Insulin resistance

Insulin resistance is when cells in your muscles, body fat and liver start resisting or ignoring the signal that the hormone insulin is trying to send out—which is to grab glucose out of the bloodstream and put it into our cells.

In Alzheimer's disease (AD), white matter degeneration begins early, increases with disease progression, and contributes to cognitive impairment, yet the mechanisms are poorly understood.

Myelin loss impairs axonal function and its breakdown promotes oxidative stress, inflammation, and lipid peroxidation, further compromising the structure and function of axons. Oligodendrocyte dysfunction impairs homeostatic mechanisms needed to maintain myelin. Microvascular disease with endothelial cell pathology leads to thrombin activation and pro-inflammatory cytokine release, oxidative stress, and increased vascular permeability. Progressive fibrotic replacement of smooth muscle cells reduces vaso-responsiveness to metabolic demands. Fibrotic thickening of vessel walls narrows the lumens, rendering them more susceptible to occlusion, endothelial cell injury, and thrombin activation. Since normal physiological functions of oligodendrocytes and microvascular endothelial cells rely on intact insulin/insulin-like growth factor (IGF) signaling through cell survival, metabolic and anti-inflammatory pathways, conceivably, WM degeneration in AD is mediated by insulin and IGF resistance with attendant pathogenic targeting of oligodendroglia and endothelial cells. The apolipoprotein E-ε4 genotype may serve as a cofactor in AD-associated glial-vascular WM degeneration due to its role as a mediator of insulin resistance [1].

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de la Monte SM, Grammas P. Insulin Resistance and Oligodendrocyte/Microvascular Endothelial Cell Dysfunction as Mediators of White Matter Degeneration in Alzheimer's Disease. In: Wisniewski T, editor. Alzheimer's Disease [Internet]. Brisbane (AU): Codon Publications; 2019 Dec 20. Chapter 8. Available from http://www.ncbi.nlm.nih.gov/books/NBK552145/ PubMed PMID: 31895517.