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Exercise Increases Neural Stem Cell Number in a Growth Hormone-Dependent Manner, Augmenting the Regenerative Response in Aged Mice

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ABSTRACT

The exercise-induced enhancement of learning and memory, and its ability to slow age-related cognitive decline in humans led us to investigate whether running stimulates periventricular (PVR) neural stem cells (NSCs) in aging mice, thereby augmenting the regenerative capacity of the brain. To establish a benchmark of normal aging on endogenous NSCs, we harvested the PVR from serial vibratome sections through the lateral ventricles of juvenile (6-8 weeks), 6-, 12-, 18-, and 24-month-old mice, culturing the cells in the neural colony-forming cell assay. A significant decline in NSC frequency was apparent by 6 months (~40%), ultimately resulting in a ~90% reduction by 24 months. Concurrent with this decline was a progressive loss in regenerative capacity, as reflected by an incomplete repopulation of neurosphere-forming cells following gamma cell irradiation-induced depletion of the PVR. However, voluntary exercise (i.e., 21 days of running) significantly increased NSC frequency in mice ≥ 18 months of age, augmenting the regeneration of irradiation-ablated periventricular cells and restoring NSC numbers to youthful levels. Importantly, and consistent with the demonstrated ability of growth hormone (GH) to increase NSC proliferation, and the elevated secretion of GH during exercise, exercise failed to stimulate NSCs in GH receptor-null mice. These findings now provide a novel basis for understanding the ability of exercise to delay the onset and rate of decline in neurodegenerative conditions not typically associated with the hippocampus and suggest that the GH-dependent activation of endogenous NSCs may be effective in reversing or preventing age-related neurodegeneration in humans. STEM CELLS *2009;27:2044–2052*

Disclosure of potential conflicts of interest is found at the end of this article.

INTRODUCTION

In addition to its beneficial effects in humans such as enhanced memory and learning and improved executive function, physical exercise is known to increase brain volume in regions prone to age-related cognitive decline, suggesting a biological basis for its ability to reduce the risk of developing neurodegenerative disorders including Alzheimer's disease [1, 2]. Rodent studies have corroborated human trials by demonstrating that voluntary running in both young and aged mice increases hippocampal neurogenesis, resulting in improved performance in water and radial arm mazes, and in object recognition [3–6]. Moreover, running can also prevent the age-related decline in hippocampal progenitors and slow the decline in hippocampal neurogenesis that accompanies old age [7]. Because neural stem cells (NSCs) are considered to underpin the regenerative capacity of the brain, we hypothesized that running would increase NSC frequency in aged mice, resulting in an augmented regenerative response.

The absence of specific NSC markers has traditionally limited direct investigation of the effects of age on endogenous NSCs, forcing investigators to rely on indirect functional readouts such as the neurosphere assay. As such, only three studies have attempted to address this question to date, with agreement that aging results in a decline in proliferating (i.e., bromodeoxyuridine-positive, $BrdU^{+ve}$) cells in the rostral periventricular region (PVR, a 3- to 5-cell-thick region lining the lateral ventricles enriched in stem and progenitor cells) [8, 9], but disagreement that a decline in neurosphere-forming cells (SFCs) also occurs [10]. Therefore, we undertook a systematic analysis of the effects of age on stem and progenitor cells in the mouse brain by examining the number of $BrdU^{+ve}$ cells (assaying all dividing cells) and SFCs (assaying NSCs and more restricted progenitor cells) within the PVR along the lateral ventricles. Given our recent demonstration that

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