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Research Paper

IN VIVO ANTIMANIC ACTIVITY OF LITHIUM AND CARBAMAZEPINE IN KETAMINE INDUCED MANIA IN WISTAR ALBINO RATS

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Bipolar Disorder (BD) is an affective disorder that causes unusual shifts in a person's mood energy and ability to function. It is characterized by manic or depressive episodes such as euphoria irritability, aggressiveness or hyperactivity. The present study investigate effect of the mood stabilizers lithium and carbamazepine (CBZ) in ketamine induced hyperactivity as novel animal model of mania. In the reversal treatment, rats were treated with ketamine (25 mg/kg i.p) and saline for 14 days. Between the 8th and 14th day, animals from control and ketamine only group were treated with lithium carbonate (47.5 mg/kg; i.p, twice a day) and carbamazepine (25 mg/kg; i.p, twice a day). In reversal treatment, lithium ($p < 0.01$) and CBZ ($p < 0.001$) significantly decreases the ketamine induced hyperactivity when tested using actophotometer. In dominance test, lithium and CBZ treated animals were found to be less dominated (33%) and (50%) when compared to ketamine treated animals (100%). Lithium and CBZ significantly reverses the ketamine induced TBARS formation ($p < 0.001$), but no significant rise in catalase activity was observed in lithium and CBZ groups. The lithium and CBZ showed significant reduction in the serum FSH level ($p < 0.05$) but no significant change in the level of serum prolactin, cortisol and LH concentration was observed. CBZ significantly reduces serum cortisol level ($p < 0.05$) as compare to control group. The studies confirm the antimanic activity of lithium and carbamazepine against ketamine induced mania.

Keywords: Mania, Carbamazepine, Ketamine, Lithium

INTRODUCTION

Bipolar Disorder (BD) is an affective disorder which also known as manic depressive illness, is a brain disorder that causes unusual shifts in a person's mood, energy, and ability to function. The main diagnosing criteria is the presence of manic symptoms (American Psychiatric

Association, 1994; Belmaker, 2004, Correa *et al.*, 2007), thus an adequate animal model of BD should have some similar characteristic of the manic episodes such as euphoria, irritability, aggressiveness, hyperactivity, insomnia or increased sexual drive. The prevalence rate of BD is about 1-3% of the worldwide population and

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is associated with higher rates of suicide and general medical illnesses (Bruning *et al.*, 2012). The BD mainly occurs in youngs but sometimes it may get developed in childhood in old age person (Judd *et al.*, 2002).

The pathophysiology of BD is poorly understood. The glutamate receptor theory indicates the involvement of glutamate receptors in pathophysiology of mood disorders. Results of some studies shows that, there are changes in glutamate receptor activity (Maeng and Zarate, 2007) and reduced expression of n-methyl D-aspartate (NMDA) receptor in brain region such as hippocampus (Mccullumsmith., 2007). The administration of ketamine recently had shown its role in framing the animal model of mania (Ghedium *et al.*, 2012). The agents that antagonized the NMDA receptor such as ketamine, phencyclidine produce acute psychotic state in normal individuals that resembles some symptoms of BD or mania (Breier *et al.*, 1997). Ketamine antagonized the glutamate inotropic receptors in brain. It induces a substantial release of presynaptic glutamate, increasing the firing rate of neurons after disinhibition of GABA ergic inputs (Moghaddam *et al.*, 1997). Ketamine produces focal increase in metabolic activity in the prefrontal cortex and an acute psychotic state. Human study had also supported the induction of the altered cerebral metabolic activity and acute psychotic state upon administration of subanesthetic doses of ketamine (Breier *et al.*, 1997).

The Electroconvulsive Therapy (ECT) was only available effective treatment of mania until the discovery of lithium. The application of every ECT increases the seizure threshold. The manic patients show similar symptoms. These observations may supply a clinical rationale for using anticonvulsant in the acute treatment of mania or bipolar disorders (Grunze *et al.*, 2010).

The anticonvulsant drugs which are used for treatment of bipolar disorder include carbamazepine, sodium valproate, etc. The carbamazepine is used as alternative to lithium carbonate for treatment of mania (Tripathi, 2010). The main mode of action of carbamazepine is, to inhibit the voltage gated sodium, potassium and calcium channel, or it antagonized GABA, serotonin and glutamate receptor (Grunze *et al.*, 2010).

