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REVIEW

# Interaction of Cellular and Molecular Mechanisms in Diabetes-Associated Neurodegeneration and Alzheimer's Disease

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**ABSTRACT:** Diabetes, inflammation, and neurodegeneration, particularly Alzheimer's disease (AD), are deeply interconnected (brain diabetes). Type 2 diabetes mellitus (T2DM) acts as a significant risk factor for neurodegenerative diseases like Alzheimer's (AD) and Parkinson's (PD) by inducing chronic inflammation, oxidative stress, and metabolic dysfunction. Hyperglycemia drives neuroinflammation and damages the blood-brain barrier (BBB), exacerbating cognitive decline and neuronal loss. Chronic inflammation acts as a central bridge, linking high blood sugar, insulin resistance, and metabolic dysfunction in the brain to the buildup of amyloid plaques, tau tangles, and neuronal damage due to shared insulin signaling issues in the brain. Diabetes accelerate AD risk through inflammation-driven mitochondrial damage and impaired insulin pathways, which hinder amyloid clearance and disrupt normal brain function. Insulin resistance and impaired glucose metabolism accelerate brain aging and neurodegeneration. This narrative review aims to summarize the underlying molecular and cellular mechanisms in the pathophysiology of hyperglycemia-associated neurodegeneration with a focus on Alzheimer's disease as a manifestation of type 3 diabetes mellitus (type 2 diabetes in the brain).

**KEYWORDS:** Diabetes; obesity; inflammation; neurodegeneration; Alzheimer's disease

## 1 Introduction

Type 2 diabetes mellitus (T2DM) is increasingly recognized as a multisystem disorder in which chronic hyperglycemia, insulin resistance, and nutrient overload drive cellular stress extending beyond dysregulated glucose homeostasis [1]. During early disease stages, pancreatic β-cells partially compensate for insulin resistance through increased insulin secretion. However, chronic hyperglycemia, endoplasmic reticulum (ER) stress, and inflammatory signaling ultimately impair β-cell function and promote progressive insulin insufficiency [2]. Obesity is a major upstream contributor to T2DM pathogenesis, with excess adiposity promoting systemic insulin resistance through altered lipid accumulation and eventual β-cell dysfunction [3–5]. The strong biochemical and pathophysiological overlap between obesity and T2DM has led to the term "diabesity", emphasizing their causal link [6]. Diabesity combines "diabetes" and "obesity", highlighting that increased fat, specifically visceral fat, drives insulin resistance, which in turn causes the pancreas to work harder and produce less effective insulin. Diabesity exponentially increases the risk of severe metabolic diseases, including cardiovascular disease, hypertension, fatty liver disease (MAFLD), and chronic renal failure. In obesity, adipose tissue expansion is accompanied by inflammatory remodeling

characterized by adipocyte hypertrophy, macrophage recruitment, and adipokine imbalance, which together reinforce systemic insulin resistance [5]. Hypertrophic adipocytes and infiltrating immune cells promote a shift toward pro-inflammatory M1-polarized macrophages and increased secretion of cytokines such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, and IL-1β, establishing a chronic low-grade inflammatory state that directly impairs insulin signaling in metabolic tissues [3,5,7].

Beyond classic microvascular and neuropathic complications, diabetes also confers a substantially increased risk for central nervous system (CNS) injury and neurodegeneration [8]. Diabetes increases the risk for neurodegenerative diseases like Alzheimer's disease (AD) and Parkinson's disease (PD), primarily through mechanisms like insulin resistance, hyperglycemia, and inflammation, which can cause brain damage and cognitive decline [9]. These metabolic issues can lead to impaired insulin signaling in the brain, damage to blood vessels, and neuropathological changes [10,11]. However, diabetes may have a different effect on other conditions, such as amyotrophic lateral sclerosis (ALS), where it might offer a protective effect [12–14]. Diabetes is associated with metabolic disturbances, including insulin resistance, hyperglycemia, and dysregulation of carbohydrate, protein, and lipid metabolism. These metabolic disturbances converge on the nervous system through several interconnected mechanisms contributing to neuropathy. Impaired insulin signaling disrupts neuronal mitochondrial function and synaptic plasticity; excess reactive oxygen species (ROS) and lipid intermediates damage mitochondrial DNA, $Ca^{2+}$ handling, and energy production; and chronic inflammation and advanced glycation end-products-receptor for advanced glycation end-products (AGE-RAGE) signaling degrade vascular integrity, producing endothelial dysfunction and blood–brain barrier breakdown. These changes increase CNS exposure to cytokines and toxic metabolites while simultaneously impairing the clearance of misfolded proteins such as amyloid beta (Aβ), tau, and α-synuclein. Together, these pathways create a biochemical environment that links diabetes to neuroinflammation, white-matter injury, and the protein-aggregation processes underlying AD, PD, and related neurodegenerative disorders, including Huntington's and ALS [12,13,15]. This narrative review focuses on the pathophysiology of T2DM, molecular and cellular interactions with AD, potential therapeutic targets, and future directions.

## 2 β-Cell Dysfunction and Insulin Resistance

Pancreatic β-cells play a central role in maintaining glucose homeostasis by regulating insulin secretion in response to cues triggered by metabolic demand. In early T2DM, β-cell dysfunction is recognized as a key pathogenic event; although insulin resistance is a hallmark of the disease, hyperglycemia is ultimately precipitated by a dysfunctional response to elevated glucose in β-cells, leading to failure to sustain adequate insulin secretion [16,17]. β-cells initially compensate for hyperglycemia by secreting more insulin and undergoing hyperplasia. As β-cell dysfunction progresses and insulin secretion becomes insufficient to meet metabolic demand, fasting and postprandial hyperglycemia emerge and intensify, which further aggravates systemic insulin resistance in classical glucose-recipient tissues (muscle, liver, adipose) [16]. Chronic exposure to hyperglycemia and hyperlipidemia leads to glucolipotoxicity, which induces oxidative and endoplasmic reticulum (ER) stress, reduces insulin synthesis and secretion, and promotes β-cell apoptosis [16,17] (Fig. 1). Although these mechanisms have been well supported by experimental models, the extent to which glucolipotoxicity causes β-cell failure *in vivo* in humans remains less clearly understood.

The major driver of β-cell dysfunction is chronic hyperglycemia. Prolonged exposure to supraphysiologic glucose levels is cytotoxic and overwhelms ER protein-folding capacity, triggering the unfolded protein response (UPR). As ER stress persists, the UPR becomes maladaptive, contributing to β-cell dysfunction and death [2,16,17]. In mouse pancreatic β-cells, acutely elevated glucose exposure elicits a mild, adaptive UPR via inositol-requiring enzyme 1α (IRE1α) that supports glucose-stimulated insulin biosynthesis, whereas loss

of IRE1α blunts glucose-stimulated insulin production [18]. However, in INS-1 832/13 rat β-cell cultures, sustained elevated glucose induces ER stress, reduces insulin mRNA and proinsulin synthesis, and impairs insulin secretion, through glucotoxic-mediated ER stress, driving β-cell dysfunction [16,17,19].

