Modulation of catalase, copper and zinc in the hippocampus and the prefrontal cortex in social isolation-induced depression in male rats

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Depression is a chronic illness of unknown etiology. Trace elements, such as copper and zinc, and defense antioxidants, such as catalase, are important factors that determine the clinical course of brain diseases. Furthermore, altered glucose metabolism in hippocampus and prefrontal cortex has been associated with depression. Identifying factors that can precipitate depressive-like behavior is of particular importance as it can direct clinicians towards the etiology of the disease. In this study, 16 male Sprague-Dawley rats were randomly divided into two groups: socialized and socially isolated. After one week of acclimatization, animals were housed in isolation for 14 days. Rats in the social group were socialized together for 14 days. On day 15, the forced swim test was performed and blood sugar was analyzed. The brain was removed immediately for biochemical analysis. Socially isolated rats showed more pronounced depressive-like behavior in the forced swim test than socialized rats. Moreover, socially isolated rats demonstrated significantly lower copper and zinc concentrations, as well as a marked reduction in catalase activity, in both prefrontal cortex and hippocampus compared to socialized rats. Additionally, blood sugar levels were higher in socially isolated animals. Isolation causes reduction in copper and zinc levels and catalase activity, which may precipitate depressive-like behavior in these animals.

Key words: copper, zinc, catalase, depression, glucose, prefrontal cortex, hippocampus

INTRODUCTION

Depression is a psychiatric illness with diverse clinical manifestations. It's presentation can include loss of sleep, appetite and sense of pleasure and loneliness (Kapfhammer, 2006). Moreover, in many neurological and psychiatric disorders, depression is found to be co morbid (Sherbourne et al., 1996; Moussavi et al., 2007; Raskind, 2008). In some cases, it manifests itself in periods of relapse (Morgan, 2003; Ma and Teasdale, 2004). Considering the burden of depression, exploring factors that regulate this complex disease can be of great importance in controlling the illness. Environmental and genetic factors contribute to the occurrence and relapse of psychiatric diseases (Meyer-Lindenberg and Weinberger, 2006). Although both factors are important, the precise roles of environment and genetics have yet to be determined. In this study, we hypothesized that social isolation can favor mechanisms leading to the occurrence of depressive-like behavior.

Social isolation has been linked previously to the occurrence of depression and, by definition, depression has been described as loneliness (Cacioppo et al., 2006). Social isolation is described as the lack of physical contact with society members, but loneliness is a subjective feeling of distress that is the result of an inadequate social relationship (de Jong Gierveld and Havens, 2004; Tomaka et al., 2006). Loneliness can occur in any stage of life. There are many poten-

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tial causes of loneliness and social isolation (Choi et al., 2015). Moreover, genetic factors play an important role in determining an individual's response to social isolation and loneliness (Sullivan et al., 2000). Studies have shown that trace elements are crucial for brain development and, in later stages of life, necessary for certain structural and functional aspects of brain function (Frederickson et al., 2000). Disturbances in levels of trace elements have been linked to various psychiatric diseases (Eby and Eby, 2006). The cause of depression in socially isolated people is not fully understood. In this study, we hypothesized that fourteen days of social isolation would lead to a reduction in zinc and copper levels and catalase activity in the hippocampus and prefrontal cortex that may contribute to the occurrence of depression.

The prefrontal cortex is a brain region often investigated in psychiatric illnesses (Vostrikov et al., 2007). The hippocampus is also of particular importance for studying depressive and anxiety behavior (Tanti and Belzung, 2013). Trace elements like copper and zinc have been shown to regulate the metabolism of neurotransmitters that are important for psychiatric diseases (Frederickson etal., 2000; Takeda et al., 2007; Scheiber et al., 2014).

The brain is highly susceptible to oxidative stress, and the progression of numerous neurological disorders has been linked to oxidative stress (O'Donnell, 2012). In this study, catalase activity was assessed in the hippocampus and the prefrontal cortex in order to explore what role changes in the activity of this antioxidant enzyme play in social isolation.

The interplays between blood sugar, antioxidant defense and trace elements have been investigated in previous studies. High blood glucose levels have been shown to increase antioxidants in endothelial cells, reflecting the importance of antioxidant defense in neutralizing the toxic effect of high glucose (Ceriello et al., 1996). In contrast, the high blood glucose levels observed in diabetes mellitus (DM) patients have been shown to disturb the balance of trace elements, sugar and antioxidants (Navarro-Alarcon et al., 2013; Habib et al., 2015). In this study, the interplay between sugar, trace elements and catalase activity has been assessed during a period of social isolation. The forced swim test, a well-known behavioral test for analyzing the occurrence of depression-like behavior, was also utilized (Castagné et al., 2010).

