v. 3, n. 6, 2022

International Journal of Health Science

PROMISING ACTION OF IRISIN IN THE TREATMENT OF ALZHEIMER'S DISEASE

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Abstract: Oxidative stress plays a central role in the initiation and progression of Alzheimer's Disease (AD) due to its high oxygen utilization rate; high content of polyunsaturated lipids that are susceptible to lipid peroxidation; and poor concentrations of antioxidants. Studies suggest that amyloid beta plaques cause cognitive damage by interrupting synaptic function leading to an underregulation of these networks and compromising anatomically and functionally interconnected brain areas. Irisin is an exercise-induced myokine released upon cleavage of the membrane-bound precursor protein fibronectin type III containing protein 5 (FNDC5), also expressed in the hippocampus. FNDC5/irisin dysfunction impairs long-term potentiation and recognition memory. On the other hand, increasing brain levels of FNDC5/irisin increases synaptic plasticity and memory. Thus, FNDC5/irisin is an important mediator of the beneficial effects of exercise capable of opposing memory impairment in AD. Regarding the Methodology, a qualitative exploratory study was carried out, with a bibliographic character and a theoretical survey based on scientific articles on the implications of irisin in the treatment of AD. For the result and discussion: Studies indicate that the brain with AD has a smaller amount of irisin and that this substance has a protective potential for neurons, preventing the amyloid β protein from binding to them, preventing neuronal loss. that FNDC5/irisin levels are reduced in the hippocampus and cerebrospinal fluid being a promising alternative in the treatment of AD, however, there is a need for further studies to prove its effectiveness.

Keywords: AD. FNDC5. BDNF. irisin. Neurodegeneration.

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia characterized by cognitive impairment, neurodegeneration, β-amyloid deposition, neurofibrillary tangle formation, neuroinflammation, and alteration in hippocampal neurogenesis.

The main neuropathological characteristics include the extracellular deposit of β-amyloid peptide (βA) plaques in the cerebral cortical regions, accompanied by the presence of intracellular neurofibrillary tangles, composed of hyperphosphorylated tau protein. βA accumulation leads to microglia activation and consequent production and release of cytokines with activation of glial cells producing inflammatory mediators such as nitric oxide, interleukins and nuclear transcription factor kappa B that are related to the neuroinflammatory process (ALZHEIMERS ASSOCIATION. 2021).

Within the pathophysiology of AD, aggregation of β-amyloid in the brain may be one of the causes of the disease, as it increases levels of reactive oxygen species and oxidative stress. Amyloid β plaques arise after the cleavage of the amyloid precursor protein (APP) present in the cell membrane of the neuron, via the BACE-1 enzyme (responsible for the cleavage of APP at the β site). In contrast, FNDC5 (irisin precursor) can reduce β-amyloid formation (JIN et al., 2018).

Irisin is a myokine with 112 amino acids, secreted with the domain of the fibronectin transmembrane protein (FNDC5) in skeletal muscles through physical exercise capable of protecting the hippocampus, a region of the brain centrally involved in learning and memory, by stimulating the expression of neurotrophic factors, such as Brain-Derived Neurotrophic Factor (BDNF) which is involved in neuroplasticity, neurogenesis, neuronal survival, synaptogenesis and cognition (JIN et al., 2018).

Furthermore, the protective effects of irisin on hippocampal neurons can also be attributed to a lower release of inflammatory cytokines by astrocytes (DI LIEGRO et al., 2019). According to the current panorama of the scientific literature, irisin has potential for the treatment of AD, as it demonstrates efficacy in neurophysiology and metabolism.

RESULT AND DISCUSSION

Recent research suggests a relationship between AD and systemic metabolic changes, such as lipid imbalance, hyperglycemia and insulin resistance, given that impaired glucose uptake in the brain triggers brain atrophy and neuronal dysfunction.

According to previous studies, there is an endocrine loop between the muscle and the brain, through peptides and metabolites released during physical exercise that can directly alter the function of the hippocampus or stimulate the expression of neurotrophic factors, such as BDNF (PEDERSEN, 2019).