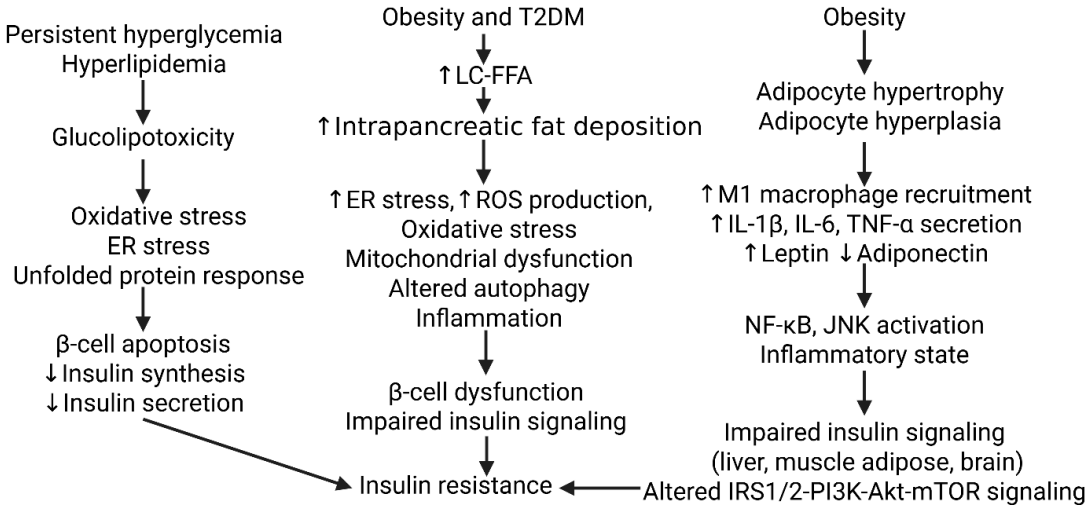


**Figure 1:** Cellular and molecular mechanisms of β-cell dysfunction and insulin resistance. T2DM, type 2 diabetes mellitus; LC-FFA, long chain free fatty acid; ER, endoplasmic reticulum; ROS, reactive oxygen species; IL, interleukin; TNF, tumor necrosis factor; NF-κB, nuclear factor kappa beta; JNK, c-Jun N-terminal kinase; IRS1/2, insulin receptor substrate 1 and 2; PI3K, phosphoinositide 3-Kinase; mTOR, mammalian receptor for rapamycin. ↑ indicates an increase and ↓ indicates a decrease. Created in BioRender. Rai, V. (2025); https://BioRender.com/mzm27zz.

This compromising of β-cell structure and function drives the transition from compensated insulin resistance to overt T2DM. This positions β-cell failure as a primary determinant of systemic metabolic dysregulation [2,16]. In parallel, adipose tissue expansion in obesity and T2DM promotes macrophage recruitment, shifting towards a chronic, low-grade inflammatory state. In mouse models of diet-induced and genetic obesity, and in adipose biopsies from obese humans, enlarged fat depots show marked accumulation of adipose tissue macrophages that are a major source of TNF-α and other cytokines, and these inflammatory mediators contribute to insulin resistance in classical insulin target tissues [20]. Impaired insulin signaling through the insulin receptor substrate (IRS)1/2 phosphoinositide 3-kinase (PI3K)-protein kinase B (Akt)-mammalian target of rapamycin (mTOR) pathway (Fig. 1) in the brain alters neuronal metabolism and synaptic function, linking peripheral metabolic disease to central nervous system dysfunction. Consistent with this, male Wistar rats rendered insulin resistant by 12 weeks of high-fat diet feeding show impaired neuronal insulin receptor function, evidenced by attenuated insulin-induced long-term depression in hippocampal CA1 and reduced insulin-stimulated Akt (Ser473) phosphorylation, together with brain mitochondrial swelling, membrane depolarization, and increased ROS production [21]. Meanwhile, reduced peripheral insulin availability and chronic insulin resistance limit insulin signaling within the brain, where insulin normally supports neuronal glucose uptake, energy metabolism, and synaptic plasticity. This supports how brain insulin resistance contributes to cognitive vulnerability and Alzheimer's disease-like neurodegeneration [16,17,22].

Elevated long-chain free fatty acids (LC-FFA) are widely accepted contributors of β-cell dysfunction in genetically susceptible individuals with T2DM and obesity. *In vivo* human studies tend to show that increased plasma FFA and increased intrapancreatic fat are associated with impaired insulin secretion and β-cell dysfunction [23] (Fig. 1). However, findings are heterogeneous and influenced by FFA profile, sex,

and ethnicity. In human islets, acute LC-FFA exposure can transiently augment glucose-stimulated insulin secretion, whereas chronic exposure impairs insulin release and promotes apoptosis, accompanied by ER stress, mitochondrial and oxidative stress, altered autophagy, inflammatory signaling, and transcriptional changes that weaken β-cell identity (Fig. 1). In a study using a human β-cell line (1.1B4) and isolated human islets, palmitate induced oxidative/ER stress and pro-apoptotic signaling, whereas oleate increased neutral lipid storage and insulin secretion and partially mitigated palmitate's stress effects, supporting a buffering role for lipid sequestration/desaturation pathways [24]. Lipid droplet formation and stearoyl-CoA desaturase activity appear to buffer saturated LC-FFA and may confer partial protection relative to rodent β-cells. However, prolonged LC-FFA exposure remains harmful *in vitro*, and the extent to which β-cell lipotoxicity occurs *in vivo* in humans is still not fully defined [23].

## 3 Diabetes, Obesity, and Inflammation

As adipose depots expand in obesity and diabetes through adipogenesis and adipocyte growth, adipose tissue undergoes coordinated immune remodeling. In the lean state, resident immune cells maintain a type 2 environment with M2-polarized macrophages that secrete IL-10 and support insulin sensitivity. With obesity, this balance shifts such that the total number of macrophages increases, largely due to recruitment of proinflammatory M1-polarized macrophages, and the M1:M2 ratio rises. This macrophage accumulation is a hallmark of obesity-associated adipose tissue inflammation and reflects activation of an innate immune program that becomes chronically engaged during adipose expansion, demonstrated by increased adipose tissue macrophages in diet-induced and genetically obese mice and in adipose biopsies from obese humans [20]. The resulting proinflammatory environment establishes tonic, low-grade inflammation that closely tracks with the severity of insulin resistance and other metabolic complications of obesity [25] (Fig. 2). While this provides a plausible causal route from obesity to systemic insulin resistance via sustained cytokine signaling, longitudinal human evidence demonstrating that adipose-driven inflammation drives brain insulin signaling malfunction is still needed to establish a stronger case for causation [25].

In obesity, adipocytes and adipose tissue macrophages release proinflammatory cytokines such as TNF-α, IL-6, and IL-1β that act locally on adipose tissue, liver, and muscle to activate inflammatory signaling. These cytokines stimulate stress-responsive serine kinases, including c-Jun N-terminal kinases (JNK) and inhibitor of κB kinase β (IKKβ) in insulin target cells, which in turn activate transcription factors activator protein (AP)-1 and nuclear factor kappa beta (NF-κB), upregulating additional inflammatory genes [26]. Mice with conditional deletion of IKKβ in myeloid cells showed that myeloid IKKβ loss preserved global insulin sensitivity in an obese state [27]. These same kinases phosphorylate insulin receptor substrate (IRS) proteins, insulin receptors, and other insulin signaling molecules on serine residues, and these phosphorylation events interfere with normal insulin signaling, producing a state of cellular insulin resistance [26] (Fig. 2). This supports a causal role for myeloid IKKβ/NF-κB signalling in driving systemic insulin resistance in obesity, but longitudinal human data are needed to show that this inflammatory pathway precedes and impairs brain insulin signaling [26].

The adipokine profile in obesity shifts toward a proinflammatory, insulin-resistant state. Circulating adiponectin, an adipocyte-derived hormone with potent anti-inflammatory and insulin-sensitizing actions, is reduced in obese humans and rodents. Inflammatory signals such as TNF-α, IL-6, ROS, and hypoxia suppress its expression. In adiponectin/ACRP30-knockout mice, the loss of adiponectin was shown to produce severe high-fat, high-sucrose diet-induced insulin resistance with decreased muscle IRS-1/PI3K activity and increased plasma and adipose TNF-α, while adenoviral adiponectin expression reversed these abnormalities [28]. Adiponectin normally activates AMP-activated protein kinase (AMPK) via AdipoR1/2

to enhance fatty acid oxidation and glucose uptake in muscle and to inhibit hepatic gluconeogenesis (Fig. 2). Loss of adiponectin promotes diet-induced inflammation and insulin resistance. In contrast, leptin levels are elevated in obesity, and leptin acts as a proinflammatory cytokine-like hormone that activates monocytes and macrophages to produce TNF-α, IL-6, and IL-12 and skews T cells toward a Th1 phenotype. Chronic hyperleptinemia and reduced adiponectin together favor persistent inflammation and ultimately impaired insulin sensitivity [28] (Fig. 2). This establishes a causal relationship between adiponectin loss and insulin resistance with increased inflammatory tone, but without models showing that restored adiponectin signaling prevents these defects, this only shows indirect linkage to neurodegeneration [28].

