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Exercise copes with prolonged stress-induced impairment of spatial memory performance by endoplasmic reticulum stress

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Jong-Seok Kang. Exercise copes with prolonged stress-induced impairment of spatial memory performance by endoplasmic reticulum stress. *JENB.*, Vol. 19, No. 3, pp.191-197, 2015 **[Purpose]** The present study demonstrates that prolonged restraint administration for 21 days caused memory impairment and induced hippocampal endoplasmic reticulum (ER) stress-mediated apoptosis. On the contrary, this change was revered by treadmill running for 8 weeks. Repeated psychological stress caused an increase in escape latency time in the water maze test, accompanied by the induction of glucose-regulated protein 78 (GRP78), CCAAT/enhancer-binding protein homologous protein (CHOP), and cleaved/active caspase-12 protein in the hippocampus. The expression pattern of ER stress response-related proteins were counter-regulated by chronic exercise, as indicated by a reduction in GRP78, CHOP, and cleaved caspase-12, along with a decrease in escape latency time. In addition, the hippocampal expression pattern of phospho-cAMP response element-binding protein (CREB) and brain-derived neurotrophic factor (BDNF) opposed that of ER stress response components. Accordingly, chronic exercise may attenuate prolonged stress-induced hippocampal ER stress and memory deficit, likely through CREB/BDNF signaling. **[Key words]** prolonged stress, exercise, endoplasmic reticulum stress, glucose-regulated protein 78, CHOP, memory

INTRODUCTION

A growing body of evidence suggests that the chronic exposure to stressful stimuli detrimentally impacts brain functions such as emotional disturbance, mood fluctuation, and memory impairment [1-3]. Sustained high levels of corticosteroid by chronic stress or exogenous glucocorticoid treatment in rodents caused a change in the hippocampal structure and function, including reduced volume, decreased synaptic plasticity, and adult neurogenesis, thereby altering behavioral consequences such as cognitive deficits and a depressive phenotype [2-5]. Chronic stress is a precipitating factor for the development of mood disorders and cognitive deficits. The chronic restraint stress model has been extensively applied in psychiatric and cognitive insults because of the simple experimental procedure. Repeated stress-induced hippocampal neuronal insult is thought to be a contributing factor for hippocampal-dependent learning and memory impairment. Several studies have shown that chronic restraint stress resulted in enhanced hippocampal apoptotic or degenerative cells, along with cognitive deficits, suggesting that long-lasting exposure to psychological and physical stress can impair hippocampal-dependent memory performance, concomitant with hippocampal neuronal loss [6-7].

The ER is a major subcellular compartment for secretory protein synthesis and maturation, intracellular calcium homeostasis, and lipid biosynthesis [8]. Under intracellular stress, the accumulation of unfolded and misfolded proteins in the ER lumen triggers an adaptive cellular stress response to restore normal ER function. However, prolonged and severe stress promotes the disruption of ER homeostasis and eventually causes cell apoptosis [9-11]. Recently, some studies have demonstrated a role of ER stress in chronic stress-related neuropathogenesis. For instance, social defeat stress for 10 days upregulated glucose-regulated protein 78 (GRP78) and CCAAT/enhancer-binding protein homologous protein (CHOP) expression in several limbic structures including the prefrontal cortex, hippocampus, and amygdala, along with behavioral defects [12]. Furthermore, repeated restraint stress impaired learning and memory function as well as facilitated neuronal

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ER stress in the prefrontal cortex and hippocampus [6-7]. As addressed above, chronic stress-induced affected behavior such as memory deficit are considered to be intimately related to neuronal ER stress.

Chronic exercise exerts a beneficial impact on cognitive impairment. Long-term voluntary or treadmill running improved memory performance, enhanced hippocampal neurogenesis, and strengthened long-term potentiation in aged rodents [13-14]. In addition, the 21 consecutive days of restraint stress led to cognitive decline and augmented hippocampal oxidative damage, which were reversed by treadmill running for 12 weeks [15].

