Physical activity for the promotion of cognitive functions: The role of the exercise-induced Brain Derived Neurotrophic Factor in muscle-brain crosstalk

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Abstract
During physical activity, the contracting skeletal muscle acts as an endocrine organ for its ability to secrete molecules called myokines, mostly cytokines and growth factors, which modulate metabolic and cellular functions in different organs and tissues. Some of the most relevant for the brain include Brain-Derived Neurotrophic Factor, Insulin-like growth factor-1, Interleukin-6, Irisin, cathepsin B, and vascular endothelial growth factor, which are involved in muscle-brain crosstalk. Brain-Derived Neurotrophic Factor improves cognitive functions by neurogenesis, and the increase of plasticity in the hippocampus region. This review aims to provide recent insights on the role played by physical activity and diet in ameliorating cognitive functions, focusing on the effects involving Brain-Derived Neurotrophic Factor.

Keywords: Physical activity; cognitive functions; myokines; brain-derived neurotrophic factor (BDNF); muscle-brain crosstalk; neurodegenerative disorders.

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Introduction

In the last few decades, the recent and rapid progress in bio-medical research and socio-economic improvements have led to an increase in life expectancy which, however, has greatly increased dementia and

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neurodegenerative disorders, especially in the elderly population (Davis *et al.,* 2022). In addition, sedentary behaviors, which are characterized by a low energy expenditure (≤ 1.5 metabolic equivalents, METs) contribute to the risk factors linked to cognitive decline and dementia (Tremblay *et al.,* 2017). To prevent neurodegenerative disorders or reduce their harmful effects on cognitive functions in older adults, several non-pharmacological interventions, such as physical activity (PA), are used. Indeed, the regular practice of PA emerged as the most useful approach for positively influencing health, well-being, and enhancing cognitive functions in humans (Montesano *et al.,* 2013; Erickson *et al.,* 2019; Nazlieva *et al.,* 2019; Nasso *et al.,* 2024). For example, PA enables healthy older adults to improve their executive functions and memory, whereas only global cognition is improved in their peers with cognitive impairments (Sanders *et al*., 2019). The same finding was observed for several cognitive functions (Memory, executive functions, processing speed and global cognition) in sedentary older adults (Zhao *et al.,* 2022). At the macroscopic level, the beneficial effects of PA on cognitive functions are explained by neurogenesis, synaptogenesis, and angiogenesis (Lista and Sorrentino, 2010). The key molecular mechanisms underlying these macro-level changes that induce the beneficial effects of PA on cognitive functions involve myokines, including proteins and peptides secreted by contracting skeletal muscle, which acts as an endocrine organ (Iizuka *et al.,* 2014; Pedersen and Febbraio, 2012; Severinsen *et al.,* 2021). Myokines act in a hormone-like manner modulating metabolism and cellular functions in different organs (Severinsen *et al.,* 2021). Among these myokines, Brain-Derived Neurotrophic Factor (BDNF) exerts a pivotal role in improving cognitive functions. Furthermore, PA and/or an appropriate diet can reduce the age-related cognitive decline associated to neurodegenerative disorders, such as Alzheimer's disease (AD) and Parkinson's disease (PD) (Chieffi *et al.,* 2017; Miranda *et al.,* 2019). This review aims to provide recent insights on the role played by PA and diet in ameliorating cognitive functions, focusing in particular on the effects involving BDNF.

1. Myokines involved in muscle-brain crosstalk and cognitive improvement

Myokines are signaling molecules secreted by contracting skeletal myofibers (Iizuka *et al.,* 2014; Severinsen *et al.,* 2021). Up to now, about 1,110 myokines have been identified which can act in an autocrine, paracrine and endocrine manner modulating energy metabolism and plasticity of the

skeletal muscle cell, that includes hypertropia, hyperplasia and the repair process of damaged tissues (Lee *et al.,* 2019; Bortoluzzi *et al.,* 2006; Pedersen and Febbraio, 2012). Among these myokines, BDNF, Interleukin-6 (IL-6), Insulin-like Growth Factor-1 (IGF-1), irisin, Leukemia Inhibitory Factor (LIF) have been identified as mediators of brain neuroplasticity and cognitive functions (Miranda *et al.,* 2019; Pedersen, 2019; Vints *et al.,* 2023). However, BDNF is the major myokine involved in muscle-brain cross-talk whose expression level can be up-regulated PA and an appropriate diet, thus improving cognitive functions (Liu and Nusslock, 2018; Miranda *et al.,* 2019; Vints *et al.,* 2023).

