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REVIEW

Physical exercise, neuroplasticity, spatial learning and memory

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Abstract There has long been discussion regarding the positive effects of physical exercise on brain activity. However, physical exercise has only recently begun to receive the attention of the scientific community, with major interest in its effects on the cognitive functions, spatial learning and memory, as a non-drug method of maintaining brain health and treating neurodegenerative and/or psychiatric conditions. In humans, several studies have shown the beneficial effects of aerobic and resistance exercises in adult and geriatric populations. More recently, studies employing animal models have attempted to elucidate the mechanisms underlying neuroplasticity related to physical exercise-induced spatial learning and memory improvement, even under neurodegenerative conditions. In an attempt to clarify these issues, the present review aims to discuss the role of physical exercise in the improvement of spatial learning and memory and the cellular and molecular mechanisms involved in neuroplasticity.

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Introduction

Higher organisms have an exceptional ability to adapt to the environment using modifications in behavior resulting from new learning and past experiences. This ability, called memory, and the process of acquiring new information, called learning, became vital throughout species evolution. There are distinct types of memory, which can be briefly classified in accordance with either retention time (short- and long-term memories) or the nature of the memory (working memory and declarative or non-declarative memories). Over the decades, our knowledge regarding the neuronal and molecular basis of memory has advanced greatly. Such knowledge has made it possible to understand future therapies for neurodegenerative diseases that affect learning and memory and the cognitive decline related to aging in humans. Several conditions may influence the consolidation process and memory retention, modulating their outcomes as attention, mood, the sleep–wake cycle and physical exercise.

A large amount of data has suggested that physical exercise can reduce the risk for cardiovascular diseases, obesity, type 2 diabetes, cognitive decline and other diseases and chronic conditions [1]. To improve health, the American College of Sports and Exercise recommends the practice of aerobic and resistance exercises most days of each week. Studies on these types of physical exercise (aerobic and resistance) and their relationship to cerebral health have been gaining the attention of the scientific community. In fact, evidence showing the benefits of practicing physical exercise for health, regardless of age,

has grown in recent years [2]. In addition, majority of evidence has indicated that physical exercise can be an efficient way of preserving brain health and cognitive function under normal or disease conditions, even protecting against cognitive decline and neurodegenerative diseases [3, 4]. Recent studies have linked physical exercise to spatial learning and memory, which critically rely on the hippocampus. For instance, a number of studies have detected an association between cardiovascular conditioning and performance on relational binding [5, 6]. In another study, a positive association between physical exercise and performance in the Virtual Morris Water Maze task was reported in adolescents. Moreover, these studies have also reported a positive association between associative memory and hippocampal volume [6, 7]. Cassilhas et al. have found that physical exercises (both aerobic and resistance) were able to improve spatial learning and memory both humans [8] and rodents [9]. Despite the quantity of literature suggesting the beneficial effects of physical exercise on the brain, only a few studies have specifically targeted the effects of aerobic and resistance physical exercise on spatial learning and memory and the cellular and molecular mechanisms underlying such effects. The present review aims to discuss the role of physical exercise in the improvement of spatial learning and memory and the cellular and molecular mechanisms involved.

Spatial learning and memory, the hippocampus and physical exercise

In past years, the scientific community believed that the mammalian central nervous system (CNS) became structurally stable soon after birth and that only a few modifications could occur throughout life. As techniques improved over the decades, this paradigm began to change. Currently, it is believed that the mammalian brain exhibits persistent plasticity throughout all stages of life [10]. Neuronal plasticity allows the CNS to learn new skills, to consolidate and retrieve memories, to reorganize neuronal networks in response to environmental stimuli and to recover after lesions [11]. Neuronal plasticity may occur using neurogenesis, cellular apoptosis, synaptic-dependent activity and the reorganization of neuronal networks [12, 13]. Changes in the frequency of synaptic activation may lead to an increase or decrease in the long-term efficiency of these synapses through phenomena known as long-term potentiation (LTP) and depression (LTD) [13]. Activity-dependent alterations may occur at all excitatory synapses where glutamate is the neurotransmitter and in some of the inhibitory gamma-aminobutyric acid (GABA)ergic synapses [13].

