Enhancing Neurogenesis in the Aging Brain through mTOR Pathway Activation

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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 become 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. Following stimulation of the mTOR signaling pathway with Ketamine, we found a significant increase in the number of mature neurons. In order to determine whether or not a further increase in hippocampal neurogenesis is possible, we will next examine the ratio of newborn neuron survival.

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