REVIEW ARTICLE

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Cross talk mechanisms of aerobic exercise training on obesity, type 2 diabetes, and Alzheimer's disease: the role of insulin resistance

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INTRODUCTION

Obesity is characterized by the presence of excessive white adipose tissue, inflammation, and insulin resistance[1]. It is known that a sedentary lifestyle, commonly seen in subjects with type 2 diabetes (T2D) and obesity, is associated with many deleterious health outcomes. The overexpression of white adipose tissue is associated with higher levels of insulin resistance, which, in turn, is crucial for cognitive impairment and mental health[1,2]. T2D main feature is insulin resistance, which occurs mainly due to molecular impairments in the phosphatidylinositol 3-kinase (PI3K) pathway[3,4]. Disruption of normal functioning of insulin receptor substrates 1 (IRS-1) and 2 (IRS-2) in PI3K pathway can lead to T2D[5]. The changes in IRS-1 and IRS-2 in the brain mediate the alterations in glucose metabolism[6]. However, failure of activating any protein of PI3K pathway can lead to insulin resistance, obesity, and T2D[7]. Insulin resistance is also a common feature present in Alzheimer's disease (AD). Thus, T2D and obese individuals are at increased risk for dementia, particularly AD[7,8].

AD is the most common type of dementia worldwide[9]. The impairment of the insulin signaling increases the amyloidogenic processing of the amyloid precursor protein, leading to the increased generation of the neurotoxic protein amyloid beta (Aβ). Cognitive impairment and memory deficits have been attributed to the aggregation of these insoluble amyloid fibrils and brain insulin resistance[10]. Another important hallmark of AD is the overexpression of Tau protein, which also favors the development of insulin resistance[11]. Inflammation is also present concomitantly to insulin resistance and hyperphosphorylation of Tau protein during the development and establishment of AD[6]. Thus, insulin resistance, hyperphosphorylation of Tau protein, and inflammation contribute to the development of AD. The development and progression of obesity, T2D, and AD can lead to cognitive decline and mental health impairment, which can be overcome by performing aerobic exercise training (AET), which is characterized by performing exercises where the utilization and transport of oxygen are predominant and occur concomitantly to the recruitment of red fibers, also known as type I fibers, or fibers of slow contraction. In this study, we aimed to review some of the most important molecular mechanisms that can be changed by the practice of AET in obesity, T2D, and AD.

ROLE OF AEROBIC EXERCISE TRAINING ON OBESITY

AET can contribute to fight and avoid the development of obesity. AET activates the beta-oxidative pathway, which is a multienzymatic pathway that degrades fat to produce energy in skeletal muscle12. Gene expression is modulated by peroxisome proliferator-activated receptor alpha (PPAR-α), and a co-activator (PGC-1α)13. PGC-1α is a member of a family of transcription co-activators that plays an important role in the regulation of cellular energy metabolism14. It has been reported that PGC-1α would play a role in the occurrence of white tissue browning by exercise in mice, but this is still a controversial topic regarding humans15. PGC-1α induces the expression of fibronectin type III domain-containing 5 (FNDC5), which is cleaved at the C-terminal to produce Irisin16. Irisin is a myokine which was identified for its ability to induce browning of the white adipose tissue, increasing energy expenditure, and protecting against insulin resistance17. AET can induce positive changes in the mental health of overweight and obese individuals18.

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ROLE OF AEROBIC EXERCISE TRAINING ON TYPE 2 DIABETES

Physical exercise, specially AET, has a crucial role on the glucose metabolism because it leads AKT to signalize to cytoplasmic vesicles that carry GLUT4, a glucose transporter found inside these vesicles, to be translocated to the cell membrane by these vesicles to catch and take glucose to the adipose and muscle tissues[4]. This glucose will be stocked and used as energy fuel to perform daily activities. AET reduces and manages blood glucose in T2D, controlling hyperglycemia and hyperinsulinemia through insulin-dependent and insulin-independent pathways[19,20]. The insulin-independent pathway that activates translocation of GLUT4 to the muscle membrane is not impaired in T2D, hence the surprising value of exercise. These physiological changes contribute to a higher VO_{2max}, and this higher oxidative contributes to energy generation at a particular exercise workload, improves the blood pressure, and lowers the risk of developing cardiovascular diseases in T2D individuals[4,21].