The hippocampus is a highly plastic region (even in adulthood) located in the medial temporal lobe of the CNS [10]. The hippocampus is also one of the most studied neurological structures associated with spatial memory. In addition, this region is central to declarative memory consolidation [14]. Two main areas form the hippocampus: the cornus ammonis (CA1, CA2, CA3) and the dentate gyrus (DG) [15]. Each area exhibits neuroplasticity and harbors specific cell types that may respond distinctly to physical exercise, contributing separately to spatial learning and memory processes in the hippocampus [16]. The DG is the only hippocampal region able to generate new neurons; the DG can double or triple in size after physical exercise in rodents [17, 18]. The DG and some areas of CA3 are considered vital for the pattern of dissociation or the differential storage of associations between stimuli and experience [19]). In mice, it was verified that voluntary exercise had better performance on pattern separation capacity (measured on a touchscreen-based spatial discrimination task) compared to sedentary animals; these results suggested that the spatial discrimination improvement was due to exercise-induced neurogenesis [20].

In health young adults, better performance was demonstrated on visual pattern separation task for those who were submitted to chronic aerobic exercise [21]. Cassilhas et al. reported short- and long-term spatial memory improvements (among other cognitive functions) in elderly subjects subjected to 6 months of resistance training [8]. Using aerobic exercise, Erickson et al. [22] demonstrated that short-term spatial memory improved with greater cardiovascular conditioning. These results were associated with an enlarged volume of the left hippocampus that was proportional to the cognitive findings. Measures of aerobic conditioning, cerebral flow, and analogous paradigms for evaluating hippocampal function, along with virtual navigation and pattern separation tasks, may allow researchers to begin bridging studies in animal and human models. Future studies should focus on examining the neuronal networks underlying spatial memory and the effects of physical exercise throughout life in different species.

Physical exercise-induced improvements in learning and memory: the role of neurotrophins

Various events, such as physical exercise, may induce hippocampal plasticity [11]. Evidence has demonstrated that both forced (treadmill) and non-forced (activity wheel) physical exercise increase hippocampal neurogenesis, cell proliferation [23–25] and dendritic branching [26, 27]. Modulation of the release and utilization of neurotransmitters, such as monoamines [3, 28], may also be related to

physical exercise-induced neuroplasticity. Other possible mechanisms include the neurotrophic action of brain-derived neurotrophic factor (BDNF) [25, 29, 30] and growth factors that can act in the CNS, such as insulin-like growth factor-1 (IGF-1) [31, 32].

BDNF is one of the major modulators of brain plasticity [33, 34]. Apart from its action on the CNS, BDNF may also influence peripheral systems, such as reduced food intake, increased glucose oxidation rate, decreased blood glucose level and increased insulin sensitivity [35, 36]. Together, this evidence indicates that BDNF is not only critical for the nervous system but also interconnects central and peripheral processes related to metabolism regulation and homeostasis [11]. Thus, it is proposed that peripheral levels of this neurotrophin are associated with cognition, metabolic diseases and psychiatric disorders [37–40].

BDNF cellular signaling is triggered by the activation of the tropomyosin-related kinase B (TrKB) receptor, a member of the tyrosine kinase receptor family [41]. The interaction of BDNF with the receptor leads to phosphorylation of the tyrosine residues in the tyrosine kinase domain, facilitating adaptor protein binding. For example, phosphorylation of the tyrosine domain at position 515 activates Shc or FRS2 adaptor molecules that may compete for binding at this site [41]. Subsequently, these adaptor molecules activate the Ras-protein kinase pathway via Ras-mitogen-activated protein kinase (Ras-MAPK), thus promoting neuronal differentiation and proliferation [41].

Alternatively, TrKB phosphorylation may activate the phosphoinositide 3-kinase (PI3K) pathway and stimulate neuronal proliferation and survival [41]. Phosphorylation at position 816 of the C-terminal portion leads to activation of phospholipase Cγ (PLCγ), which induces the production of inositol-1,4,5-trisphosphate Ins(1,4,5P3) and diacylglycerol (DAG) [41]. DAG stimulates protein kinase C (PKC) isoforms, and Ins(1,4,5P3) leads to Ca^{2+} release and subsequent activation of Ca2+/calmodulin-dependent protein kinases (CaMKII, CaMKK and CAMKIV) [41]. These proteins in turn activate cyclic AMP response element-binding protein (CREB), which can lead to LTP and/or other types of synaptic plasticity [41]. PI3K may also activate the serine–threonine kinase (AKT) pathway, promoting cellular survival [41]. In addition to TrKB, pro-BDNF (an immature form of the neurotrophin) may bind to another type of receptor, the pan-neurotrophin receptor (P75ntr). Such binding triggers a signaling cascade that leads to caspase 3 activation-mediated apoptosis [42]. Cell death induced by pro-BDNF/p75ntr signaling occurs only when the BDNF/TrkB pathway is inhibited or absent [43].