The medical literature survey showed the increased level of products of lipid peroxidation and alterations of the major antioxidant enzymes in people with BD. It has been widely demonstrated that the generation of Reactive Oxygen Species (ROS) plays a critical role in the pathophysiology of several neuropsychiatric disorders. The BD is associated with mitochondrial dysfunction and abnormalities in respiratory complex activity and energy production may lead to cellular degeneration (Frey *et al.*, 2006).

It has been widely described that the dysregulation of Hypothalamic Pitutary Axis (HPA) in bipolar disorder or manic patient, which include the change in cortisol level (Valiengo *et al.*, 2012), prolactin level and affect the growth hormone secretion such as Lutenising Hormone (LH) and Folical Stimulating Hormone (FSH) (Kusalic and Frank, 1996).

The present study was carried out with the aim to investigate the antimanic activity of lithium and carbamazepine in ketamine induced mania in wistar albino rats.

MATERIALS AND METHODS

Animals

Adult wistar albino rats (200-250 g) were obtained from animal house facility of Smt. Kashibai Navale

College of Pharmacy, Kondhwa (Bk) Pune – 48. They were housed in polypropylene cages with groups of six animal per cage, free access to food and water and were maintained on a 12 h light-dark cycle, at temperature of $22\pm 1^\circ\text{C}$ and relative humidity of 55-65%. All experimental procedure were carried out in accordance with CPCSEA guidelines, with the approval of animal ethical committee. The IAEC protocol number was IAEC 10-50/2012.

Drugs

Lithium as (carbonate) (Thomus Baker), Carbamazepine (Sun Pharma) and ketamine injection (Sun Pharma)

Experimental Methods

Reversal Treatment

The reversal treatment was designed in order to reproduce the management of an acute manic episode. Wistar albino rats of either sex ($n=24$) were used for study. Animals were divided into four groups. Group I was treated with normal saline (1 ml/kg) for 14 days, Group II was treated with ketamine (25 mg/kg; i.p) for 14 days, Group III was treated with ketamine (25 mg/kg; i.p) for 14 days and lithium (47.5 mg/kg; i.p, twice a day) (Correa *et al.*, 2007, Freye *et al.*, 2006, Valvassori *et al.*, 2008) was administered from day 8 to day 14 with time interval of 30 min. Group IV was treated with ketamine (25 mg/kg; i.p) for 14 days and carbamazepine (25 mg/kg; i.p, twice a day) (Rao *et al.*, 2007; Basselin *et al.*, 2008) was administered from day 8 to day 14 with time interval of 30 min. On 15th day, locomotor activity and dominance tube test was performed. At the end of study blood samples were collected from retro-orbital plexes for serum GH, prolactin, cortisol estimations. Rats were sacrificed by decapitation and brain were isolated for quantify

the extent of lipid peroxidation (TBARS) and catalase activity.

Locomotor Activity

On 15th day, the locomotor activity was assessed by using Photo-Actometer (Inco). The individually each animals were placed in the activity cage for 5 min. Note the number of counts of all the animals (Correa *et al.*, 2007, Valvassori *et al.*, 2008).

Dominance Tube Test

The dominance tube test measure the changes in animal hierarchy formed through animal social interaction. The test was used to assess tendencies of social dominance and aggressive behavior in rodents.

The dominance tube apparatus is constructed out of plexiglass and consists of a 40 cm long tube with a diameter of 6 cm (slightly modified) that is attached on either end to a start box (measuring 20×15×12 cm) (Malatynska *et al.*, 2007). At the center the tube has a clear gate with perforations that allow for olfactory and visual investigation, but not physical contact. Animals were housed in group ($n=1$) per cage for a period of 3 days to avoid social interaction. At the beginning of experiment, animals were individually placed in the apparatus for 15 min during first two experimental days. A single housed rat and an unfamiliar group-housed rat were placed in opposite start boxes and allowed to acclimatize to the apparatus for 3 min. When the animals met in the middle of the tube after the acclimation period the center gate was lifted for 5 min. The diameter of the tube was such that the rat cannot pass one another. Typically tendency of one rat to force another rat to back out of the tube and into their start box was recorded by 5 mega pixel camera (Sony Ericsson)

mounted parallelly in front of dominance tube. The test was concluded dominance, when one rat has forced the other back (Kovacsics and Gould, 2010).

