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Commented Article

Comment on: Bente Klarlund Peddersen, Physical activity and muscle-brain crosstalk

Comentário sobre: Bente Klarlund Peddersen: Atividade física e interação-ação músculo-cerébro

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In the recent article published in Nature Reviews Endocrinology – "**Physical activity and muscle-brain crosstalk**" [1], the author - Bente Klaurlund Peddersen, a great reference in the study of skeletal muscle cell biology, contextualizes the theme by citing great philosophers of the past and their perceptions about the link between physical activity and the mind. Emphasizing the phrase of the German philosopher Friedrich Nietzsche: "All great thoughts are conceived by walking".

Thus, since our ancestors, when starting to walk in a bipedal way, human beings use a large amount of skeletal muscles as propelling agents for this action. Muscles correspond to ~ 40% of the body mass of healthy adults, with percentage changes throughout life. Muscles have functions beyond the mechanics of movement, for example, endocrine. Thus, the stimulation of this tissue through physical exercise (PE) promotes a great systemic impact [2,3].

Among these impacts, Peddersen BK [1] highlights the growing volume of evidence converging that PE promotes brain health benefits. In humans, PE increases blood flow to the hippocampus region and even the size of the hippocampus [4]. The author points out that PE is also essential to promote activation and increase of neural connections, in addition to impacting the basic cognitive, motor and physiological functions involved in mental health, such as appetite, sleep and mood [5-9].

For the effects of PE on the brain take place, two factors may be involved: a) neurotrophins produced within the brain and b) peripheral factors circulating in the bloodstream that may be due to muscle-brain interaction [10]. One category of these circulating factors that allow crosstalk between active muscles and brain function are the myokines. Myokines are cytokines produced and secreted by the skeletal muscle, that may act in an autocrine, endocrine or paracrine manner (they were baptized with this name by Peddersen in 2003) [11].

Among the crosstalk pathways approached in the article, we have separated three to detail in this article: 1) Cathepsin B – BDNF pathway, 2) PGC1α - FNDC5 – BDNF pathway and 3) PGC1α – Kynurenine axis pathway.

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I - Cathepsin B – BDNF pathway

Cathepsin B is a myokine involved in improving the processes of neurogenesis, cognition and memory mediated by PE in the hippocampus region. The energy consumption promoted by the PE activates the AMP-activated protein kinase (AMPK), which promotes the expression of the Ctsb gene. The gene encodes cathepsin B, which is secreted into skeletal muscle and released into the bloodstream [10].

Cathepsin B can cross the blood-brain barrier (BBB), where it stimulates the expression of the messenger ribonucleic acid (mRNA) of the brain-derived neurotrophic factor (BDNF). BDNF has a neuroprotective role against anxiety and depression [10,12]. In addition, from exercise, concomitantly, there is also an increase in doublecortin levels, which together with BDNF stimulate neurogenesis [10,13].

The evidence mainly deals with aerobic exercise of moderate to high intensity in animal models and in humans. In the article by Moon *et al*. [10], cathepsin B levels increased significantly in humans who underwent interval training on a treadmill at 70-90% of the maximum heart rate for 16 weeks.

On the other hand, when analyzing individuals who practice amateur rugby in a chronic way (35 ± 15 years of practice), De la Rosa *et al*. [14] found a lower serum concentration of cathepsin B in trained individuals, compared to untrained ones, which may suggest chronic adaptation to PE and greater efficiency of cathepsin signaling in trained individuals. In the same study, BDNF was also measured, finding a similar response, lower serum concentration in trained individuals than in untrained ones. In this case, the authors consider that the lower concentration is due beyond better signaling, to the fact that BDNF is also used for tissue repair, regulating satellite cell differentiation and muscle regeneration [15].

Despite the robust evidence in the literature, about the ability of resistance exercise to promote an increase in BNDF in humans [16,17], there is no evidence in the about its efficiency in promoting neurogenesis in humans, and in animal models, there are controversies [18,19]. Still, in our opinion, this method of exercise should be encouraged to improve and maintain mental health, as it promotes considerable cognitive gains in humans. For this, volume seems to be an important variable, as evidenced in the study by Fortes *et al*. [20], when investigating inhibitory control, a component of cognition, in young individuals (18-31 years), demonstrated that greater volume (3 sets) was better than lower volume (1 set) to stimulate adaptations in inhibitory control.