As mentioned, depression is a prevalent disease with many burdens and it requires a much fuller understanding. For this purpose, social isolation as a cause of depression was investigated. In this regard, copper and zinc, as two important elements in brain, and catalase activity, as an important antioxidant, was studied.

METHODS

Animal care

Sprague-Dawley rats weighing approximately 200-250 g (8 to 10 weeks old) were housed individually (socially isolated) in standard small polycarbonate cages (27×15×21 cm) or together (socialized) in large (42×15×21 cm) polycarbonate cages. Animals had free access to food and water. Animals were housed in a temperature- (22±1°C) and humidity-controlled (40-70%) environment with a 12 h light/dark cycle (lights on at 7:00 a.m.). All behavioral assessments were conducted during the light phase of the cycle (specifically, from 11:00 a.m. to 3:00 p.m.) in the experimental room. All rats were habituated to the animal house of Tehran University of Medical Science at least 7 days before the experiments. All experimental protocols were in accordance with the Animal Ethics Committee of Tehran University of Medical Sciences. In each group, 8 rats were used. We did not put 8 rats together in the same cage in the social group but, rather, an additional 8 rats were used for socializing each rat. In other words, the animals were socialized in pairs, therefore 24 animals were used in total.

Experimental procedure and preparation of samples

After 14 days, rats in isolation and socialized groups were studied for depression-like behavior using the forced swim test. In the socialized group, the animals were housed in pairs, whereas in the isolated group the animals were housed alone. After the behavioral experiments, the rats were anesthetized using xylazine (10 mg/kg) and ketamine (100 mg/kg). Blood was taken from heart and serum was obtained after centrifugation. The brain was removed from the skull and immediately frozen in liquid nitrogen. For the preparation of homogenized tissue, the hippocampus and the prefrontal cortex were isolated from the brain and homogenized in buffer phosphate (50 mmol/L).

Assessment of copper and zinc in tissues

The homogenized sample was diluted with 65% nitric acid and 65% perchloric acid to the total volume of 5 ml. Then, copper and zinc were assessed with an

atomic spectrophotometer (Vivian). The wavelength was corrected with a standard curve and final concentrations were obtained (Yang and Wong, 2001).

Assessment of copper and zinc in serum

The serum was diluted with 65% nitric acid and 65% perchloric acid to the total volume of 5 ml. Then, copper and zinc were assessed with an atomic spectrophotometer (Vivian). The wavelength was corrected with a standard curve and final concentrations were obtained (Yang and Wong, 2001).

Catalase activity

Catalase activity was assessed based using the Claiborne method (1985), wherein the breakdown of H_2O_2 is measured. Briefly, the assay mixture consisted of 1 ml of phosphate buffer (pH=7), 10 µM H_2O_2 and 20 µM tissue homogenate supernatant. The change in absorbance was recorded for 1 min with 30 s interval at 240 nm using a spectrophotometer. The results were expressed as a unit of an enzyme that can degrade 1 µmol of H_2O_2 in 1 milligram of protein (Unit/mg-Protein) (Genet et al., 2002).

Blood sugar

Blood was obtained from the tail of rats. Next, blood was placed over a strip and glucose level was assessed by the aid of a glucometer.

Forced swim test

In this study, the forced swim test was used to assess mood state on day 15 of social isolation. Here, the rats were forced to swim in a water-filled cylindrical shaped container (29 cm diameter × 50 cm tall), containing 25°C water 40 cm deep. The experiment had two phases. On day 1,rats swam for 15 minutes in an opaque cylindrical-like container (pre-session test). The water was changed after experiment-induced olfactory cues. On day 2, the experiment was repeated in the same conditions for 5 min (test session). In this experiment, two variables were considered as the index of depressive-like behavior: number of stops and immobility time. Immobility was considered as the absence of movement, passively floating, while the paws are immobile. The experiments were videotaped for scoring (Menezes et al., 2008).

Statistics

Independent two-tailed sample t-test was performed for comparing two groups of the experiments (Socialized × Socially Isolated (SI)). Graph Pad Prism 5 and SPSS version 22 were used for statistical analysis. Data were represented as mean ± SEM. $P<0.05$ was considered significant.