According to Souza (2019), irisin performs autocrine, paracrine and endocrine functions, being produced in different tissues, such as bone and adipose tissue, but its greater production affects skeletal muscles. Due to the stimuli of physical exercise, there are responses of increased transcription and activation of the co-activator that will culminate in the production of irisin via cleavage of FNDC5.

In the findings of Jin et al., (2018), aerobic exercise reverses the loss of hippocampal volume causing a 2% increase, followed by an improvement in memory function, in addition to delaying the decline in executive functioning induced by neurodegeneration.

During exercise, FNDC5 expression in skeletal muscle increased, leading to a subsequent increase in irisin, similarly, exercise increases FNDC5 expression in the hippocampus. In addition to the hippocampus, the authors below analyzed that FNDC5/irisin is highly expressed in Purkinje cells of the cerebellum, whereas irisin was identified in the cerebrospinal fluid, in the hypothalamus, especially in paraventricular neurons (ISLAM et al., 2017; JIN et al.., 2018; LOURENCO et al., 2019; YOUNG, et al., 2019).

According to Islam et al., (2017) the effects of exercise on the brain are most apparent in the hippocampus and dentate gyrus, a part of the brain involved in learning and memory. The results indicate that the beneficial effects of exercise on the brain include increases in the size and blood flow of the hippocampus in humans, morphological changes in dendrites and dendritic spines, increased plasticity of synapses and, most importantly, neurogenesis.

Young et al. (2019), corroborates the study above, in which the hippocampus is one of the brain areas most benefited by physical exercise, since there is a reduction in neuroinflammation and an increase in neurogenesis provided by BDNF.

The BDNF produced in the periphery is able to cross the blood-brain barrier and perform its actions centrally, but this factor is also produced directly in the brain from the action of other molecules, some even produced in the periphery in a manner dependent on physical exercise. Therefore, BDNF is involved in several important aspects with regard to neuroplasticity, neurogenesis, neuronal survival, synaptogenesis and cognition (MORRIS et al., 2017).

According to Di Liegro et al., (2019), the benefits observed in the first patients with AD after aerobic exercise are due to the exercise-dependent increase in cardiorespiratory fitness, which in turn is associated with better memory performance and reduced hippocampal atrophy..

In AD, FNDC5/irisin levels are lower in the hippocampus and cerebrospinal fluid in patients with this advanced-stage neurodegenerative disease when compared to

age-matched controls, as well as in transgenic mice (TARI et al., 2019).

Some studies have investigated chronic neuroinflammation in the pathophysiology of AD, relating the increase in plasma levels of tumor necrosis factor alpha (TNF-α) and interleukin-6 and, on the other hand, a decrease in irisin. In this sense, evidence suggests that irisin may be a new target to reduce pro-inflammatory mediators in the prevention or treatment of this disease. Thus, irisin may be mediating neuroprotective effects via astrocytes, decreasing the release of inflammatory mediators (DI LIEGRO et al., 2019; YOUNG et al., 2019).

Other findings suggest that irisin modulates signal transducer and transcription activator 3 (STAT3) signaling after exercise, contributing to decrease the risks of AD. This way, the irisin axis can enhance neurogenesis (JIN et al., 2018).

Choi et al. (2018) states that exercise-induced adult hippocampal neurogenesis improved cognition and memory, along with reduced β-amyloid burden and increased levels of BDNF, FNDC5, and synaptic markers in AD.

Morris et al. (2017) evaluated the effect of aerobic exercises on memory, executive function and on depression at the onset of AD. The study showed that physical exercise is associated with better memory performance and reduced hippocampus atrophy.

Kuster et al. (2017) evaluated BDNF and irisin as blood biomarkers of cognition, stress, and physical or cognitive training in elderly people at risk of dementia. The study showed that, after exercise or cognitive training, serum levels of BDNF and irisin were positively correlated with global cognition and episodic memory, while the neurotoxic metabolite kynurenine was negatively correlated with executive functions.

Evidence from animal and in vitro studies suggests irisin connections with BDNF in the central nervous system, as part of the relationship between physical exercise and cognition promoting neurogenesis as well as neuroplasticity. (JIN et al., 2018).

Irisin and BDNF serum levels may become possible biomarkers. In this sense, it has been shown that high serum concentrations of BDNF alleviate cognitive impairment (CONTI et al., 2019).

