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Research report

Psychological stress induced hippocampus zinc dyshomeostasis and depression-like behavior in rats

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HIGHLIGHTS

- PS could result in depression-like behavior.
- PS induced low zinc contents and high free zinc contents in hippocampus.
- PS-induced depression might be correlated with zinc dyshomeostasis in hippocampus.
- PS-induced zinc dyshomeostasis was related to changes in ZnT, ZIP and MT expressions.

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ABSTRACT

There are strong evidences showed that psychological stress (PS) could result in depression. Recently, many attentions were paid to the roles of corticosterone (CORT) and zinc dyshomeostasis in the development of depression. In this study, we investigated the zinc level in rat hippocampus after exposure to PS and accompanied behavior change. Male SD rats were randomly divided into the control and PS groups. Each group had two subgroups: 7-d group and 14-d group. A communication box was used to produce the PS model in rats. Compared to control group, the PS-treated group showed decreased total zinc levels and increased free zinc levels observed by TSQ staining in hippocampus. Meanwhile, there were significant decreases in mRNA expressions of zinc transporters including ZnT1, ZnT3 and ZIP1 and metallothionein (MT) contents in hippocampus. Moreover, the increased immobility time in forced swim test (FST), lower movement time and total movement distance and longer immobile time in spontaneous activity test were demonstrated in rats after PS exposure. These results suggested that the depression-like behavior in PS-treated rats might be correlated with zinc dyshomeostasis including decreased zinc contents and increased free zinc in hippocampus which was related to changes in zinc transporters and MT expressions.

1. Introduction

Psychological stress (PS) has attracted much attention because its significant negative effects can increase the risk of various diseases, including diabetes, cardiovascular neurodegenerative diseases, and aging [1–3]. Under the stress condition the hypothalamic–pituitary–adrenal (HPA) axis is activated and the function of cognition and mental health are affected [4]. Decades of research have shown that stress is the primary precipitating factor in depression [5]. Stress causes the adrenal cortex secretion corticosterone (CORT) which could access the blood-brain-barrier and affects learning and memory processes [6]. Rats repeated exposure to CORT showed depression-like behavior in the forced swim test (FST) [7]. The hippocampus has the highest density of glucocorticoids receptors, and it is also the region which significantly participates in learning and memory [8].

Interestingly, zinc-deficient diet also can induce high level of serum CORT concentration in rats [9]. Zinc, as an essential trace element, is very important to organisms. Both clinical studies and animal experiments have demonstrated that zinc deficiency is connected to clinical depression and the depression-like behavior of animals [10,11]. And more interesting, the

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serum zinc concentration could be normalized through effective anti-depressant therapy [12,13]. Recent investigations into the molecular mechanisms responsible for mood disorders suggested a role of zinc in the regulation of neurotransmitter systems, antioxidant mechanisms, neurotrophic factors, and neuronal precursor cells [14]. Zinc is rich in central nervous system (CNS), especially in the hippocampus and cortical gray matter [15]. The hippocampus involves in cognition and also takes part in the respond of stress [16]. Researches already showed that the hippocampus involves in the pathogenesis of depression [17]. The brain of depressed patients has shown a significant reduction in hippocampus volume, which is proposed to be a result of decreased hippocampal neurogenesis [14,18].

Zinc serves as a cofactor for enzymes that are involved in critical biochemical processes and it plays many structural roles as well. At the cellular level, zinc is tightly regulated and disruption of zinc homeostasis results in serious physiological or pathological issues. Despite the high demand for zinc in cells, free or labile zinc must be kept at very low levels. Two families of zinc transporters are involved in zinc homeostasis in the cellular zinc homeostasis, SLC30 (ZnT, zinc transporter) and SLC39 (ZIP, Zinc (Zn^{2+})–Iron (Fe^{2+}) Permease). The two zinc transporter family members function in opposite directions to maintain cellular zinc homeostasis. ZnT proteins contribute to the cytoplasmic zinc balance by exporting zinc out to the extracellular space or by sequestrating cytoplasmic zinc into intracellular compartments when cellular zinc levels are elevated. In contrast, ZIP proteins function to increase cytoplasmic zinc concentrations when cellular zinc is depleted [19,20].

