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Research Report

Regular treadmill running improves spatial learning and memory performance in young mice through increased hippocampal neurogenesis and decreased stress

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ABSTRACT

A substantial amount of evidence has shown that treadmill running enhances neurogenesis, improves cognitive function, and protects the brain against neurodegenerative disorders. However, treadmill running is a type of forced exercise that could increase the level of corticosterone, which subsequently down-regulates neurogenesis and impairs cognitive function. The purpose of this study was to investigate if regular treadmill running provides a balance between the positive and negative effects of treadmill running. The mice were divided into four groups: controls (CON), regular runners (RR), irregular duration runners (IDR) and irregular time-of-day runners (ITR). The RR mice ran daily on the treadmill at the same time-of-day, speed and duration. The IDR mice ran at the same time-of-day and speed, but for a different duration. The ITR mice ran at the same speed and duration, but at different time-of-day. The results showed that regular treadmill running could increase neurogenesis and improve spatial learning and memory performance, as well as decrease the level of corticosterone. The present finding emphasizes the importance of regular physical exercise on cognition.

1. Introduction

Neurogenesis in the adult mammalian brain occurs throughout life. Many epigenetic and genetic factors are associated with differential regulation of adult hippocampal neurogenesis. Enriched environments and exercise are known to enhance neurogenesis and improve learning and memory (van Praag et al., 1999a, 1999b; Fuss et al., 2010a), whereas

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aging and stress impair neurogenesis and cause learning deficits (Gould et al., 1997; Tanapat et al., 2001; Drapeau et al., 2007).

Two common types of exercise regimes have been used in previous studies, voluntary wheel running (Dunn et al., 1996; Van Praag et al., 1999a, 1999b) and forced treadmill running (Anderson et al., 2000; Kim et al., 2003; Ra et al., 2002). Both paradigms have been shown to enhance neurogenesis, learning and memory (Clelland et al., 2009; Fordyce and Farrar, 1991; Ang et al., 2006; Van Praag, 2008). In the voluntary wheel running model, the animals can freely run when they desire, while forced treadmill running is characterized by having the animals run in adherence to specific experimental designs (i.e., predetermined time, duration and intensity), which is arguably more objective in terms of the outcome measure as it allows for a more accurate correlation between the amounts of exercise and any potential benefits arising therefrom.

Studies have suggested that the effect of exercise on neurogenesis is modulated by both the time-of-day and intensity of the daily exercise (Holmes et al., 2004; Tamai et al., 2008). Regular exercises have vast beneficial effects on a variety of biological systems. Research interests on the neurological implications of regular exercise have also intensified, yielding evidence demonstrating positive effects on brain function (van Praag et al., 2005; Wolf et al., 2006). Conversely, corticosterone release appears to be enhanced in association with running regardless of the circadian time (Sellers et al., 1988). Exercise-induced increases in neurogenesis may be counterbalanced by stress, which has a suppressive effect on neurogenesis (Snyder et al., 2009), while study has showed that beneficial effects of running on neurogenesis are not negatively influenced by the increased corticosterone levels (Fuss et al., 2010b). Acute stress increases hippocampal cell proliferation and improves the adaptive capacity of brain (Kirby et al., 2013). Furthermore, animals, including humans, show improved coping with stressful events after regular performance of moderate physical exercise (Steptoe et al., 1989; Byrne and Byrne, 1993; Salmon, 2001).

Stress is a rapid and direct response to extrinsic/intrinsic stimuli. As a corresponding response, the system generally returns to a basic homeostatic state within hours or days by means of intrinsic adaptation mechanisms. This notion is supported by the observation that long-term treadmill running does not change basal levels of serum corticosterone and downregulates the level of hippocampal mineralocorticoid receptor (Wu et al., 2007; Droste et al., 2003).

Previous studies have investigated the effects of running within the circadian rhythm and utilized a voluntary running paradigm. Varying run durations, run velocities, and circadian rhythms have made it difficult to discern the effect of time-of-day from the duration of activity. We divided mice into four groups according to time-of-day and duration of activity: controls (CON), regular runners (RR), irregular duration runners (IDR) and irregular time-of-day runners (ITR). The RR mice ran daily on the treadmill at the same time-of-day, speed and duration. The IDR mice ran at the same time-of-day and speed, but for a different duration. The ITR mice ran at the same speed and duration, but at different time-of-day. The objective of this study was to evaluate the effects of regular treadmill running on neurogenesis in the dentate gyrus of young mice, and associated cognition ability. We also measured the levels of plasma corticosterone in the short and long term, and attempted to associate their levels with neurogenesis. We selected treadmill running as an exercise paradigm to precisely control the intensity, duration and time-of-day of running. The purpose of this study was to gain an understanding of which specific training regimes were more beneficial to cognitive function (Fig. 1).

2. Results

2.1. *Short-term and long-term survival of BrdU-labeled dentate cells*

The number of BrdU-labeled cells was assessed at two time-points: day 8 and day 29. The number of BrdU-labeled positive cells on day 8 was used as a short-term indicator of cell survival in the hippocampus; the number of BrdU-labeled positive cells on day 29 was estimated as the long-term survival of newborn cells. On day 8, a significant difference was found between the groups ($F(3,28)=690.49$, $p<0.001$). Post-hoc comparisons showed that the RR group had more BrdU-positive cells than those of any of the other groups examined ($p<0.001$, Fisher test). In addition, there were fewer BrdU-positive cells in the CON group than those of the three treadmill running groups ($p<0.001$, Fisher test; see Fig. 2A, C). The results suggested that treadmill running could increase cell genesis in the dentate gyrus of mice.

On day 29, cells in the dentate gyrus of the hippocampus were analyzed for the expression of BrdU and for co-expression of BrdU and NeuN. A higher number of surviving cells were observed in the RR group than in any of the three other groups ($F(3, 28)=186.23$, $p<0.001$; see Fig. 2B, C). In addition, the number of surviving cells was higher in the three running groups than in the CON group ($F(3, 28)=186.23$, $p<0.001$; see Fig. 2B, C).

A higher number of BrdU/NeuN-positive co-labeled cells were observed in the three running groups than in the CON group ($F(3,28)=5.92$, $p<0.05$; see Fig. 2B, D). The percentage of BrdU/NeuN-positive cells was significantly greater in the RR group than in the IDR group ($F(3,28)=5.92$, $p=0.022$) or CON group ($F(3,28)=5.92$, $p<0.001$) (See Fig. 2B, D). Thus, we speculated that the regularity of running along with the duration of running produced a synergistic effect promoting neuronal differentiation and survival in cells of the hippocampal dentate gyrus of young mice.

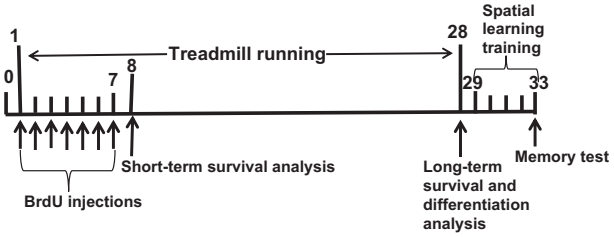

Fig. 1 – Experimental timelines (see methods for details).

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