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PHYSICAL ACTIVITY AND COGNITIVE FUNCTIONS: ROLE OF THE BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF)

ATTIVITA' FISICA E FUNZIONI COGNITIVE: RUOLO DEL FATTORE NEUROTROFICO DEL CERVELLO (BDNF)

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Abstract

The skeletal muscle is considered an endocrine organ as it secretes various myokines. The myokines are produced during skeletal muscle contraction and exert autocrine, paracrine, and endocrine effects even on different organs and tissues. Up to now, many myokines have been described, including the brain-derived neurotrophic factor (BDNF), interleukin-6 (IL-6), irisin, leukemia inhibitory factor (LIF), and insulin-like growth factor1 (IGF-1) are the most relevant also for brain functions. In particular, it is well known that BDNF ameliorates cognitive functions via neuronal differentiation and plasticity in the hippocampal region. Therefore, myokines represent key molecules in the cross-talk between skeletal muscle and brain.

Il muscolo scheletrico è considerato un organo endocrino in quanto secerne varie miochine. Le miochine sono prodotte durante la contrazione del muscolo scheletrico ed esercitano effetti autocrini, paracrini ed endocrini, anche su diversi organi e tessuti. Fino ad oggi, sono state identificate un gran numero di miochine, come il fattore neurotrofico del cervello (BDNF), l'interleuchina-6 (IL-6), l'irisina, il fattore inibitorio della leucemia (LIF) e il fattore di crescita insulino-simile1 (IGF-1) sono i più rilevanti anche per le funzioni cerebrali. In particolare, è noto che il BDNF migliora le funzioni cognitive attraverso la differenziazione neuronale e la plasticità nella regione dell'ippocampo. Pertanto, le miochine rappresentano molecole chiave nella comunicazione tra muscolo scheletrico e cervello.

Key-words
Physical exercise; myokines; brain-derived neurotrophic factor (BDNF); cognitive functions.
Esercizio fisico; miochine; fattore neurotrofico di derivazione cerebrale (BDNF); funzioni cognitive.

Introduction

Skeletal muscle is not only specialized for muscle contraction, but it also acts as an endocrine organ, by production of numerous cytokines, called myokines, during physical activity (Chen, et al., 2021; Pedersen, & Febbraio, 2012). Myokines are proteins, that like hormones, regulate metabolic homeostasis, muscle regeneration, modulate the aging process and are also involved in cognitive functions (Pedersen, 2019).

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1. Myokines

Up to now, numerous myokines have been characterized and numerous evidences indicate that their production is induced by muscle contraction (Bortoluzzi et al., 2006; Pedersen & Febbraio, 2012). Furthermore, their secretion appears to be related to the type and duration of physical activity as well as to the extent of the muscle mass involved (Görgens et al., 2015). Myokines act in an autocrine, paracrine and endocrine manner, modulating the energy mechanisms involved in physical activity, inducing cellular effects such as muscle hyperplasia, hypertropia and intervening in the repair process of damaged tissues (Pedersen & Febbraio, 2012; Lee, & Jun, 2019).

Among myokines, IL-6, known as a cytokine for its pro-inflammatory role (Pagliara, et al., 2018) and activation of T cells, shows an increase in circulating levels during and after acute physical exercise with an intensity > 65% of maximal aerobic capacity (VO_{2max}), depending on muscle glycogen depletion and damage. IL-6 also acts on the insulin signaling pathway, improving its affinity to muscle receptors and reducing its sensitivity in hepatocytes and adipocytes. Furthermore, IL-6 induces an increase in fatty acids oxidation through AMPK phosphorylation (Pagliara et al. 2018) in skeletal muscle and adipose tissue. The release of IL-6 also produces effects on other tissues, stimulating the production of anti-inflammatory cytokines, such as IL-10, and suppressing the formation of TNF-α (Arcone, et al. 2016) that is involved in systemic inflammation and insulin resistance in insulin-dependent tissues

Recent studies report that BDNF, IL-6, irisin, LIF and IGF-1 also mediate beneficial effects on brain function (Miranda, et al., 2019; Pedersen, 2019).