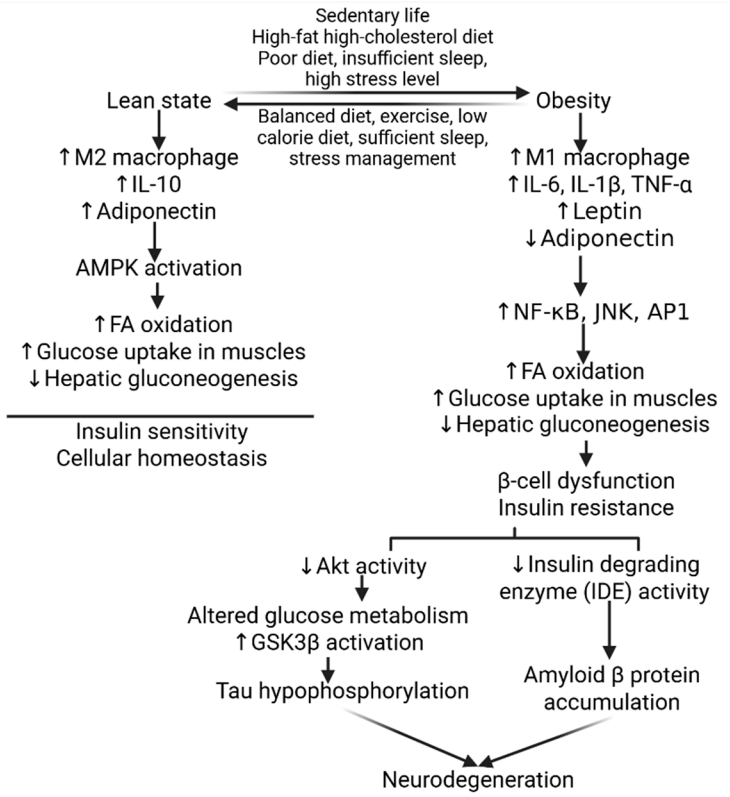


**Figure 2:** Molecular mechanisms of obesity-associated neurodegeneration. Obesity contributes to adipocyte hyperplasia and hypertrophy, leading to an increased M1:M2 ratio. This contributes to increased pro-inflammatory cytokines, fatty acid oxidation, and beta cell dysfunction, finally leading to insulin resistance and neurodegeneration. ↑-increase and ↓-decrease. Created in BioRender. Rai, V. (2026) https://BioRender.com/79lk9hk.

### *Signaling Pathways*

Signaling pathways link obesity, inflammation, and diabetes through a cascade of events that disrupt normal cellular function. As described in Section 3, obesity establishes a chronic low-grade inflammatory state characterized by activation of NF-κB and JNK signaling, which directly impairs insulin signaling and promotes insulin resistance, a key feature of T2DM (Figs. 1 and 2). Other pathways involved include Wnt, toll-like receptor (TLR), mitogen-activated protein kinase (MAPK), and extracellular signal-regulated kinase (ERK), which are activated by metabolic stresses and inflammatory signals [29,30] (Fig. 3).

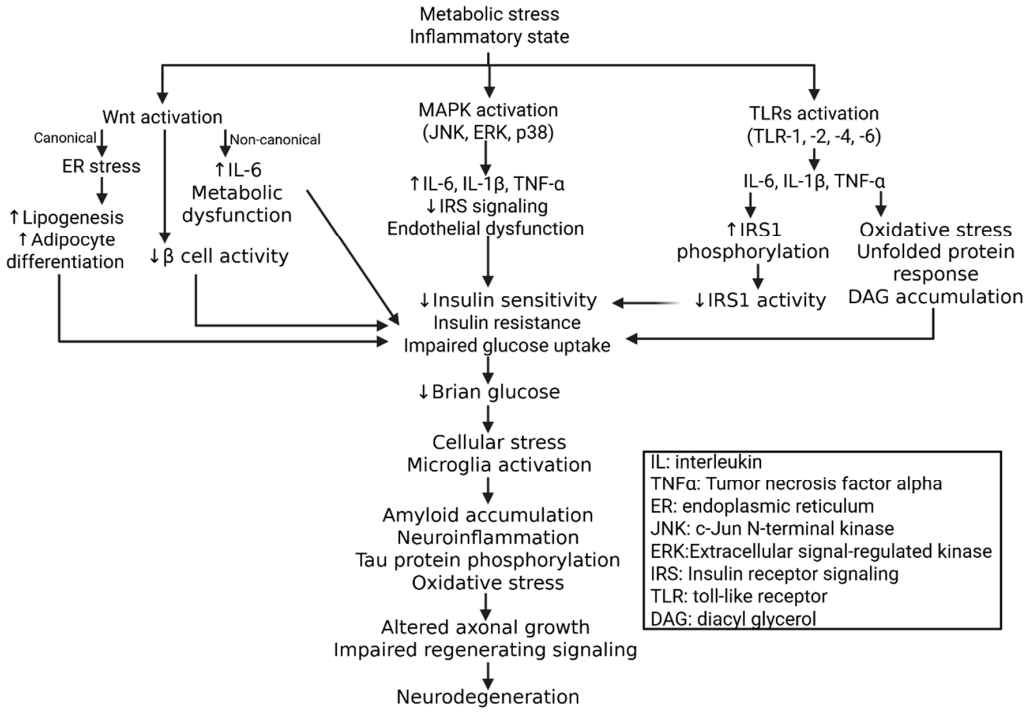


**Figure 3:** Signaling pathways involved in hyperglycemia-associated neurodegeneration. Wnt, MAPK, and TLR activation leads to activation of cytoplasmic kinases and secretion of pro-inflammatory cytokines, contributing to metabolic dysfunction, impaired insulin sensitivity, and insulin resistance. This results in decreased brain glucose, cellular and oxidative stress, and inflammation in the brain tissue, contributing to neurodegeneration. ↑-increase and ↓-decrease. Created in BioRender. Rai, V. (2026) https://BioRender.com/oojvxx5.

The activated inflammatory pathways interfere with the insulin signaling pathway, a process crucial for glucose, lipid, and energy homeostasis, contributing to insulin resistance and the development of T2DM [31–33]. The MAPK family integrates metabolic and inflammatory signals to regulate glucose metabolism and immune activation. Dysregulation of the Wnt pathway is linked to obesity-induced inflammation and diabetes [29]. Inflammatory cytokines induce suppressors of cytokine signaling (SOCS) proteins, which can negatively regulate insulin signaling [30] (Fig. 3).

Stress-activated MAPKs, particularly p38, amplify cytokine production in response to metabolic stress, sustaining chronic inflammation in insulin-sensitive tissues such as skeletal muscle and endothelium. MAPKs are activated by various stressors in diabetes (high glucose, lipids, oxidative stress, and inflammatory signals), mediating cellular responses that often become pathological, contributing to metabolic syndrome. Activated MAPKs, particularly p38, interfere with insulin signaling by phosphorylating key components (like IRS proteins) on serine/threonine residues, disrupting normal glucose uptake and utilization, contributing to insulin resistance (Fig. 3). Hyperactivation of MAPK pathways contributes to oxidative stress and apoptosis in pancreatic β-cells (impairing insulin production) and endothelial cells (leading to vascular complications) [34,35].

Alzheimer's disease and T2DM are closely linked, sharing common pathways involving impaired brain insulin signaling (PI3K-AKT), chronic inflammation, glucose/lipid metabolism dysfunction, and mitochondrial issues, leading to amyloid-beta buildup, tau hyperphosphorylation, and neurodegeneration. Deficient PI3K-AKT signaling links to tau hyperphosphorylation and increased activity of tau-kinase GSK-3β. Chronic inflammation (via inflammatory cytokines) contributes to synapse loss and memory

impairment [14,36,37]. Peripheral insulin resistance from T2DM triggers brain inflammation and impairs neuronal insulin signaling, increasing AD risk and severity. AD involves reduced glucose metabolism (hypometabolism), potentially linked to down-regulated glucose transporters (GLUTs) in T2DM-related insulin resistance. Insulin resistance can increase amyloid-beta (Aβ) production/aggregation and tau hyperphosphorylation, partly by affecting enzymes like insulin-degrading enzyme (IDE) and altering the balance of normal protein modification (O-GlcNAcylation) [14,36,37].