RESULTS

Copper in hippocampus and prefrontal cortex: For investigating the difference of copper in socially isolated
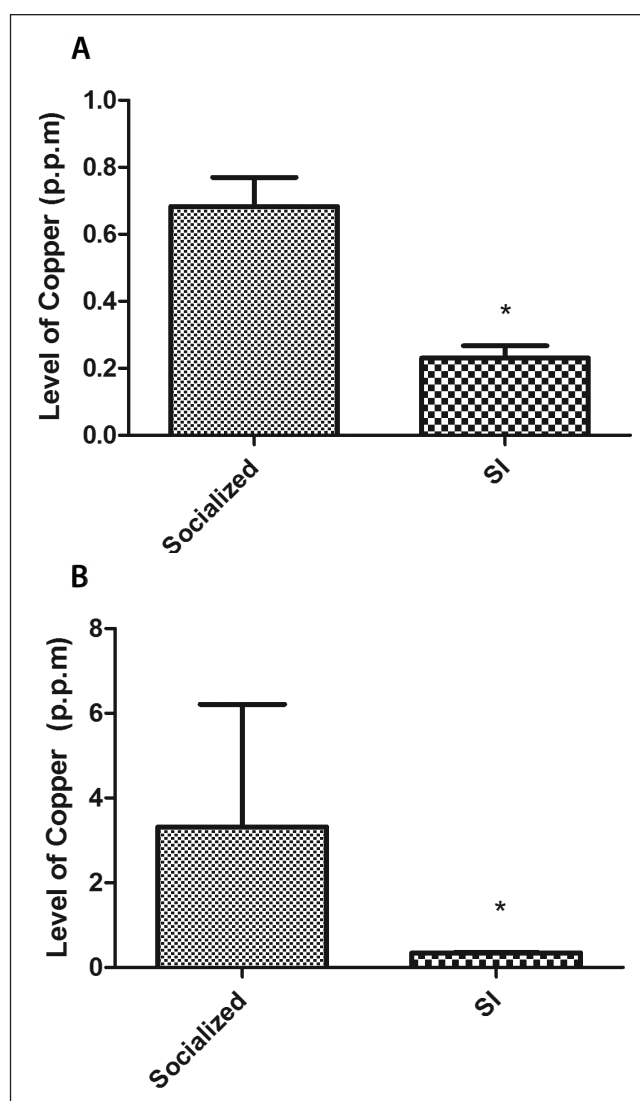

Fig. 1. Concentrations of copper in the hippocampus (A) and the prefrontal cortex (B) as measured by spectrophotometer after preparation for analysis. The wavelength was corrected with a standard curve to determine concentration. Data were presented as mean ± SEM. * denotes P<0.05. SI: socially isolated.

rats and socialized rats in hippocampus and prefrontal cortex regions, an independent sample t-test was performed. In socially isolated rats, copper in hippocampus and prefrontal cortex was reduced compared to socialized rats (0.68±0.078 *vs.* 0.227±0.013, P=0.019 and 3.4±2.52 *vs.* 0.33±0.04, P=0.039, respectively) (Fig. 1A and B).

Zinc in hippocampus and prefrontal cortex: For investigating the difference in zinc among experimental groups in hippocampus and prefrontal cortex regions, an independent sample t-test was performed. In socially isolated rats, zinc in hippocampus and prefrontal cortex was reduced compared to socialized

rats (5.56±0.71 *vs.* 2.77±0.317, P=0.028 and 8.2±0.55 *vs.* 2.9±0.4163, P=0.001, respectively) (Fig. 2A and B).

Serum level of copper and zinc: For investigating the differences in the serum level of copper and zinc among experimental groups, an independent sample t-test was used. In socially isolated rats, zinc was reduced in serum compared to socialized rats. Paradoxically, copper was increased in socially isolated rats (9.13±0.18 *vs.* 7.4±0.17, P=0.0005, 2.26±0.10 *vs.* 3.61±0.15, P=0.002, respectively) (Fig. 3A and B).