Conti et al., (2019), evaluated that serum irisin is significantly decreased in patients with AD. Thus, the aforementioned author proposed that myokines may represent interesting results in patients with dementia with psychological symptoms and behavioral changes.

To corroborate this hypothesis, in another study, the levels of irisin and BDNF in the brain of patients with AD are below average and may be related to memory loss, demonstrating that physical exercises and replacement of irisin synthetically in the brain, the loss of memory has been significantly reversed. However, it was not possible to find out how irisin acts to prevent neurons from being affected by amyloid β plaques (ABRAZ, 2019).

Zhang's results (2014) corroborate the present study by suggesting that irisin favors neurogenesis when it is released by skeletal muscle when performing physical exercises. Thus, the action of irisin increases the expression of BDNF contributing to learning, memory as well as the aging process.

Lourenco et al (2019) demonstrated the reduced level of FNDC5/irisin in individuals with AD, demonstrating that its influence is on the neuroplasticity of the hippocampus. Analyzes of the in vitro methodology indicate that irisin prevents the amyloid β protein from binding to neurons.

In a later study, Lourenco et al (2020) investigated the presence of irisin in the cerebrospinal fluid (CSF) of 39 elderly people

aged 60 years or older, with and without AD. The results were related to the amount of irisin in the CSF, identifying that the elderly with higher serum concentrations of irisin had a better score on the test. According to the author, the higher the concentration of irisin, the higher the levels of BDNF - considered a predictive marker of mental health.

Food can also contribute to the production of irisin through the consumption of polyunsaturated fatty acids, such as omega 3. In addition, there is the possibility of developing irisin-based drugs indicated for individuals who cannot exercise, however, more studies need to be carried out, therefore, the best way to increase irisin levels is in the regular practice of physical exercises.

In a study carried out with individuals supplemented with ursolic acid, there was an increase of 23% in the production of circulating irisin when a dose of 1,000mg/ day was used. The results suggest that ursolic acid, associated with physical exercise, may represent a better strategy to increase plasma levels of irisin (KUNKEL, 2012).

Arcoverde et al (2014) carried out a randomized study, on an ergometric treadmill, with 20 elderly people with AD, where the training group underwent 3 months of aerobic exercise, twice a week, lasting 30 minutes and observed that, after the During the training period, patients showed improvements in global cognitive functions, balance and mobility.

FINAL CONSIDERATIONS

Irisin is able to protect the hippocampus - brain region involved in learning and memory - by stimulating the expression of BDNF involved in neuroplasticity, neurogenesis and synaptogenesis. However, due to the reduced number of studies in the current literature, there is a need for further investigation so that more robust evidence can be presented. In addition, the high cost to carry it out and the need for specific equipment may be some of the factors that hinder its execution.

In view of the results of the present study, we suggest clinical trials on a larger scale to clarify the action of irisin in the treatment of AD. Thus, future studies need to be carried out for further clarification on the effects of physical exercises, the release of the hormone irisin and its benefits as a possible predictive marker or the production of a drug or nutrients from food to potentiate its action in the neurogenesis of the system. central nervous.

REFERENCES

ALZHEIMERS ASSOCIATION. **Alzheimer's disease facts and figures. Alzheimer's and Dementia**. v. 17, n. 3, p. 327–406, 2022.

BEAR MF, CONNORS BW, PARADISO MA (2002) **Neurociências: desvendando o sistema nervoso**. Artmed Editora S.A 2:22-49.

BELVIRANLI M, OKUDAN N, KABAK B, ERDOĞAN M, KARANFILCI M (2016) **The relationship between brain-derived neurotrophic factor, irisin and cognitive skills of endurance athletes**. The Physician and Sportsmedicine 44:290-296.

BLOOMER, Richard J et al. **Impact of the Dietary Supplement CLOCK® on BDNF and Other Biochemical Measures Related to Cognitive Function and Health in Men and Women. Alternative, Complementary & Integrative Medicine**, [S.L.], v. 3, n. 3, p. 1-7, 18 out. 2017. Herald Scholarly http://dx.doi.org/10.24966/acim-7562/100034.