In 1995, Neeper et al. [44] reported that voluntary exercise on the activity wheel for 7 days could enhance BDNF gene expression in the hippocampus and the caudal region of the neocortex in rodents. This study was pioneering in demonstrating that physical exercise could influence neurotrophic factors. Among all of the neurotrophins, BDNF seems to be the most sensitive to the effects of physical exercise; however, other trophic factors may be influenced by physical exercise, even if only transiently [45–48], such as nerve growth factor (NGF), vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF-2). Vayman et al. [49] have shown that blocking TrKB in the brain abolished the effects of physical exercise on the activity wheel for 5 days on spatial memory, synapsin-1, CaMKII and MAPKII. Similar results have been obtained in other studies that subjected mice and rats to aerobic physical exercise [29, 50–52]. Some studies have suggested that peripheral BDNF can be enhanced by aerobic physical exercise in humans [47, 48, 53, 54].

IGF-1 and molecular aspects on learning and memory

IGFs are peptides that can be stimulated by growth hormone (GH) or act independent of GH. These peptides may promote growth, differentiation and cellular survival [55]. Among these peptides, IGF-1 can be highlighted due to its central and peripheral physiological effects [56]. The expression of IGF-1 mRNA occurs in specific regions of the adult brain, such as the hippocampus [57]; however, insulin-like growth factor 1 receptor (IGF-1R), a tyrosine kinase type receptor, is distributed throughout the CNS [58]. IGF-1/IGF-1R activation is vital for various biological processes because it is the main antiapoptotic pathway, inhibiting the death of neurons, fibroblasts and other cells [59, 60]. When these peptides are phosphorylated, the IGF-1R intracellular beta domains interact with adaptor proteins called insulin receptor substrates (IRSs), activating the Ras-MAPK pathway [61]. There are three isoforms of IRSs (IRS1, IRS2 and IRS4). All of the isoforms are found in the CNS and may have distinct roles in neuronal function and development [62]. IRS binding activates the PI3K/AKT [61] pathway. AKT mediates cellular survival by inhibiting glycogen synthase kinase 3 (GSK3) and consequently preventing apoptotic signaling. AKT can also stimulate master regulator of muscle differentiation (MyoD), which controls cellular differentiation, especially in striated skeletal muscle [63]. MyoD is a mammalian target of rapamycin (mTOR) and P70 S6K, proteins that can trigger protein synthesis during cellular proliferation and hypertrophy [61, 63].

IGF-1 can be considered a molecule that acts as a neurotrophic factor in the CNS, as it is responsible for the maintenance of brain cells and is involved in differentiation, proliferation, synaptic plasticity and neurogenesis. IGF-1 is directly and indirectly involved in spatial learning

and memory [31, 61, 62, 64]. Because of the involvement of IGF-1 in neurogenesis, studies that aimed to correlate its peripheral levels with cognitive function were conducted in humans. Positive correlations have been reported between increased blood IGF-1 levels and cognitive function improvement [65–71].

Physical exercise-induced improvements in learning and memory: the role of synaptic plasticity

Improvements in spatial learning and memory are closely related to adaptations at the synapses of hippocampal neurons or in neurons that make synapses with hippocampal neurons. LTP was observed in the young rodent DG after running. Similarly, a reduction in aging-associated LTP loss was detected in running old rodents [72]. Exercise-induced LTP seems to be related to neurogenesis observed after physical exercise. In accordance with LTP induction, upregulated *N*-methyl D-aspartate receptor subtype 2B (NMDAR2B) gene expression in the DG has been reported in running rats [73]. Previous studies demonstrated that this receptor is able to increase the capacity of cells to exhibit LTP. In addition, the expression of the glutamate receptor 5 (GluR5)-linked gene is also higher in the DG of running rats.

LTD is considered a model of forgetting due to its property of reducing the synapse's capacity to potentiate responses [74]. This form of plasticity is associated with spatial memory improvement. Although physical exercise does not seem to alter LTD, it has been reported that LTD induction depends on the activation of NR2A-containing NMDA receptors in running (but not sedentary) mice. These data suggest that physical exercise may modify the role of NMDA receptor subunits in LTD [75].

After physical exercise, considering both LTP and LTD, there are changes in synapse morphology (spine density) in the entorhinal cortex, CA1 pyramidal cells and the DG [26]. Granule cells from the DG of runners exhibited increased length, spine density, volume and complexity of their dendrites. Synaptic density of new neurons was not significantly different in young and old mice [76].