The potential role of exercise in chronic stress-induced memory deficit has been extensively explored, nevertheless the underlying mechanism is poorly understood. In particular, there is little evidence to suggest that chronic stress-induced ER stress-related memory decline is coped with by long-term exercise. Accordingly, here, we investigate whether 8 weeks of treadmill running relieves chronic stress-induced hippocampal ER stress and improves memory performance.

METHODS

Experimental animals

7-week-old male C57BL/6J mice were obtained from Daehan Biolink, Inc. (Eumsung, Chungbuk, Korea) and housed in clear plastic cages under specified pathogen-free conditions and light-dark cycles of 12/12 hours (lights on at 0600 and off at 1800). All mice had free access to standard irradiated chow (Purina Mills, Seoul, Korea). All animal procedures were approved by the Animal Care and Use Committee of Ewha Women's University, (Seoul, Korea).

Experimental design

The mice were divided into 3 groups (control: CON, restraint stress: RST, and exercise combined with restraint stress: RST + Ex; 17 mice per group). Mice were subjected to treadmill exercise (Myung Jin Instruments Co., Seoul, Korea) at 19 m/min for 60 min/day, 5 days/week from week 0 to week 8 [15]. To induce restraint stress, 8-week-old mice were individually placed into a well-ventilated 50-ml conical tube that prevented forward or backward movement. Restraint stress was delivered at set times from 1000 to 1600 for 6 hours. Control mice remained undisturbed in their home cages. This was repeated for 21 days unless otherwise indicated. Mice were subjected to restraint stress from 1000

to 1600 for 6 hours, followed by treadmill running 2 hours later. Treadmill running was administrated from week 1 to week 8 and restraint stress was started at week 5 and ended at week 8.

Water maze test

The water maze test was performed using the SMART-CS (Panlab, Barcelona, Spain) in a 1.2-m-diameter plastic circular pool with water at 22℃, in an air-conditioned room. Powdered milk was dissolved in the water to obstruct visibility of the platform. Escape latency was monitored using the SMART-LD program by a computer that was connected to a ceiling-mounted camera directly above the pool. The training schedule consisted of two trials per day over 5 test days, and each trial assessed the ability of the mouse to reach the platform within 60 seconds. On day 6, the mice were subjected to three probe trials, where they would swim for 60 seconds with no platform. The time required to reach the previous platform location (escape latency) was recorded.

Annexin V and propidium iodide (PI) staining

Apoptosis was measured by an annexin V FITC Apoptosis Detection Kit TDS (BD biosciences, CA, USA) according to manufacturer's instructions. After dissection, the hippocampus was prepared for a single-cell suspension using mechanical trituration. The cell suspension was sifted through a mesh strainer (pore size, 75 μm), centrifuged at 1000 rpm for 5 minutes, and the pellet was resuspended in 0.01 M phosphate-buffered saline (PBS). Cells were washed twice with cold PBS and then resuspended in 1X binding buffer. The diluted cell suspension was incubated with 5 μl annexin V and 2 μl PI in the dark for 15 minutes. The fluorescence was analyzed using a flow cytometer (FACS Calibur, Becton-Dickinson, Germany). Early apoptotic cells stained positive for annexin V but negative for PI, and late apoptotic or necrotic cells stained positive for both annexin V and PI.

Western blotting analysis

Mouse hippocampus was extracted according to the Paxinos mouse brain Atlas (from the bregma to the AP, -2.0 mm; ML, -2.9 mm; DV, -3.7 mm) using a micro puncture. Protein samples (15 μg) were separated in each lane of a 12% polyacrylamide gel by electrophoresis and transferred to a nitrocellulose membrane (Amersham bioscience, Buckinghamshire, UK). The membrane was incubated with primary antibodies in blocking buffer overnight at room temperature,

washed in washing buffer, and incubated with a horseradish peroxidase-conjugated secondary antibody for 2 hours at room temperature. The optical density of each band was measured using the SCION program (NIH Image Engineering). Anti-BDNF (1: 1,000) and anti-β-actin (1: 3,000) antibodies were obtained from Santa Cruz Biotechnology (Santa Cruz, CA, USA), anti-phospho-cAMP response element-binding protein (CREB; 1: 2,000), anti-CREB (1: 1,000), anti-CHOP (1: 500), and anti-GRP78 (1: 500) antibodies were obtained from Cell Signaling Tech. Inc. (Danvers, MA, USA).

