# Bidirectional Pathophysiological Mechanisms and Shared Cascades Coordinating Type 2 Diabetes, Central Insulin Resistance, and Cognitive Decline

The epidemiological convergence of type 2 diabetes mellitus (T2D) and neurodegenerative diseases represents a major public health challenge.[1] Population-based longitudinal cohort studies have established that individuals with T2D face a significantly elevated risk of cognitive decline, exhibiting an approximate twofold increase in the risk of developing Alzheimer's disease (AD) and a comparable risk elevation for vascular dementia (VaD).[1] Global demographic projections indicate that the population living with diabetes will rise from 536.6 million in 2021 to 783 million by 2045, while dementia cases are forecasted to exceed 140 million by 2050, highlighting the urgent need to understand the molecular bridges connecting these disorders.[6]

This pathophysiological link has historically been conceptualized as "type 3 diabetes," which describes the state of localized insulin resistance and impaired glucose transport that develops in the brain parenchyma during AD.[4] More recently, this metabolic-neurodegenerative continuum has been extended to include the aging process through concepts such as Senescence-Associated Gluco-Endocrinopathy Diabetes Mellitus (SAGE-DM), or "type 4 diabetes," which characterizes the progressive decline in systemic glycemic homeostasis that occurs in lean or older individuals with sarcopenic obesity.[9] This age-related state is driven by a steady decline in beta-cell secretory capacity of approximately 1% per year, delayed insulin secretion kinetics, and a 40% to 50% reduction in total insulin output, coupled with impaired mitochondrial oxidative metabolism and cellular wear-and-tear.[9]

Importantly, the relationship between peripheral metabolic dysfunction and central cognitive decline is highly bidirectional.[10] While systemic metabolic conditions promote neurovascular damage, neuroinflammation, and amyloidogenesis, the progressive decay of central regulatory networks in AD disrupts systemic glucose, lipid, and inflammatory control, completing a destructive, self-perpetuating feedback loop.[11]

## Systemic Mediators of Neurodegeneration: The Adipose-Gut-Liver-Brain Axis

The translocation of metabolic dysfunction from peripheral tissues to the central nervous system is mediated by key endocrine, metabolic, and immunogenic networks that link adipose tissue, the gastrointestinal tract, and the liver to the brain.

### Adipose Tissue-Derived Exosomes and the Adipose-Brain Axis

Systemic obesity and insulin resistance in T2D alter the endocrine profile of adipose tissue,

driving the pathological secretion of adipose tissue-derived exosomes (Ad-EXs).[13] These circulating microvesicles cross the blood-brain barrier (BBB) and interact directly with brain microvascular endothelial cells.[13] Under diabetic conditions, Ad-EXs promote neurovascular unit impairment by delivering pro-inflammatory microRNAs and proteins that trigger local oxidative stress, mitochondrial dysfunction, and neurovascular inflammation, rendering the brain increasingly susceptible to ischemic stroke and progressive cognitive decline.[13]

### The Gut-Brain Axis and Symbiotic Metabolites

Systemic glucose and insulin homeostasis are heavily modulated by gut-segment-dependent nutrient sensing, gut-derived hormones, and host-microbe symbiosis.[14] Under physiological conditions, short-chain fatty acids (SCFAs) and bile acids produced by the intestinal microbiota engage G-protein-coupled receptors to stimulate the release of glucagon-like peptide-1 (GLP-1), which enhances pancreatic beta-cell efficiency and modulates systemic glucose clearance.[14]

Under conditions of high-fat feeding, the gut microbiome becomes dysregulated, increasing the concentration of taurochenodeoxycholic acid in the plasma and the dorsal vagal complex, which induces hypothalamic insulin resistance.[14] Conversely, the activation of small intestinal sirtuin 1 (SIRT1) has been shown to reverse high-fat-induced hypothalamic insulin resistance via a gut-brain neuronal pathway, suggesting a direct, neural link between gastrointestinal metabolic sensing and central insulin action.[14] Furthermore, systemic innate immune sensing of gut-derived lipopolysaccharides (LPS) and bacterial cell wall components promotes a chronic, low-grade inflammatory state that impairs both peripheral and central insulin sensitivity.[14]

