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EXERCISE PREVENTS AGE-RELATED MEMORY DECLINE: THE ROLE OF NEUROTROPHIC FACTORS

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ABSTRACT

Increasing aging population causes an increased prevalence of neurodegenerative diseases such as dementia that is associated with memory decline. Developing strategies for the prevention and therapy of age-related dementia is important to reduce the burden of treatment costs. Physical exercise is known to prevent cognitive decline and improve cognitive abilities. Thus, physical exercise appears as a simple, inexpensive, and affordable non-pharmacological therapy for most people. The processes of neurogenesis and neuronal survival involve the role of neurotrophic factors including BDNF, IGF-1 and VEGF, which are the three main neurotrophic factors that are known to increase after exercise. Many publications discuss about these neurotrophic factors, but their mechanism of signals and changes related to aging and exercise have not been completely studied.

Keywords: Exercise, aging, BDNF, IGF-1, VEGF

Introduction

Aging is unavoidable and unalterable process. The increasing aging population in the world is caused by improved medical care and decreased fertility. World Health Organization reported that there were 900.9 million people aged 65 years or above in 2015 and the number was expected to increase up to 2092 million by 2050.¹ Aging is the major risk factor for neurodegenerative diseases, such as dementia which is initially characterized by memory decline.² The population of dementia will continue to increase along with the increasing number of aging population. There are approximately 36.6 million people suffering from dementia, and it was expected to double up by 2030. Therefore, one of the greatest health threats in many countries is aging-related dementia, which costed US \$ 818 billion in 2015 worldwide.³

Developing strategies for the prevention and treatment of age-related dementia is important to reduce the burden of treatment costs. Unfortunately, until now there has been no effective pharmacological therapy for aging-related dementia. Therefore, the development of non-pharmacological prevention and treatment is a potential alternative therapy for these neurodegenerative disorders. Physical exercise can be an inexpensive and affordable non-pharmacological therapy in preventing age-related cognitive decline. Prior studies have revealed that exercise or physical activity were able to give neurological advantage and

preservative effects on the brain, prevent cognitive decline and improve cognitive performance.⁴⁻⁶ Research using animal models showed that exercise increased neurotrophic factors, glial cells activity and cerebral blood flow which led to increased neurogenesis and neuron cell survival.⁴⁻¹⁰

Neurotrophic factors such as brain derived neurotrophic factor (BDNF), insulin-like growth factor (IGF-1) and vascular endothelial growth factor (VEGF) are known to be the main mediators of neurogenesis in the adult brain. Physical exercise causes an increased BDNF gene expression in the hippocampus. In addition, physical exercise also causes increased levels of IGF-1 and VEGF in the peripheral, subsequently enters the brain through the blood brain barrier and triggers the process of neurogenesis, thus maintaining cognitive function.¹¹ These neurotrophic factors including BDNF, IGF-1 and vascular VEGF have been widely studied, with evidence of the large number of publications discussing these neurotrophic factors. However, the mechanism of signals and changes of these neurotrophic factors related to aging and exercise have not been completely studied. In this article the mechanism of signals and changes of these neurotrophic factors related to aging and exercise are highlighted.

Neurotrophic Factors, Aging Brain and Exercise

Neurotrophic factors are proteins that function as mediators for the neuronal proliferation, differentiation, and survival. The three main neurotrophic factors that are known to increase after exercise and can further the neuronal growth and proliferation are brain-derived neurotrophic factor (BDNF), insulin-like growth factor-I (IGF-1) and vascular endothelial growth factor (VEGF).¹² The aging process is associated with a decreased activity of these neurotrophic factors activity.

