology of several neuropsychiatric diseases, including BD (Amanda et al. 2010). The lower antioxidant capacity, high levels of free iron and polyunsaturated fatty acid content and higher oxygen consumption of brain render it more susceptible to oxidative damage when compared to other tissues (Ter-Minassian 2006, Berk et al. 2011). Increasing oxygen radicals in tissues can lead to neurodegeneration in psychiatric diseases by compromising cell membrane transport, signal transmission mechanisms and mitochondrial energy production and neuroplasticity by leading to lipid peroxidation and protein and nucleic acid injury (Mahadik et al. 2001). Experimental studies have shown that antioxidant substances have beneficial effects on mania by reducing oxidative stress in the PFC and HP (Brüning et al. 2012, Gazal et al. 2014, Souza et al. 2014). This study also investigated the effects of the antioxidant edaravone on antioxidant mechanisms in the rat PFC and HP.

Edaravone is a potent antioxidant molecule, with neuroprotective effects in experimental models of Parkinson's disease and dementia and it has been shown to have beneficial effects against oxidative stress in experimental models of cerebral ischemia and in clinical practice. In the light of these evidence, it is anticipated that edaravone might be effective in the treatment of BD, the etiology in which oxidative stress has been implicated.

SOD is an enzyme group that reduces superoxide anion (O_2^-) to hydrogen peroxide (H_2O_2) which is later converted into H_2O and O_2 by the enzyme catalase. In our study, levels of SOD and CAT in the rat PFC increased with ketamine administration, while the activities of these enzymes decreased with edaravone administration, albeit not statistically significantly so. The application of lithium chloride, used as the positive control, significantly reduced hyperlocomotion. The SOD and CAT activities in PFC and HP were lower in Lithium chloride-ketamine group when compared to those of vehicle-ketamine group but the difference was not statistically significant.

In addition, no variation was observed in this study in TBARS levels in the PFC and HP regions with ketamine, edaravone and lithium chloride administration. In agreement with our results, SOD and CAT activities in the PFC and HP in a ketamine-induced experimental schizophrenia model have been shown to rise with ketamine administration, but the activities of these enzymes decreased with the addition of the antioxidant omega-3 (Zugno et al. 2013). Another study reported that SOD and CAT activities in the PFC and HP in a mania model increased with ouabain and that enzyme activities decreased with antioxidant substance administration (Brüning et al. 2012). Inconsistent results have been reported concerning the effects of antioxidant

substances on antioxidant enzymes in experimental mania models. For example, some studies have reported a rise in TBARS levels, and a rise in antioxidant enzyme activities and superoxide formation with oxidative stress in the brain (Riegel et al. 2009, Brocardo et al. 2010, Jornada et al. 2011, Brüning et al. 2012).

In this study, edaravone used as an antioxidant agent exhibited a similar effect to lithium chloride used as the positive control, leading to lower levels of SOD and CAT enzyme activities in PFC and HP in comparison to saline-ketamine treatment group. The result that the lower levels did not reach to a statistical significance may be due to sample group constitution. The optimal edaravone dose in this study was determined referring to previous studies in order to prevent side-effects. However, studies involving higher doses of edaravone might reveal a more marked effect on antioxidant enzymes.

Various biochemical pathways with effects on oxidative stress in different psychiatric disorders are not yet fully understood. Clinical and experimental studies of oxidative stress in BD have reported controversial results. Further studies with larger sample size are required in order to better elucidate the probable protective effects of edaravone in BD.

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