### The Liver-Brain Axis and Metabolic Dialogue

The liver and brain coordinate systemic energy balance through a complex bidirectional dialogue known as the liver-brain axis.[12] The liver acts as both a supplier of essential nutrients to the brain and an endocrine organ capable of secreting hepatokines and clearing neurotoxic cerebral proteins during senescence.[12] In the afferent direction, hepatokines, metabolites, and sensory signals from the vagus nerve communicate the nutritional status of the splanchnic bed to the hypothalamus.[12] In the efferent direction, the autonomic nervous system projects from the hypothalamus to autonomic nuclei and the liver, modulating hepatic macronutrient metabolism, lipid storage, and inflammatory pathways.[11]

Disruptions along this axis are common in NAFLD and T2D, where impaired hepatic clearance of toxic proteins and abnormal hepatokine secretion exacerbate central insulin resistance and neuroinflammation.[11]

## Neurovascular and Blood-Brain Barrier Breakdown

The blood-brain barrier serves as the physiological gatekeeper of the brain, composed of capillary endothelial cells, tight junctions, pericytes, and astrocytic end-feet.[4] In T2D, chronic hyperglycemia and fluctuating glycemic levels trigger mitochondrial superoxide overproduction in the brain capillary endothelial cells, initiating a cascade of microvascular

damage.[4]

## Hyperglycemia-Induced Microvascular Damage Pathways

Mitochondrial superoxide overproduction activates four classical pathways of microvascular disease: the polyol and hexosamine pathways, protein kinase C (PKC) activation, and the accelerated formation of advanced glycation end-product (AGE) ligands.[4] This biochemical signaling results in capillary basement membrane thickening, abnormal endothelial cell proliferation, and low microvascular perfusion rates, which collectively compromise BBB transport.[4]

These microvascular changes are not confined to the brain; clinical evaluations of prediabetic and diabetic populations have demonstrated that microvascular dysfunction in the retina and skin correlates with, and often precedes, the onset of cognitive decline.[5] Crucially, while Jansen et al. ruled out frank, large-scale capillary collapse as a prerequisite for early cognitive loss in a cohort of 41 T2D patients, more subtle alterations in microvascular permeability and endothelial function are heavily implicated in early cognitive impairment.[5]

During cerebral ischemia, hyperglycemia acts as a potent driver of mortality and tissue damage by accelerating tissue plasminogen activator (tPA) activation and superoxide production, which direct destructive paracellular leakage and expand hematomas.[4]

## Tight Junction Disruption and Macrophage Infiltration

The physical integrity of the BBB is maintained by inter-endothelial tight junctions consisting of claudin-5, occludin, and zonula occludens-1 ($\mathrm{ZO\text{-}1}$).[4] Well-controlled T2D is associated with significantly elevated BBB permeability.[5] Under diabetic conditions, the down-regulation of these tight junction proteins, combined with the up-regulation of intercellular adhesion molecule-1 ($\mathrm{ICAM\text{-}1}$), permits the paracellular entry of polar substances and circulating pro-inflammatory cytokines into the brain parenchyma.[4]

In leptin receptor-deficient, insulin-resistant mouse models ($db/db$), this breakdown of BBB integrity is accompanied by significant cerebral macrophage infiltration, which is facilitated by an interleukin-1 beta ($\mathrm{IL\text{-}1}\beta$)-dependent pathway.[5] In hybrid transgenic models crossing amyloid-precursor protein/presenilin-1 ($\mathrm{APP/PS1}$) mice with $db/db$ mice, these BBB alterations occur concurrently with the onset of T2D (around 14 weeks of age) and precede the deposition of parenchymal amyloid-beta ($\mathrm{A}\beta$) plaques, indicating that vascular barrier failure is an early, causative step in AD pathogenesis.[5]