Statistical analysis

Significant differences among groups were determined using a one-way analysis of variance (ANOVA) and an independent t-test (SPSS for Windows, version 18.0, Chicago, IL, USA). Post-hoc comparisons were made using Newman-Keuls tests. All values are reported as the mean ± standard error (SE). Statistical significance was set at $p < 0.05$.

RESULTS

Repeated restraint stress upregulated hippocampal levels of GRP78 and CHOP proteins

To investigate whether repeated restraint stress induced hippocampal ER stress, hippocampal GRP78 (an ER stress marker) and CHOP (an ER stress-mediated apoptotic transcription factor) protein expression levels were measured in mice subjected to restraint stress for 7 days using western blotting. GRP78 (CON: $100 ± 5.30\%$; RST: $160.03 ± 10.15\%$, $p < 0.01$) and CHOP (CON: $100 ± 4.47$; RST: $147.40 ± 6.65\%$, $p < 0.01$) were significantly upregulated in response to repeated restraint stress administration (Fig. 1).

The 21 consecutive days of restraint stress induced memory impairment and hippocampal apoptotic cell death, which were restored by 8 weeks of treadmill running

We found that escape latency was significantly enhanced in response to restraint stress for 21 days, which was reversed
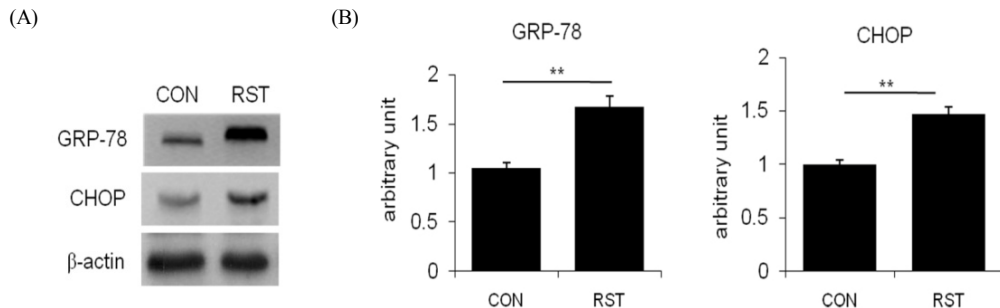

Fig. 1. Repeated restraint stress induces an increase in hippocampal GRP78 and CHOP proteins. (A) Photomicrographs showing GRP78 and CHOP immunoreactivity. (B) Diagram showing the quantitative analysis for GRP78 and CHOP immunoreactivity. (C) Diagram showing body weight change during restraint exposure. Data are presented as the mean ± SE. * and ** denote differences at $p < 0.05$ and $p < 0.01$, respectively.
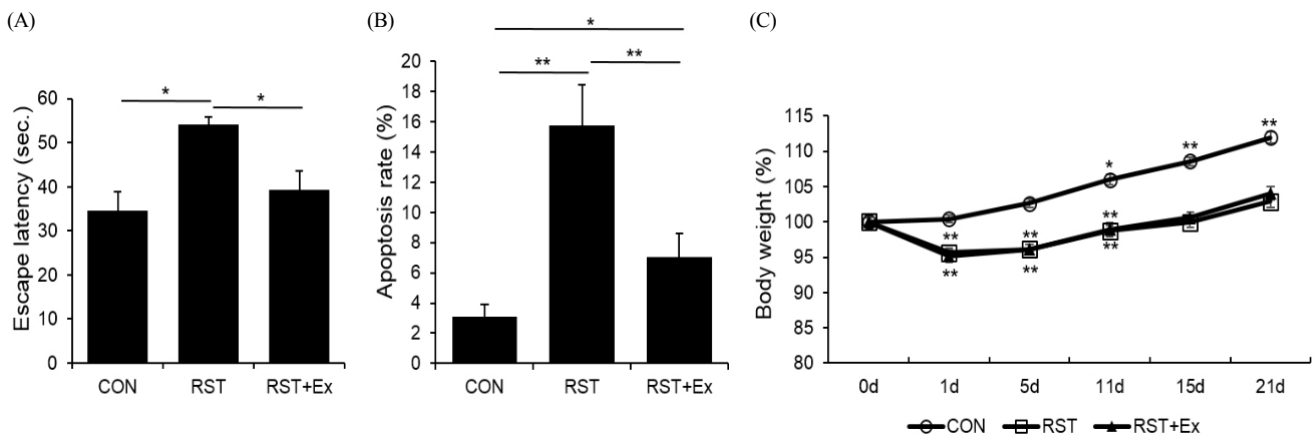