However, the effects of PS on hippocampal zinc homeostasis and its possible mechanism are not fully understood. In this study, we investigated how zinc content changed in hippocampus after exposure in PS and accompanied behavior alteration. We hope establishing a viable experimental reference for further study including how stress influences zinc homeostasis in hippocampus and the following consequences on physiological and biochemical property of the organism.

2. Materials and methods

2.1. Animals

Male SD rats from Shanghai-BK Co., Ltd., Shanghai, China, eight weeks old, weighed 200 ± 20 g, one in a cage at a temperature of 25 ± 1 °C, a humidity of 55 ± 5% in a natural light/dark cycle, and free access to food and water. All the objects treated according to the international ethical guidelines and the National Institutes of Health Guide concerning the Care and Use of Laboratory Animals, and the experiments carried out under the supervision of the Committee of Experimental Animal Administration of the Second Military Medical University. The content of zinc in the chow given to the rats was 50 mg/kg. After an adaptive phase of 3 d, the rats were randomly divided into three groups: the control group, the foot-shock group, and the PS group. Both of the control and PS groups had two subgroups: 7-d group (7dG) and 14-d group (14dG) (each subgroup had 10 rats in it).

2.2. PS exposure

A communication box had been used to produce the PS model in rats as described previously [21,22]. To put it simply, a communication box was separated into several cells with transparent acrylic boards, we divided the cells into two groups: group A and group B, each group has 10 cells. The cells in group A have a plastic board-covered floor for electric insulation and cells in group B have a metal grid-exposed floor for electric conduction. Rats in cell B (foot-shock group) were randomly given electrical shocks (0.6 mA for 1 s) for 30 min (60 times) through the floor and exhibited nociceptive stimulation-evoked responses, such as jumping up, defecation, and screaming; rats in cell A (PS group) were only exposed to the responses of rats in cell B to establish PS model. PS was given to rats at 10:00 to 10:30 every morning. After the PS test, the rats were still stayed in the cells for another 4 min until they were taken out. The control group animals were only kept in the cells for 4 min without receiving any stress. After every test, all the cells had been cleaned to prevent the smell leaved affecting the later experiment. During the experiment, weight was monitored daily.

2.3. Behavioral tests

2.3.1. FST

On the first day of the FST, rats were individually placed into a plastic tank (diameter, 30 cm; height, 40 cm), in which the depth of the water (25 °C) was 30 cm. The test lasted for 6 min until we got the rat out and dried it. The water was changed between tests to minimize interference. On the second day, all the conditions were the same as the day before. Then we traced the movement of the rats with a video camera for 4 min to record immobility time exactly. The immobility was defined as the rat floating on the surface of the water without the movement of its head, claws or tail. The total immobile time of each rat was counted manually [23].

2.3.2. Spontaneous activity test

The spontaneous activity is used to measure the behavior and locomotor activity of rats. The arena (50 cm × 50 cm × 70 cm) made of black plastic box, in which the subject had never been placed in before, illuminated with an infrared camera. Test of each rat in the arena lasting for 3 min was recorded by the camera and the image was transmitted to the computer. The Ethovision XT 4.0 software had been used to analysis the videos. The arena had been cleaned between tests.

2.4. Zinc assay

At the end of PS exposure period, all rats were deeply anesthetized by intraperitoneal injection of 7% chloral hydrate as soon as possible. Then the rats were perfused through the left cardiac ventricle with ice-cold phosphate-buffered saline (pH 7.4). Then the hippocampus was quickly removed and snaps frozen in liquid nitrogen, then kept in a −80 °C freezer till use. Each sample was weighed and wet-acid digested with a concentrated nitric/perchloric acid mixture (4:1 ratio) for 24 h. Zinc contents in the hippocampus were measured using a zinc flame atomic absorption spectrophotometer (AAS, Z-8100, Hitachi, Tokyo, Japan).