## The Endothelial AGE-RAGE Influx Axis

RAGE is a type I membrane protein expressed on the luminal surface of brain microvascular endothelial cells.[4] It serves as a transport receptor that translocates circulating $\mathrm{A}\beta$ from the

bloodstream across the BBB into the brain parenchyma.[4] Under conditions of chronic hyperglycemia, the non-enzymatic glycation of proteins and lipids yields abundant AGE ligands that bind to endothelial RAGE.[4] This interaction upregulates RAGE expression, creating a feedforward loop that accelerates the influx of peripheral $\mathrm{A}\beta$ into the brain and impairs the clearance of central $\mathrm{A}\beta$.[4]

The systemic and clinical relevance of this pathway was demonstrated in the STEADFAST phase III trials of azeliragon (TPP488), an oral small-molecule RAGE antagonist.[19] Although the trials failed to meet their co-primary endpoints (ADAS-Cog11 and CDR-SB) in the overall mild AD cohort, exploratory post-hoc subgroup analyses revealed that patients with baseline $\mathrm{HbA1c} \geq$ experienced significantly less cognitive decline when treated with azeliragon.[19] This clinical finding supports the hypothesis that the AGE-RAGE axis serves as a functional, pathological bridge linking diabetic hyperglycemia to the progression of AD neuropathology.[19]

# Central Autonomic Failure and Systemic Metabolic Decay

The brain directly regulates systemic glucose, lipid, and inflammatory homeostasis through specialized neuroendocrine hubs located within the hypothalamus and brainstem.[11] Under conditions of central insulin resistance and neurodegeneration, the progressive decay of these neural pathways disrupts the brain's ability to coordinate peripheral metabolic homeostasis, creating a pathological feedback loop.[11]

## Neuromodulation of Glycemia and Lipids

The lateral hypothalamus and ventromedial hypothalamus ($\mathrm{VMH}$) monitor circulating glucose, insulin, and leptin to coordinate autonomic nervous system outflow to peripheral organs.[11]

- **Glycemia Regulation:** In response to elevated portal vein glucose levels, the lateral hypothalamus stimulates parasympathetic outflow, promoting hepatic glycogen synthesis to store excess glucose.[11] Conversely, during hypoglycemia, the $\mathrm{VMH}$ activates sympathetic outflow to stimulate hepatic glycogen catabolism, releasing glucose back into the systemic circulation.[11]
- **Lipid Regulation:** Central neuroendocrine pathways, including leptin and melanocortin signaling, act via the vagus nerve to suppress hepatic lipogenesis and limit fat accumulation in the liver.[11] Parasympathetic activation also directly modulates hepatic bile acid metabolism, optimizing fat absorption and preventing ectopic lipid deposition.[11] Simultaneously, sympathetic activation enhances hepatic glucose uptake and stimulates lipolysis in brown adipose tissue ($\mathrm{BAT}$) to regulate systemic energy expenditure.[11]

Under conditions of central neurodegeneration, damage to these hypothalamic nuclei

decouples autonomic outflow, leading to uninhibited hepatic glucose production, NAFLD, lipid accumulation, and systemic lipotoxicity, which further exacerbates peripheral insulin resistance.[11]

### Autonomic Regulation of Systemic Inflammation

Beyond energy metabolism, the CNS directly modulates systemic and hepatic inflammatory responses.[11] Sympathetic neurotransmitters, such as norepinephrine and epinephrine, act on hepatic stellate cells and kupffer cells to regulate local and systemic inflammatory cascades.[11] Because chronic, low-grade metabolic inflammation is a key driver of both T2D and AD, the failure of these central immunomodulatory pathways removes an important physiological check on systemic inflammatory responses, leading to uninhibited cytokine production that feeds back to accelerate neurovascular injury.[8]

### Perinatal Reprogramming and Early Causal Steps

Central insulin and leptin resistance, hypothalamic inflammation, and impaired autonomic control in the brainstem frequently precede the onset of overt systemic hyperglycemia.[20] This indicates that neuroendocrine dysfunction is an early, causal step in systemic metabolic deterioration.[20]

Furthermore, early-life environmental exposures can induce perinatal reprogramming of these hypothalamic pathways; perinatal perturbations in central insulin or leptin signaling can permanently alter the hypothalamic control of glucose metabolism, predisposing individuals to metabolic and neurodegenerative disease in adulthood.[20]