BOSTRÖM P, WU J, JEDRYCHOWSKI MP, KORDE A, YE L, LO JC, RASBACH KA, BOSTRÖM EA, CHOI JH, LONG JZ, KAJIMURA S, ZINGARETTI MC, VIND BF, TU H, CINTI S, HØJLUND K, GYGI SP, SPIEGELMAN BM (2012) **A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis**. Nature 481:463-468.
CHEN X, GAN L (2019) **An exercise-induced messenger boosts memory in Alzheimer's disease**. Nature medicine 25:20-23.

CUMMINGS JL, VINTERS HV, COLE GM, KHACHATURIAN ZS (1998) **Alzheimer's disease: etiologies, pathophysiology, cognitive reserve, and treatment opportunities**. Neurology 51:2-17.

GOLDE TE, ECKMAN CB, YOUNKIN SG (2000) **Biochemical detection of Aβ isoforms: implications for pathogenesis, diagnosis, and treatment of Alzheimer's disease**. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease 1502(1): 172-187.

KUNKEL, SD. et al. **Ursolic Acid Increases Skeletal Muscle and Brown Fat and Decreases Diet-Induced Obesity, Glucose Intolerance and Fatty Liver Disease**. Plos One, [S.L.], v. 7, n. 6, p. 332, 20 jun. 2012. Public Library of Science (PLoS). http://dx.doi.org/10.1371/journal.pone.0039332.

LOURENCO MV, FROZZA RL, FREITAS GB, ZHANG H, KINCHESKI GC, RIBEIRO FC, GONÇALVES RA, CLARKE JR, BECKMAN D, STANISZEWSKI A, BERMAN H, GUERRA LA, FORNY-GERMANO L, MEIER S, WILCOCK DM, SOUZA JM, ALVES-LEON S, PRADO VF, PRADO MAM, ABISAMBRA JF, TOVAR-MOLL F, MATTOS P, ARANCIO O, FERREIRA ST, FELICE FG (2019) **Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models**. Nature medicine 25:165-175.

LOURENCO MV, RIBEIRO FC, SUDO FK, DRUMMOND C, ASSUNÇÃO N, VANDERBORGHT B, TOVAR-MOLL F, MATTOS P, FELICE FG, FERREIRA ST (2020) **Cerebrospinal fluid irisin correlates with amyloid-β, BDNF, and cognition in Alzheimer's disease. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring** 12:1-5.

NODA Y, KUZUYA A, TANIGAWA K, ARAKI M, KAWAI R, MA B, SASAKURA Y, MAESAKO M, TASHIRO Y, MIYAMOTO M, UEMURA K, OKUNO Y, KINOSHITA A (2018) **Fibronectin type III domain-containing protein 5 interacts with APP and decreases amyloid β production in Alzheimer's disease**. Molecular brain 11:1-13.

PHILLIPS C, BAKTIR MA, SRIVATSAN M, SALEHI A (2014) **Neuroprotective effects of physical activity on the brain: a closer look at trophic factor signaling. Frontiers in cellular neuroscience** 8:170

ABRAZ. Associação Brasileira de Alzheimer. **Irisina e a doença de Alzheimer**. 2019 Disponível em: http://abraz.org.br/web/2019/01/25/irisina-e-a-doenca-de-alzheimer.

AMERICAN PSYCHIATRIC ASSOCIATION DSM-5 - **Manual Diagnóstico y Estadístico de los Trastornos Mentales**. Madrid: Panamericana. 2014.

ARCOVERDE, C.; DESLANDES, A.; MORAES, H.; ALMEIDA, C.; BOM DE ARAÚJO, N.; VASQUES, P.E.; SILVEIRA, H.; LAKS, J. **Treadmill training as an augmentation treatment for Alzheimer's disease: a pilot randomized controlled study**. Arquivos de Neuropsiquiatria, v.72, n.3, p.190-196, 2014.

BHERER, L. **Cognitive plasticity in older adults: effects of cognitive training and physical exercise**. Ann N Y Acad Sci. Mar;1337:1-6 2015.

LOURENCO, M.V.; FROZZA, R.L.; FREITAS, G.B. **Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's model**s. Nat Med v. 25, p: 165–175, 2019.

