OVERCOMING THE AGE-ASSOCIATED DECLINE IN NEURAL STEM CELL PROLIFERATION

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The U.S. population is aging. Age-related cognitive decline is a major public health problem. Developing an approach to treat or delay cognitive decline is critical. Neurogenesis by neural stem/progenitor cells (NSCs) in the hippocampus is related to cognitive function, and is greatly affected by the aging process. The molecular signaling that regulates age-related decline in neurogenesis is still poorly understood. Here we took the advantage of a transgenic mouse, Nestin-GFP, to assess neurogenesis and molecular signaling related to age-related decline in neurogenesis. We found that the total number of NSCs, including quiescent neural progenitors (QNPs) and amplifying neural progenitors (ANPs) decreased as the mice aged, but more importantly, ANPs are more significantly affected than QNPs, leading to further reduction in number and proliferation of ANPs. We further found that the mTOR signaling pathway is impaired in NSCs as mice age. Activating the mTOR signaling pathway through Ketamine injections increased NSC proliferation in aged mice. In contrast, inhibiting the activity of the mTOR signaling pathway by rapamycin is sufficient to reduce ANP proliferation in young mice. These results indicate that NSCs becomes more quiescent when the activity of mTOR signaling is compromised in aged mice, and stimulating the activity of mTOR signaling can overcome the age-associated decline in NSC proliferation. This data suggests that promoting stem cell proliferation to enhance neurogenesis may be a potential approach for attenuating cognitive decline in the aging brain.

This work was supported by funding from the Ralph W. and Grace M. Showalter Research Award, Indiana University Biological Research Grant, NIH grants RR025761 and 1R21NS072631-01A, and Undergraduate Research Opportunities Program (UROP).