BDNF, aging brain and exercise

¹⁹ Brain-derived neurotrophic factor (BDNF) is a member of neurotrophin family that is expressed in the hippocampus, cortex, hypothalamus, septum, and in adrenergic brain stem nuclei and is highly concentrated in the hippocampus.^{12,13} BDNF play a role for neuronal growth, differentiation, and survival, synaptic plasticity, proliferation of dendritic arbor, axonal sprouting, regulates LTD (long-term depression) and LTP (long-term potentiation).^{31,2,14} The expression of this neurotrophic factor in the peripheral and central nervous systems is influenced by stress, nutrition, behavior and metabolism.¹⁴

BDNF is derived from pro-isoform BDNF which will form a mature BDNF protein after undergoing proteolytic breakdown in neurons or after being released. BDNF protein will bind to protein-kinase neurotrophin receptors – tropomyosine-related kinase (Trk) receptors. The interaction between BDNF and its receptors causes the activation of several major signaling pathways that play a role in stimulating synaptic plasticity, neuronal proliferation, differentiation and survival, including PI-3 kinase, MAP kinase and phospholipase-c- γ .^{15,16} The binding of BDNF with Trk receptor subsequently activates cAMP-responsive element-binding protein (CREB). CREB is a transcription factor that plays a role in regulating the process of neuronal proliferation, differentiation and survival. Therefore, CREB plays an important role in neuronal plasticity, memory and learning.^{15,17,18} Contrastingly, pro BDNF binding with its receptor, p75 neurotrophin receptor (p75 NTR) activates the apoptotic pathway of neurons and glial cells.¹⁴

Petzold and his colleagues found BDNF protein levels in the hippocampus (without distinguishing between mature BDNF and pro BDNF) were relatively stable in mice aged 3, 5, 7 and 9 months.¹⁹ This finding can be explained by research by

Calabrese and colleagues comparing mature BDNF and pro BDNF levels in mice aged 18 months and 3 months. Based on the study, there were reduced mature BDNF levels and elevated pro BDNF levels in the hippocampus and prefrontal cortex of old mice.²⁰ Increased pro-BDNF levels is related to a decreased activity of pro-BDNF cleaving extracellular protease plasmin due to decreased proteolytic activity of tissue type plasminogen activator (tPA).²¹ Therefore, the total BDNF protein in the brain is relatively stable. However, aging will change the ratio of pro BDNF and mBDNF which represents the decrease of mBDNF levels and increase of pro BDNF levels. This resulted in an increase of apoptotic pathways for neurons and glial cells and a decrease of neuronal proliferation, differentiation and survival.

In addition to its influence to the BDNF protein, aging also affects the TrkB receptor. Research by Florence and colleagues which observed TrkB expression in pituitary rats at age of 1 month, 2 months, 4 months, 10 months and 22 months showed a decrease of TrkB expression along with the increase of rat age.²² This was also supported by other studies that showed a decreased expression of TrkB in the hippocampus along with the increased age of mice.¹⁹

Exercise causes an increase of BDNF levels. Marlatt and colleagues showed an increase of neurogenesis and BDNF levels in female mice (9 months) after wheel running. The increase of BDNF levels and the number of new neuron cells causes an improvement in memory retention and spatial memory. Although specific molecular mechanisms underlying the increased BDNF gene expression due to exercise were not clearly elucidated, recent studies showed that there was a role of ketone body D- β -hydroxybutyrate (DBHD) in increasing BDNF gene expression due to exercise. DBHB is a major metabolite which is increasingly secreted in the liver after prolonged exercise. DBHB is produced from acetyl coA derived from the β -oxidation of fatty acids in the liver. DBHD from the liver enters the blood circulation and enter the brain to be used as an energy source. In addition, DBHD is known to inhibit histone deacetylation (HDAC), specifically HDAC2 and HDAC3 that causes an increased BDNF gene expression.²³ Therefore, exercise increases the expression of BDNF genes through HDAC inhibition by DBHD.