Catalase in hippocampus and prefrontal cortex: For investigating the difference in catalase activity in
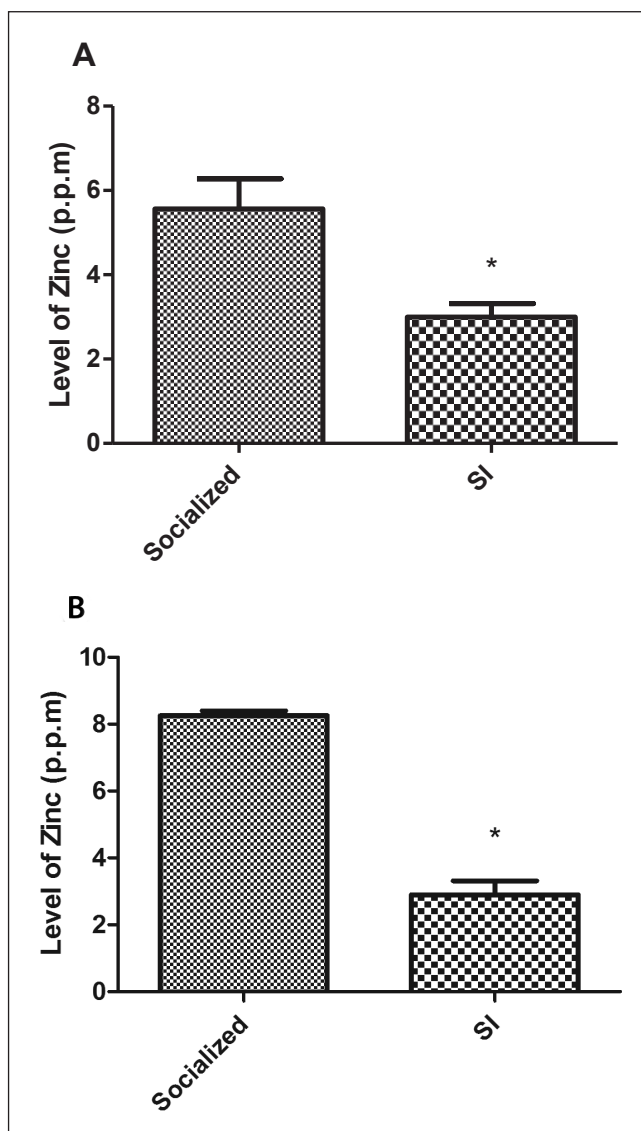

Fig. 2. Concentrations of zinc in the hippocampus (A) and the prefrontal cortex (B) as measured by spectrophotometer after preparation for analysis. The wavelength was corrected with a standard curve to determine concentration. Data were presented as mean ± SEM. * denotes P<0.05. SI: socially isolated.
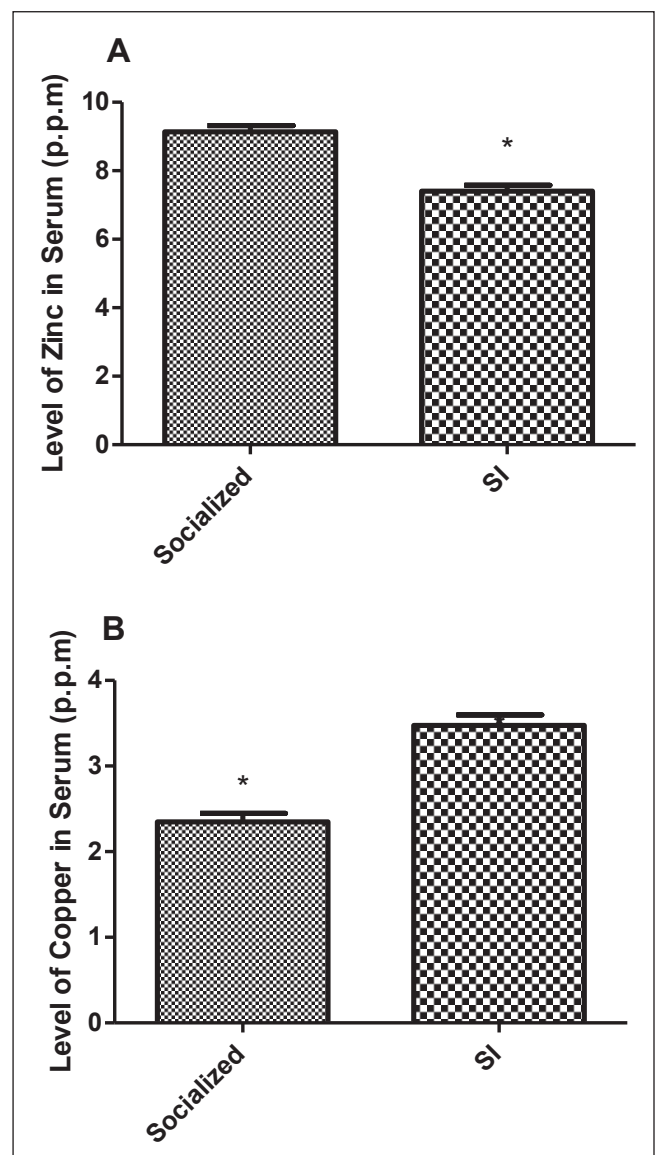