## 4 Neuroinflammation

Diabetes is increasingly recognized as a chronic low-grade inflammatory state in which adipose tissue functions as a dysregulated inflammatory organ [38]. Adipocytes and infiltrating immune cells release cytokines and adipokines, including TNF-α, IL-6, C-reactive protein (CRP), monocyte chemoattractant protein (MCP)-1, leptin, and resistin, that support systemic inflammation [39]. Hyperglycemia-induced oxidative stress contributes to blood–brain barrier (BBB) dysfunction and increased permeability, enabling peripheral inflammatory signals to enter the CNS. These cytokines and metabolic stressors reach the brain and promote a primed state of microglial activation along with reactive astrocyte dysregulation, leading to activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome and release of pro-inflammatory cytokines such as IL-1β and IL-18 [40]. In parallel, advanced glycation end-product (AGE) formation and binding to RAGE on endothelial and neural cells amplify NF-κB signaling, oxidative stress, and downstream pathogenic processes [41] (Fig. 4). Together, these mechanisms directly link diabetes to CNS immune activation through the NLRP3 inflammasome, which activates caspase-1 and subsequently the proinflammatory cytokines IL-1β, IL-18, and neuronal damage [42]. This resulting neuroinflammation is associated with an increased risk of neurodegenerative diseases such as AD [43] (Fig. 4).

Microglial cells and astrocytes are the central nervous system's primary innate immune responders, and BBB breakdown in diabetes (section on BBB) exposes them to chronic peripheral inflammatory signals that drive their activation and dysregulation [44]. Microglia are the predominant-NLRP3-expressing cells in the CNS and act as a key intermediary in diabetes-induced neuroinflammation [42]. Activation of the NLRP3 inflammasome follows a two-signal model. First, a priming signal—typically mediated by pattern-recognition receptors responding to microbial ligands or inflammatory cytokines, which activates NF-κB, leading to upregulation of NLRP3 and the pro-forms of IL-1β and IL-18 [40]. These priming pathways are markedly elevated in the diabetic microenvironment, where systemic inflammation persistently "licenses" NLRP3 in CNS immune cells [45] (Fig. 4). A second activation signal is then triggered by danger-associated stimuli such as $K^+$ efflux, extracellular ATP, lysosomal destabilization, mitochondrial dysfunction, calcium flux, or cytosolic RNA sensors [46]. With both signals in place, NLRP3 undergoes conformational activation and assembles with apoptosis-associated speck-like protein containing a caspase recruitment domain to recruit pro-caspase-1, which subsequently processes pro-IL-1β and pro-IL-18 into their mature, secreted forms [47] (Fig. 4). These activation pathways map closely onto the metabolic and oxidative stresses characteristic of diabetes.

The AGE-RAGE axis is a peripherally mediated inflammatory pathological process that is upregulated in diabetes. AGEs are formed when proteins, lipids, or nucleic acids become non-enzymatically glycated in the setting of hyperglycemia. RAGE is a receptor on many cells, namely endothelial cells and neurons, that, when bound, triggers a chronic inflammatory signaling cascade. Hyperglycemia is the primary factor in which AGEs are upregulated. Although beginning in the peripheral system, the AGE-RAGE axis extends to the blood-brain barrier and remodels the extracellular matrix, ultimately causing neuroinflammation [41]. AGEs binding to RAGE triggers downstream activation of the central mediator NF-kB, which is a central

mediator that expresses multiple inflammatory factors through a complex system of cross-talk, including MAPKs, JNK, ERK1/2, and the canonical IKK complex that collectively promote phosphorylation and nuclear translocation of the NF-κB RelA/p50 heterodimer. Once activated, NF-κB orchestrates a broad inflammatory program by inducing transcription of cytokines (IL-1β, IL-6, TNF-α), chemokines, adhesion molecules, and components required for NLRP3 inflammasome priming [48,49]. Beyond generic NF-KB signaling, AGE-RAGE signaling proceeds with a distinct RelA phosphorylation and acylation pattern that selectively drives expression of collagen I, priming innate immune cells more aggressively than generic inflammation stimuli [50]. Furthermore, the binding of AGEs to RAGE also generates ROS, further generating downstream inflammation (Fig. 4).

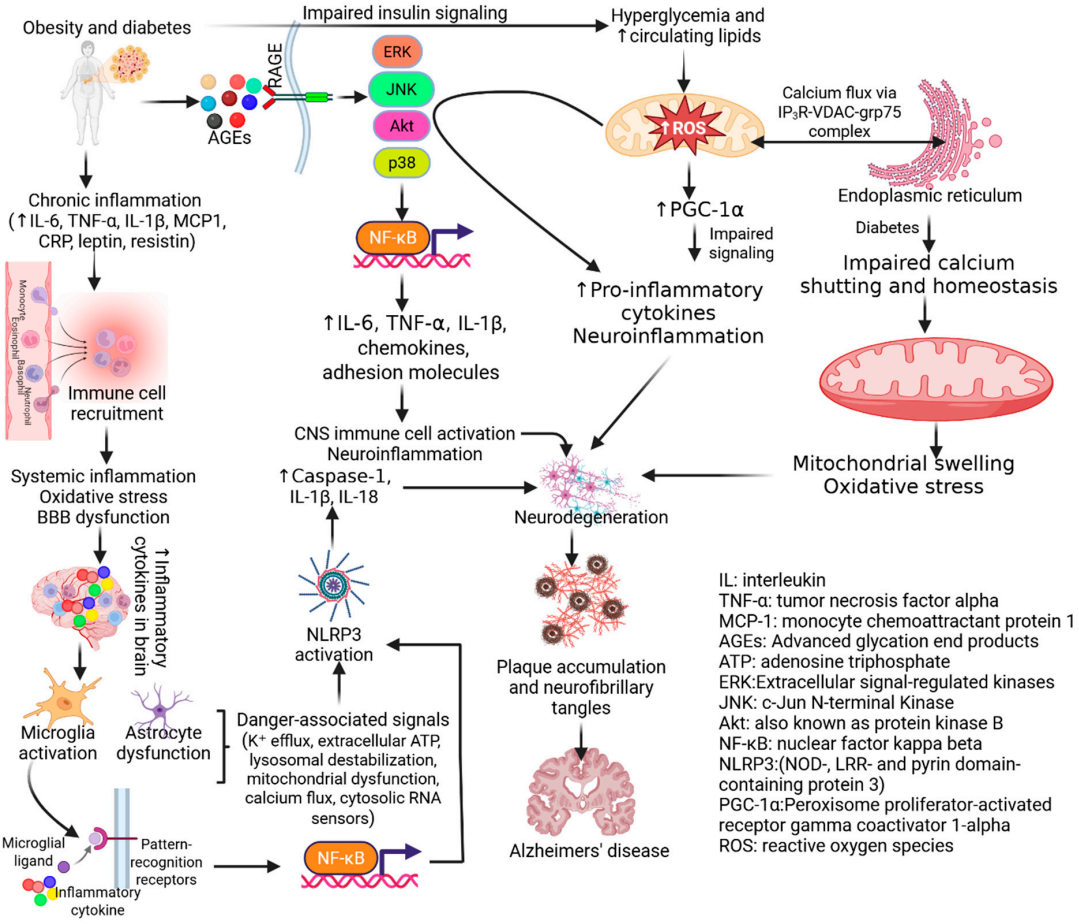


**Figure 4:** Molecular and cellular mechanisms of neuroinflammation and neurodegeneration. Chronic inflammation, oxidative stress, impaired blood-brain barrier, immune cell recruitment, impaired insulin sensitivity, insulin resistance, and mitochondrial and endothelial dysfunction play a critical role in neuroinflammation and neurodegenerative diseases, including Alzheimer's disease. ↑-increase. Created in BioRender. Rai, V. (2026) https://BioRender.com/zbdafjg.

Furthermore, the binding of AGEs to RAGE also generates ROS, further generating downstream inflammation. It does so in a two-step process by first stimulating the NADPH oxidase complex (NOX2), driving a surge in cytosolic superoxide, which amplifies NF-kB signaling and transcription of NLRP3 and pro-IL-1β B [51]. In parallel, RAGE signaling disrupts electron transport, leading to excess mitochondrial ROS (mtROS). mtROS is a potent stimulator for NLRP3. mtROS also facilitates mitochondrial DNA release into the

cytosol, which further accelerates inflammasome assembly [52]. Together, the priming through NOX2 and activation through mtROS make the AGE-RAGE axis a driver for NLRP3 inflammasome signaling in diabetes.

