

INSULIN RESISTANCE AND NEURODEGENERATION: A METABOLIC LINK

Miguel Antonio de Souza

Carolina Souza Marçal; Gustavo Silveira Pires; Isabella Cristina Rosetto; Sandra M. Barbalho

RESUMO

Introduction: Insulin plays fundamental roles in the central nervous system (CNS), regulating glucose metabolism, supporting cognitive functions, synaptic plasticity, and neuronal survival (Pliszka et al., 2026). Cerebral insulin resistance (BIR) refers to a reduction in the cellular response to insulin in the CNS and can occur independently of peripheral diabetes. Epidemiological studies indicate that patients with Type 2 Diabetes Mellitus (T2DM) have an approximately 56% higher risk of developing dementia, highlighting a critical link between systemic metabolism and neuronal health (Tseng et al., 2026). **Objectives:** This study synthesizes evidence on how failure in insulin signaling contributes to the pathogenesis of neurodegeneration. The focus is on the mechanisms of amyloid plaque accumulation, Tau pathology, mitochondrial dysfunction, and neuroinflammation, as well as exploring therapeutic strategies to restore insulin sensitivity. **Methods:** A search was conducted in the PubMed database using MeSH descriptors such as "Insulin Resistance," "Alzheimer's Disease," and "Metabolic Syndrome," combined with Boolean operators. Articles published between 2025 and 2026 were included, selected based on reading titles, abstracts, and relevance to the topic. **Results:** BIR is associated with the early accumulation of beta-amyloid (A β) peptides and hyperphosphorylation of the Tau protein (Chamorro et al., 2025). The risk of dementia in diabetics follows a dose-response pattern related to the burden of vascular complications. Clinical and observational trials suggest that strict glycemic control (HbA1c < 7%) and the use of antidiabetic drugs, such as metformin, GLP-1 agonists, and SGLT2 inhibitors, are associated with a reduced risk of dementia and improved mitochondrial function (Ken et al., 2025). **Discussion:** The central mechanism involves the disruption of the PI3K/AKT signaling pathway. Failure in this pathway results in the overexpression of the GSK-3 β enzyme, which is primarily responsible for Tau hyperphosphorylation and the formation of neurofibrillary tangles (Verma et al., 2026). At the same time, BIR interferes with neuronal bioenergetics by exacerbating mitochondrial dysfunction and oxidative stress. Humoral mediators, such as inflammatory cytokines (TNF- α , IL-6), and extracellular vesicles propagate inflammation from the periphery to the brain by breaking down the blood-brain barrier. Additionally, BIR alters dopamine signaling, linking metabolic dysfunction to neuropsychiatric symptoms (Izuo et al., 2026). **Conclusion:** Cerebral insulin resistance is an early pathogenic factor and a vital therapeutic target in neurodegeneration. Strategies that normalize metabolic pathways, such as intranasal insulin or drug repositioning, are essential to slow disease progression and preserve cognitive health.

Palavras-chave: Insulin Resistance; Alzheimer's Disease; Metabolic Syndrome.