2. Physical activity and BDNF

Physical activity plays an important role in the prevention of age-related cognitive decline, in reducing the risk of dementia and in increasing the general quality of life (Chieffi, et al., 2017; Mandolesi, et al., 2018). In fact, physical activity increases the levels of serotonin and beta-endorphins, such as the endocannabinoid arachidonoylethanolamide (Pietrelli, et al., 2018; Fuss, et al., 2015). Brain regions that benefit from physical activity overlap with those affected by dementia. Studies on animal models describe that exercise-enhanced neuroplasticity is due to angiogenesis and growth factors, especially BDNF (Mandolesi, et al., 2018; Colucci-D'Amato, et al. 2020). During physical activity, BDNF levels rise in the brain, blood, muscles and in patients with schizophrenia, an increase of hippocampal region has been revealed (Miyamoto, et al., 2017; Pedersen, 2019). In addition, regular aerobic exercise is associated with structural and functional neuroplastic changes and with improved cognitive functions (Pietrelli, et al., 2017; Mandolesi et al., 2018). It has also been reported that moderate-intensity exercise is associated with the improvement of memory and cognitive flexibility, while high-intensity exercise increases the speed of information processing (Chang et al., 2019).

3. BDNF structure and biological functions

Brain-Derived Neurotrophic Factor (BDNF) is a homodimeric protein with a molecular weight of 25-28 kDa belonging to the neurotrophin family, and its gene encodes the proBDNF precursor (Leibrock, et al. 1989). BDNF is predominantly expressed in the brain, particularly in the hippocampus and cerebral cortex, but also in non-neurogenic tissues such as the aortic walls, endothelium, heart, kidneys, submaxillary glands, ovaries, dorsal ganglia, lungs and skeletal muscle.

BDNF induces neuronal survival and promotes the growth and differentiation of new neurons and synapses. Further, BDNF plays a vital role not only in the metabolic pathways of the central nervous system, but also acts as a metabolic regulator of muscle tissue (Leal, et al., 2014). At a central level, BDNF acts at hypothalamic region by regulation of energy homeostasis, plasticity, learning and memory (Colucci, et al. 2020). At the muscle level, BDNF is involved in energy metabolism control, improving glucose catabolism, particularly in diabetic subjects. Furthermore, BDNF stimulates satellite cell differentiation and muscle regeneration, and its expression increases in myocytes after both acute and chronic aerobic physical activity (Mackay, et al. 2017).

4. BDNF cell signaling and cognitive functions.

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, 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).

The decreased neurogenesis with impaired neuroplasticity, depression and neurogenerative diseases, such as Alzheimer's disease, observed during aging, have been correlated to a reduction of BDNF levels (Miranda, et al., 2019). In this scenario, exercise derived BDNF can contribute to ameliorate the impairment of these brain functions.

5. Effects of diet on BDNF levels

In addition to physical exercise, also diet can modulate BDNF levels. In fact, a correlation between nutritional factors and BDNF circulating level has been observed; in fact, a reduction in carbohydrate intake can increase BDNF levels. Vice versa, a high sugar and fats intake is associated with low levels of BDNF. It is noteworthy that among fats, omega-3 fatty acids from fish and vegetable oils sustain BDNF levels, also during a brain injury. Finally, even a calory restriction diet or intermittent fasting, has been linked to numerous beneficial effects, including the increase in BDNF levels. The mediterranean diet, rich of plant and fruit can influence the health status by the presence of polyphenols, molecules that show anti-oxidant, anti-inflammatory and anticancer properties (Arcone, et al., 2016; Nasso, et al. 2021). Among polyphenols, the flavonoid 7,8-dihydroxyflavone (7,8-DHF), abundant in fruits and vegetables, acts as an agonist of the BDNF TrkB receptor (Agrawal, et al., 2015). Its binding to TrkB extracellular domain causes dimerization and self-phosphorylation, leading to a signaling cascade similar to that caused by BDNF. In fact, 7,8-DHC has been shown to induce neuro-protective effects counteracting the oxidative stress caused by glutamate toxicity (Chen et al., 2011). These evidences confirm that the protection from oxidative damage is essential to maintain brain functionality (Chen, et al., 2011).

Conclusions

This brief review describes the role that exercise induced BDNF can exert on brain functions. BDNF can be produced during both aerobic and anaerobic activity, showing paracrine and endocrine function. BDNF can both cross the blood-brain barrier from the bloodstream or it can be produced by the brain itself during physical activity. At a central level, it was observed that physical activity improves memory, learning and synaptic plasticity, especially in the hippocampus region. This suggests that this myokine can play a role in improvement of cognitive functions, prevention of depression and neurodegenerative diseases (Colucci-D'Amato, et al., 2020). In particular, aerobic physical activity leads to increased BDNF and 5-HT levels in various areas of the brain, improving the performance of spatial memory, learning and energy expenditure. These results clearly indicate that physical activity can improve physical and mental health. Furthermore, the property of the flavonoid 7,8-DHF to act as an antioxidant that protect nerve cells from free radicals induced damage, as well as improving brain plasticity and memory confirm that even a correct diet promotes healthy mental functions.

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