## 5 Mitochondrial Dysfunction

### *5.1 Mitochondrial Damage*

Nutrient excess and elevated circulating lipids initiate a cascade of metabolic stress in insulin-sensitive tissues, including the generation of ROS, which damage mitochondrial DNA and electron-transport chain enzymes, shifting mitochondria from ATP producers to pro-oxidant organelles. This process begins with nutrient overload and excess lipid intermediates that generate diacylglycerol (DAG), ROS, ceramide accumulation, and ER stress [28]. Experimental studies in cultured adipocytes and rodent models demonstrate that inflammatory and lipid-induced signaling interfere with insulin-induced phosphorylation of insulin receptor substrate 1 (IRS-1), which is critical in the insulin signaling cascade [28] (Fig. 4). As IRS-1 signaling is progressively impaired, hepatic, adipose, and skeletal muscle cells become increasingly insulin resistant. Sustained metabolic stress initially drives compensatory β-cell hyperactivity, which predisposes β-cells to oxidative injury and apoptotic loss over time, resulting in chronically elevated blood glucose and reinforcing the metabolic dysfunction [53].

This sustained metabolic stress is associated with oxidative stress, mitochondrial dysfunction, and cellular injury that characterize diabetes pathology across multiple tissues [54]. The presence of ROS disrupts oxidative phosphorylation pathways and ATP synthesis by uncoupling proton gradients and overloading oxidative phosphorylation complex enzymes. Reduction in ATP further impairs glucose uptake and fatty acid metabolism, allowing intermediate lipid byproducts to freely circulate and disrupt insulin signaling cascades [55]. In the nervous system, this mechanism is particularly critical: mitochondrial dysfunction and ROS act as upstream key drivers of synaptic failure, neuronal loss, and protein aggregation in neurodegenerative diseases [56].

### *5.2 Impaired Energy Production*

Coactivator proteins are closely linked to mitochondrial function and efficiency, such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α). PGC-1α plays a critical role in directing mitochondrial function and efficiency [57]. In peripheral tissues such as skeletal muscle, adipose tissue, and cardiomyocytes, metabolic signaling pathways, including PI3K/Akt-linked growth-factor signaling, promote PGC-1α activation. This increase in PGC-1α assists in mitochondrial biosynthesis and efficiency by providing transcription signals for replication machinery, OXPHOS complexes, and genes for fatty acid oxidation. All of which may assist in maintaining efficient energy use [58]. In the brain, PGC-1α plays a similar role in mitochondrial efficiency. Impaired signaling pathways for PCG-1α in the brain and in peripheral tissues (Fig. 4) may contribute to further neurodegeneration in diabetic patients [58].

Mitochondria and ER are tightly associated at mitochondria-associated membranes (MAMs), where controlled transfer of $Ca^{2+}$ takes place via $IP_3R$-VDAC-grp75 complex. In healthy cells, the ER releases $Ca^{2+}$ based on the energy demand of the mitochondria via calcium-sensitive dehydrogenases (Fig. 4). This coordinated mechanism is essential for maintaining adequate ATP production [59]. In diabetes, this shuttling system is disrupted by oxidative stress and lipid-induced organelle dysfunction, particularly at the $IP_3R$-VDAC complex, causing an inability to control $Ca^{2+}$ influx into the mitochondria. This impaired $Ca^{2+}$ handling leads to increased cytosolic $Ca^{2+}$ levels, which accumulate and induce the opening of the mitochondrial permeability transition pore (PTP). Constitutive opening of PTP leads to mitochondrial swelling, loss of membrane potential, and initiation of apoptosis, a catastrophic cascade that is amplified

under diabetic conditions of oxidative stress. In neurons, this degenerative process is particularly harmful, accelerating neurodegenerative conditions like Alzheimer's, Parkinson's, and dementia [60].

## 6 Vascular Damage

T2DM exerts widespread injury on the cerebral vasculature, extending beyond its typical metabolic effects. Chronic hyperglycemia and insulin resistance promote systemic endothelial dysfunction, arterial stiffening, and a pro-inflammatory, pro-thrombotic environment. In the brain, these disturbances manifest as microvascular remodeling and BBB disruption, with impaired vasoreactivity and cerebral autoregulation that ultimately led to cerebral small vessel disease and hypoperfusion. Together, these vascular alterations interact with neurodegenerative processes to accelerate cognitive decline and increase the risk of vascular cognitive impairment and dementia in individuals with diabetes [61].

### *6.1 Endothelial Dysfunction*

In healthy tissue, insulin activates the insulin-PI3K-eNOS signaling pathway, increasing nitric oxide (NO), which promotes vasodilation. Insulin resistance leads to selective impairment of this PI3K pathway while MAP-kinase pathways and endothelin-1 (ET-1) production remain active, shifting signaling towards ET-1-mediated vasoconstriction. This shift was seen in isolated porcine coronary arteries and small resistance arteries from obese, insulin-resistant humans when PI3K was under inhibition, but was prevented by ET-1 receptor blocking [62]. This is exacerbated by chronic hyperglycemia, which also decreases NO through oxidative stress. This leads to uncoupling of eNOS and rapid scavenging of NO by reactive oxygen species. Furthermore, in patients with diabetes and in streptozotocin-diabetic rats, an elevated ADMA and a reduced L-arginine/ADMA ratio were observed, which is associated with impaired endothelium-dependent vasodilation [63]. Elevated levels of eNOS inhibitors such as asymmetric dimethylarginine (ADMA), inflammatory mediators, and angiotensin II further inhibit NO synthesis. All of the defects in tandem severely limit NO activity and favor a vasoconstrictive, pro-inflammatory endothelial state [64]. Both human and vascular studies support mechanisms suggesting that insulin-signaling defects and eNOS uncoupling play a partly causal role in endothelial dysfunction, but more studies evaluating this mechanism in cerebral vasculature specifically would connect eNOS uncoupling in T2DM more strongly with cerebral injury [64].

Another consequence of unbalanced MAP-kinase activity is increased expression of adhesion molecules (ICAM-1 (Intercellular Adhesion Molecule-1) and VCAM-1 (Vascular Cell Adhesion Molecule-1)) and chemokines that promote leukocyte adhesion and vascular inflammation as seen in human brain microvascular endothelial cells when exposed to high glucose and advanced glycation end products (AGE-RAGE) [65]. Inflammatory cytokines (IL-1β, IL-6, TNF-α) and AGE-RAGE signaling damage the blood-brain barrier, causing a reduction in tight-junction integrity. This allows albumin and inflammatory mediators to more easily cross into the brain parenchyma [66]. The use of human brain cells in these models strongly supports how unbalanced MAP-kinase activity creates a pro-inflammatory vascular environment. However, *in vivo* data linking this pathway to long-term cognitive decline would connect this mechanism to neurodegeneration [66].

### *6.2 Advanced Glycation End-Products*

In chronic hyperglycemia, an increased amount of vascular proteins undergo nonenzymatic glycation, which forms AGEs. These AGEs accumulate in the extracellular matrix, forming intra- and intermolecular cross-links on elastin and collagen, especially in basement membranes and connective tissue. This stiffens vessel walls and hinders normal proteolytic turnover. This is manifested by diminished arterial and

myocardial compliance, which is linked to diastolic dysfunction and systolic hypertension [67]. AGE-RAGE binding promotes oxidative stress and inflammation through activation of cytoplasmic kinases, activating transcription factors NF-κB, signal transducer and activator of transcription 3 (STAT3), hypoxia inducible factor (HIF)-1α, and activator protein (AP)-1. This increases production of ROS, which ultimately overwhelms endogenous antioxidant mechanisms, creating sustained oxidative stress. This was seen in cultured bovine brain microvascular endothelial cells, where exposure to glyceraldehyde-derived AGEs increased intracellular ROS more than in bovine aortic endothelial cells, while the free radical scavenger edaravone attenuated both ROS generation and tissue factor induction [68]. The activation of NF-κB upregulates inflammatory cytokines (IL-1β, IL-6, TNF-α) and adhesions and matrix molecules (VCAM-1, ICAM-1, plasminogen activator inhibitor (PAI)-1, MCP-1, matrix metalloproteinase (MMP)-2), promoting leukocyte recruitment, extracellular matrix (ECM) remodeling, and vascular calcification in diabetes-prone vessels [69]. Because most mechanistic data on AGE-RAGE signaling and oxidative stress come from vascular and *in vitro* brain endothelial models rather than longitudinal human brain studies, AGE-driven vascular injury is best interpreted as a biologically plausible, partly causal contributor to vascular dysfunction in T2DM, while its downstream impact on cognitive decline and neurodegeneration remains indirect and only partially defined [69].