II - PGC1α – FNDC5 – BDNF pathway

Higher levels of Peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC1α) increase the expression of the membrane protein Fibronectin type III domain containing 5 (FNDC5) in the muscle, also present in highly oxidative tissues such as the heart and brain. During PE, FNDC5 undergoes proteolytic cleavage by a protease not yet identified and is secreted into the circulation in the form of the myokine irisin [17]. Irisin is best known for its modulating effect on white adipose tissue, increasing thermogenesis and energy expenditure, in addition to improving glucose tolerance [22].

An interesting study has shown that cyclic aerobic exercise promotes

increased expression of the FNDC5 gene in the hippocampus of animal models [23]. Another study demonstrated that the delivery of FNDC5 to the liver, increased the concentration of circulating irisin and induced the expression of the BNDF gene in the hippocampus [22]. This finding raised the hypothesis that irisin can cross the BBB to stimulate the production of BDNF in the brain and play a neurogenic, learning and reward-rewarding role.

The first question to ask is: After PE, would irisin released into the bloodstream be, in fact, able to cross the BBB to stimulate the expression of BDNF? The second, considering that FNDC5 is expressed not only in skeletal muscle, but also in other oxidative tissues, if the first question is true: Which tissue would contribute more to the expression of BDNF in the central nervous system?

It is important to note that the discovery of the relationship between exercise and FNDC5/irisin is recent [22], and there have even been questions raised as to whether irisin was in fact an existing myokine in humans or a myth derived from the low specificity of antibodies during analyzes by methods such as western blot and ELISA [24]. The controversy was resolved after studies demonstrated the detection of circulating irisin using mass spectrometry, a robust method that does not depend on the quality of antibodies [25,26].

Two human studies found a correlation between serum irisin concentration and cognition [21,26], however, a third study found no positive correlation [27]. Although the author points out that the increase in irisin in the blood is controversial, in our view, irisin seems to be a promising myokine due to its diversified action. However, more research is needed analyzing irisin, PE and its possible effects on the brain, especially in humans after cyclical aerobic and resistance exercises, at different volumes and training intensities.

III - PGC1α – Kynurenine axis pathway

Tryptophan is an essential amino acid for protein synthesis, in addition being the precursor of the neurotransmitter serotonin, fundamental for the proper functioning of the brain and involved in the processes of regulating mood, anxiety and cognition. Deficiency of serotonin is linked to development of depression and, therefore, the prescription of physical exercise is extremely important for people with mental health problems [28].

Most (~95%) of bioavailable tryptophan is metabolized to kynurenine, a neurotoxic protein, which is commonly elevated in individuals with depression [29]. This protein can cross the BBB, accumulating in the central nervous system and may be related to neuronal death and neuroinflammation. An enzyme called kynurenine aminotransferase converts kynurenine into kynurenic acid, which in turn is not able to cross the BBB, thus exercising a neuroprotective role [30].

PE promotes increased expression of PGC1α in skeletal muscle, this protein mediates the metabolic effects of exercise on muscle and is also a transcriptional co-activator of mitochondrial biogenesis and lipid metabolism [31]. The increased expression of PGC1α stimulates the production of kynurenine aminotransferase in skeletal muscle, increasing the conversion rate of kynurenine to kynurenic acid, consequently reducing the levels of kynurenine in the central nervous system, promoting a balance between neurotoxic and neuroprotective substances, thus, presenting an antidepressant effect.

The literature points out that women produce more kynurenine than men, this factor could help explain the two-fold rate of depression in women. In addition, women who use oral contraceptives have a higher rate of depression and a lower concentration of kynurenine acid than women who do not use it [32].

As with the first pathway presented, the evidence is concentrated on cyclic aerobic exercise, requiring further studies analyzing the effect of resistance exercise on this pathway, since resistance exercise activates PGC1α1, while cyclic aerobic exercise activates another isoform, PGC1α4, and may, thus present different results. Obese and type 2 diabetic individuals present low levels of PGC1α expression [33]. The same takes place in elderly individuals, therefore, studies evaluating the kynurenine/kynurenic acid balance in these populations would be of great importance.

Conclusion

In the article, the author presents some important pathways of interaction between skeletal muscle and the brain. Among which are the three pathways highlighted in this article, which through myokines released by the skeletal muscle from PE stimulus, are transported to the central nervous system and can promote cognitive and memory improvements, in addition to stimulating the process of neurogenesis and promote neuroprotective effect.

Research aiming to reveal the peripheral mechanisms of muscle-brain crosstalk and the ability of exercise to modulate brain functioning, presents great prospects for the future. The more in-depth knowledge of the molecular processes of these and other pathways, can help direct the prescription of PE in a more assertive way as prevention and treatment of diseases that affect the central nervous system, as well as for other beneficial effects in different populations.

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