Exercise is also known to be able to inhibit the activity of enzymes β and γ secretases through BDNF. These enzymes function to break down

amyloid precursor protein (APP) to produce amyloid β peptide ($A\beta$), which is a toxic substance that causes age-related neurodegenerative diseases, such as Alzheimer's disease. Exercise and BDNF cause an increase in the activity of α secretase. The α secretase is one of the three types of secretase which functions in breaking down amyloid precursor proteins and forming sAPP α . sAPP α is a secreted form of APP

which will be secreted outside neuron cells. In addition, β secretase activity will be inhibited by sAPP α , thus preventing the formation and accumulation of $A\beta$. Therefore, sAPP α is also known as intracellular neuroprotective APP peptide. Therefore, exercise and BDNF have neuroprotective effects by increasing α secretase activity.²⁴

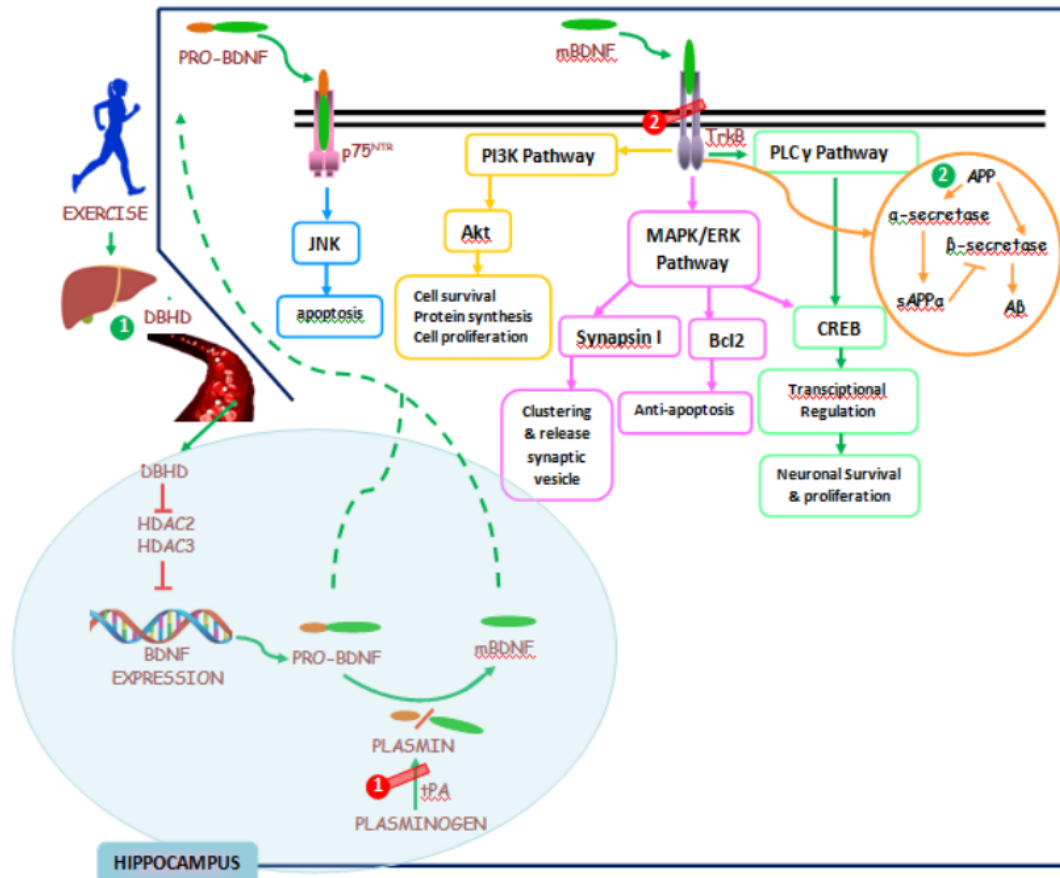


Fig.1. Aging causes (1) an increase of pro-BDNF levels compared to BDNF due to decreased activity of tPA, which results in increased cell apoptosis and (2) decreased expression of TrkB receptors and decreased signaling pathways that function as neuronal survival, proliferation and anti apoptotic pathway. Exercise is able to counteract the effects of aging by: (1) increasing DBHD secretion in the liver which will cause increased BDNF expression, thereby increasing BDNF signaling activity and (2) increasing α secretase activity by inhibiting the activity of β secretase to form $A\beta$.