Biochemical Parameter

Measurement of Thiobarbituric Acid Reactive Substances (TBARS)

In this procedure, 2 ml of freshly prepared 10% w/v trichloroacetic acid (TCA) was added to 2 ml of the tissue homogenate (supernatant). The mixture was allowed to cool in an ice bath for 15 min and then centrifuged at 2500 rpm for 15 min. From this take 2 ml of clear supernatant and mixed with 2 ml of freshly prepared 0.67% w/v TBA. The resulting solution were heated in a boiling water bath for 10 min and then immediately cooled in an ice bath for 5 min. The color absorbance were measured at 532 nm using 1, 1, 3, 3-tetraethoxypropane as a standard (Esterbauer and Cheeseman, 1990).

Measurement of Catalase Activity (CA)

To determine CAT activity, the brain tissue was sonicated in 50 mmol/L phosphate buffer (pH 7.0), and the resulting suspension was centrifuged at 3000 g for 10 min and add 2.9 ml of 30 mM H_2O_2 in phosphate buffer pH 7.0 to supernatant. CAT activity was measured by the rate of decrease in hydrogen peroxide absorbance at 240 nm. An extinction coefficient for H_2O_2 at 240 nm of 39.4 M⁻¹ cm⁻¹ was used for the calculation. The specific activity of catalase were expressed as mMoles of H_2O_2 reduced per minute (Frey *et al.*, 2006).

Estimation of Serum Hormonal Level

On 15th day of treatment all animals was anaesthetized by using anaesthetic ether. The

blood sample was collected by retro orbital method. The collected blood sample was centrifuged at 3000 rpm for 5 min. All serum hormonal levels were estimated by Clia method (Advia Centaur).