2. BDNF and cognitive functions

2.1. BDNF structure and functions

BDNF is a 25-28 kDa homodimer protein, belonging to the neurotrophin family which also includes Nerve Growth Factor (NGF), Neurotrophin (NT) -3 and NT-4, structurally related members playing crucial roles in the survival and differentiation of neurons in the nervous system (Hernández *et al.,* 2024). BDNF is one of the major neurotrophins essential for neuron growth and survival; it is mostly involved in the synaptic plasticity which controls memory and learning processes (Liu and Nusslock, 2018; Miranda *et al.,* 2019). Mechanisms underlying cognitive enhancement exerted by exercise-induced BDNF include neurogenesis, increased synaptic plasticity which allows for better communication between neurons and neuroprotection during neurodegeneration process (Miranda *et al.,* 2019; Vints *et al.,* 2023).

2.2. BDNF expression, regulation and bio-signaling pathways

BDNF is synthetized by various cell types, and its expression and secretion are regulated in response to different factors, such as age, pathological conditions, PA (Brigadski and Leßmann, 2020). The alteration of BDNF concentration in tissue and serum is associated with neurodegenerative, neurological, or even cardiovascular diseases (Brigadski and Leßmann, 2020). In the central nervous system, BDNF is predominantly detected in the brain, particularly in the hippocampus, cerebral cortex, amygdala, striatum and hypothalamus (Edelmann *et al.,* 2014).
BDNF is expressed by nervous cell types such as glutamatergic neurons, astrocytes and microglia (Marie *et al.,* 2018). In non-neurogenic tissues,

BDNF is expressed in (Cefis *et al.,* 2020), heart, kidneys, submaxillary glands, ovaries, dorsal ganglia, lungs and skeletal muscle (Gass and Hellweg, 2010).

Like many hormones and growth factors, BDNF is synthetized as proBDNF precursor (32-35 kDa) (Koshimizu *et al.,* 2009) which is subsequently cleaved either intracellularly by serine proteases such as PC1/3 or furin, or extracellularly by plasmin and/or matrix metalloproteases (MMPs) to form mature protein (Matsumoto *et al*., 2019). ProBDNF and mature BDNFs show opposite effects interacting respectively with the p75 neurotrophin receptor (p75NTR) or Trk tyrosine kinase receptors; in fact, ProBDNF induces synaptic weakening, apoptosis and long-term depression whereas BDNF exerts vital functions (Koshimizu *et al.,* 2009). However, further research is needed to fully understand the proBDNF role and functions.

Mature BDNF binds to the low affinity receptor tyrosine kinase TrkB and to the p75 receptor with high affinity; the binding to TrkB stimulates the dimerization and phosphorylation of the receptor with activation of the intracellular tyrosine kinase domain that interacts with different intracellular targets such as MAP kinases and phosphatidyl-inositol 3 kinase (Sasi *et al.,* 2017).

Within the brain, BDNF receptor activation increases synaptic plasticity, the number of dendritic spines, and the release of the neurotransmitters glutamate, γ-aminobutyric acid (GABA), dopamine and serotonin (Leal *et al.,* 2014).

2.3. BDNF in neurodegenerative disorders

In neurodegenerative diseases, such as AD, PD and Huntington's disease, the cognitive impairment, including memory, thinking and judging skills, has been linked to the reduced expression of BDNF level (Narisawa-Saito, *et al.,* 1996; Hock, *et al.,* 2000; Zuccato, *et al.,* 2008). Alterations of BDNF expression have been described in the brain area responsible for memory processes, such as the hippocampus and parahippocampal, which are involved in psychiatric and neurodegenerative disorders (Miranda *et al.,* 2019). In AD disease, the decreased neurogenesis with impaired neuroplasticity leading to depression and memory loss have been correlated to a decrease in BDNF levels (Miranda, *et al.,* 2019).

3. Strategies targeting BDNF for the treatment of cognitive decline

Since a decrease in BDNF expression levels has been linked to the

cognitive decline observed in aging and neurodegenerative, neurological and psychiatric disorders (Miranda *et al.,* 2019), new strategies for cognitive improvement aimed at increasing BDNF expression level have been developed (Nicastri *et al.,* 2022). Here we highlight the major pharmacological or non-pharmacological approaches usefull to enhance BDNF levels.

3.1. Pharmacological strategies for improving cognitive functions

Up to now, many efforts have been employed to find pharmacological therapies for the treatment of AD which can also ameliorate cognitive functions and delay further progression. Cholinesterase inhibitors, which prevent the breakdown of acetylcholine, primarily used for the treatment of AD and PD, such as Donepezil, Galantamine and Rivastigmine can ameliorate the symptoms of the disease, however they only induce a modest improvement of cognitive function, exerting side-effects and without being able to revert the diseases (Miculas *et al.,* 2023). Glutamate antagonists such as memantine, a N-methyl-D-aspartate (NMDA) receptor antagonists, act by regulating glutamate activity and improving dopamine transmission; they can increase memory and attention but induce side-effects (Wesnes *et al.,* 2015).

However, considering low efficacy in memory improving and of side effects exerted by these drugs, several studies investigated alternative approaches focusing on the increase of BDNF exerted by PA and nutritional interventions.