Fig. 3. Concentrations of zinc (A) and copper (B) in serum as measured by spectrophotometer after preparation for analysis. The wavelength was corrected with a standard curve to determine concentration. Data were presented as mean ± SEM. * denotes P<0.05. SI: socially isolated.

socially isolated rats and social rats in hippocampus and prefrontal cortex regions, an independent sample t-test was performed. In socially isolated rats, catalase in hippocampus showed a marked reduction in comparison with socialized rats. Similarly, in socially isolated rats catalase in prefrontal cortex was lower than in socialized rats (7.75±0.47 *vs.* 5.0±0.57, P=0.014, 7.0±0.40 *vs.* 4.0±0.57, P=0.007, respectively) (Fig. 4A and B).

Blood glucose level: For investigating the difference in blood glucose levels, an independent sample t-test was applied. In isolated rats, glucose in serum was higher compared to the socialized rats (95.0±1.52 *vs.* 131.4±8.15, P=0.035) (Fig. 5).

Fig. 5. The amount of glucose in the blood is depicted. Data were represented as mean ± SEM. * denotes P<0.05. SI: socially isolated.

Food intake: For investigating the difference in food intake in among experimental groups, an independent sample t-test was applied. In socially isolated rats, food intake was reduced in comparison with socialized rats (23.93±1.88 *vs.* 16.88±0.7447, P=0.025) (Fig. 6).

Forced swim test for assessing depression-like behavior: For investigating the difference in immobility time and the number of stops in socially isolated rats and socialized rats, an independent sample t-test was performed. Both the number of stops and the immobility time were greater in socially isolated rats compared to socialized rats (1.5±0.86 *vs.* 8.25±1.25, P=0.0397, 1.750±0.8539 *vs.* 10.75±2.097, P=0.0286, respectively) (Fig. 7A and B).
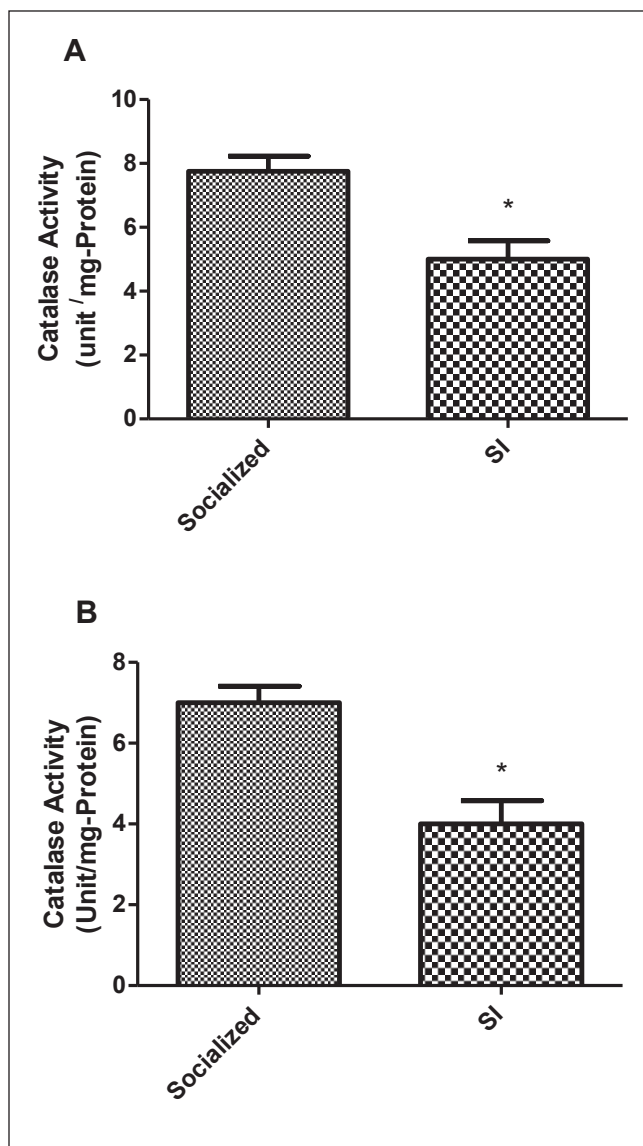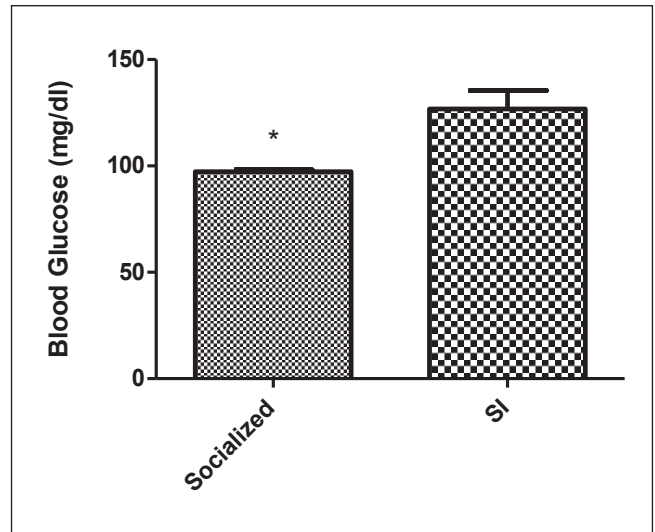