## Intracellular Cascades: From Insulin Resistance to Synaptic Collapse

At the cellular level, central insulin signaling is essential for preserving neuronal survival, synaptic plasticity, glucose uptake, and mitochondrial function.[7]

### The Canonical Insulin Signaling Pathway

In the healthy brain, insulin crosses the BBB via a saturable transporter and binds to the insulin receptor ($\mathrm{INSR}$), a member of the receptor tyrosine kinase superfamily located on the membranes of neurons and glial cells.[22] Normal fasting brain insulin levels range between $2.55$ and $18.4\ \mu\mathrm{IU/mL}$.[23] Binding initiates autophosphorylation of the $\mathrm{INSR}$, recruiting and phosphorylating insulin receptor substrate-1 and -2 ($\mathrm{IRS\text{-}1/2}$).[22] Phosphorylated $\mathrm{IRS\text{-}1/2}$ activates the phosphatidylinositol 3-kinase ($\mathrm{PI3K}$)/Akt pathway and the mitogen-activated protein kinase ($\mathrm{MAPK}$)/extracellular signal-regulated kinase ($\mathrm{ERK}$) pathway.[22]

Active Akt phosphorylates Glycogen Synthase Kinase-3 beta ( $\mathrm{GSK\text{-}3}\beta$ ) on its inhibitory serine residue ( $\mathrm{Ser}^{9}$ ), keeping this enzyme inactive.[8] Simultaneously, Akt signaling stimulates the translocation of $\mathrm{GLUT4}$ vesicles to the plasma membrane, facilitating localized glucose transport to support the energetic demands of synaptic transmission.[23]

## Disruption of PI3K-Akt and MAPK-ERK Cascades

In the insulin-resistant brain, this signaling network is disrupted at several critical nodes.[1] Soluble $\mathrm{A}\beta$ oligomers bind to hippocampal neurons, triggering the rapid internalization and removal of $\mathrm{INSRs}$ from the plasma membrane.[1] Simultaneously, pro-inflammatory cytokines ( $\mathrm{TNF\text{-}}\alpha$ , $\mathrm{IL\text{-}1}\beta$ ) released by activated microglia activate stress kinases such as c-Jun N-terminal kinase ( $\mathrm{JNK}$ ), which phosphorylate $\mathrm{IRS\text{-}1}$ on inhibitory serine residues (such as $\mathrm{Ser}^{312}$ or $\mathrm{Ser}^{616}$ ), uncoupling the receptor from downstream $\mathrm{PI3K\text{-}Akt}$ activation.[1] This uncoupling prevents the inhibitory phosphorylation of $\mathrm{GSK\text{-}3}\beta$ , leading to its hyperactivation.[8] Unchecked $\mathrm{GSK\text{-}3}\beta$ hyperphosphorylates tau proteins in the neuronal microtubules.[8] Hyperphosphorylated tau detaches from microtubules, self-assembling into paired helical filaments and neurofibrillary tangles (NFTs) that disrupt axonal transport, impair synaptic plasticity, and induce apoptotic cell death.[8]

In parallel, the uncoupling of the $\mathrm{MAPK/ERK}$ cascade directly impairs synaptic plasticity and memory formation.[10] Insulin regulates ERK, which serves as a central integrator of hippocampal plasticity.[10] In early AD, $\mathrm{A}\beta$-mediated neuroinflammation induces insulin resistance, uncoupling this cascade and causing immediate deficits in hippocampus-dependent memory.[10]

This process is further exacerbated by age-dependent calcineurin upregulation, which leads to the downstream downregulation of peroxisome proliferator-activated receptor-gamma ( $\mathrm{PPAR}\gamma$ ) at approximately 9 months and AMP-activated protein kinase ( $\mathrm{AMPK}$ ) at approximately 13 months, as demonstrated in animal models of AD, causing progressive metabolic stress and synaptic collapse.[10] Furthermore, metabolic irregularities and insulin resistance can overactivate the brain's mitochondrial target of rapamycin (TOR) pathway, resulting in direct neuronal injury and mitochondrial dysfunction.[6]

