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THE BRAIN AS A MASTER REGULATOR OF GLUCOSE: INSULIN ACTION ON ASTROCYTES

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The classical model of glucose homeostasis describes insulin as a peripheral hormone that reduces blood sugar by having action on muscles, fat, and the liver. However, this paradigm does not provide a clear explanation of important observations. Fasting glucose is tightly controlled despite minimal peripheral insulin, hepatic glucose production is impaired in obese individuals, and Alzheimer's disease is strongly linked with type 2 diabetes.

This review examines the novel role of brain astrocytes in insulin-mediated glucose regulation. It also explores clinical implications of brain insulin resistance. A literature search was conducted using PubMed and Scopus. A landmark study by New and colleagues was the first to demonstrate the release of endozepines in response to insulin by astrocytes in the nucleus tractus solitarius (NTS) (New et al., 2025). Insulin signaling in astrocytes is associated with nutrient availability and brain glucose uptake (García-Cáceres et al., 2016). Derakhshan et al. (2020) demonstrated obesity-related brain insulin resistance in humans. A critical analysis of intranasal insulin in Alzheimer's was carried out by Craft et al. (2020).

Recent findings have revealed a new pathway. After crossing the blood-brain barrier, insulin binds to receptors on astrocytes in the NTS. Endozepines are then released and act on $GABA_a$ receptors on nearby neurons, reducing inhibition and activating descending vagal pathways. The vagus nerve then signals the liver to suppress glucose production.

Three lines of experimental evidence confirm this pathway. First, genetic knockout of insulin receptors on NTS astrocytes abolishes insulin's effect on the liver, proving astrocytes are essential (New et al., 2025). Second, direct endozepine infusion into the NTS reduces liver glucose output even without insulin, demonstrating these molecules are sufficient mediators (New et al., 2025). Third, subdiaphragmatic vagotomy eliminates both effects, confirming the vagus nerve as the essential conduit (Pocai et al., 2005; Rosario et al., 2016).

Human studies confirm clinical relevance. PET imaging shows obese individuals have reduced brain insulin sensitivity, which correlates with higher fasting glucose and increased hepatic glucose production. Brain insulin resistance may precede peripheral resistance, repositioning type 2 diabetes as a neuroendocrine disease (Chen, Kullmann and Rhea, 2025; New et al., 2025).

Alzheimer's disease risk is increased by type 2 diabetes. Insulin promotes memory and synaptic plasticity, and brain insulin resistance contributes to hippocampal atrophy and amyloid-β accumulation. This explains why some researchers refer to Alzheimer's as type 3 diabetes (New et al., 2025).

Intranasal insulin bypasses the blood-brain barrier and delivers insulin directly to the brain. Clinical trial evidence shows improved memory in mild cognitive impairment and reduced hepatic glucose synthesis with this approach (Erichsen et al., 2025).

In conclusion, a paradigm shift is revealed by the way insulin acts on brain astrocytes. The astrocyte-endozepine-vagus axis establishes the brain as a master regulator of glucose homeostasis through central mechanisms that complement peripheral insulin action. Type 2 diabetes and Alzheimer's disease are linked by brain insulin resistance, bridging neurology and endocrinology. Intranasally administered insulin is a potentially effective treatment approach.