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CHRONIC STRESS-INDUCED MEMORY DEFICITS ARE REVERSED BY REGULAR EXERCISE VIA AMPK-MEDIATED BDNF INDUCTION

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Abstract—Chronic stress has a detrimental effect on neurological insults, psychiatric deficits, and cognitive impairment. In the current study, chronic stress was shown to impair learning and memory functions, in addition to reducing in hippocampal Adenosine monophosphate-activated protein kinase (AMPK) activity. Similar reductions were also observed for brain-derived neurotrophic factor (BDNF), synaptophysin, and post-synaptic density-95 (PSD-95) levels, all of which was counter-regulated by a regime of regular and prolonged exercise. A 21-day restraint stress regimen (6 h/day) produced learning and memory deficits, including reduced alternation in the Y-maze and decreased memory retention in the water maze test. These effects were reversed post-administration by a 3-week regime of treadmill running (19 m/min, 1 h/day, 6 days/week). In hippocampal primary culture, phosphorylated-AMPK (phospho-AMPK) and BDNF levels were enhanced in a dose-dependent manner by 5-amimoimidazole-4-carboxamide riboside (AICAR) treatment, and AICAR-treated increase was blocked by Compound C. A 7-day period of AICAR intraperitoneal injections enhanced alternation in the Y-maze test and reduced escape latency in water maze test, along with enhanced phospho-AMPK and BDNF levels in the hippocampus. The intraperitoneal injection of Compound C every 4 days during exercise intervention diminished exercise-induced enhancement of memory improvement during the water maze test in chronically stressed mice. Also, chronic stress reduced hippocampal neurogenesis (lower Ki-67- and doublecortin-positive cells) and mRNA levels of BDNF, synaptophysin, and PSD-95. Our results suggest that regular and prolonged exercise can alleviate chronic stress-induced hippocampal-dependent memory deficits. Hippocampal AMPK-engaged BDNF induction is at least in part required for exercise-induced protection against chronic stress.
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Key words: chronic restraint stress, treadmill running, learning and memory, AMPK, BDNF.

INTRODUCTION

Stress causes widespread changes to the neurochemical, neurobiological, and behavioral responses of the brain. Accumulating evidence also suggests that chronic stress negatively affects neural plasticity to produce deficits in memory and learning processes (Sandi and Pinelo-Nava, 2007; Krishnan and Nestler, 2008). The detrimental effect of chronic stress on cognitive function is suggested to be modulated by corticosterone (CORT), neurotrophins, oxidative stress, and various neurotransmitters (McGaugh and Roozendaal, 2002; Yamada and Nabeshima, 2003; Sandi and Pinelo-Nava, 2007; Calabrese et al., 2012; Kwon et al., 2013). Among the brain structures affected, the hippocampus is a region commonly implicated in repeated or chronic stress-triggered abnormalities of neural plasticity. Such abnormalities include hippocampal atrophy, decreased neurogenesis, and impaired synaptic plasticity (Watanabe et al., 1992; Sousa et al., 2000; Pham et al., 2003; Han et al., 2015).

Since a large amount of energy is required to fulfill the physiological demands of neurons in the central nervous system (CNS), dysregulation of energy metabolism will deleteriously affect their survival and function. Adenosine monophosphate-activated protein kinase (AMPK) is an energy metabolite-sensing protein kinase that contributes to regulating cellular energy homeostasis (Spasic et al., 2009; Steinberg and Kemp, 2009). The phosphorylation of AMPK on threonine 172, producing phosphorylated-AMPK (phospho-AMPK), stimulates catabolic processes such as glucose uptake, glycolysis, and fatty acid oxidation. Correspondingly, AMPK phosphorylation also suppresses anabolic process, including the synthesis of fatty acid, cholesterol, and protein, to restore cellular energy levels (Hadad et al., 2008; Ronnett et al., 2009). The activation of AMPK through phosphorylation is triggered by ATP depletion (increased AMP/ATP ratio), metabolic stresses (hypoxia, glucose deprivation, oxidative stress), and exercise (Culmsee et al., 2001; Hardie, 2007). Furthermore, AMPK is also

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Abbreviations: ACTH, adrenocorticotrophic hormone; AICAR, 5-amimoimidazole-4-carboxamide riboside; AMPK, adenosine monophosphate-activated protein kinase; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CORT, corticosterone; EGTA, ethylene glycol tetraacetic acid; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; HPX, hypothalamic–pituitary–adrenal; phospho-AMPK, phosphorylated-AMPK; PSD-95, post-synaptic density-95.