3.2. Physical activity and BDNF

Many studies have investigated whether different types of PA could affect BDNF expression levels, by evaluating the effects of a single exercise (acute effects) or the regular practice of physical exercise (chronic effects) in humans. In studies analyzing the acute effects of PA on BDNF levels, it has been demonstrated that in men, 40 min of vigorous exercise increases circulating BDNF levels (Schmolesky *et al.,* 2013). This enhancement of BDNF levels was not associated to the type of exercise (aerobic or resistance) (Arazi *et al.,* 2021) or to the health status (healthy or with AD) in elderly adults (Coelho *et al.,* 2014). Apart from these results, several meta-analyses from studies aiming to evaluate the acute effect of PA on BDNF levels, have confirmed the increase of serum or plasma BDNF concentration (Dinoff *et al.,* 2017; Szuhany *et al.,* 2015). In addition, studies investigating the chronic effect of PA on BDNF levels, demonstrated that a one-year

aerobic intervention resulted in a growth of BDNF concentration which was correlated to an increase of volume in the right and left hippocampal regions (Erickson *et al.,* 2010). A six-month aerobic intervention (45 to 60 minutes, 4 times per week, 75% to 85% of heart rate reserve) showed an increase in BDNF in women with mild cognitive impairment (MCI) but not in their male peers (Baker *et al.,* 2010). The meta-analysis by Szuhany and colleagues confirms these results, highlighting the increase in plasma or serum BDNF concentration after a 3-week to 2-year aerobic program at an intensity of 50-80% of VO_2max (Szuhany *et al.,* 2015). The increase of BDNF concentration induced by PA involves the PGC-1α/FNDC5/BDNF signaling pathway (Wrann *et al.,* 2013). Taken together, these studies indicated that both acute and chronic effects exerted by PA up-regulated BDNF expression, and its circulating form at the peripheral level can cross the blood-brain barrier influencing brain specific regions involved in cognitive performance (Pan *et al.,* 1998).

3.3. Diet and BDNF

Among life-style interventions, diet plays a crucial role exerting beneficial effects on human health and brain functions modulating BDNF concentrations (Gravesteijn *et al.,* 2022). Evaluation of dietary patterns has revealed that the Mediterranean diet, characterized by high consumptions of vegetables, fruit, whole grains, nuts, fish and olive oil, has been associated to a reduced risk of cognitive decline and dementia (Arcone *et al*., 2023; Maiuolo *et al.,* 2023; D'Errico *et al.*, 2024), particularly through the increase of BDNF expression levels (Fu *et al.,* 2022; Tirani *et al*., 2024; Fekete *et al.,* 2025). The most effective dietary components of the Mediterranean diet include polyphenols, such as flavonoids (in grains, vegetables, fruit, olive oil, and beverages such as red wine, tea, chocolate, coffee) and other nutritional factors such as omega-3 fatty acids (fish, almonds, walnuts) (Román *et al.,* 2019; Ziaei *et al.,* 2024). Also, vitamins B6, B12, and folate are crucial for neurological functions because their deficiencies are associated with cognitive impairment and dementia (Agnew-Blais *et al*., 2015).

Diet polyphenols may induce BDNF upregulation through different mechanisms, which encompass their anti-oxidant and anti-inflammatory properties effect thus supporting BDNF-supporting neuronal survival (Grabska-Kobyłecka *et al.,* 2023). These effects are exerted by various bio signaling pathways, including the cAMP response element-binding protein (CREB) pathway, leading to enhanced BDNF transcription (Jalouli *et al.,* 2025).

Conclusion and future perspectives

In this review, we discuss the role of physical activity in promoting brain health, mostly increasing the production BDNF by contracting skeletal myofibers. BDNF acts enhancing plasticity, cognition, learning, and memory. BDNF behaves as a key regulator of neuroplasticity and cognitive functions, acting through complex bio signaling pathways which regulate energy metabolism and brain functions. The increase of BDNF expression during physical activity highlights its therapeutic potential for cognitive decline linked to aging and neurodegenerative disorders. In addition, the adoption of dietary pattern as the Mediterranean diet constitutes a promising strategy to enhance BDNF's benefits for brain function, and prevention of cognitive impairments.

These lifestyle interventions enhance BDNF expression level thus preventing, delaying cognitive decline and ameliorating learning and memory functions. Cognitive functions are fundamental to human behavior, learning, and adaptation, enabling individuals to apply knowledge, problem solving and intellectual development. The research in the neuroscience field demonstrated the role of brain regions, such as hippocampus, cerebral cortex, and neurotrophic factors, mostly the exercise-induced BDNF in the regulation of cognitive processes. Although further research is needed to better understand the relationship among PA, diet and BDNF expression, current evidence indicates that adopting healthy lifestyle certainly contributes to enhancing cognitive abilities and overall well-being.

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