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Exercise and Enrichment Recruit Positive Factors for Hippocampus Plasticity and Cognitive Enhancement

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Short Communication

The hippocampus plays critical roles in consolidation of information from short- to long-term memory, as well as spatial navigation, which are defined as cognitive function. A number of lifestyle interventions are proven to be cognitive enhancers, such as physical exercise, Environmental Enrichments (EE) including mental stimulation, social stimulation, such as reading a favorite book, playing games, participation in group activities or a targeted cognitive training. These non-pharmacological cognitive enhancers circumvent the ethical considerations associated with pharmaceutical or technological cognitive enhancement. Meanwhile, they are low in cost and low risk to health and well-being. The effects of exercise and EE on enhancing cognitive function have been attributed to the hippocampal plastic changes including *neurogenesis*, *synaptogenesis* and *angiogenesis*. Some of the cellular mechanisms, such as the increased expression of growth factors, signal pathway, likely underlie each of these changes.

Neural Stem/Progenitor Cells (NSPCs), the major role in *neurogenesis*, are present throughout life in the Subgranular Zone (SGZ) of Dentate Gyrus (DG) and Subventricular Zone (SVZ). Approximately 700 newborn granular neurons are formed every day in the adult human DG [1]. NSPCs in the SGZ differentiate into the granular cells which anchor within the granular layer of the DG establishing synaptic connections with the neighbor neurons to maintain the hippocampal functions. It has been reported that exercise exerts positive effect the adult hippocampal *neurogenesis* in all aspects, including cell proliferation, survival, differentiation and recruitment in the DG [2-5]. Researchers discovered that exposure to EE also showed significantly high differentiation of newborn cells into granular neurons in hippocampus [6,7]. More recently, several reports suggested that the notable EE-induced increase in adult *neurogenesis* was attributed to physical activity associated with exercise [8,9].

Formation of new synapses is much critical to store new information in the brain. Granular cells in the DG sprout mossy fibers targeting and forming synaptic connect with neurons in the Cornu Ammonis 3 (CA3) area of the hippocampus, which is an important part of the neural trisynaptic circuit in maintaining cognitive function. It has been reported that exercise significantly increased the levels of synaptic vesicle proteins synaptophysin and synapsin-I indicating the exercise-induced *synaptogenesis* [10-12]. As well, the common exercise running increases the density of dendritic spines and mossy fibre sprouting in granule cells in DG and CA1 pyramidal neurons in hippocampus and layer III pyramidal neurons in entorhinal cortex [13,14].

There are evidences to support the exercise or EE-induced *angiogenesis* in the hippocampus, motor cortex and cerebellum [2,15-18]. It has also been suggested that *angiogenesis* increases circulation which deliver more nutrient metabolites, hormones, growth factors and oxygen to the cognition-related brain regions, and also facilitate metabolic waste disposal, leading to increased cell survival and enhanced *neurogenesis* [19]. Thus, *angiogenesis* could be another key mechanism mediating exercise or EE-induced cognitive enhancement (Figure1).

According to the studies, it is speculated that the molecules such as nutrient metabolites, hormones, growth factors and oxygen in circulation or the local brain region may attribute to the exercise or EE-induced hippocampal plasticity. The following potential trophic factors whose expression can be induced by exercise and EE likely show the critical effects during the plastic processes.