Fig. 2. Chronic treadmill running suppresses sustained restraint stress-induced memory impairment and hippocampal apoptosis. (A) Diagram showing escape latency in a water maze test. (B) Diagram showing the apoptotic rate in annexin V/PI staining. Data are presented as the mean ± SE. * and ** denote differences at $p < 0.05$ and $p < 0.01$, respectively.
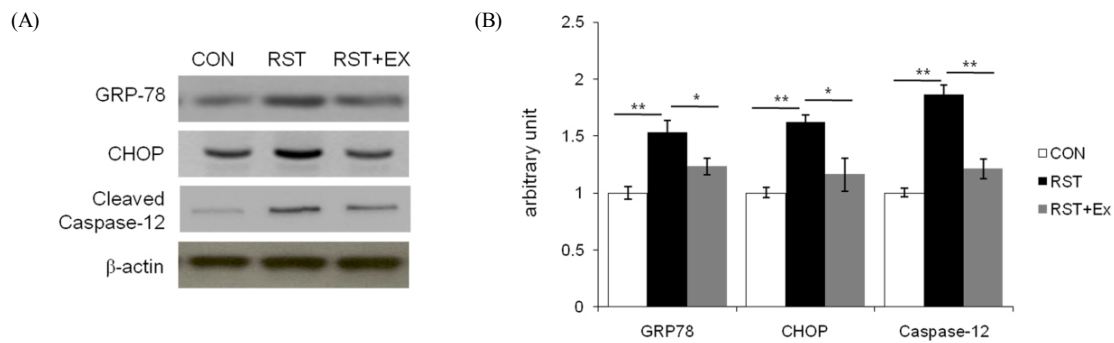
(A)

(B)

Fig. 3. Chronic treadmill running suppressed the induction of hippocampal GRP78, CHOP, and cleaved caspase-12 proteins. (A) Photomicrographs showing GRP78, CHOP, and cleaved caspase-12 immunoreactivity. (B) Diagram showing the quantitative analysis for GRP78, CHOP, and cleaved caspase-12 immunoreactivity. Data are presented as the mean ± SE. * and ** denote differences at $p < 0.05$ and $p < 0.01$, respectively.
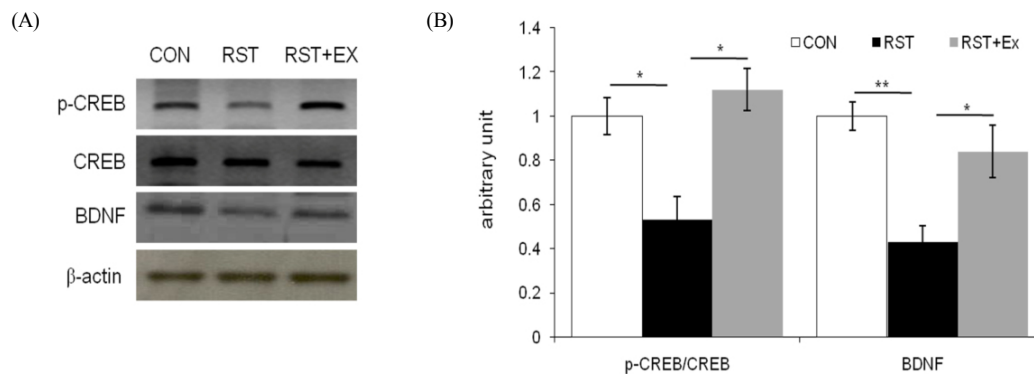
(A)

(B)