2.5. Real-time PCR

The Trizol reagent (Invitrogen) has been used to extract the total RNA from hippocampus following the instruction. All RNA samples were dissolved in RNase and DNase-free water (Promega), and 1 μl RNA solution was then reverse transcribed into cDNA with 2.5 pmol oligo (dT) 18 primer and 5 U avian myeloblastosis virus reverse transcriptase XL (TaKaRa) in 25 μl reaction mixture at 42 °C for 40 min according to manufacturer's recommendations. The ZnT1, ZnT3 and, ZIP1 mRNA levels were quantified by the real-time PCR technique using a Thermal Cycler Dice Real Time System (Rotor-gene 3000) with rat ZnT3 forward: 5′-CCACAGCTCCTACACTTCGAG-3′; reverse: 5′-GAATCCAAACCGGGAATAGAG-3′; ZnT1 forward: 5′-AGACCAACACGCTAGTGGCTA-3′, reverse: 5′-ACACGGGTTCACACAAAAGTC-3′; ZIP1 forward: 5′-GGTGATGGAGCAGATCACACT-3′, reverse: 5′-ATGCCCAGAGGTGTCATACAG-3′ a SYBR Premix Ex Taq kit (Takara).

2.6. Enzyme-linked immunosorbent assay (ELISA)

Metallothionein (MT) in hippocampus was analyzed using commercially available ELISA kits (R&D Systems, Inc., USA) for ELISA. Total protein concentration was determined with bovine serum albumin as the standard.

2.7. TSQ (N-(6-methoxy-8-quinolyl)-4-toluenesulfonamide) staining

Four rats were executed as described above. The brain was removed and frozen in liquid nitrogen immediately, and then cryosections (10 μm) were prepared (Heraeus, Germany). The hippocampus slices air-dried in room temperature for 2 h, then immersed in TSQ solution (100 ml solution of sodium acetate 1.9 g and sodium barbital 2.9 g were mixed with 100 ml TSQ 1.5% solution (w/v) dissolved in hot ethanol) for 60 s, then washed it with 0.9% normal saline for 60 s in a dark room [24]. The TSQ fluorescence was observed using a fluorescence microscope (Leica, Germany) (excitation, 360 nm). Only deionized water (Millipore Ltd., America) was used for the tissues and preparation for all the solutions.

2.8. Statistical analysis

All results were expressed as means ± SD. Statistical analysis was carried out by using SPSS 11.0. One-way ANOVA was used to determine whether differences were statistically significant in groups. A P value less than 0.05 was considered statistically significant difference.

3. Results

3.1. Hippocampal zinc concentration

The effects of PS on the hippocampal zinc concentration are shown in Fig. 1. The zinc level decreased significantly in rats exposed in PS circumstance for 7 d ($P = 0.002$) and 14 d ($P = 0.032$) compared with the control group.

3.2. Free zinc in hippocampus

TSQ staining showed that fluorescence was brighter in PS group than that in control group, which indicated the increased free zinc in hippocampus after exposure in PS (Fig. 2).

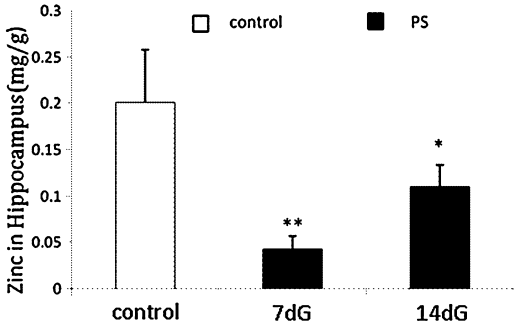

Fig. 1. The effect of PS exposure for 7-d and 14-d on zinc concentration in hippocampus. Values were expressed as means ± SD, $n = 6$. *$P < 0.05$, **$P < 0.01$ vs. control.

