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Opinion

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Is alzheimer's disease a type of diabetes?

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Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by loss of memory and impairment of multiple cognitive functions, to the detriment of hippocampal and cortical neurons. It is reported that neuronal loss may contribute to a 20-30% decrease in brain weight loss in patients with AD. This impairment in the counting and functionality of neurons occurs as a consequence of the accumulation of β-amyloid protein (β-A) and neurofibrillary tangles. B-A protein is found in neuritic plaques of the brain with AD and is generated by abnormal processing of amyloid precursor protein (APP) in neurons. The process of generation of APP occurs through two pathways: the amyloidogenic pathway, in which APP undergoes a sequential proteolysis through the β and γ secretases enzymes, originating the β-A protein; and the non-amyloidogenic pathway, in which cleavage occurs through the α-secretase enzyme within the β-A domain, generating soluble and non-amyloidogenic fragments that are cleaved by the enzyme γ-secretase.

The cause of abnormal APP processing and subsequent accumulation of β-A protein is unknown. However, factors such as genetics, age, lifestyle, diet, metabolic diseases and other pathologies such as Down syndrome are considered to be at risk for the onset of the disease. The β-A protein is generated in neurons, where APP and β and secrete enzymes are present in many intracellular sites, such as the Golgi complex, endoplasmic reticulum, endosome-lysosome system and multivesicular bodies. Studies have shown that β-A protein represents the central cause of the development and progression of AD, since it causes a series of events such as oxidative stress, synaptic loss and deterioration, inhibition of synaptic plasticity and hyperphosphorylation of Tau protein reported as one of the main biomarkers of the disease, together with the β-A2 protein [1-3].

In the central nervous system (CNS), IGF / insulin signaling plays a critical role in the regulation and maintenance of cognitive function. Insulin, insulin-like growth factors 1 and 2 (IGF-1 and IGF-2) and receptor genes are expressed in glia cells and neurons throughout the brain, with the highest levels of expression being found in structures that are usually targets of degenerative diseases[4]. The IGF / insulin signaling axis exerts several functions, such as growth, survival, differentiation, migration, energetic metabolism, gene expression, protein synthesis, cytoskeletal assembly, synapse, neurotransmitter function and neuronal plasticity [4].

There has been a growing number of studies that support the concept that AD essentially represents a metabolic disease with impairment in energy production and utilization of glucose by the brain [5]. The metabolic abnormalities present in the disease in question are related to insulin resistance and insulin-like growth factor (IGF), and thus to the breakdown of signaling pathways that regulate the survival of neurons, energy production, gene expression and plasticity. It is reported that brain inhibition of IGF / insulin may increase APP expression, β-A protein accumulation, enzyme activity responsible for phosphorylation of Tau protein and generation of reactive oxygen and nitrogen species that cause protein damage, DNA, RNA and lipids; in addition, it promotes mitochondrial dysfunction and activates pro-inflammatory and pro-apoptotic cascades [4]. Furthermore, IGF / insulin resistance in the brain promotes a decrease in the expression of key genes required for homeostasis cholinergic, compromising systems that mediate neuronal plasticity, memory and cognition [6].

It is shown that the early stages of AD are characterized by cerebral deficit in the use of glucose, and the physiological and metabolic abnormalities related to energetic impairment worsen with the progression of the disease. The expression of genes related to IGF / insulin synthesis that mediates cholinergic / cognitive and metabolic functions is suppressed in AD [6]. In patients with AD, deficiency in insulin signaling is due to the combined effect of their deficiency and brain resistance. These events are manifested by reduced responsiveness to the stimulation and functionality of their receptor, whereas IGF deficiency is associated with reduced gene expression and insulin levels in cerebrospinal fluid and brain. Thus, AD is considered a form of cerebral diabetes mellitus characterized by deficiency and insulin resistance, being called diabetes mellitus type 3 [4]. In addition, it is shown that the molecular, biochemical and signal transduction abnormalities present in AD are identical to those that occur in the presence of type 1 and type 2 diabetes mellitus 2 [4-6]. It is reported that the toxicity of β-A protein promotes insulin resistance in brain with concomitant oxidative stress and neuroinflammation [7,8].

In addition, insulin stimulation accelerates the mobilization of the Golgi complex β-A protein, where it is generated, to the plasma membrane, which causes greater stimulation of insulin secretion [4]. In addition, it is reported that insulin signaling in the brain may prevent both processing of APP and clearance of β-A protein. The accumulation of β-A protein exacerbates this picture, since β-A protein causes disruption of insulin signaling by competition or reduction of insulin affinity with its receptor [2-4]. Studies have shown that individuals who present with glucose intolerance, insulin secretion deficiency or type 2 diabetes mellitus have a significantly higher risk of developing AD, since peripheral insulin resistance is a triggering factor for their resistance cerebral [9,10]. These events promote neuroinflammation and increase APP expression. Through the action of the β and γ secretases enzymes, the protein in question is cleaved, and the exaggerated generation of neurotoxic peptides and oligomers that promote increased oxidative

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stress and GSK-3β activation: glycogen synthase kinase-3β; CDK5: cyclin-dependent kinase-5; P38 MAPK: mitogen-activated protein kinase P38; JNK: N-terminal c-Jun kinase; PP2A: protein phosphatase 2; EROS: reactive oxygen species [13,14]. It is reported that individuals with impaired glucose tolerance, insulin secretion, type 2 diabetes mellitus, dyslipidemic diseases or obesity present a significant increase in the risk of developing mild cognitive impairment or dementia [11,12].

Thus, it is suggested that therapeutic strategies designated for treatment of type 2 diabetes mellitus, obesity and insulin resistance may be useful in slowing the progresion or reducing the severity of AD.

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