IGF-1, aging brain and exercise

Insulin-like growth factor-1 (IGF-1) is a major growth factor and its production is stimulated by growth hormone (GH). IGF-1 is mainly produced in the liver and is subsequently bound to IGF binding protein (IGFBP) in the blood circulation before eventually entering the blood brain barrier into the central nervous system.²⁵⁻²⁷ The ability of IGF-1 to penetrate the blood-brain barrier explains the relationship between IGF-1 levels in circulation and IGF-1 levels in cerebrospinal fluid. Decreased IGF-1 levels in the circulation will cause a decrease of IGF-1 levels in the cerebrospinal fluid.²⁶ IGF-1 can cross the blood-brain barrier through 3 mechanisms: (1) by binding to IGF-1 receptors in endothelial cells and then taken directly by neuron cells or through astrocyte cells and then transferred to neuron cells; (2) by binding to low-density lipoprotein receptor-related protein-2 (LRP2) into the cerebrospinal fluid (CSF); and (3) by metalloproteinase 9 activity which will break IGF-1 and IGFBP bonds to form free IGF-1 that can enter the central nervous system (CNS).^{25,28-30} IGF-1 which has crossed the blood-brain barrier plays a role in increasing BDNF activity, activating c-fos and activating various major signaling pathways similar to BDNF.^{12,31} Thus, IGF-1 activity in the brain is important for neuronal proliferation, differentiation and survival, neurotransmission, synaptic density, synaptic plasticity and adult neurogenesis.

Aging causes a decrease of IGF-1 and IGF-1R levels.^{32,33} Study by Hyun et al. showed a decrease of IGF-1 and IGF-1 receptor levels in the hippocampus and somatosensory cortex of mouse at age of 24 months compared to mouse at age of 6 months.³⁴ Other studies have shown a decrease of IGF-1 levels and IGF-1R expression in gerbil olfactory bulbs at age of 24 months compared to age of 3 and 6 months.³⁵ Thus, a decrease of IGF-1 levels and IGF-1R expression causes a decreased activity of BDNF activity and the activity of various major signaling pathways associated with neuronal survival, neurogenesis and synaptic plasticity. This results in decreased cognitive function and memory in the elderly.

Age-related decrease of IGF-1 also causes a decrease of expression and NMDA receptor activity. NMDA receptors are receptors that play a role in maintaining LTP expression and generating action potentials in neurons which play an important role in hippocampal-dependent learning and memory. The NMDA receptor is a tetramer that consists of different subunits. Within the hippocampus, the

NMDA receptor consists of two GluN1 subunits and two other subunits consisting of GluN2A or GluN2B. Aging causes a significant decrease of GluN2B expression. This subunit reduction is associated with age-related cognitive disorders. This is proved by over expression of GluN2B correcting cognitive impairment in old rats. IGF-1 supplementation in older rats successfully corrected the expression of GluN2A/GluN2B, suggesting that IGF-1 played an important role in NMDA expression and activity.³⁶

In addition to its effect to NMDA expression, decreased IGF-1 levels and age-related ular sensitivity to IGF-1 also play a role in the accumulation of dangerous compounds such as β -amyloid peptides (β A) in the brain. β A is a compound that plays a role in age-related dementia, including Alzheimer's and vascular dementia. IGF-1 plays a role in protecting nerve cells from the toxicity of β A, increasing the release of these compounds from cells and stimulating the clearance of these compound in brain tissues. Another newly revealed mechanism is IGF-1 increases the entry of β A carrier proteins, such as albumin, transthyretin and apolipoprotein J into cells, and subsequently binds to β A and carries β A out of the brain parenchyma into the blood circulation through cerebrospinal fluid.³⁷