## 7 Impaired Insulin Signaling in the Brain

Neuronal insulin receptors are widely expressed in the cortex and hippocampus, where insulin binding activates IRS1/2-PI3K-Akt-mTOR signaling. This pathway regulates synaptic plasticity, neuronal survival, neurotransmitter trafficking, and mitochondrial metabolism rather than bulk glucose uptake [70]. Although most brain glucose entry is mediated by insulin-independent transporters (GLUT1/3), insulin can still modulate glucose handling by promoting GLUT3 translocation in neurons and enhancing GLUT1-dependent glucose uptake in astrocytes. Elevating insulin signaling using a constitutively active human insulin receptor β subunit (IRβ) in mixed primary rat hippocampal cultures increased neuronal uptake of $^{3}$H-glucose and selectively upregulated membrane GLUT3 [70]. In obesity, T2D, and Alzheimer's disease, brain insulin resistance is characterized by reduced IR/IGF1R signaling, impaired PI3K-Akt-mTOR activation, mitochondrial dysfunction, lower oxidative phosphorylation and ATP production, and increased ROS, changes that correlate with defective hippocampal long-term potentiation (LTP) and spatial memory [70]. Complementary work in high-fat diet mice shows that hippocampal insulin resistance impairs LTP and spatial memory via FoxO3a-dependent upregulation and autopalmitoylation of the palmitoyltransferase zDHHC3, which increases GluA1 palmitoylation, reduces synaptic AMPA receptor surface expression, and weakens glutamatergic transmission [71]. Thus, reduced neuronal insulin receptor and PI3K-Akt-mTOR signaling is shown to indirectly limit glucose utilization and compromise synaptic plasticity, contributing to cognitive decline in rat and mouse models, but reproducing these studies in human models may serve to strengthen the applicability of these findings [70].

Brain insulin resistance has been linked to age-related declines in memory and executive function and to Alzheimer's disease-like pathology [72]. In high-fat diet mice, brain insulin resistance in hippocampus and cortex tissue reduces mitochondrial respiratory capacity and ATP production, but improves with aerobic exercise [73]. Brain insulin signaling supports healthy cognition partially through its effects on mitochondrial function and brain energy metabolism. When insulin signaling is impaired, mitochondria generate less ATP, and neural energy production is compromised, which can weaken synaptic function and cognitive performance. Regular exercise is highlighted as a strategy that can improve brain insulin

sensitivity and thereby help preserve mitochondrial function and cognition in the setting of obesity-related metabolic disease [72].

### *7.1 Blood-Brain Barrier (BBB) Breakdown*

In particular, the BBB is impaired due to these inflammatory changes, which cause weakened tight junctions and injured pericytes. Chronic hyperglycemia and its associated oxidative stress, inflammation, and hypertension downregulate tight junction proteins, including occludin, claudin-5, and zonula occludens-1, in brain microvessels, which is shown to increase paracellular leakage [74]. Furthermore, hyperglycemia and AGEs, in tandem with VEGF, increase matrix metalloproteinases, which further damage tight junctions and basement membranes, ultimately increasing brain-blood barrier permeability [74]. Cerebrovascular pericytes, damaged by oxidative stress and AGE exposure, also contribute to loss of BBB stability. Diabetes also directly injures cerebrovascular pericytes, which undermines BBB stability. Old T2DM rats demonstrated reduced pericyte and claudin-5/occludin coverage of cortical capillaries with thickened basement membranes, greater BBB leakage, and impaired cerebral blood-flow autoregulation, changes linked to elevated mitochondrial ROS and reduced ATP in pericytes; high-glucose-treated human brain pericytes similarly showed increased ROS and AGEs, induction of TGF-β1, vascular endothelial growth factor (VEGF), and fibronectin, and reduced mitochondrial respiration and integrin β1 expression, consistent with weakened pericyte endothelial adhesion and basement-membrane hypertrophy [75]. This data indicates that hyperglycemia-induced pericyte dysfunction is mechanistically plausible as a driver of BBB dysfunction, but is limited to rodent and *in vitro* cell models [74].

This disruption in BBB function allows for the leakage of circulating inflammatory and neurotoxic signals to enter the brain. Systemic and CNS inflammation activate NF-κB, JAK-STAT, and MAPK signaling in cerebrovascular cells, amplifying production of cytokines such as TNF-α, IL-1β, IL-6, and TGF-β. NF-κB signaling increases endothelial VCAM-1 and ICAM-1 expression and pro-coagulant/vasoactive factors, which promote leukocyte adhesion, transmigration, and microvascular dysfunction. At the BBB, these cascades downregulate tight-junction proteins (claudin-5, occludin, ZO-1, caveolin-1) and alter transcytosis and transporter profiles, including upregulation of influx transporters for TNF-α and lysosomal enzymes [76]. This was similarly seen in short-term high-fat diet mice who showed increased hippocampal BBB permeability to sodium fluorescein within 1–2 days of TNF-α and IL-6 induction [77]. As barrier integrity falls, peripheral cytokines, immune cells, and fibrin cross into the CNS, where they disrupt glial and neuronal homeostasis and contribute to cognitive decline in metabolic syndrome, including obesity and T2DM [76]. The data support that inflammatory BBB disruption is contributory to cognitive decline, but the timing and reversibility of BBB changes relative to neurodegeneration remain uncertain.

In the case of circulating amyloid-β (Aβ), the BBB provides a receptor-mediated route of entry via the RAGE expressed on endothelial cells. In Alzheimer-model mice infused with pathophysiologically relevant concentrations of radiolabeled Aβ(1-40), substantial RAGE-dependent uptake in brain microvessels and transport across the BBB into brain parenchyma was observed [78]. RAGE-specific antibodies or soluble RAGE almost completely blocked this influx, and RAGE-null mice exhibited undetectable BBB transport of Aβ. RAGE-mediated Aβ entry was accompanied by increased expression of pro-inflammatory cytokines and endothelin-1 in the brain, causing vasoconstriction and reduced cerebral blood flow. These experiments identify vascular RAGE as a key mechanism by which plasma Aβ accumulates in brain parenchyma, driving neuroinflammation and neurovascular dysfunction [78].

### *7.2 Cerebral Hypoperfusion and Vascular Dementia*

T2DM produces cerebral hypoperfusion through both microvascular and large-artery mechanisms. Chronically elevated glucose and blood pressure remodel brain capillaries, causing basement-membrane thickening, aberrant angiogenesis, and ultimately microvascular rarefaction (reduction in density) [79]. In hyperglycemic mouse models with and without insulin resistance, these changes are reflected by basement-membrane thickening, loss of pericyte coverage, decreased numbers of perfused vessels, abnormal non-functional angiogenesis, and increased albumin leakage together with perivascular collagen and elastin remodeling, consistent with structurally mediated reductions in microvascular perfusion [80]. These structural changes, along with endothelial dysfunction, decrease vasodilatory capacity and impair neurovascular coupling and autoregulation, such that cerebral arterioles cannot appropriately dilate to meet metabolic demand or buffer systemic pressure changes. Furthermore, diabetes, insulin resistance, and hypertension accelerate atherosclerosis and stiffening of central arteries, which increases pressure and flow pulsatility transmitted into the low-resistance cerebral circulation. Clinical data from patients with type 2 diabetes demonstrate that greater aortic stiffness, quantified by carotid-femoral pulse wave velocity, is associated with a higher burden and progression of cerebral white-matter lesions, and systematic review and meta-analysis link arterial stiffness more broadly to cerebral small vessel disease and cognitive impairment [81]. This shows that increased pulsatile load further damages small vessels and is closely associated with cerebral small vessel disease, white-matter lesions, and cerebral hypoperfusion. These experimental and clinical data support diabetic microvascular remodeling and large-artery stiffening as important contributors to chronic cerebral hypoperfusion and small vessel disease, although in humans, they likely act alongside other vascular and neurodegenerative processes, and their exact timing remains uncertain [79].