## Astrocytic Insulin Resistance and Glycolytic Deprivation

Astrocytes are essential for maintaining the brain's energetic homeostasis through the Astrocyte-Neuron Lactate Shuttle (ANLS).[24] They convert glucose into pyruvate during

glycolysis, which is then converted into lactate.[24] This lactate is transported into the extracellular space via monocarboxylate transporters ($\mathrm{MCTs}$) and taken up by neurons, where it is oxidized to fuel the tricarboxylic acid ($\mathrm{TCA}$) cycle and generate $\mathrm{ATP}$.[24] This metabolic shuttle relies on intact astrocytic insulin signaling.[24] In vitro and in vivo studies using inducible astrocyte-specific insulin receptor knockout ($\mathrm{iGIRKO}$) mice crossed with $5\mathrm{xFAD}$ amyloid models have demonstrated that the loss of astrocytic insulin signaling causes:

- Reduced mitochondrial mass, decreased mitochondrial respiration, and impaired glycolysis [25]
- Impaired astrocytic capacity to uptake and degrade extracellular $\mathrm{A}\beta$ plaques [25]
- Accelerated tau hyperphosphorylation, altered mitophagy, and exacerbated cognitive and behavioral deficits, underscoring the critical neuroprotective role of astrocytic insulin signaling [25]

### Microglial Reactivity and Immunometabolic Polarization

Microglia, the resident immune cells of the CNS, undergo functional and metabolic polarization in response to changes in their microenvironment.[15] In T2D and AD, exposure to hyperglycemia, AGEs, and soluble $\mathrm{A}\beta$ oligomers shifts microglia from a highly phagocytic, ramified homeostatic state to a chronic, pro-inflammatory disease-associated microglia ($\mathrm{DAM}$) phenotype.[17] This pro-inflammatory polarization is characterized by a metabolic shift toward glycolysis, mitochondrial fragmentation, and the secretion of neurotoxic cytokines ($\mathrm{TNF}\text{-}\alpha$, $\mathrm{IL}\text{-}1\beta$, $\mathrm{IL}\text{-}6$).[17]

These microglia lose their capacity to clear $\mathrm{A}\beta$ plaques and instead drive localized neuroinflammation, which further impairs insulin receptor sensitivity in surrounding neurons and astrocytes, creating a chronic, neurodestructive cycle.[10]

## Comparative Analysis of Therapeutic Interventions

Given the shared pathophysiological pathways linking T2D and dementia, repurposing established classes of antidiabetic agents represents a promising strategy for clinical translation.[1]

### Systemic Insulin Therapy versus Intranasal Delivery

Systemic insulin therapy has shown conflicting associations with cognitive outcomes in clinical studies.[6] While insulin is required to manage advanced T2D, chronic peripheral hyperinsulinemia can downregulate the blood-brain glucose transport capacity and cause systemic

hypoglycemia.[6] Furthermore, systemic insulin therapy is associated with a $21\%$ to $58\%$ increased risk of dementia in pooled observational cohorts.[6] This is hypothesized to be due to peripheral hyperinsulinemia, where excess insulin competes with $\mathrm{A}\beta$ as a substrate for insulin-degrading enzyme (IDE), preventing the clearance of central $\mathrm{A}\beta$ and promoting plaque deposition.[6]

In contrast, intranasal insulin (INI) bypasses the BBB to engage the CNS directly without altering systemic blood glucose or insulin levels, avoiding the risk of hypoglycemia.[1] INI improves memory in healthy adults, enhances verbal memory in memory-impaired subjects, and regulates peripheral energy homeostasis.[1] Preclinically, INI reduces cerebral $\mathrm{A}\beta$ and phosphorylated tau pathology and preserves mitochondrial function.[18]

Clinically, a 12-month trial in adults with MCI or AD showed that twice-daily INI ($20\ \mathrm{IU}$) significantly reduced white matter hyperintensity progression and preserved global brain volume compared to placebo, although a larger multi-center trial of $289$ adults failed to demonstrate cognitive benefits, a finding likely impacted by a change in the nasal delivery device mid-trial.[18] In acute settings, preoperative INI significantly reduced the incidence of postoperative delirium and attenuated systemic cytokine surges.[28]