The specific molecular mechanism underlying the improvement of memory by IGF-1 is still unknown, but it is known that IGF-1 corrects age-memory disorders through synapse formation in the hippocampus. Studies on the profile of total synaptic, postsynaptic density (PSD) and multiple spine bouton (MSB) complexes in the CA1 region in the hippocampus of rats aged 4, 18 and 29 months showed that aging caused a decrease of total synapses but retained the length of PSD and the MSB complex. IGF-1 infusion for 28 days did not improve the reduction in total synapses due to aging. However, it successfully increased the number of MSD synapses and PSD length.³⁸ This suggested that both aging and IGF-1 showed complementary functions and affected different parts of the synapse.

Exercise causes an increase of IGF-1 levels by increasing growth hormone (GH) levels. Plasma GH levels will increase within 10-20 minutes after exercise, and GH is the main regulator of IGF-1 synthesis in the liver.³⁹ Many studies have shown that exercise plays a role in increasing IGF-1 activity. Carro and colleagues showed that wistar rats treated with treadmill running of 17m/min for 1 hour could induce uptake of IGF-1 from blood to neurons in the brain, and accumulation of IGF-1 in neuron cells caused an increase in sensitivity to prolonged afferent

stimulus. Systemic injection of IGF-1 in sedentary rats will resemble the effect of exercise on the brain, which shows the same pattern of IGF-1 accumulation in the brain after exercise or after intracarotid injection of IGF-1. The accumulation of IGF-1 in the brain also causes an increase of c-Fos neuronal activity and the number of new neurons in the hippocampus. The mechanism generated by IGF-1 is

similar to stimulation of brain-derived neurotrophic factor in the hippocampus. Increased expression of c-Fos was inhibited after exercise, if IGF-1 uptake by brain cells was inhibited by antiserum IGF-1. This suggested that IGF-1 in circulation was important and exercise caused an increase of IGF-1 activity in the brain by stimulating IGF-1 uptake in circulation to the brain.

