CAPSTONE

An overview of exercise-induced hippocampal neurogenesis

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Exercise is widely recognized as an essential component in the maintenance of one's physical health, including clinical benefits in the prevention of obesity and cardiovascular disease. A promising area of developing research is exploring the neurophysiological effects of physical activity on neurogenesis and cognitive enhancement. Research suggests there are a diverse number of potential mechanisms that can explain how exercise is involved in the mediation of neurogenesis and the resulting effects on cortical plasticity and cognitive enhancement.[1] The hippocampus provides an excellent model to study the role of exercise in relation to neurogenesis, as other mammalian species exhibit neurogenesis in the hippocampus throughout adulthood.[2] The bulk of current research seems to conclude that exercise and neurogenesis are intertwined, but that relationship is still poorly understood. The adult hippocampal dentate gyrus is an area where neurogenesis occurs and is sensitive to extrinsic and intrinsic factors, i.e. exercise or genetic disposition.

There are two zones where neurogenesis is known to occur, the olfactory bulb and the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG).[3] In the hippocampus, neural progenitor cells undergo division, differentiate, migrate, and integrate into the existing circuitry.[4] The dendrites of these newborn cells migrate to the molecular layer of the dentate gyrus and their axons migrate to the cornus ammonis 3 (CA3) region via the mossy fiber pathway. The addition of new neurons in existing circuitry can aid in synaptogenesis. Research suggests a relationship between important neurotrophins such as brain-derived neurotropic factor (BDNF), insulin-like growth factor 1 (IGF-1), and vascular endothelial growth factor (VEGF) and exercise-induced adult neurogenesis.[1] It is likely that interplay between multiple mechanisms contribute to neurogenesis and cortical plasticity. The following review will attempt to provide clarity on the roles of BDNF, IGF-1, and VEGF in relation to exercise-induced hippocampal neurogenesis.

Hippocampal neurogenesis

While there is some controversial research that suggests adult hippocampal neurogenesis ceases throughout adulthood, there is research that suggests otherwise.[5,6] The dentate gyrus (DG) subregion of the hippocampus is associated with memory, pattern recognition and mood regulation.[7] The generation of new neurons in the DG is a form of neural plasticity that occurs throughout life.[8] One study provided evidence of adult neurogenesis in the human brain that came by showing the presence of positive staining for 5-bromo-2′-deoxyuridine (BrdU) in the DG of postmortem brain sections from cancer patients who had received BrdU injections in life.[9] Another study using radiocarbon dating to track cell division in the brain found consistent neural turnover in the hippocampus and estimates approximately 700 new neurons are added to the adult human hippocampus each day.[6] Newly generated neurons in this region are sensitive to synaptic plasticity during their maturation and can account for up to ten percent of the entire granule cell population.[10,11] In the DG, newborn neurons migrate approximately 20 to 25 μm from the subgranular zone (SGZ) to the granule cell layer (GCL), where they are integrated.[3] The newborn hippocampal neurons are believed to aid in the functioning of the hippocampus and may play an integral role in hippocampal-dependent learning, memory, and pattern separation.[12]

In response to these findings, the major point of interest is in addressing how to support neurogenesis in the hippocampus.

Linking exercise to hippocampal neurogenesis

It has been demonstrated that moderate exercise increases the size of the hippocampus in humans.[13] BDNF, IGF-1, and VEGF have been recognized as primary mediators of adult neurogenesis, though there are many potential factors associated with the benefits of exercise on hippocampal neurogenesis.[14,15,16,17] BDNF is vital for many factors contributing to neurogenesis, including proliferation, differentiation, maturation, and survival.[17] One study reported that physical exercise in aging populations effectively aided in the reduction of age-related loss in hippocampal volume in addition to increased levels of BDNF.[13] Another study demonstrated that metabolic derivatives from muscles and endurance factors stimulate BDNF expression in the brain and lead to improved spatial memory in mice.[18] Another factor, IGF-1, appears to be upregulated following physical exercise in rodents.[19] Additionally, transgenic overexpression of IGF-1 during postnatal development promotes neurogenesis and synaptogenesis in the DG, though it is important to note the relationship between IGF-1 and neurogenesis is still poorly understood. VEGF is expressed in the CNS and is shown to be upregulated following acute exercise.[15,20,21] VEGF is associated with an increase of new vasculature tissue in the hippocampus, and it is reasonable to suspect a necessity for increased nourishment via blood flow to support newborn neurons.[20] The interplay between neurotropic factors such as BDNF, IG-1, and VEGF, among others, are vital in the proliferation, maturation, and survival of newborn neurons in the hippocampus.

In humans, exercise-related research demonstrated enhancements in spatial learning, pattern separation, executive function, working memory, and processing speed.[22] Additionally, a meta-analysis study demonstrated that 1 to 12 months of exercise in healthy adults induces behavioral benefits, such as increases in memory, attention, processing speed, and executive function.[23] Midlife exercise intervention has been associated with reduced risks of developing dementia, suggesting that exercise may aid in the prevention of developing age-related cognitive decline. [24]

Future directions

With a prevalence of cognitive decline associated with neurodegenerative diseases among the aging populations, physical exercise, a potent enhancer of adult hippocampal neurogenesis, has emerged as a potential preventative approach to reduce cognitive decline. Research suggests that neurogenesis in the DG plays an important role in hippocampal-dependent learning and memory.[1] Further understanding of this relationship could lead to therapies focused on cognitive preservation of healthy aging individuals and potential therapeutic remedies for those suffering from neurodegenerative disorders, such as Alzheimer’s or Parkinson’s disease. Several clinical human studies and abundant animal studies have attempted to understand the functional role of adult hippocampal neurogenesis in specific forms of hippocampal-dependent learning and memory, but there is much research to be conducted in humans to assess this relationship. Using cognitive learning assessments after exercise in humans does not point to hippocampal neurogenesis, and so, future directions may find clarity to this dilemma in post-mortem assessments of subjects that have engaged in exercise-related research prior to death. Additionally, there is preliminary research that suggests neurogenesis may also occur in other brain regions, including the amygdala and hypothalamus, which may explain the broad scope of exercise-induced benefits.[25] This promotes the idea that exercise is an essential aspect in the maintenance and physiological success of healthy adults. Exercise is a cost-effective, low-tech method of preserving and increasing cognition and warrants further explanation and clarity to determine where future research could be focused, i.e. via human studies that can help guide potential therapeutic strategies for cognitive decline. While concrete links between physical exercise, increase adult hippocampal neurogenesis and improved cognition are remain unclear due to the current technical limitations, there is enough evidence to support the notion that exercise is worth investing time in.

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