Table 1
The effects of PS exposure on spontaneous activity in rats.

Group	Distance moved (mm)	Immobile time (s)	Moving time(s)
Control group	8116.64 ± 2186.18	52.68 ± 28.44	127.3 ± 28.4
PS 7-d group	4332.82 ± 2259.01**	89.65 ± 35.52*	90.4 ± 35.5*
PS 14-d group	1928.15 ± 1693.47***	134.11 ± 32.61***	45.5 ± 34.7***

* $P < 0.05$ vs. control group.
** $P < 0.01$ vs. control group.
*** $P < 0.001$ vs. control group.

3.3. ZIP1, ZnT1 and ZnT3 mRNA levels in hippocampus

Fig. 3 shows that a significant decrease in ZnT1, ZnT3 and ZIP mRNA levels in hippocampus after 7-day ($P = 0.011$, 0.01, and 0.009 respectively) and 14-day ($P = 0.001$, 0.007, and 0.002 respectively) exposure in PS.

3.4. MT contents in hippocampus

Compared with the control group, the concentrations of MT in the hippocampus after PS for 7 d ($P = 0.0007$) and 14 d ($P = 0.0004$) decreased apparently (Fig. 4).

3.5. FST

The immobility time of the PS group increased respectively in FST after 7-day ($P = 0.014$) and 14-day ($P = 0.002$) period (Fig. 5).

3.6. Locomotor activity

Table 1 shows the total movement distance and movement time were lower in PS group than those in the control group

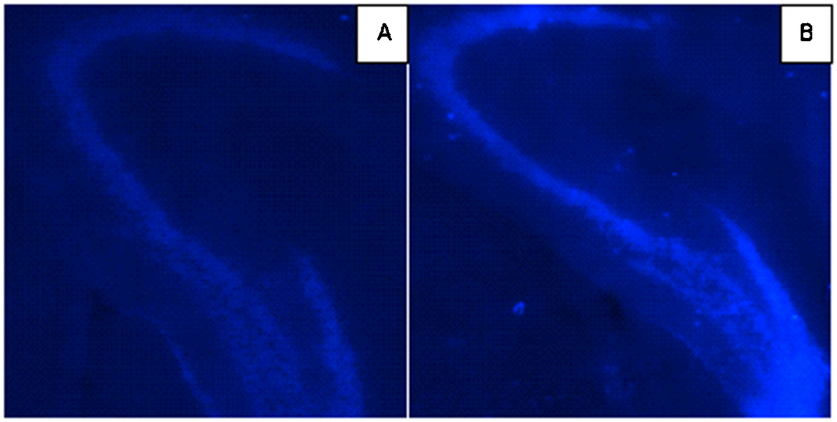

Fig. 2. TSQ staining of Zn(2+) in control group (A) and PS group (B).