Brain-Derived Neurotrophic Factor: Studies have shown that exercise significantly increases peripheral and central levels of Brain-Derived Neurotrophic Factor (BDNF) [20-22], which have been reported to be involved in several functions such as enhancing neuronal survival, *neurogenesis*

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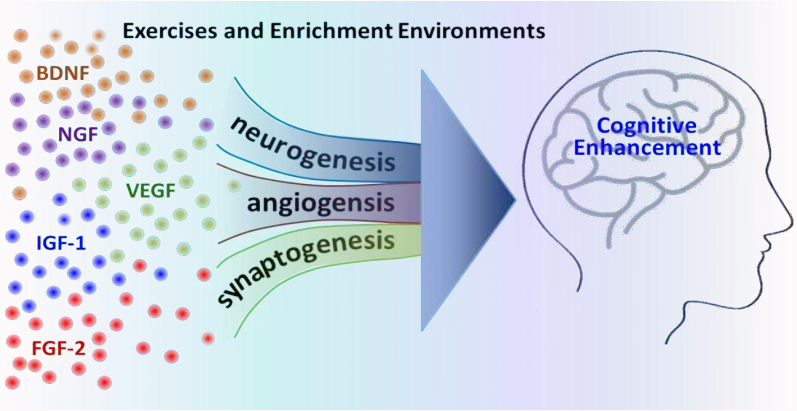

Figure: The trophic factors mediate exercise and EE-induced cognitive enhancement.

and cognition [21,23]. BDNF administration can induce a form of LTP and improve hippocampus-dependent learning [24-26]. BDNF is able to regulate neuronal growth and survival, which was reported to be involved in the exercise-increased brain's resistance to damage and degeneration [27]. BDNF was found to be robustly involved in *neurogenesis* because the *neurogenesis* was attenuated by BDNF knockdown in the adult DG, but increased in response to exogenous BDNF injection [28,29]. Dendritic growth in adult hippocampal neurons was also decreased after BDNF deletion and increased after BDNF overexpression [30]. The evidences indicate that exercise-induced *synaptogenesis* may be a BDNF-dependent process [10-12].

Basic Fibroblast Growth Factor: In the adult CNS, the basic Fibroblast Growth Factor (FGF-2) and its receptors (FGFR) are expressed by astrocytes and neurons located in the SVZ and SGZ, as well other brain regions [31,32]. After birth, FGF-2 is concentrated primarily in the hippocampal subfields CA1-3, and in neurons of the medial septum and the vertical limb of the diagonal band nuclei. Within the mature hippocampus, the CA2 region is the primary area of neuron-derived FGF-2 expression [33], suggesting that FGF-2 may play a role in the development and function of the adult hippocampus. Studies suggested that exercise and EE both increased peripheral and central level of FGF-2, which showed the positive effect on hippocampal *neurogenesis*. For example, loss of FGF-2 in animals caused decrease in adult hippocampal *neurogenesis*. However, these defects could not be rescued by exogenous FGF-2 [34]. Yoshimura et al. reported that hippocampal *neurogenesis* increased in normal adult mice after brain injury, but this phenomenon did not appear in FGF-2 knockout adult mice [35]. These results indicated that endogenous FGF-2 is necessary to stimulate *neurogenesis* in the adult hippocampus. Genetic deletion of FGFR1 resulted in reduced proliferation of hippocampal NSPCs and reduced hippocampal volume during embryonic and postnatal development [36]. These studies suggested that the FGF-2/FGFR system mediates *neurogenesis* in the adult hippocampus. FGF-2 is also a strong pro-angiogenic factor acting as a stimulator of endothelial cell migration, proliferation, sprouting, and tube formation [37,38]. FGF-2 was also proven to be able to enhance hippocampal *synaptogenesis*, including increase of excitatory synapses and synaptic cycling vesicles on hippocampal neurons [39].

Nerve Growth Factor: Early studies confirmed that Nerve Growth Factor (NGF) is crucial for neuronal survival and growth, especially the cholinergic neurons, and neurotransmission in both the CNS and peripheral nervous system [40,41]. Recent reports indicated that continuous NGF infusion promotes proliferation and *synaptogenesis* in the hippocampus and enhanced survival of new neurons in the DG granule cell layer of young adult rats [42,43]. Neurogenic conditions in the hippocampus may be enhanced by the synergistic interactions of NGF and its receptor, TrkA, as well as by NGF-mediated cholinergic regulation. Finally, intracerebroventricular NGF infusion rescued hippocampal *neurogenesis* deficiencies in a transgenic mouse model of Huntington's disease [44], suggesting that the effects of NGF on neuroplasticity likely support the treatment of this disease through exercises or EE.