Fig. 4. Chronic treadmill running restored the repeated restraint stress-induced deficit in the CREB/BDNF cascade of the hippocampus. (A) Photomicrographs showing phospho-CREB, CREB, and BDNF immunoreactivity. (B) Diagram showing the quantitative analysis for phospho-CREB and BDNF immunoreactivity. Data are presented as the mean ± SE. * and ** denote differences at $p < 0.05$ and $p < 0.01$, respectively.

by chronic treadmill running (CON: $100 \pm 11.98\%$; RST: $156.28 \pm 4.90\%$; RST + Ex: $113.48 \pm 12.16\%$, CON vs. RST $p < 0.05$; RST vs. RST + Ex $p < 0.05$, Fig. 2A). Restraint-induced memory deficit allowed us to assess hippocampal apoptotic cell death. In annexin V/PI staining (Fig. 2B), the apoptotic rate in the restrained hippocampus was higher than that of both the control and restraint with treadmill running, although that of restrained mice with treadmill running for 8 weeks was significantly increased relative to that of control mice (CON: $3.09 \pm 0.35\%$; RST: $15.75 \pm 1.20\%$; RST + Ex: $7.02 \pm 0.70\%$, CON vs. RST $p < 0.01$; RST vs. RST + Ex $p < 0.01$; CON vs. RST + Ex $p < 0.05$). The body weight of control mice was progressive during the experimental period. Restraint stress caused body weight loss regardless of exercise intervention, suggesting that body weight loss can be regarded as a physiological marker of stress.

The 21 consecutive days of restraint stress profoundly enhanced hippocampal GRP78 and CHOP protein levels, which was reversed by 8 weeks of treadmill running

To investigate whether chronic exercise alleviated the

sustained stress-induced ER stress-mediated hippocampal apoptotic pathway, hippocampal GRP78 and CHOP expression levels were determined (Fig. 3). GRP78 expression in restrained mice was significantly enhanced compared with control mice, and this increase was reduced by chronic exercise (CON: $100 \pm 5.54\%$; RST: $153.21 \pm 10.62\%$; RST + Ex: $123.51 \pm 7.50\%$, CON vs. RST $p < 0.01$; RST vs. RST + Ex $p < 0.05$). Hippocampal CHOP protein levels corresponded well to GRP78 expression data (CON: $100 \pm 4.47\%$; RST: $162.38 \pm 6.65\%$; RST + Ex: $116.92 \pm 14.7\%$, CON vs. RST $p < 0.01$; RST vs. RST + Ex $p < 0.05$). Cleaved caspase-3 protein levels were markedly enhanced by restraint stress, which were reduced by chronic exercise (CON: $100 \pm 3.84\%$; RST: $186.51 \pm 8.47\%$; RST + Ex: $121.78 \pm 8.45\%$, CON vs. RST $p < 0.01$; RST vs. RST + Ex $p < 0.01$).

The 21 consecutive days of restraint stress markedly reduced hippocampal phospho-CREB and BDNF levels, which was reversed by 8 weeks of treadmill running

Finally, we measured the hippocampal CREB/BDNF cascade that plays a crucial role in neuronal survival and

cognitive function (Fig. 4). Sustained restraint stress suppressed the phosphorylation of hippocampal CREB, which was averted by chronic treadmill running (CON: $100 \pm 8.40\%$; RST: $53.24 \pm 10.60\%$; RST + Ex: $112.19 \pm 9.51\%$, CON vs. RST $p < 0.05$; RST vs. RST + Ex $p < 0.05$). Hippocampal BDNF levels were also reduced by sustained restraint stress, however this change was reversed in response to chronic treadmill running (CON: $100 \pm 6.50\%$; RST: $43.85 \pm 7.40\%$; RST + Ex: $84.11 \pm 12.00\%$, CON vs. RST $p < 0.01$; RST vs. RST + Ex $p < 0.05$).