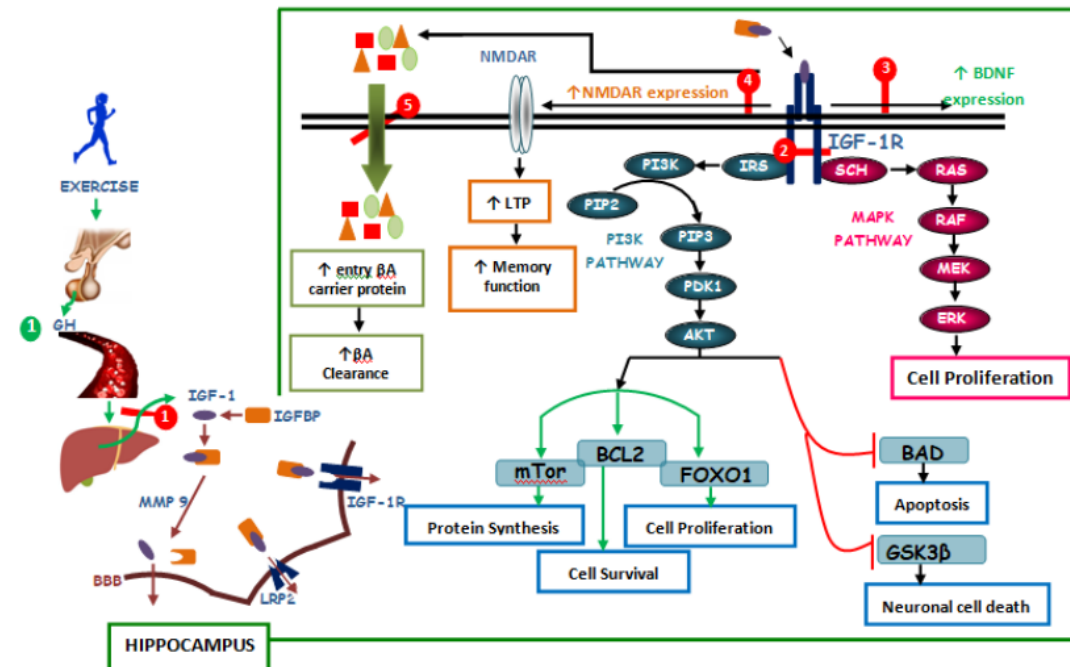


Fig.2. Aging causes (1) decreased IGF-1 levels and (2) decreased IGF-1R expression, thus inhibits proliferation, cell survival, and anti apoptosis signaling pathway; (3) inhibits increased BDNF expression; (4) inhibits increased NMDAR expression; (5) inhibits clearance from β A. Exercise can counteract the effects of aging through: (1) an increase of growth hormone which causes an increase in IGF-1 levels by the liver.

VEGF, aging brain and exercise

VEGF is a hypoxia-induced protein which plays an important role to stimulate the growth and formation of blood vessels. VEGF can be secreted by a variety of cells and tissues, including glial cells, macrophages, endothelial cells, and smooth and skeletal muscle.¹² VEGF binding with VEGF receptor 2 (VEGFR2) causes an increase in angiogenic, mitogenic and neurogenic activity.⁴²

Studies evaluating the VEGF response in older mice showed that injection adeno-associated viral vector expressing VEGF (AAV-VEGF) caused an three

times increase of vascular density in brain of mice aged 3 and 12 months three times compared to mice aged 24 months. In addition, there was an increase in the number of endothelial cells and neuroprogenitors in the subventricular area in mice aged 3 and 12 months compared to 24 months. AAV-VEGF injection also increased the expression of VEGF receptor 2 in the brains of mice aged 3 and 12 months, but not in mice aged 24 months.⁴² Other studies have shown that there was a decrease in the VEGFR2 protein in the coronary arteries and a decrease in the phosphorylation of Akt induced by VEGF in older mice compared with young mice.⁴³ This suggested that aging caused a decrease in response to VEGF stimulation and impairment of

VEGFR2/PI3-kinase signaling, which was likely due to decreased VEGF receptor function and expression.

Exercise causes an increase of several growth factors including VEGF. There was an increase of neuronal proliferation in the subgranular zone (SGZ) in the hippocampus of mice after having exercise on a running wheel for 1 week. Blocking peripheral VEGF with soluble Flt-1 fusion protein (sFlt) caused a decrease in neuronal proliferation in the hippocampus. This showed that peripheral VEGF played an important role in the process of neurogenesis in the hippocampus.⁴⁴ It was estimated that 60-90% of peripheral VEGF was produced by muscles. Therefore, skeletal muscle may be the main source of VEGF that was involved in exercise-induced neurogenesis. This was proven by research that observed the number of neuronal precursor cells in the hippocampal dentate gyrus of mice with normal skeletal myofiber VEGF production (VEGF^{fl/fl} mice) and transgenic mice with decreased levels of

skeletal myofiber VEGF (VEGF^{hsa-/-} mice). It was shown wheel running for 2 weeks caused increased neurogenesis in VEGF^{fl/fl} mice but no effect was found in VEGF^{hsa-/-} mice.⁴⁵

In addition to increasing VEGFR and neural stem cell (NSCs) activity, treadmill exercise in rats also showed significantly increased Caveolin-1. Caveolin-1 is protein that mediates cell and tissue regeneration. Inhibition of caveolin-1 by daidzein was reported to decrease caveolin-1 and VEGF levels. It was known that caveolin-1 was involved in following mechanism: (1) caveolin-1 was thought to mediate the VEGF signaling pathway; (2) caveolin-1/VEGF signaling pathways via VEGFR2 after exercise induced NSC differentiation and proliferation, (3) increased caveolin-1 activity caused a decrease in VEGF expression, thus inhibiting stimulation of VEGFR2 phosphorylation by VEGF and inhibits several major signaling pathways such as PLC γ 1, AKT and ERK.^{46,47}