Fig. 4. Concentrations of catalase in the hippocampus (A) and the prefrontal cortex (B) as measured by spectrophotometer after preparation for analysis. Data were presented as mean ± SEM. * denotes P<0.05. SI: socially isolated.
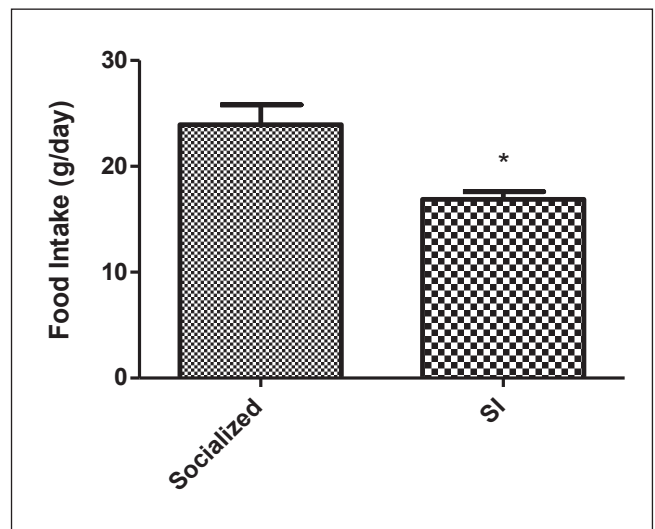
Fig. 6. The amount of food intake is depicted. Data were represented as mean ± SEM. * denotes P<0.05. SI: socially isolated.
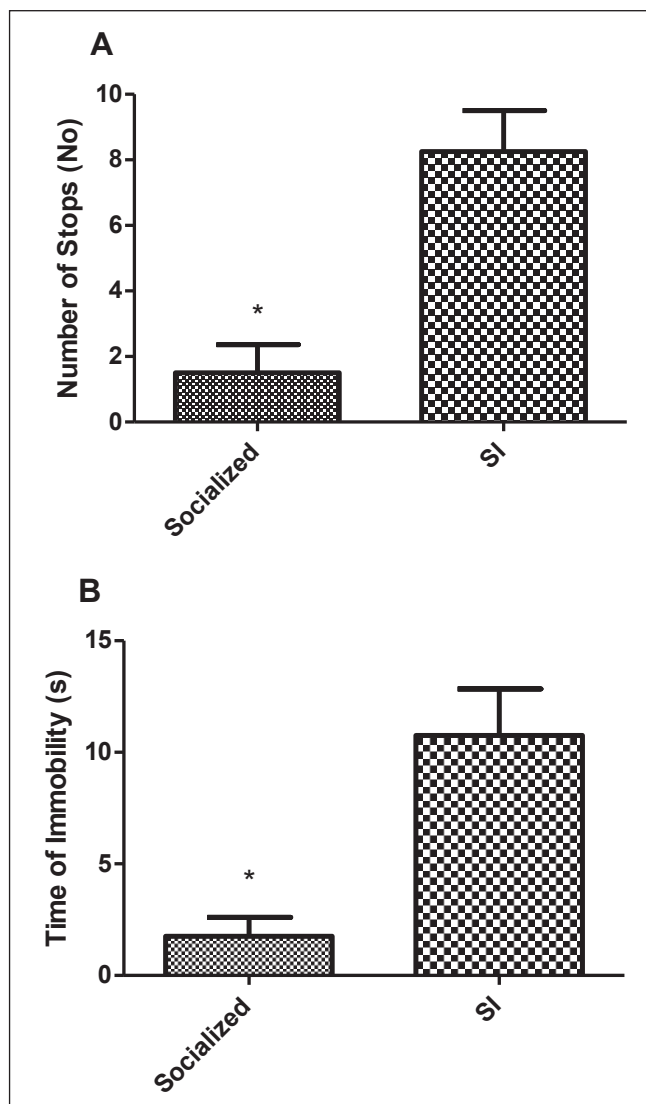
Fig. 7. Performance in the forced swim test. The number of stops is shown in (A). The time of immobility is shown in (B). An increase in number of stops and time of immobility is indicative of greater depressive behavior. Data were presented as mean ± SEM. * denotes $P<0.05$. SI: socially isolated.