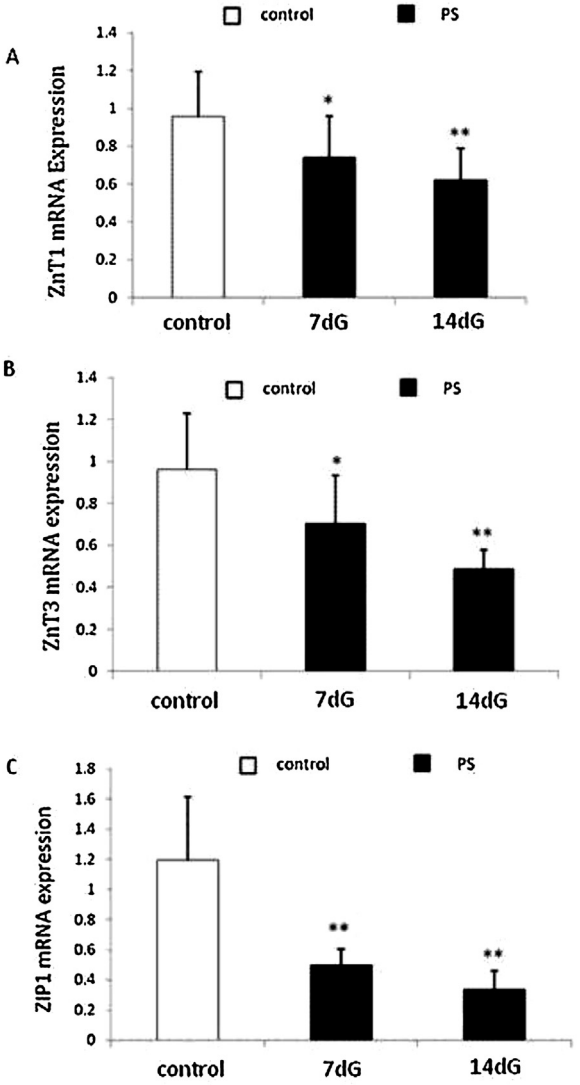

Fig. 3. The influence of exposure in PS for 7-d and 14-d on ZnT1 (A), ZnT3 (B), and ZIP1 (C) mRNA expressions in hippocampus. Values were expressed as means ± SD, $n = 6$. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. control.

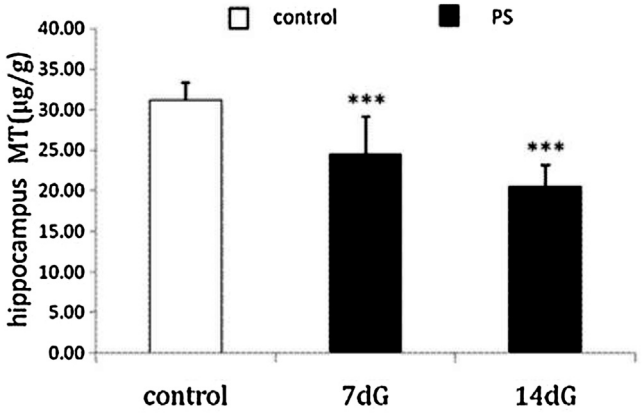

Fig. 4. The effects of PS 7-d and 14-d PS exposure on MT contents in hippocampus. Values were expressed as means ± SD, $n = 6$. $^{***}P < 0.001$ vs. control.

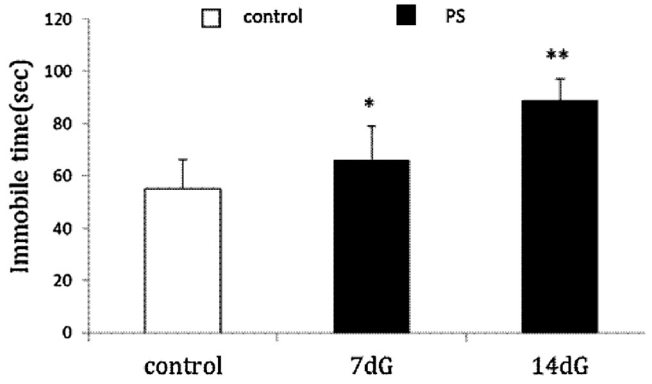

Fig. 5. The influence of exposure in PS for 7-d and 14-d on immobile time of FST in rats. Values were expressed as means ± SD, $n = 6$. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. control.

after 7 d ($P = 0.001$ and 0.019 respectively) and 14 d ($P = 0.0004$ and 0.0005 respectively). On the contrary, the immobile time was longer ($P = 0.017$ and 0.0004 respectively).