Statistical Analysis

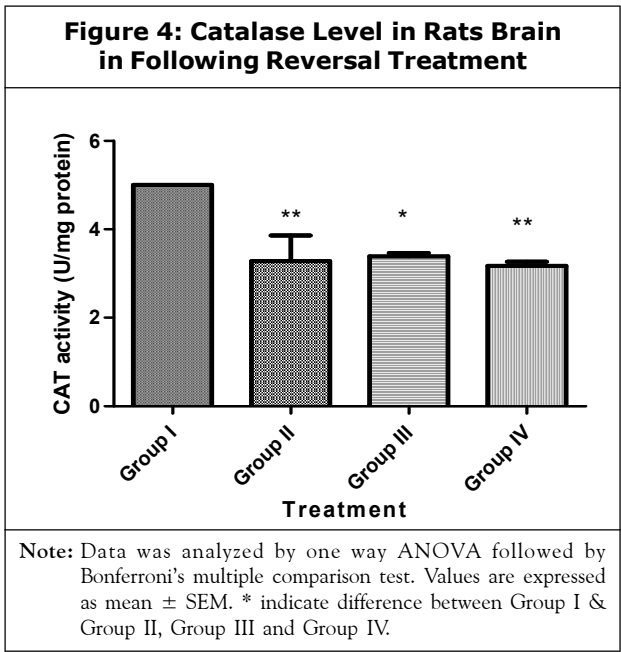
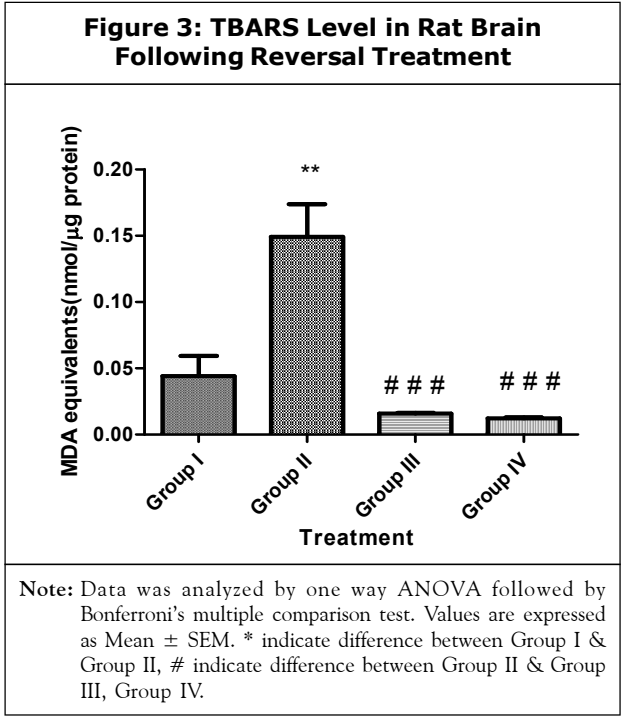
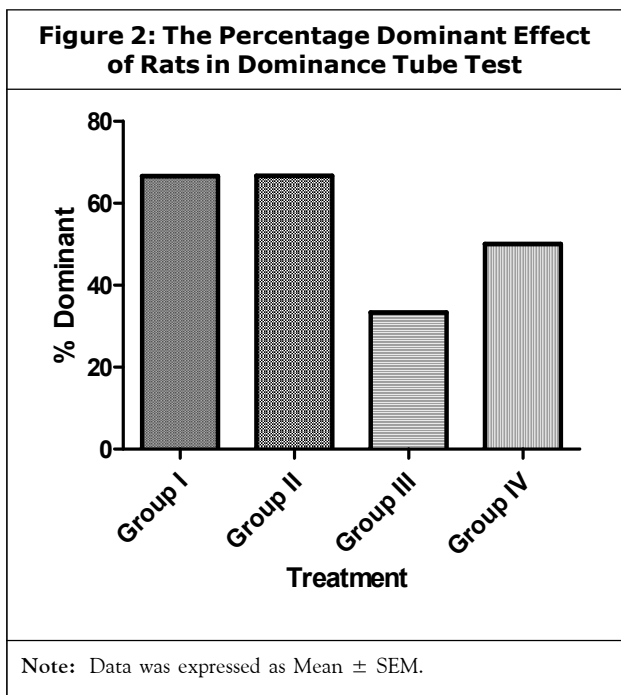
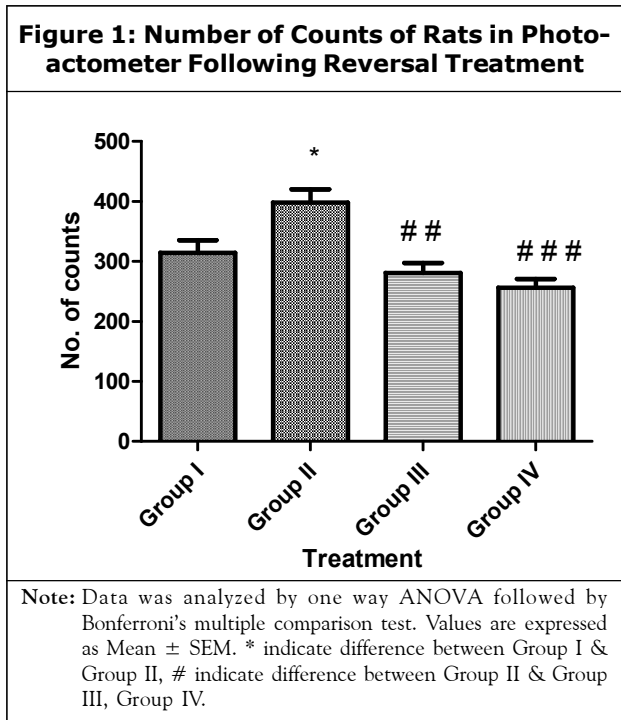
The comparison between control and treatment groups were done by one-way analysis of variance followed by Bonferroni's multiple comparison test. All results are expressed as Mean \pm SEM.

RESULTS

In reversal treatment, group II showed significant increase ($p < 0.05$) in locomotor activity after ketamine treatment as compare to control group. Hyperlocomotion was found to be reduced by lithium ($p < 0.01$) and CBZ ($p < 0.001$) as presented in Figure 1. In the dominance tube test, lithium and CBZ treated animals were found to be less dominated (33%) and (50%) when compared to ketamine treated animals (100%) as indicated in Figure 2. As illustrated in Figure 3, group II showed significant elevation ($p < 0.01$) in TBARS formation after ketamine administration as compare to group I. The group III and group IV showed significant decrease ($p < 0.001$) in TBARS level in rat brains as compare to group II. In comparison to group I, group II, III, IV showed significant ($p < 0.01$), ($p < 0.05$) and ($p < 0.01$) reduction in catalase level respectively in rat brain as shown in Figure 4. Table 1 showed changes in serum hormonal levels. Group II showed significant elevation of serum prolactin and FSH level ($p < 0.05$) as compared to group I. The lithium and CBZ significantly ($p < 0.05$) reduces

DISCUSSION

In present study we revealed, for the first time, the use of carbamazepine as mood stabilizer against the ketamine induced hyperactivity in experimental animals.



the serum FSH level. Significant decrease ($p < 0.001$) in serum LH level was observed as compared to other groups. Cortisol level was found to be controlled by CBZ as significant reduction in serum cortisol level ($p < 0.05$) was observed.

