

Hyperglycemia Induced Neurovascular & GLP-1 Receptor Dysfunction Precede Cognitive Decline In Alzheimer's Disease.

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Background

Emerging evidence suggests that vascular dysfunction precedes classical amyloid pathology in the early stages of Alzheimer's disease (AD). Metabolic disorders such as diabetes and insulin resistance accelerate these vascular changes, implicating driver of cognitive decline. Glucagon-like peptide-1 (GLP-1) signaling has recently gained attention as a key modulator of metabolic and vascular homeostasis in the brain.

Method

An screening yielded publications of which relevant articles were selected after an evaluation of their titles & abstracts. And then full text of these articles was obtained & compared about above respective subjects thoroughly.

Results

Fig.1

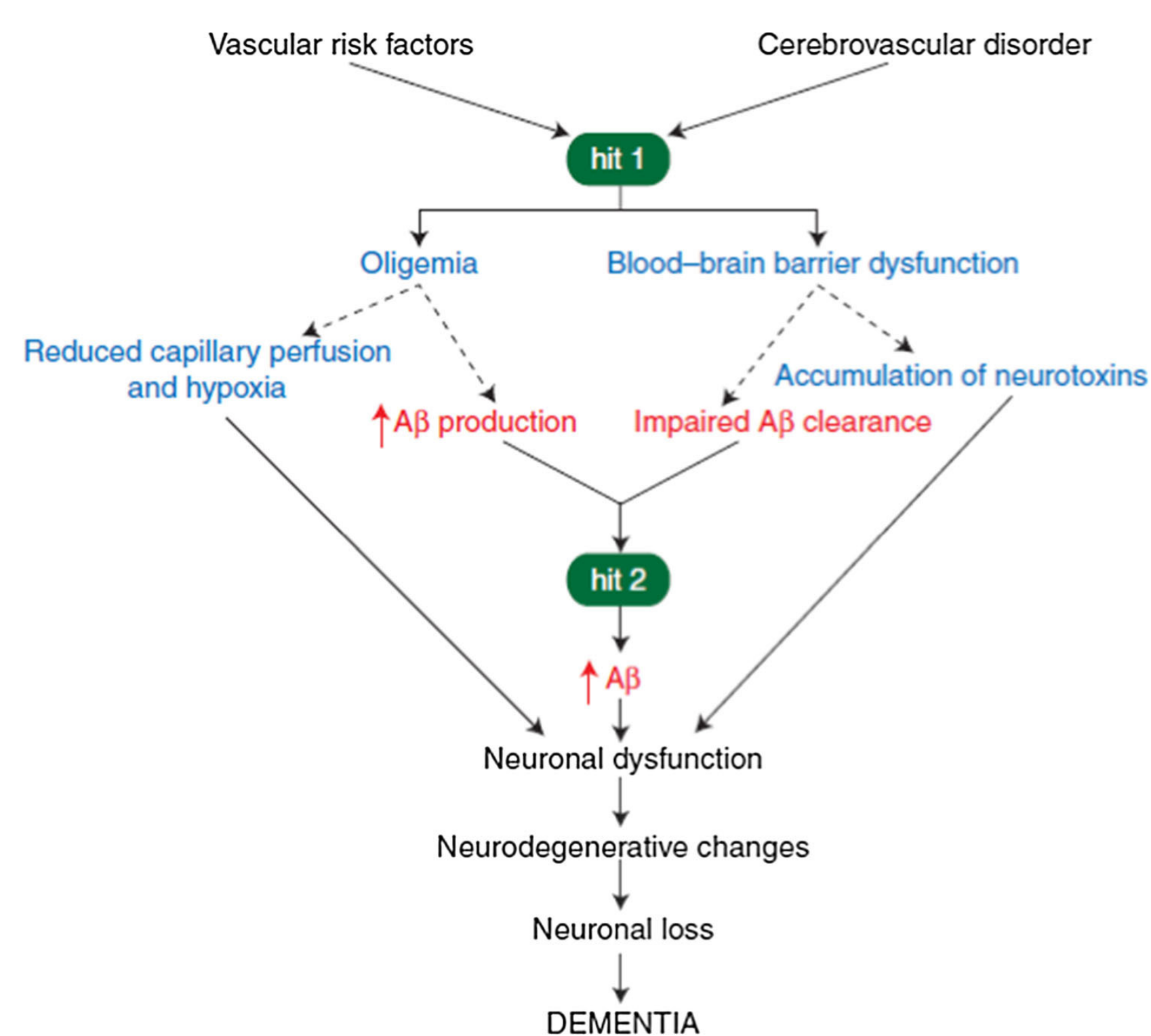
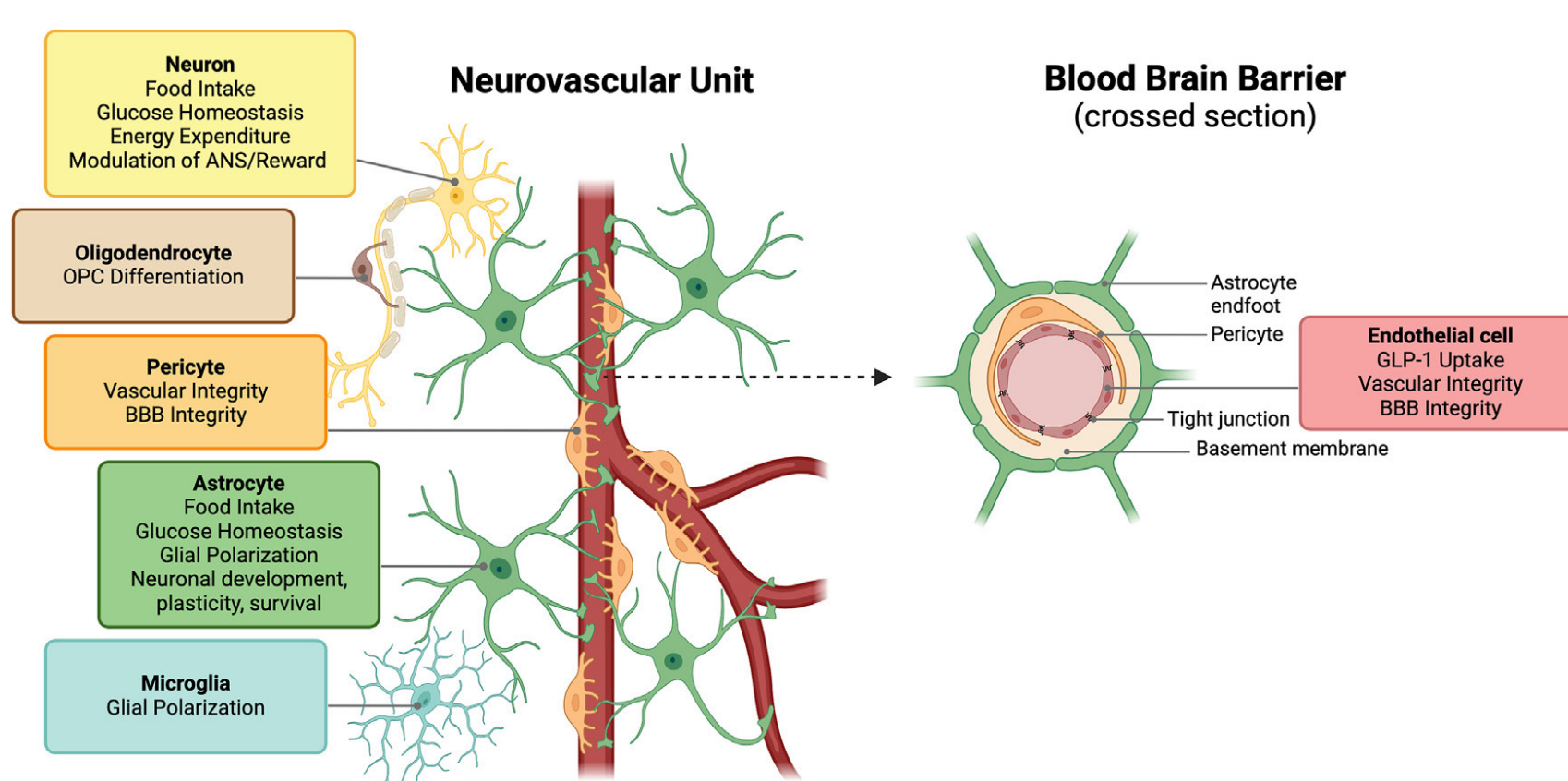