Chronic cerebral hypoperfusion (CCH) produces the white matter injury that characterizes vascular cognitive impairment, including vascular dementia. White matter lesions are a major pathological hallmark of vascular cognitive impairment (VCI). White matter tracts normally maintain neural circuit signaling, so their disruption is closely linked to cognitive dysfunction. In both CCH models and VCI patients, these lesions demonstrate demyelination, astrogliosis, axonal loss, and venular damage due to oxidative stress, inflammation, and blood-brain barrier breakdown. Excitotoxicity and pro-inflammatory cytokines damage oligodendrocytes via loss of cellular function, mitochondrial dysfunction, and pro-apoptotic signaling. This leads to primary or secondary myelin destruction in white matter regions [82]. Remyelination is limited as a result of the chronic hypoxic, pro-oxidative environment of CCH, which blocks differentiation of oligodendrocyte progenitor cells. This is further hindered by endothelial damage and astrogliotic scarring [82]. This was consistent with a mouse model of subcortical ischemic vascular dementia induced by right unilateral common carotid artery inclusion, which showed that early IL-1β (pro-inflammatory cytokine) upregulation in the corpus callosum impairs oligodendrocyte precursor cell recruitment and remyelination, which led to a deficit in object recognition and spatial memory [83]. Together, these mechanisms create persistent white matter lesions that correlate with cognitive decline in VCI. Overall, these findings support a mechanism of chronic hypoperfusion-induced inflammation as a contributory factor to persistent white matter lesions and cognitive impairment, but the application of these results towards human VCI and its timing still requires longitudinal human data [82].

### *7.3 Protein Misfolding and Aggregation*

In a healthy individual, glycogen synthase kinase-3 (GSK-3β) and cyclin-dependent kinase 5 (CDK5) have essential and closely regulated roles in neurons, functioning to support cell structure, signaling, and survival. GSK-3β is a ubiquitous serine/threonine kinase. In addition to glycogen synthase, it has

many substrates that are involved in metabolism, gene transcription, neurogenesis [84], and neuronal plasticity through phosphorylation of the protein tau, which binds microtubules [85]. The main pathological hallmarks of AD include extracellular neuritic plaques (NPs) composed of toxic aggregates of β-Amyloid (Aβ) peptide, and intracellular neurofibrillary tangles (NFTs) composed of misfolded tau proteins [86]. GSK-3β is regulated by insulin via the AKT pathway [87]. Thus, insulin resistance leads to an increase in GSK-3β activity as well as a decrease in tau phosphatases, both leading to hyperphosphorylation of tau [88]. Insulin resistance also leads to hyperactivation of CDK5 through p25 overexpression, leading to increased phosphorylation of tau proteins like Tau217, which impairs neuronal synaptic structure and exacerbates cognitive impairment in AD [89]. The hyperphosphorylation and truncation of tau proteins lead to the formation of paired helical filaments and straight filaments that subsequently form the pathological aggregates that comprise NFTs [90].

Aβ plaques in AD are surrounded by dendritic and axonal changes that include spine loss, axonal swellings, and distorted neurite trajectories, and have been shown to activate GSK-3β [91]. Insulin resistance increases neuroinflammation and production of reactive oxygen species, triggering Aβ protein accumulation. Insulin, along with Aβ protein, is metabolized by insulin-degrading enzyme (IDE), a metalloprotease [92]. Insulin resistance, causing both the lowering of expression of IDE as well as impaired enzymatic activity, lays a basis for the accumulation of Aβ protein and its disruption of synaptic function, promotion of oxidative stress, and mitochondrial dysfunction, which all contribute to neuronal damage [93]. Genetic polymorphisms in the IDE gene that potentially cause reduced enzymatic activity have also been linked with increased risk of T2DM and AD, although the mechanisms by which they reduce such activity are not fully understood [94–96]. It is also worth noting that the efficacy of IDE clearance of Aβ protein *in vivo* remains debated [94].

There is growing evidence that suggests that T2DM and hyperglycemia are linked to Lewy-body pathology through their effects on alpha-synuclein. Alpha-synuclein is a small, highly charged protein encoded by the SNCA gene and is primarily expressed in CNS neurons [97]. Chronic high glucose has been shown to promote alpha-synuclein accumulation and Ser129 phosphorylation in mouse models, accelerating nigrostriatal neurodegeneration [98]. Metabolic stress induced by hyperglycemia can involve the production of reactive aldehydes like methylglyoxal, which promotes glycation of alpha-synuclein, leading to misfolding and aggregation [99]. Hyperglycemia and metabolic stress may also impair proteostatic functions like autophagy, leading to the dysregulation of post-translational modifications, further destabilizing alpha-synuclein and other amyloid proteins [100]. Cross-seeding, also known as heterologous seeding, occurs when oligomers composed of one misfolded protein can promote the polymerization of another protein [101]. Misfolded alpha-synuclein can cross-seed with proteins such as tau [102]. Recent studies suggest that α-synuclein and tau directly interact through the microtubule-binding region of tau and the C-terminus of α-synuclein, promoting aggregation [103]. Such cross-seeding induces proteostatic stress in neurons, providing a link between metabolic disturbances in T2DM and pathologies of synuclein and tau proteins.

### *7.4 Preclinical Models Linking Diabetes and Neurodegeneration*

Several preclinical studies strongly support a link between metabolic disturbances and the development of neurodegenerative diseases like Alzheimer's disease. In Drosophila melanogaster expressing human amyloid-β with the familial Arctic mutation, a high-sucrose diet increased Aβ aggregation, caspase-3 activation, and endoplasmic reticulum stress, resulting in impaired locomotor performance and reduced lifespan. These findings support the idea that Alzheimer's disease can be viewed as a "type 3 diabetes" condition, potentially mediated through the PERK-eIF2α pathway [104]. In another study using a Drosophila

tauopathy model, genetic induction of insulin resistance through loss of Chico (the fly ortholog of IRS) led to increased tau hyperphosphorylation, worsened rough-eye phenotype, and decreased phototactic behavior. In contrast, maintaining insulin signaling via Chico overexpression was neuroprotective, highlighting the role of intact insulin pathways in preventing tau-mediated neurodegeneration [105].

Rodent models further provide a mechanistic basis. Male Wistar rats with streptozotocin (STZ)-induced hyperglycemia showed elevated brain and serum Aβ, increased total and phosphorylated tau, higher neurofilament light levels, increased oxidative stress, and elevated acetylcholinesterase activity. Treatment with antidiabetic agents such as metformin and donepezil decreased many of these neurodegeneration markers, suggesting that metabolic interventions can protect the brain [106]. High-fat diet studies in transgenic mice expressing human islet amyloid polypeptide (hIAPP) revealed that aggregated hIAPP caused cytotoxic and pro-inflammatory effects on islet endothelial cells. Amyloid-laden islets demonstrated decreased capillary density, increased capillary diameter, and increased pericyte number, linking type 2 diabetes–associated amyloid pathology directly to vascular damage and B-cell dysfunction [107].

Other rodent studies combining high-fat diets with low-dose STZ have shown similar cognitive changes and molecular findings seen in diabetes-related neurodegeneration. In Sprague-Dawley rats, this model caused impaired cognitive performance in the Morris water maze and increased hippocampal and cortical Aβ levels, while enhancement of nitric oxide–mediated metabolic signaling via L-arginine provided neuroprotection [108]. In Wistar rats, a similar protocol increased phosphorylated tau, elevated dephosphorylated GSK-3β, and reduced hippocampal insulin and adiponectin levels. High-intensity interval training (HIIT) reversed these changes, demonstrating neuroprotective effects through metabolic and adiponectin-dependent pathways [109]. Of note, intracerebroventricular STZ in Wistar rats impaired cognitive function in both Morris water maze and passive avoidance tests without detectable change in Aβ levels, and low-dose SGLT-2 inhibition did not rescue diabetes-related cognitive function or amyloid pathology, indicating that not all metabolic interventions may equally influence neurodegeneration [110].