Insulin-like Growth Factor 1: IGF-1, primarily produced in the liver, plays a major role in brain development. It may link the systemic and the central changes induced by exercise. IGF-1 deletion or blockage of its receptors markedly impaired exercise-induced cognitive enhancement that would be ameliorated by exogenous IGF-1 administration [11,45]. Reports showed that IGF-1 directly or indirectly improves the proliferation, survival, and neuronal differentiation of NSPCs, as well prevents their apoptosis in the SGZ of the adult mammalian [46-48]. Zhu and colleagues not only demonstrated its neurotrophic property, but also showed that IGF-1 could enhance neurovascular regeneration in a mouse model of permanent focal cerebral ischemia [49]. The evidences that IGF-1 stimulates an increase in the density of spines in the basal dendrites of CA1 pyramidal neurons while a decrease in the serum IGF-I levels causes a reduction of glutamatergic boutons in the hippocampus [50,51]. This finding suggests that IGF-I can promote hippocampal synapse formation and/or maintenance.

Vascular Endothelial Growth Factor: Peripheral Vascular Endothelial Growth Factor (VEGF) is mainly produced by skeletal muscles. Exercises can increase level of VEGF in skeletal muscle and hippocampus [52]. However, effect of exercise on VEGF expression in the hippocampus is very little. Peripheral VEGF must cross the Blood-Brain Barrier (BBB) to show the functions in the brain. The BBB permeability may increase in response to exercise, providing a potential route for signaling proteins to enter the brain parenchyma from the circulation. VEGF is a strong *angiogenesis* factor, as well shows neurotrophic and neuroprotective effects [53-56].

As the most important mitogen in the process of *angiogenesis*, VEGF plays a role in the angiogenic effects of exercise [57,58]. Pharmacological blockade of *angiogenesis* in the hippocampus impairs spatial learning [59]. The *angiogenesis* is mediated by the binding of VEGF to its receptors on the surface of endothelial cells

through activation of intracellular tyrosine kinases and the multiple downstream signals.

In concert with the *neurogenesis*, VEGF also play an important role in exercise-induced adult hippocampal *neurogenesis* because the increased number of newborn neuronal precursor cells in the hippocampus were not present in adult conditional skeletal myofiber-specific VEGF gene-ablated mice [60,61], suggesting that VEGF expressed by skeletal myofibers may directly or indirectly regulate hippocampal *neurogenesis*. In addition, VEGF secreted in the adult hippocampal NSPCs are known to functionally maintain the neurogenic niche [62]. Specific loss of VEGF in NSPC resulted in impairment of stem cell maintenance although VEGF produced from other cell types was still present [62]. Evidence from knockout mice indicated that hippocampal *neurogenesis* was impaired in VEGF B-KO mice, whereas intraventricular administration of VEGF B restored *neurogenesis* to control levels [63]. These findings suggested that VEGF is involved in *neurogenesis* in the adult hippocampus. Indeed, increasing evidence has shown that VEGF acts as a molecular mediator for adult hippocampal *neurogenesis* and is upregulated by antidepressant treatments including drugs, electroconvulsive seizure [64,65], exercise, and enriched environments [66,67], indicating that VEGF is a promising target for treatment of neural disorders.

In conclusion, the processes of *neurogenesis*, *synaptogenesis* and *angiogenesis* are known as the main mechanisms mediating the exercise or EE-induced cognitive enhancement. The upregulation of these factors may be the critical molecules promoting the above processes. Certainly, it appears that exercise or EE simultaneously stimulates upregulation of several growth factors who would exert the angiogenic, neurogenic and synaptogenic promotion effects at the same time. Keeping exercises and enrichments keep youth.

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