Fig.2

GLP-1R Signaling effects on Neuro-Glial-Vascular Unit



Early vascular alterations in AD include blood-brain barrier disruption, pericyte degeneration, endothelial dysfunction, and impaired neurovascular coupling. According to an alternative two-hit vascular hypothesis, A β accumulation in the brain is a second pathology(hit 2)initiated by vascular damage.(hit 1;Fig.1) Neurovascular dysfunction and hypoperfusion/hypoxia can reduce A β vascular clearance across the BBB and increase A β production from A β precursor protein(APP), respectively, causing A β accumulation in the brain. Elevated levels of A β in the brain may in turn accelerate neurovascular and neuronal dysfunction and promote self-propagation, leading to cerebral β -amyloidosis. These changes compromise cerebral perfusion and amyloid clearance, creating a permissive environment for cognitive impairment. GLP-1 receptors are expressed in cerebral endothelial cells, pericytes, and neurons, where GLP-1 signaling exerts anti-inflammatory, antioxidative, and vasculoprotective effects.(Fig. 2) Chronic hyperglycemia and insulin resistance attenuate GLP-1receptor expression and signaling, thereby weakening endogenous neurovascular defense mechanisms. Preclinical and early clinical studies demonstrate that GLP-1 receptor agonists restore blood-brain barrier integrity, preserve pericyte viability, improve endothelial nitric oxide signaling, and enhance cerebral microcirculation. These vascular benefits are accompanied by improved neurovascular coupling and reduced neuroinflammation, suggesting that GLP-1-based therapies may target amyloid-independent pathways of early cognitive impairment.

Conclusion

GLP-1 signaling represents a critical link between metabolic dysfunction and vascular-driven early brain changes in Alzheimer's disease. Targeting GLP-1-mediated neurovascular protection may offer a promising strategy for early intervention, particularly in individuals with hyperglycemia, insulin resistance, and cognitive impairment.