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phosphorylated by Ca^{2+}/calmodulin-dependent protein kinase β, suggesting that the kinase activity of this molecule is regulated indirectly by intracellular Ca^{2+} levels (Woods et al., 2005). As addressed above, AMPK is considered to play a crucial role in CNS neuronal responses to various physiological and pathological stimuli, particularly within the hippocampus. Supporting this, modest activation of AMPK in the hippocampus by diet restriction improves cognitive function and enhances hippocampal neurogenesis (Dagon et al., 2005). Similarly, Resveratrol treatment elicits activation of hippocampal AMPK and alleviates prenatal stress-induced memory impairment in pups (Cao et al., 2014). These articles suggest a potential role for hippocampal AMPK activation in the modulation of cognitive function. Furthermore, a recent study showed that the induction of unpredictable chronic mild stress for a 4-week period results in the inactivation of AMPK and the emergence of abnormal mood-related behaviors (Zhu et al., 2014). The anti-depressive actions of ketamine appear to require both availability of brain-derived neurotrophic factor (BDNF) and AMPK activation, with the activation of AMPK causing induction of BDNF expression (Yoon et al., 2008; Autry et al., 2011; Xu et al., 2013). The neuroprotective role of BDNF and its link to cognitive function is well established. BDNF contributes to the promotion of long-term potentiation, enhanced synaptic plasticity, and improved cognitive function (Conner et al., 1997; Duman and Monteggia, 2006). Judging from these studies, alterations in hippocampal AMPK activity may be linked to stress-induced memory impairment.

Physical exercise is renowned for its ability to improve brain function, influencing both cognitive function and mood (Hillman et al., 2008). In particular, the effect of exercise on performance in hippocampal-dependent memory tasks is believed to be associated with hippocampal neurogenesis, synaptic plasticity and neurotrophins (Eadie et al., 2005; Gomez-Pinilla et al., 2008; Hillman et al., 2008; van Praag, 2008). In addition, AMPK is highly expressed in brain regions such as the hippocampus and plays a crucial role in exercise physiology (Hardie, 2004; Spasic et al., 2009). However, the

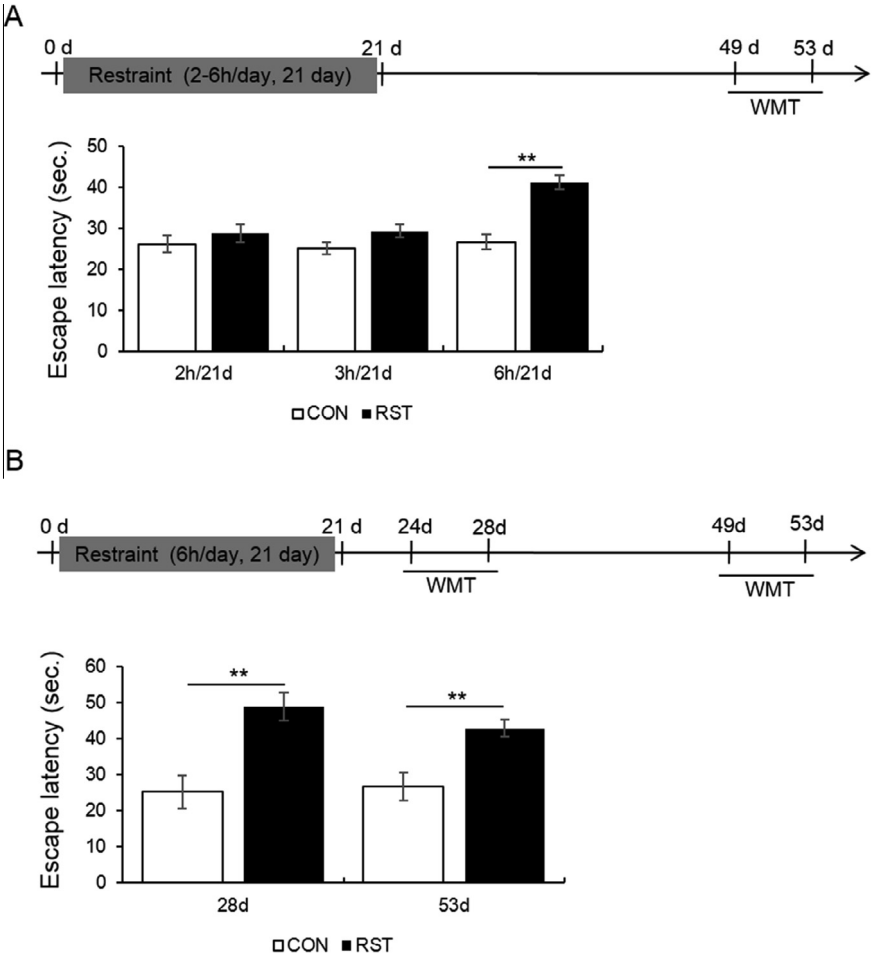

Fig. 1. A 21-day restraint stress (6 h/day) caused memory decline and this effect continued up to 4 weeks, but not 2–3 h/day. (A) Quantitative analysis of the escape latency on the final day of water maze testing. The escape latency of stressed mice was enhanced compared with that of control mice on day 28 (for 2 h/21 days $t_{14} = -0.87$, $p > 0.05$; for 3 h/21 days $t_{14} = -1.90$, $p > 0.05$; for 6 h/21 days $t_{14} = -5.71.90$, $p > 0.01$). (B) Quantitative analysis of the escape latency on the final day of water maze testing. The escape latency of stressed mice was enhanced compared with that of control mice on days 28 ($t_{14} = -11.20$, $p < 0.01$) and 53 ($t_{14} = -9.98$, $p < 0.01$). Data are presented as mean ± SEM. **Denote differences at $p < 0.01$.

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