DISCUSSION

In this investigation, copper and zinc were found to be reduced in the hippocampus and prefrontal cortex of the socially isolated animals. Additionally, isolation caused a marked deterioration in catalase activity in these brain regions. Concomitant with these reductions, depressive behavior occurred.

Copper is an important element in the brain with specific and non-specific functions. Copper-dependent enzymes perform diverse functions in the brain, such as energy production, antioxidant defense, iron metabolism, neurotransmitter metabolism and neuropeptide synthesis (Scheiber et al., 2014). Active transport produces an enormous amount of free radicals and, for this reason, production of a correspondingly high antioxidant defense is needed (Vergun et al., 2007). Copper is delivered to the brain via blood circulation, as it can cross the BBB as a free ion, and is present in higher levels in extracellular fluid than in intracellular fluid (Hopt et al., 2003). It is also present at higher concentrations in glial cells than neurons, suggestive of copper storage in glial cells (Becker and Salber, 2010). The copper in neurons is mostly found in bound form rather than as free ions. Chaperones store free copper to keep it accessible for cellular functions, as free copper rapidly absorbs to metallothioneins and glutathione (Robinson and Winge, 2010). Copper dysregulation has been implicated in many neurologic and psychiatric diseases, such as Alzheimer's disease and depression (Waggoner et al.,1999). In this study, reduction of copper in socially isolated rats may be attributed to the reduced storage of this ion. This reduction might be due to the brain's limited capacity for long-term storage of copper. A reduction in copper can affect process cognition and other brain functions, thereby producing clinical symptoms such as depression and mood disturbances. Since there is relatively high copper in extracellular fluid, increased copper in serum may be indicative of impaired neuronal transport of copper. In line with this study's findings, copper levels have been found to be elevated depressed patients (Ni et al., 2018). An additional study, investigating chronic treatment with an antidepressant, found the zinc to copper ratio to be an important factor in predicting the outcome of depression (Mlyniec et al., 2014).Our results suggests that copper is an antagonist to zinc in depressed rats and suggest that copper elevation and zinc reduction in serum are associated with the emergence of depression after 14 days of social isolation.

Zinc is also an essential element in the brain. Neurons containing zinc are mostly glutamatergic, therefore zinc is more likely to be involved in the storage, release, and uptake of glutamate. These neurons are more concentrated in cerebral cortex and amygdala. It has been postulated that zinc deficiency causes memory decline (Frederickson et al., 2000). Also, zinc is essential for associational neurons, not long-axon neurons. Previously, it was thought that zinc had three routes of transport in the brain including 1) presynaptic release along with glutamate, 2) voltage-gated L-type Ca^{2+} channels and glutamate-gated channels and 3) a plasma membrane transporter potentially present in all neurons which is important for cellular zinc homeostasis (Frederickson and Danscher, 1990). Recently, specific transporters have also been identified for zinc uptake in the brain (Colvin et al., 2000). Expression of