DISCUSSION

The present study demonstrates that chronic exercise coped with prolonged stress-induced memory impairment, which occurred concomitantly with an attenuated ER stress response. Repeated or long-lasting psychological stress is well-known to affect the neuronal function and structure of the hippocampus, as evidenced by the production of dendritic atrophy of CA3 pyramidal neurons, the promotion of hippocampal neuronal loss, and the induction of cognitive deficits [4-7]. The hippocampus, a limbic structure, is closely linked to emotional and cognitive functions, which is susceptible to repeated stress [16-17]. Firstly, to elucidate the correlation between repeated stress and the ER stress response, hippocampal GRP78 and CHOP protein levels were measured in mice subjected to restraint stress for 7 days (6 hours/day) using Western blotting. Hippocampal GRP78 and CHOP protein levels were markedly elevated by the 7 consecutive days of restraint stress. Various stimuli that perturb ER homeostasis lead to interference with protein folding, which causes deposits of unfolded and misfolded proteins in the ER lumen, promoting the ER stress response [18]. The unfolded protein response (UPR), one of the ER stress responses, induces the synthesis of ER chaperone GRP78 and enhances the transcriptional activity of CHOP and activating transcriptional factor 6 (ATF6), which maintain normal ER homeostasis [18-19]. However, sustained ER stress activates three ER stress sensors, inositol-requiring kinase 1 (IRE1), protein kinase-like ER kinase (PERK), and ATF6. These different signaling pathways of UPR induce CHOP transcription, thereby triggering caspase-12-mediated apoptotic cell death [20-21]. This result suggests that repeated restraint stress can induce hippocampal ER stress. Next, we investigated whether prolonged stress-induced ER stress and memory deficit were restored by chronic exercise. The escape latency in restrained mice was significantly higher than that of control mice, which is in agreement with other studies reporting that 21 consecutive days of restraint stress induced memory impairment [7,15]. In various neuropathophysiological conditions, neuronal cell death is regarded as a contributing episode to the decrease in hippocampal volume involved in cognitive function [22]. Behavioral data corresponded well to the pattern of apoptotic neuronal cell death in the present study. These results suggest that prolonged stress-induced memory impairment is at least in part attributed to hippocampal neuronal loss. However, this change by prolonged stress was reversed by chronic exercise, suggesting that prolonged stress-induced impairment of memory and enhancement of hippocampal apoptosis can be suppressed by chronic exercise.

Given that prolonged restraint stress induced hippocampal neuronal loss, we investigated whether chronic exercise attenuated ER stress-mediated apoptosis in the hippocampus. Notably, the upregulation of GRP78, CHOP, and cleaved caspase-12 protein levels in restrained mice were profoundly reduced by chronic exercise, suggesting that chronic exercise attenuated prolonged stress-induced ER stress-mediated hippocampal neuronal loss.

To further investigate the mechanism involved in the protective effects of chronic exercise on ER stress-mediated neuronal loss, the hippocampal CREB/BDNF cascade was determined. The phosphorylation of CREB and BDNF levels were significantly lower in restrained mice compared with control mice, and these decreases were enhanced by exercise. Exercise is well-known to activate hippocampal CREB/BDNF signaling, as indicated by increased BDNF levels and CREB phosphorylation [23-24]. BDNF contributes to neuronal survival, synaptic plasticity, and development in the central nervous system [25-26]. In addition, BDNF exerts protective effects on diverse neurodegenerative diseases and neuronal damage [23,25,27-28]. Several studies have demonstrated the potential role of BDNF in ER stress-mediated cell death. For instance, homocysteine-induced ER stress-induced neuronal death was inhibited by hydrogen sulfide through the BDNF-TrkB pathway in the rat hippocampus [29]. The neuroprotective effects of BDNF on ER stress are related to the suppression of CHOP activation, as indicated by the repression of CHOP induction and nuclear translocation, the blocking of the ATF6/CHOP pathway, and the inhibition of death receptor 5 (DR5) induction [30]. Based on previous findings and our present results, exercise-induced BDNF induction may attenuate ER stress-mediated hippocampal neuronal loss through the suppression of CHOP activation.

Collectively, prolonged psychological stress can promote ER stress-mediated hippocampal neuronal loss, thereby causing hippocampal-dependent memory impairment, whereas chronic

exercise can counteract ER stress-induced hippocampal insults through BDNF induction. However, further study is needed to investigate the detailed molecular events by which exercise can ameliorate ER stress.

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