4. Discussion

With the development of society and the acceleration in the pace of life, people are typically in a constant state of stress. Numbers of neuropsychiatric disorders, such as depression, post-traumatic stress disorder (PTSD) and addiction, are related to stress [25–28]. We observed depression-like behavior changes such as increased immobile time in FST and decreased moving distance in locomotor activity in those objectives after PS exposure in present study. Depression is a commonly occurring psychiatric disorder, which can be debilitating and even life threatening. In recent years, a substantial amount of experimental and clinical data has supported the notion that dysregulation of the HPA axis is involved in the pathogenesis of depression [5,7,9,23,25]. In our previous study, we found that under the PS condition serum CORT concentration was higher in PS group than those in control group [21,22]. Several researches already showed that constant injection of CORT caused rats or mouse depression-like behavior changes, like increased immobile time in FST and tail suspension test (TST) [23,29,30]. And the hippocampus is abundant in corticosteroid receptors, which is impressionable to corticosteroids. Thus, the hippocampus is a vulnerable area during the stress circumstance. Stress-induced high CORT level could strongly inhibit the hippocampal neurogenesis which is relevant to the affective symptoms of depression [31–33]. It seems that CORT could modify the homeostasis of synaptic Zn^{2+} and glutamate, and their dyshomeostasis may have disadvantage on hippocampus and a possible role in pathogenesis of depression [34,35]. Clearly, the mechanism of stress-induced hippocampal zinc dyshomeostasis observed in present study will develop our understanding on stress-induced depression.

As a trace element, zinc is very important in enzymatic function, cellular signal transduction, and the neurotransmission regulation, which is required for many parts of physiological functions. At the molecular level, zinc adjusts transcription factor to modulation gene expression and is in charge of enzymatic activity in neurometabolism. In the cellular perspective, zinc is involved in synaptic function and neuroplasticity [36]. Plasmatic zinc concentration decreased in a number of circumstances, such as infection, trauma and stress [37]. In our previous studies, we found that serum zinc level decreased in rats after PS exposure, simultaneously, zinc in liver was accumulated [21,22]. Importantly, in present study, PS induced the total zinc concentration decreased in the hippocampus. The brain presences the highest concentration of zinc, especially the hippocampus and cerebral cortex,

major in the form of protein bound and free zinc or that can be detected histochemically [38–40]. Synaptically-released zinc modulates glutamatergic, γ-aminobutyric acid (GABA) and glycinergic transmission [41]. Adequate zinc is necessary for the important function of the hippocampus. Zinc deficiency elicits the neurochemical and metabolic changes in the hippocampus [42]. A growing body of evidence demonstrates that experimental zinc deficiency can induce depressive-like behavior in animals, which can be effectively reversed by zinc supplement [10,11].

The precise molecular mechanisms underlying the pathophysiology of depression and therapeutic efficacy of antidepressant drugs and zinc are currently not well understood. Several studies suggest that the antidepressant action of zinc is related to modulation of the glutamatergic system, but mostly to the inhibition of NMDA receptor activity, and can fit the NMDA/glutamate hypothesis of depression [43–45]. Zinc is thought to be an antagonist of the NMDA receptor, which itself may be involved in the psychopathology and therefore a target for the treatment of depression [45]. In addition, animal studies have reported that exposure of rats to stress can result in decreased hippocampal brain-derived neurotrophic factor (BDNF) mRNA levels but had no effect in the frontal cortex [46–48]. Repeated treatment with zinc induced a significant increase in the BDNF mRNA level in the hippocampus in the chronically stressed animals. More interesting, combined treatment of zinc and imipramine induced a 12% elevation of the BDNF mRNA level in the stressed but not in the unstressed rats. These results indicated that the stress-induced reduction in BDNF expression is antagonized by chronic treatment with zinc [48]. Besides, studies showed that zinc may activate metabotropic GPR39 receptor. It was proved that the natural ligand for the GPR39 receptor is zinc. This receptor is capable of sensing extracellular Zn^{2+}, thereby activating diverse signal-transduction pathways [49,50]. A biochemical study showed a significant reduction in GPR39 and BDNF protein expression in mice receiving the zinc deficient diet for 6 weeks, which could be upregulated by antidepressants [51,52]. These observations provides evidence that the GPR39 Zn^{2+}-sensing receptor may be responsible for lowering the BDNF protein level and in consequence may be involved in the pathogenesis of depression.