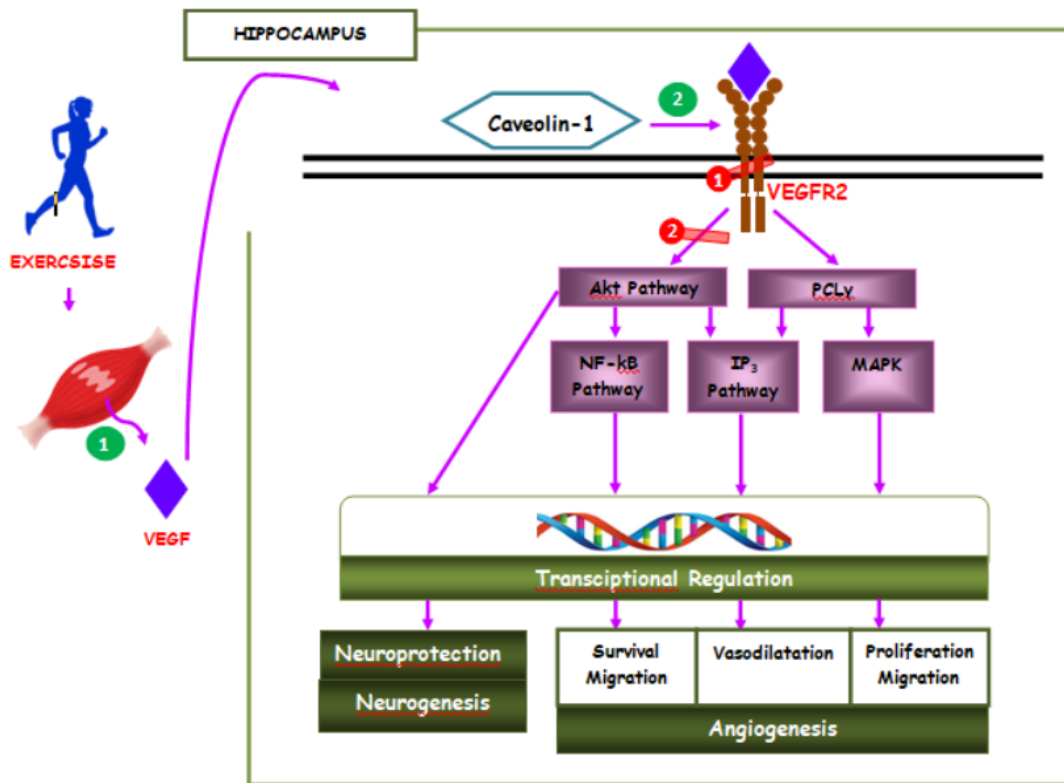


Fig.3. Aging causes (1) decreased VEGFR2 expression and (2) decreased Akt phosphorylation activity induced by VEGF, causing a decrease in signaling pathways of neuroprotective and neurogenesis. Exercise is able to counteract the effects of aging by following mechanisms: (1) increasing of VEGF levels by skeletal muscle and (2) increasing caveolin-1 activity, mediating an increase of VEGF expression thereby increasing the activity of the signaling pathway by VEGF.

Conclusion

Age-related neurodegenerative disease was caused by decreased activity, levels and expression of neurotrophic factors such as BDNF, IGF-1 and VEGF. These three factors have a role in increasing

neuronal survival and neurogenesis through the activation of various signaling pathways. Exercise has been known to stimulate expression and activity of these neurotrophic factors. Therefore, exercise can be considered as a preventive therapy to prevent age-related cognitive and memory decline.

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