ROLE OF AEROBIC EXERCISE TRAINING ON ALZHEIMER'S DISEASE: FOCUS ON COGNITIVE DECLINE AND MEMORY LOSS

Cognitive decline and memory loss are not a direct natural consequence of aging, and instead are related to heritability, illness, or damage in the brain tissue[22]. A recent meta-analysis evaluated if physical exercise programs had a significant impact in improving cognition and the ability to perform activities of daily living in people with all types of dementia, with a strong focus on AD[23]. The 16 included trials (n=937 participants) were extremely heterogeneous in terms of classifying the participants' dementia and the duration, intensity, and frequency of exercise. Only two trials included participants who were living at home. The meta-analysis suggested that all types of physical exercise programs may have a significant impact on improving cognitive function and the ability of people facing cognitive decline or memory loss to perform daily activities normally.

AEROBIC EXERCISE TRAINING REGULATES THE MOLECULAR MECHANISMS IN ALZHEIMER'S DISEASE, TYPE 2 DIABETES, AND OBESITY

AET induces changes in the expression of several genes, by altering epigenetic patterns of DNA methylation and histone acetylation, modulating signal transduction pathways and metabolic pathways, and especially promoting a more efficient stimulation of the PI3K pathway[24] and also insulin-independent pathways, such as interleukins (ILs) pathway[25]. PGC-1α/FNDC5/Irisin pathway is only activated by skeletal muscle during physical exercise and has been positively correlated with biceps circumference and insulin-like growth factor-1 (IGF-1) levels in humans[26] and growth-related genes in mice[27]. Irisin has unidentified receptors and plays a role in metabolism, synaptic plasticity, neurogenesis, cognitive function, and memory through different pathways, such as PI3K[21]. On the other hand, excessive adiposity is associated with poor mental health[28,29].

AET increases lipid oxidation via upregulating genes involved in regulating fatty acid uptake across the plasma and mitochondrial membranes[30]. AET increases carnitine palmitoyltransferase (CPT) complex activity and malonyl-CoA production is inhibited[13], which is the precursor of all fatty acids. This contributes to reduced body fat mass, thus contributing to a reduced risk of obesity and cardiovascular disease. A recent study showed that obese individuals who did bicycle training for 3 months did not lose visceral adipose tissue when a selective inhibitor of the IL-6 receptor was used, compared to the exercise group who received a placebo[31]. This study showed that loss of visceral adipose tissue mass with exercise training is dependent on IL-6, but it remains unclear whether inhibition of IL-6 also inhibited PGC-1α and/or CPT complex or how it would interfere with Irisin production and related pathways.

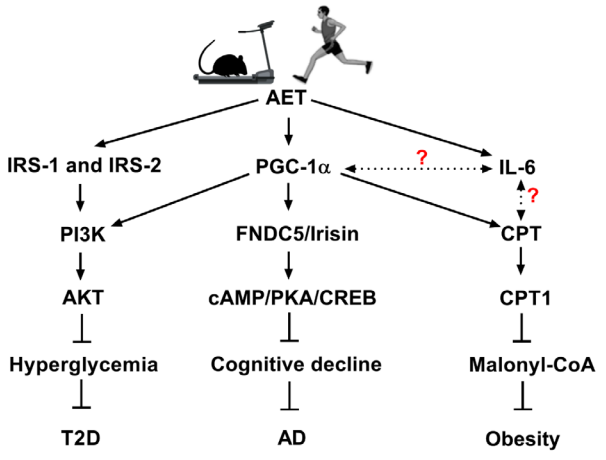
In addition, it is now clear that AET can increase the levels of brain-derived neurotrophic factor (BDNF)[32], stimulate neurogenesis[33], and improve learning and mental performance[34]. Irisin levels are diminished in the hippocampus of AD experimental models. When boosting brain or peripheral levels of Irisin through AET or injecting recombinant Irisin, in animal models and human cells, respectively, BDNF levels are enhanced, and memory and synaptic plasticity are rescued[35]. Recombinant Irisin also had neuroprotective actions in human cells stimulating cyclic AMP (cAMP), protein kinase A (PKA), and CREB, which together form a very important pathway (i.e., cAMP/PKA/CREB) that plays several roles in memory formation (Figure 1).