zinc transporters can change in response to an excessive zinc environment (Bobilya et al., 2008). On the other hand, a zinc deficient diet increases the activity of zinc transporters such as Zn T-1 and LIV -1 in the brain (Chowanadisai et al., 2005). Zinc is tightly regulated as, after a one-week zinc deprivation, zinc in plasma can fall 50% below normal (Takeda et al., 2007). Therefore, in the described condition, zinc first declines in serum, as occurred in this study, then CSF and then in hippocampus, which is one of most susceptible organs of the brain. In this regard, astrocytes are thought to act as sensors (Bertoni-Freddari et al., 2006). Zinc supplements, which act via the monoaminergic pathway, are recommended for the management of depression (Doboszewska et al., 2017). Also, dietary zinc restriction has been associated with depression (Mlyniec and Nowak, 2012). In consistent with this study, recent studies have been well showed a decline in zinc in the hippocampus and prefrontal cortex requires supplementation because zinc deficiency and deprivation can also be caused by behavioral disturbances (Takeda et al., 2007; Omata et al., 2012). It seems that regulatory mechanisms fail to restore this depletion because the depletion causes symptoms such as depression. Thus, the only remedy would appear to be the replacement of zinc through treatment. One other important factor to consider is the turnover of zinc in neurons. In this regard, consumption of both zinc and copper seems necessary. The important related issue is the question of how social isolation can cause a reduction of zinc and copper in the hippocampus and the prefrontal cortex. In isolated animals, the reduction of copper and zinc in the social isolation period, in hippocampus and the prefrontal cortex, appears to be due to a reduction in food intake. This reduction may reflect a severe depletion in zinc and copper by other mechanisms that cannot been compensated by food intake. This study suggests that a sufficient intake of copper and zinc may prevent the reduction of copper and zinc in the mentioned brain regions. Further studies are warranted to explore the primary mechanisms resulting in the reduction of copper and zinc in these brain areas.

In this study, catalase activity as an antioxidant index in the hippocampal area and prefrontal cortex was assessed. There is strong supporting evidence in the literature that glutathione is involved the interplay between antioxidants and psychiatric disease (Gawryluk et al., 2011). However, in this study catalase was assessed as an antioxidant. The relationship between the concentration of antioxidants and brain function has been well established based on the effectiveness of antioxidant treatment for the treatment of psychiatric disorders (Berk et al., 2008). Moreover, an increase in brain catalase content has been associated with im-

provement in cognition and motor disturbances (Brutman and Mhlanga, 2013). The effectiveness of catalase in the treatment of brain disorders is not fully understood but it may be due to its effect on the BBB (Wengenack et al., 1997). In addition, catalase treatment may improve the function of astroglial cells and, separately, has been shown to improve symptoms of Alzheimer's disease (Mao et al., 2012).

There is evidence that impaired glucose metabolism in the hippocampus and prefrontal cortex is one of the key factors in the development of depression (Detka et al., 2015). Changes in brain glucose levels have been found to be related to activation of the HPA axis in response to stress (Kern et al., 2008). In medication-resistant major depression, a disturbance of glucose metabolism in the prefrontal cortex has been observed (Li et al., 2015). This phenomena has also been observed in the hippocampus (Campbell and MacQueen, 2004). In diabetes mellitus, high blood sugar levels are thought to be the cause of depression (Andreoulakis et al., 2012). In this study, a social isolation-induced rise in glucose level could have contributed to depressive-like behavior. Isolation may have increased the release of stress hormones which in turn may have increased glucose and caused or accelerated the progression of depression.

The hippocampus and prefrontal cortex have been previously linked to emotions and emotional disturbances (Webster et al., 2001; Jin and Maren, 2015). Mechanisms underlying depression based on previous studies include methylation of NMDA receptors in prefrontal cortex and hippocampus (Kaut et al., 2015). In another study, the effectiveness of olanzapine in treatment-resistant depression has been attributed to cellular proliferation in the hippocampus and prefrontal cortex (Kodama et al., 2004). Indeed, both glial loss in prefrontal cortex and inadequate adult hippocampal neurogenesis may induce depression (Sahay and Hen, 2007). While people with a smaller hippocampus and prefrontal cortex were found to be more vulnerable to showing depressive-like behavior and, similarly, atrophy of the hippocampus and prefrontal cortex has been linked to the occurrence of depression (McEwen, 2005). Interestingly, ketamine can reduce depression by up regulating mTOR and BDNF in the hippocampus and the prefrontal cortex (Zhou et al., 2014). In this study, we showed several alterations in rat hippocampus and prefrontal cortex which may have led to isolation-induced depression.

CONCLUSION

In this study, it was observed that, in rats, catalase activity was reduced in both hippocampus and prefron-

tal cortex in a socially isolated group. Along with this reduction in catalase, copper and zinc levels were also found to be lower in the two brain regions. It is thus proposed that zinc, copper and catalase activity in associated areas during a period of isolation may play an important role in the occurrence of depressive behavior.

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