PHILLIPS C. **LIFESTYLE MODULATORS OF NEUROPLASTICITY: How Physical Activity, Mental Engagement, and Diet Promote Cognitive** Health during Aging. Neural Plast 2017.

PEDERSEN BK.; FEBBRAIO MA. **Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nat Rev Endocrinol**. v. 8, n. 8, p: 457-465, 2019.

SANDRI, F, R. Estudo de caso. Efeitos do exercício físico na doença de Alzheimer (2017).

SHARMA. N.; CASTORENA, C.M.; CARTEE, G.D. **Maior sensibilidade à insulina em ratos com restrição calórica ocorre com níveis circulantes inalterados de várias miocinas e citocinas importantes**. Nutr Metab (Lond), 2012.

SOUZA, C.R.R.M.; OLIVEIRA, D.J. S.; COSTA, G.A.; SANTANA, V.H.S. **Déficits de memória e plasticidade sinápticos resgatadas em modelos de Alzheimer vinculados a miocina estimulada ao exercício físico**, 2019.

WRANN, C, D.; WHITE, JP.; SALOGIANNNIS, J.; LAZNIK-BOGOSLAVSKI, D.; WU, J.; MA, D.; LIN, JD.; GREENBERG, ME.; SPIEGELMAN, BM. **Exercise induces hippocampal BDNF through a PGC1alpha/FNDC5 pathway**. Cell Metab. v. 18, n. 5, p: 649-659, 2013.

ZHANG, Y.; LI, R.; MENG, Y.; LI, S.; DONELAN, W. **Irisin Stimulates Browning of White Adipocytes Through Mitogen-Activated Protein Kinase p38 MAP Kinase and ERK MAP Kinase Signaling Diabetes** v. 63, n. 2, p: 514-25, 2012.

ZWICK, R, K. **Anatomical, physiological, and functional diversity of adipose tissue. Cell Metabolism**, New Haven, v. 27, p. 68-83, 2018.

BOSTRÖM P, et al. **A PGC1-α dependentmyokinethatdrivesbrowing of whitefatandthermogenesis**. Nature, 2012; 481: 463-468.

CHOI SH, et al. **Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer's mouse model**. Science, 2018; 361(6406).

CONTI E, et al. **Irisin and BDNF serum levels and behavioral disturbances in Alzheimer's disease**. Neurological Sciences, 2019; 40(6):1145-1150.

DI LIEGRO CM, et al. **Physical activity and brain health**. Genes, 2019; 10(9): 720.

ISLAM MR, et al. **The role of FNDC5/Irisin in the nervous system and as a mediator for beneficial effects of exercise on the brain**. Springer, 2017; 93-102.

JIN Y, et al. **Molecular and functional interaction of the myokine irisin with physical exercise and Alzheimer's disease. Molecules**, 2018; 23(12): 3229.

KIM OY, CANÇÃO J. **O papel da irisina na doença de Alzheimer**. Journal of Clinical Medicine, 2018; 7(11): 407.

KÜSTER OC, et al. **Novel blood-based biomarkers of cognition, stress, and physical or cognitive training in older adults at risk of dementia: preliminary evidence for a role of BDNF, irisin, and the kynurenine pathway. Journal of Alzheimer's Disease**, 2017; 59(3): 1097-1111.

LOURENCO MV, et al. **Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models**. Nature medicine, 2019; 25(1): 165-175.

MORRIS JK, et al. **Aerobic exercise for Alzheimer's disease: a randomized controlled pilot trial**. PloS one, 2017; 12(2): e0170547.

PEDERSEN BK. **Physical activity and muscle–brain crosstalk**. Nature reviews endocrinology, 2019; 15(7): 383-392.

TARI AR, et al. **Are the neuroprotective effects of exercise training systemically mediated?**. n, 2019; 62(2): 94-101.

YOUNG MF, et al. **A role for FNDC5/Irisin in the beneficial effects of exercise on the brain and in neurodegenerative diseases**. Progress in cardiovascular diseases, 2019; 62(2): 172-178.

ZHANG J, ZHANG W. **Can irisin be a linker between physical activity and brain function?**. Biomolecular concepts, 2016; 7(4): 253-258.