Table 1: Estimation of Serum Hormonal Level

Parameter	Group I	Group II	Group III	Group IV
Prolactin (ng/ml)	0.60 ± 0.0	5.45 ± 2.21*	1.81 ± 0.12	1.95 ± 0.26
Cortisol (mcg/dl)	3.41 ± 1.16	1.05 ± 0.08	1.68 ± 0.35	0.45 ± 0.14*
LH (miU/ml)	0.09 ± 0.0	0.03 ± 0.01***	0.02 ± 0.00***	0.01 ± 0.0***
FSH (miU/ml)	0.05 ± 0.0	1.23 ± 0.48*	0.02 ± 0.00 #	0.04 ± 0.0 #

Note: All values are expressed as Mean ± SEM. *# P < 0.05, ** P < 0.01 and *** P < 0.001 was consider significant as compare to control group. * indicate comparison between Group I and Group II and # indicate comparison between Group II and Group III, Group IV.

The manic state is associated with alteration of cortisol level, activity, consisting of an elevation of nocturnal cortisol level. Both amount and temporal organization of prolactin (PRL) and growth hormone (GH) secretions are normal (Linkowski, 1994). Ketamine significantly increases serum FSH and prolactin level. The medical literature survey indicates that the cortisol level is elevated in manic patient. Results of our study showed that ketamine does not increase serum cortisol level. Lithium and CBZ reduces the serum cortisol, and LH level as compare to control group which support the previous study. They also reduce serum FSH level as compared to ketamine group. It has been widely described that the dysregulation of Hypothlamic Pitutatry Axis (HPA) in bipolar disorder and manic patient, which include the change in cortisol level (Valiengo *et al.*, 2012). There is elevation of glutamate transmission and cortisol secretion in mood disorders that causes the reductions in gray matter volume and synaptic markers by inducing dendritic atrophy in some brain structures. The depressive subtypes such as BD, also show the regional reductions in gray matter volume and evidence of increased cortisol secretion and glutamate transmission (Wayne, 2008). In this study lithium and CBZ decreases the level of

serum cortisol (but no significant decrease was observed).

Ketamine affect glutamatergic activity by blocking of the NMDA receptor. Administration of subanesthetic dose of ketamine induces behavioral alterations in animals such as hyperlocomotion and same was observed when locomotor activity and dominance test was performed on ketamine induced animals (Bubenikova Valesova *et al.*, 2008; Gunduz, 2009; Sorce *et al.*, 2010; Oliveira *et al.*, 2011). Hence our study supports the study of (Ghedim *et al.*, 2012) for ketamine induced hyperactivity. The hyperlocomotion and dominance effect was significantly reversed by lithium and CBZ indicating the antimanic activity against ketamine induced mania.

Ketamine induced oxidative stress was reversed by the both the drugs indicating the antioxidant activity but in contrast no increase in catalase activity was observed. Thus the lithium and CBZ may act by reducing ROS formation and alteration in neurotransmitter level in the cortex which observed in manic patients. CAT activity increased in response to increased H₂O₂ production induced by amphetamine metabolism

(Frey *et al.*, 2006). Our results showed that lithium and CBZ has no effect on catalase activity.

Our finding demonstrates the effect of ketamine on serum hormonal levels and tried to correlate it with antimanic activity of lithium and CBZ. The studies confirm the antimanic activity of lithium and carbamazepine against ketamine induced mania. Antioxidant activity of lithium and CBZ may be the major pathway which could assist the antimanic activity of these drugs. The study under taken explores the possible use of lithium and CBZ in treatment of ketamine induced mania.

CONFLICT OF INTEREST

No conflict of interest.

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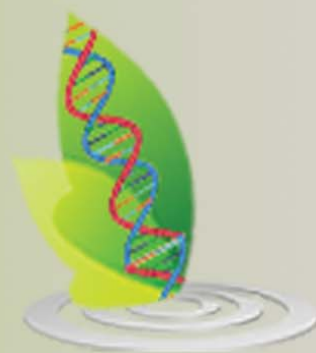
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