AEROBIC EXERCISE TRAINING STIMULATES GLUCOSE METABOLISM AND MITOCHONDRIA FUNCTION IN THE BRAIN

We have demonstrated a connection between obesity, T2D, and AD, and the role of AET in stimulating glucose metabolism and mitochondria function in the brain. These changes

will also fight the development and progression of these diseases[36-38]. The brain is also important for managing compensatory mechanisms to hypoglycemia in addition to its regulation of energy metabolism[39]. It is known that glucose is the most important circulating energy substrate for the brain and is actively oxidized to produce ATP, generating a synergistic effect with mitochondria in several metabolic pathways[40].

There is a growing body of evidence showing a crucial role of impaired mitochondrial function in pathogenesis of several neurodegenerative diseases and thus biochemical factors in mitochondria are considered promising targets for pharmacological-based therapies[41]. It is known that the activation of PGC-1α is essential for mitochondrial dynamics and function, and AET triggers the enhancement of its expression together with greater expression of BDNF and FNDC5[42,43]. Acute or chronic AET can favor greater expression of PGC-1α, mitochondria biogenesis and elongation, and autophagy, which together will also favor the enhancement of glucose uptake and utilization[44,45].



AET: aerobic exercise training; IRS: insulin receptor substrates; PGC: Peroxisome proliferator-activated receptor gamma coactivator; IL: interleukins PI3K: phosphatidylinositol 3-kinase; FNDC: fibronectin; CPT: carnitine palmitoyltransferase; AKT: Protein kinase B; COA: Coenzyme A; T2D: type 2 diabetes; AD: Alzheimer's disease.

Figure 1. Representative scheme of the influence of aerobic exercise training on different molecular pathways. Aerobic exercise training can contribute to a better functioning of the phosphatidylinositol 3-kinase pathway, thus inhibiting the development of hyperglycemia and, consequently, obesity and type 2 diabetes. Aerobic exercise training needs to activate Interleukins-6 to induce weight loss. It is not known if IL-6 plays a role in elevating the activity of the carnitine palmitoyltransferase complex and the production of PGC-1α and/or vice versa. Aerobic exercise training also favors the activation of PGC-1α/fibronectin type III domain-containing 5/Irisin and cyclic Adenosine monophosphate/protein kinase A/ Cyclic adenosine monophosphate response element-binding protein pathways, thus inhibiting, in this way, cognitive decline and development of Alzheimer's disease.

Many governments and their health research funding agencies include scientific research into the determinants of exercise behavior and its role in healthy aging as an important item on their agenda. Many studies of the practice of exercise in T2D or AD lack appropriate sample power, randomization and allocation concealment, and standardized protocols. There is also a lack of information provided in many studies about how to implement the AET (especially for long-term exercise regimens). It is essential to describe the frequency, intensity, volume, duration, rate of progression, and type of the AET performed in sufficient detail to allow replication. In addition to the physiological adaptations related to the AET, it is also necessary to describe factors such as age, gender, ethnicity, heritability, geographic location, climate temperature, nutritional habits, and emotional and psychological parameters. All these variables will influence the physiological effect of AET; however, many of the studies target just one or two of these variables, which may not be the ones mainly responsible for the physiological changes captured in the study.

Finally, AET leads to peripheral and central protective effects. Thus, AET can be seen not only as a therapeutic tool but also as a preventive strategy in order to avoid the development and/or progression of obesity, T2D, and AD. However, an accurate and individualized approach following the standards of prescribing the training based in the frequency, intensity, volume, duration, rate of progression, and type of the AET should be followed.

CONCLUSION

AET is a very useful non-pharmacological tool that can bring positive physiological adaptations to AD, T2D, and obesity. AET stimulates a better efficiency of the PI3K pathway and also insulin-independent pathways. Finally, AET can induce the enhancement of PGC-1α/FNDC5/Irisin and cAMP/PKA/CREB pathways, thus inhibiting, in this way, cognitive decline, development or progression of hyperglycemia, and weight gain.

AUTHORS' CONTRIBUTIONS

RALS: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **CODM:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Methodology, Supervision, Validation,

Visualization, Writing – original draft, Writing – review & editing. **IRD:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **LRSO:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **ACIC:** Conceptualization; data curation; formal analysis; funding acquisition; methodology; supervision; validation; visualization; roles/writing – original draft; writing – review & editing. **RCC:** Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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