The present results showed that PS increased significantly the free zinc concentration detected by TSQ staining s accompanied with decreased total zinc level in hippocampus. The total zinc concentration in the hippocampus is more than 200 μM, whereas the cytosolic free zinc (Zn^{2+}) concentration is estimated to be subnanomolar [53]. Under stress conditions a dramatic increase of free Zn^{2+} has been detected in various cell types [54,55]. It is well known that abnormal Zn^{2+} influx into post-synaptic neurons, which is induced by abnormal glutamatergic (zincergic) neuron activity, induces neuronal death and is involved in neurological disorders such as stroke/ischemia and temporal lobe epilepsy [42]. Recently, the neurotoxicity of zinc ions (Zn^{2+}) has been the subject of numerous investigations. In neurons, $[Zn^{2+}]_i$ rises are able to promote potent generation of mitochondrial reactive oxygen species (ROS), and intriguingly, this Zn^{2+}-triggered ROS production persists longer than that induced by Ca^{2+} [56]. Not only can Zn^{2+} trigger ROS generation but cellular oxidation promotes further $[Zn^{2+}]_i$ release, which likely promotes a dangerous feed-forward cycle. The imbalance of zinc released from protein-bound pools can activate calcium influx and apoptotic progress then aggravate excitotoxicity and predispose neurodegeneration [56–58]. Combined with the previous and present observations mentioned above, zinc dyshomeostasis including decreased hippocampal zinc contents and increased free zinc (Zn^{2+}) which could induce hippocampal neurons degeneration observed in present study might be the possible mechanisms of stress-induced depression.

Zinc is a trace nutrient indispensable for organisms and its homeostasis is mostly regulated by ZnT, ZIP and MT. The present results showed that the mRNA expressions of ZIP1, ZnT1, ZnT3 and MT contents decreased in hippocampus in PS group. ZnT1 is the only member of the SLC30 family that functions primarily as an exporter on the cell membrane to transport cytoplasmic zinc ions across the membrane to the extracellular space [59]. ZnT3 is essential for neuronal zinc homeostasis and is abundant in hippocampus and cortex [60]. ZIP1 was identified as a transporter that can take up zinc into human erythroleukemia K562 cells [61]. MT has a high binding affinity for zinc and is crucial in zinc homeostatic regulation and cellular protection against oxidative stress. MT increases free zinc concentration though releasing zinc ions in oxidative conditions [62]. In conversely conditions, MT combines free zinc through an increased binding affinity. MT resembles a buffering agent used to maintain zinc homeostasis in the brain. MT-mediated zinc release may act as a cell sensor mechanism to minimize neurotoxicity [63]. Glucocorticoids, zinc, activated oxygen and cytokines are primary factors increasing the MT gene expression. It was proposed from the functions of ZnT1, ZnT3, ZIP1 and MT mentioned above, the decreased ZIP1 expression resulted in decreased total zinc level in hippocampus and in consequence may induced the downregulation of ZnT1 and ZnT3 expression observed in present study. Meanwhile, oxidative stress has been found to be a key regulator of intracellular Zn^{2+} homeostasis by promoting Zn^{2+} release from MTs and in consequence may induced elevated free zinc level in hippocampus [64]. The hippocampal zinc concentration and the mRNA levels of zinc transporters and MT may play an important role in stress-induced zinc dyshomeostasis which might be the possible mechanisms of stress-induced depression. However, the exact mechanism of this procession and the effects of hippocampal zinc homeostasis in neural system need further investigation.

Collectively, zinc dyshomeostasis in hippocampus and depression-like behavior in PS-treated rats were observed in present study. The change in behavior after PS exposure might be correlated with zinc dyshomeostasis including decreased zinc contents and increased free zinc (Zn^{2+}) in hippocampus. The exact mechanism of this interaction need to be further investigated.

Acknowledgments

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