Although there is no method to directly evaluate synaptic activity in humans, indirect measures of acquisition between neuronal populations can be employed as tools for measuring synaptic activity, such as the physiological approach called paired associative stimulation (PAS) [77]. Elderly subjects displayed reduced responses following paired-pulse training relative to younger subjects. Additionally, there is an aging-dependent decrease in synaptic plasticity [78].

BDNF, IGF-1, spatial learning and memory and physical exercise

Studies using humans or animal models suggest relationships between memory, physical exercise and IGF-1 and BDNF pathways [79, 80]. Evidence has shown that rodents subjected to physical exercise on the treadmill or activity wheel performed better in the Morris water maze (a task that evaluates hippocampus-dependent spatial memory) and had higher levels of BDNF in the hippocampus, cerebellum and spinal cord [48, 81].

Ang et al. [82] subjected rodents to aerobic physical exercise on the treadmill for 12 weeks. After training, running rats performed better than the sedentary group in the Morris water maze, indicating improvements in spatial learning and memory among rats forced to perform aerobic training on the treadmill.

Ding et al. [31] subjected rats to 5 days of voluntary physical exercise. Afterward, they observed higher levels of hippocampal BDNF and IGF-1 in the rats. In the same study, a group of rats was trained, but hippocampal IGF-1R was blocked. The authors demonstrated that IGF-1R is critical for memory formation because blocking it compromised performance in the Morris water maze relative to mice that exercised and did not have their receptors blocked.

There is still a lack of evidence regarding the effects of resistance training on BDNF levels. In humans, data are restricted to evaluations at the systemic level. In recent studies, Correia et al. [83] and Goekint et al. [84] failed to find alterations in peripheral BDNF levels among individuals exposed to a single session of resistance training. Additionally, studies have shown that resistance training increases blood levels of IGF-1 [8, 85–87]. In contrast, aerobic physical exercise seems to have little or no influence on the blood levels of this growth factor [85, 88–90]. Peripheral IGF-1 is involved in processes occurring in the CNS [32] because IGF-1 is transported across the blood–brain barrier, activating its signaling cascade via the hippocampal IGF-1R receptor [31, 80, 91]. Such effects can be abolished by peripheral blockade of IGF-1 [31, 32, 80].

Neurogenesis, learning and memory

Neurogenesis in the adult hippocampal DG is well documented, and it seems to contribute to spatial learning and memory [92]. Although aging or stress may hamper neurogenesis [93], physical exercise seems to potentiate new neuronal generation [17, 24, 25]. In spite of the relationships among neurogenesis, physical exercise and memory, the mechanisms underlying exercise-elicited neurogenesis

are still unclear. Molecules such as BDNF, VEGF and IGF-1 have been proposed to promote exercise-induced neurogenesis [94]. Additionally, immunological cells (e.g., macrophages and microglia) are reputed to induce this process [95, 96], as there is evidence that neurogenesis was abolished after local ablation of microglia [97].

Neurotransmitter systems, such as the cannabinoid system, have been associated with exercise-elicited neurogenesis. In fact, blockade of the cannabinoid system abolished new neuronal formation in the DG [98]. Tryptophan hydroxylase (TPH), an enzyme involved in synthesis in the serotonergic system, may be relevant for cell proliferation but not neurogenesis. Indeed, although (TPH)2-deficient mice did not display altered hippocampal neurogenesis, they presented worse activity-induced proliferation [99]. Antidepressant drugs, such as reuptake inhibitors, can also induce neurogenesis in the DG at a lesser intensity compared to physical exercise [99]. The positive effects of physical exercise are found in animal models of aging, Alzheimer's disease (AD) and Down syndrome [100–102]. These findings corroborate clinical data describing exercise-induced cognitive improvement in normal subjects or with dementia [8, 103, 104].

A study using birds have demonstrated that hipocampal neurogenesis was involved with learning. In rats, it was noted a relationship between hippocampus-dependent learning and the neurogenesis, suggesting a function for these new neurons in certain types of learning and memory. The DG functions as a pattern separator stems from early computational modelling work, with CA3 serving as episodic memories storage [19]. For this reason, it has been investigated a specific role for neurogenesis in pattern separation. Using knock down adult mice, was found specific impairments in spatial discrimination on a spatial navigation radial arm maze task and a spatial, but non-navigable, task in the mouse touch screen. Mice with ablated neurogenesis were impaired when stimuli were presented with little spatial separation, but not when stimuli were more widely separated in space [105]. In other study, using the same touchscreen task, voluntary exercise enhanced performance on pattern separation (only for the more difficult condition). In addition, aged mice had impaired pattern separation and low neurogenesis, showing that exercise alone does not induce improvements in pattern separation [20].