## GLP-1 Receptor Agonists and Incretin Mimetics

GLP-1 receptor agonists (GLP-1RAs) are lipid-soluble small molecules that cross the BBB to exhibit neurotrophic and neuroprotective properties.[24] They activate the $\mathrm{PI3K\text{-}Akt}$ pathway to inhibit $\mathrm{GSK\text{-}3}\beta$, reducing tau phosphorylation.[27] They also promote mitochondrial biogenesis, suppress microglial activation, and enhance the clearance of toxic proteins.[27]

In the ELAD phase II trial ($52\ \mathrm{weeks}$, $n \approx 200$ patients with mild AD), liraglutide successfully improved temporal lobe and cortical volume measures and slowed gray matter loss compared to placebo, although the trial did not meet its primary metabolic endpoint of preserving cerebral glucose metabolic rate.[30]

In patients with T2D, the large-scale REWIND trial demonstrated that weekly subcutaneous dulaglutide ($1.5\ \mathrm{mg}$) over a median follow-up of $5.4\ \mathrm{years}$ led to a significant $14\%$ reduction in the hazard of substantive cognitive decline (post-hoc adjusted analysis: $\mathrm{HR} =$ , $95\%\ \mathrm{CI}\ [0.79, 0.95]$, $p = 0.0018$ ).[30]

Currently, the phase III EVOKE and EVOKE+ clinical programs are evaluating the long-term cognitive and disease-modifying efficacy of once-daily oral semaglutide in patients with early-stage symptomatic and prodromal AD.[30]

## SGLT2 Inhibitors and Immunometabolic Preservation

SGLT2 inhibitors (SGLT2i) represent a highly promising class of antidiabetic drugs for neuroprotection.[16] They are highly lipid-soluble and cross the BBB, reaching brain-to-serum concentration ratios ranging from $0.3$ (canagliflozin, dapagliflozin) up to $0.5$ (empagliflozin).[34] SGLT2i lower blood pressure, reduce arterial stiffness, improve endothelial function, and promote cerebral blood flow.[34]

They promote mild, sustained ketosis, raising circulating levels of beta-hydroxybutyrate ($\mathrm{BHB}$), which serves as an alternative energy substrate for neurons under conditions of central insulin resistance.[33] $\mathrm{BHB}$ and reduced insulin levels suppress microglial $\mathrm{NLRP3}$ inflammasome activation.[33] This suppresses the downstream $\mathrm{NLRP3/IL\text{-}1\beta/TNF\text{-}\alpha/miR\text{-}501\text{-}3p/ZO\text{-}1}$ axis, protecting endothelial tight junctions and preserving BBB integrity.[33]

Additionally, SGLT2i reduce vascular inflammation and oxidative stress, regressing early carotid atherosclerosis.[34] In a three-month study of diabetic patients, empagliflozin significantly regressed complex carotid intima-media thickness (cIMT) by $7.9\%$, a key predictor of cognitive decline in T2D.[34]

Preclinically, certain SGLT2i such as canagliflozin act as dual inhibitors of both SGLT2 and acetylcholinesterase ($\mathrm{AChE}$), enhancing synaptic acetylcholine availability and improving cholinergic transmission.[18] Epidemiologically, large-scale studies have demonstrated a lower risk of dementia in elderly T2D patients treated with SGLT2i, with a pooled meta-analysis demonstrating a hazard ratio of $\mathrm{HR} =$ , $95\%\ \mathrm{CI}\ [0.50, 0.92]$ compared to other oral antidiabetic regimens.[36]

To compare these drug classes, Table 2 summarizes their central targets, preclinical evidence, and clinical trial outcomes.

| Drug Class | Primary Central Targets & Mechanisms | Preclinical Outcomes | Key Clinical & Epidemiological Findings |
|---|---|---|---|
| **Intranasal Insulin** | Bypasses the BBB to bind neuronal/glial $\mathrm{INSR}$; restores $\mathrm{PI3K\text{-}Akt}$ and $\mathrm{MAPK/ERK}$ signaling [1] | Reduces $\mathrm{A}\beta$ plaque load, hyperphosphorylated tau, and synaptic loss [18] | Kellar et al. (2021) trial ($n =$ ) showed reduced white matter hyperintensities and global brain volume [18]; significantly reduces |

