

INSULIN RESISTANCE AS A METABOLIC LINK IN THE PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

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RESUMO

Introduction: Alzheimer's Disease (DA) is one of the most common neurodegenerative diseases, and substantial evidence has supported the relationship between peripheral insulin resistance (IR) and the development of DA. Often referred to as Type 3 Diabetes, the role of metabolic dysfunction in the pathophysiology of DA is highlighted. Insulin resistance is strongly associated with alterations in neuronal survival, synaptic plasticity, and memory formation, facilitating the progression of neurodegeneration.

Objectives: This work aims to evaluate how IR contributes to the neurodegeneration of brain areas related to memory and its relationship with the pathophysiology of DA. **Methods:** This study is a literature review in which PubMed was used as a database. Reviews and articles published within the last 5 years were included primarily. The following descriptors were used for the search: Alzheimer's disease, Insulin resistance in the brain, neurodegeneration, and Insulin receptor signaling. **Results:** The reviewed data show that insulin resistance in the brain causes the PI3K/Akt pathway to be deactivated, and consequently the GSK-3 β enzyme. This enzyme is one of the main agents responsible for the hyperphosphorylation of the Tau protein, leading to the formation of neurofibrillary tangles and collapse of the neuronal cytoskeleton, while insulin and beta-amyloid protein compete for Insulin-Degrading Enzyme (IDE), favoring the accumulation of senile plaques in states of hyperinsulinemia. In addition to protein accumulation, it was observed that metabolic failure induces severe mitochondrial dysfunction, increasing oxidative stress and activating microglia cells. This activation triggers meta-inflammation that degrades the blood-brain barrier (BBB) and accelerates the loss of synaptic connections. It was seen that it is possible to correct this metabolic environment through drugs that mimic insulin or improve its sensitivity, potentially delaying the progression of brain atrophy. **Conclusion:** Through this work, it was possible to observe that insulin resistance is an intrinsic and possibly primary component in the pathogenesis of Alzheimer's disease (DA). The transition from a healthy metabolic state to central insulin resistance precedes the symptoms of dementia, making this metabolic link a signal for early diagnosis and treatment. Understanding Alzheimer's disease in this way allows for the development of new treatment strategies that primarily act by restoring neuronal bioenergetics, offering a promising way to slow neurodegeneration.

Palavras-chave: Alzheimer's Disease; Insulin Resistance In The Brain; Neurodegeneration; Insulin Receptor Signaling.