So, it is suggested that neurogenesis is involved to classical learning and memory tests and can be influenced by some factors such age of neurons, phase of memory addressed and the type of chosen test (for reviews, see [106, 107]). Although there is much evidence to demonstrate that hipocampal neurogenesis can be increased by physical exercise, remains unclear the link and causation of this phenomenon. The neurotrophic factor and/or plasticity-related factor such as BDNF, increased by exercise, may acting as a causal determinant of both neurogenesis and learning and memory [106].

Angiogenesis and learning and memory

Physical exercise, similarly to injury, is a compelling stimulant of new vessels (angiogenesis) during development or in the adult brain [25, 45, 108]. Apart from stimulating angiogenesis and endothelial cell proliferation, physical exercise may robustly maintain these effects for long periods [109]. These effects appear to be mediated by IGF-1, BDNF and VEGF. Previous studies have found that resistance training and aerobic exercise may enhance hippocampal levels of IGF-1 and BDNF [9]. In addition, exercise is also able to increase the expression levels of IGF-1 [31, 110].

Using arterial spin labeling (ASL) with MRI in humans, an increase in the cortical hippocampal flow was verified in elderly individuals exposed to 4 months of aerobic exercise [111]. Cerebral blood volume (CBV) in the DG was also increased in young subjects after 3 months of aerobic training. In addition, correlations between cognitive improvement, aerobic training and CBV were also found [112]. Physical conditioning was positively associated with the number of small vessels (radius >0.5 mm) in elderly individuals subjected to magnetic resonance angiography (MRA), indicating angiogenesis. In contrast, sedentary individuals displayed increased numbers of vessel tortuosity (changes in direction) in both brain hemispheres [113].

Future directions and conclusions

Herein, we reiterated that both animal and human studies have reported positive effects of physical exercise on spatial learning and memory. When physical exercise is categorized according to type, such as aerobic and resistance training, it should be noted that much work remains to clarify the effects on hippocampal-dependent memory. The vast majority of studies have systematically approached the positive effects of aerobic exercise. However, studies tailored to investigate the effects of resistance exercise (such as the vertical ladder apparatus) are still needed.

Regarding the mechanisms underlying the positive effects on exercise-elicited spatial learning and memory, hippocampal plasticity can be emphasized as critical, inviting further investigation. Studies have focused on trophic mechanisms (BDNF, IGF-1 and VEGF), synaptic activity improvement (LTD and LTD), neurogenesis and angiogenesis. Although there are different mechanisms behind positive effects of exercise on brain health, it should

be noted that more studies need to be conducted to clarify if trophic activation would be a causation of enhancement of hipocampal activity and learning and memory, or just a related phenomenon. It is appear that BDNF could be crucial for exercise effects on learning memory improvement. Previous studies verified that voluntary exercise enhanced spatial learning and Memory and was associated with an increase in the mRNA levels of BDNF and TrkB receptor, suggesting that exercise predominately employed the action of BDNF to these improvements [114]. Thus, the exercise may use the BDNF to exert changes in synaptic plasticity and justify the improvement on learning and memory [52]. In addition to that, Studies also proposed that BDNF is also required for pattern separation, having a link between exercise, neurogenesis and learning and memory, in which the BDNF could be a causal determinant of both neurogenesis and learning and memory [106, 107].

Knowing that exercise use BDNF to exert changes in brain plasticity is encouraging for developing therapies to treating cognitive disturbances. This result also brings insight critical for investigations of exercise and causal effects of IGF-1 and VEGF on learning and memory and neurogenesis. In this scenario, animal models for pathological conditions and aging are interesting tools to explore and generalize the effects of physical exercise on memory and neuroplasticity in distinct populations. Even though animal models aim to shed light on neurobiological mechanisms involving memory and physical exercise, studies approaching peripheral biomarkers related to CNS activity are vital for considering the possible use in humans. Among these biomarkers, circulating growth factors, such as IGF-1 and BDNF, which possess central and peripheral actions, have been associated with cognition. Indeed, these factors have been related to altered mood, as observed in neurological and psychiatric disorders.

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