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|---|---|---|---|
| | | | postoperative delirium (POD) incidence [28] |
| **GLP-1 Receptor Agonists** | Bypasses the BBB to bind $\mathrm{GLP\text{-}1R}$; inhibits $\mathrm{GSK\text{-}3}\beta$ and suppresses microglial activation [27] | Rescues long-term potentiation; protects hippocampal neurons against $\mathrm{A}\beta_{1-42}$ toxicity [18] | Liraglutide preserves temporal lobe/cortical volume [30]; dulaglutide reduces cognitive decline risk by $14\%$ in T2D ($\mathrm{HR} =$ ) [31]; phase III semaglutide trials (EVOKE) ongoing [32] |
| **SGLT2 Inhibitors** | Crosses the BBB; induces mild ketosis ($\mathrm{BHB}$) [34]; suppresses $\mathrm{NLRP3}$ inflammasome [33]; inhibits $\mathrm{AChE}$ [34] | Increases cerebral $\mathrm{BDNF}$ [18]; preserves synaptic density and mitigates neuroinflammation [33] | Observational cohorts show up to a $42\%$ lower dementia risk [18]; pooled meta-analysis hazard ratio of $\mathrm{HR} =$ [36] |
| **RAGE Antagonists (Azeliragon)** | Competitively inhibits endothelial RAGE to block circulating $\mathrm{A}\beta$ transport across the BBB [4] | Attenuates neurovascular inflammation and microvascular amyloid deposition [4] | Phase III trials missed primary endpoints in the general AD population, but post-hoc analyses showed cognitive preservation in patients with $\mathrm{HbA1c} \geq$ [19] |

# Conclusions and Clinical Recommendations

The relationship between type 2 diabetes, central insulin resistance, and neurodegeneration is characterized by a bidirectional, pathogenic feedforward loop. Peripheral metabolic

dysfunction disrupts blood-brain barrier integrity, promotes RAGE-mediated amyloid influx, and competitively inhibits insulin-degrading enzyme through systemic hyperinsulinemia. Inside the CNS, this metabolic pressure drives central insulin resistance, initiating a cascade of neuronal energy starvation, $\text{GSK-3}\beta$ hyperactivation, tau hyperphosphorylation, astrocytic glycolytic depletion, and pro-inflammatory microglial activation.

Importantly, this central pathology feeds back to disrupt systemic homeostasis. The progressive neurodegeneration of glucose-sensing networks within the hypothalamus decouples the autonomic nervous system's control over the liver, pancreas, and adipose tissue, driving uninhibited hepatic gluconeogenesis, systemic hyperglycemia, hepatic steatosis, and systemic metabolic inflammation.

Recognizing the clinical implications of this bidirectional axis is essential for developing effective therapeutic strategies. Repurposing antidiabetic agents represents a promising avenue for disease modification in both AD and VaD. The distinct mechanisms of GLP-1 receptor agonists (restoring insulin signaling and preserving cortical volumes) and SGLT2 inhibitors (inducing neuroprotective ketosis, suppressing the $\text{NLRP3}$ inflammasome, and regressing carotid atherosclerosis) highlight the therapeutic potential of targeting systemic metabolic pathways to treat central neurodegeneration.

Future clinical trial designs must leverage this bidirectional relationship by adopting a precision health approach. Stratifying patients based on metabolic and glycemic profiles—such as specific HOMA2 indices of insulin sensitivity or baseline HbA1c levels—will be critical to identifying those most likely to benefit from metabolic interventions. Additionally, timing remains a key factor; interventions must be initiated during early prodromal or mild cognitive impairment stages, before irreversible synaptic and autonomic network loss occurs. Resolving the precise molecular mechanisms of this inter-organ crosstalk will be essential to mitigating the dual burden of metabolic and neurodegenerative disease.

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