Overall, these studies (Table 1) demonstrate that hyperglycemia, insulin resistance, and diet-induced metabolic stress are associated with increased tau and amyloid pathology, cognitive impairment, and neuronal injury. These findings support the mechanisms described in Section 7.3 and highlight metabolic pathways as potential targets for neuroprotection in diabetes-associated neurodegeneration.

**Table 1:** Evidence of diabetes-associated neurodegeneration from model organisms.

| Animal Model | Intervention | Neurological Outcome | Key Finding |
|---|---|---|---|
| Drosophila melanogaster expressing human amyloid-B (familial Arctic mutation) [104] | High sucrose diet (HSR) | Increased amyloid B aggregations Increased caspase 3 in Drosophila expressing Alzheimer's disease Impaired locomotor effects and reduced lifespan, Elevated endoplasmic reticulum stress | A high sucrose diet progresses alzheimers disease consistent with Alzheimer's disease, as a T3 diabetes (type 2 diabetes in the brain). PERK-eIFa pathway may be a pathological mechanism activated in T3 diabetes. |
| Transgenic mice expressing human islet amyloid polypeptide (hIAPP) [107] | High-fat diet | Aggregated hIAPP displayed cytotoxic and pro-inflammatory effects on islet endothelial cells. Amyloid-laden islets demonstrated decreased capillary density, increased capillary diameter, and increased pericyte number. | T2DM-induced amyloid-associated pathology directly damages islet vasculature, contributing to B-cell dysfunction. |

**Table 1:** *Cont.*

| Animal Model | Intervention | Neurological Outcome | Key Finding |
|---|---|---|---|
| Drosophila melanogaster tauopathy model [105] | Genetic induction of insulin resistance via loss of function of Chico (IRS ortholog) | Increased tau hyperphosphorylation, worsened rough-eye phenotype, and decreased phototactic behavioral performance. | Insulin resistance exacerbates tau-mediated neurodegeneration, while intact insulin signalling (overexpression of Chico) is neuroprotective. |
| Male Wistar rats [106] | Streptozotocin (STZ)-induced hyperglycemic rate model of insulin-deficient diabetes | Increased brain and serum amyloid-B, increased total tau and phosphorylated tau, increased neurofilament light, increased oxidative stress, and increased acetylcholinesterase activity. | Treatment with anti-diabetic agents metformin and donepezil decreased multiple neurodegeneration biomarkers. |
| Male Wistar rats [109] | High-fat diet followed by low-dose streptozotocin | Increased phosphorylated tau, increased dephosphorylated GSK3B, decreased hippocampal insulin and adiponectin levels, reversed by high-intensity interval training (HIIT) | HIIT exerts a neuroprotective effect through metabolic and adiponectin pathways |
| Sprague-Dawley rat model [108] | High-fat diet followed by low-dose streptozotocin | Impaired cognitive function (Morris water maze), increased hippocampal and cortical amyloid-B levels. | Enhancement of nitric oxide-mediated metabolic signaling via L-arginine exerts neuroprotective effects. |
| Male Wistar rats [111] | Intracerebroventricular streptozotocin | Impaired cognitive function (Morris water maze and passive avoidance tests), no change in amyloid-B levels | A low-dose SGLT-2 inhibitor did not rescue diabetes related cognitive function or amyloid-B levels. |

### *7.5 Oxidative Stress*

ROS in diabetic patients contribute to inflammatory signaling, cellular injury, and cognitive impairment (Fig. 4). As previously described, chronic hyperglycemia increases aerobic glycolytic flux, resulting in excessive mitochondrial electron transport chain (ETC) activity and promoting subsequent superoxide generation and mitochondrial dysfunction. However, hyperglycemia in diabetic patients also diverts glucose into several collateral pathways of glucose metabolism, including the protein kinase C (PKC) and xanthine oxidase (XO) pathways, which serve as direct, non-mitochondrial sources of ROS in diabetic patients [112]. Additionally, diabetes disrupts antioxidant defenses, which indirectly amplifies oxidative stress. Together, these direct and indirect sources of ROS buildup work synergistically with mitochondrial oxidative stress to amplify neuronal vulnerability and accelerate neurodegenerative processes [113].

Diabetic patients are directly exposed to ROS through the activation of the PKC pathway. During this process, hyperglycemia triggers activation of phospholipase C or D, which increases diacylglycerol (DAG) production. In cultured aortic endothelial cells and vascular smooth muscle cells, exposure to high glucose elevated DAGs and activated PKC within 72 h, resulting in the phosphorylation of NADPH oxidase (NOX) and subsequent generation of ROS [114]. NOX activity is markedly elevated in diabetic patients and results in the production of superoxide and hydrogen peroxide, which play a role in diabetes-related neurodegeneration [113,115]. Importantly, in cultured neurons, activation of NOX2 promotes inflammatory neurodegeneration, establishing a direct pathophysiological link from peripheral hyperglycemia to central neuronal damage [116].

Xanthine oxidase also contributes directly to the accumulation of ROS within diabetic patients. XO catalyzes the two final steps of purine degradation, oxidizing hypoxanthine to xanthine and xanthine to uric acid [110]. During these reactions, XO transfers electrons to molecular oxygen, producing superoxide and

hydrogen peroxide [117]. This is important as XO activity is elevated in T2D patients [118]. In a prospective human cohort study following 4412 diabetes-free adults over 4.7 years, elevated serum XO activity was significantly associated with an increased risk of developing T2DM [119]. Moreover, in streptozotocin-induced diabetic mice, XO inhibition with oxypurinol resulted in reduced markers of systemic and muscular oxidative stress and prevented structural and functional mitochondrial alterations in skeletal muscle, confirming the *in vivo* relevance of XO in ROS production [120]. Additionally, a 2025 meta-analysis conducted by Alenezi et al. [121] found that preclinical studies within the past decade have consistently shown that XO inhibitors, such as allopurinol, can reduce neuronal oxidative damage, dampen neuroinflammation, and improve cognitive and pathological outcomes in Alzheimer's disease models.

In addition to the direct generation of ROS through overactivity of the PKC and XO pathways, diabetic patients also experience indirect accumulation of ROS through the disruption of redox homeostasis and depletion of key antioxidant defenses. For example, hyperglycemia leads to the activation of the polyol pathway, which can result in detrimental effects on cells and tissues as a result of redox imbalances [118]. The rate-limiting step of the polyol pathways is mediated by aldose reductase (AR), which converts glucose into sorbitol [118]. This reaction depends on the donation of an electron from the cofactor NADPH, which is oxidized to NADP [122]. In turn, overactivation of this pathway depletes NADPH stores and disrupts glutathione reductases' ability to alleviate oxidative stress produced from free radicals within the human body [123]. This mechanism indirectly increases ROS levels by impairing their reduction to non-toxic byproducts and weakening antioxidant defenses. This offers a potential mechanism for treating and preventing NDD in diabetic patients, as preclinical *in vivo* rat studies have demonstrated that the AR inhibitor, cemtirestat, is able to attenuate symptoms of peripheral neuropathy with high significance [124]. Additionally, many studies have found that T2D is associated with reduced concentrations and activities of key antioxidant systems, including superoxide dismutase (SOD), catalase (CAT), and non-enzymatic antioxidants such as vitamin A and E [125,126].

Under hyperglycemic conditions, excess glucose is also diverted into the hexosamine pathway. In this pathway, fructose-6-phosphate derived from glycolysis is converted into glucosamine 6-phosphate and ultimately into UDP-N-Acetylhexosamine (UDP-GLCNac). Elevated levels of UDP-GLCNac increase activity of O-Glucosamine-N-Acetyltransferase (OGT), which modifies transcription factors and signaling proteins through O-GlcNAcylation [127]. One of these transcription factors is Sp1, whose O-GlcNAc-dependent activation upregulates various genes such as tissue-type plasminogen activator inhibitor-1 (PAI-1) and transforming growth factor-β1 (TGF-β1) [128]. These signaling molecules promote pro-inflammatory and pro-fibrotic pathways, which indirectly contribute to oxidative stress by activating downstream NOX enzymes [127].

These pathways markedly increase concentrations of superoxide and hydrogen peroxide within diabetic patients. As a result, the excess ROS overwhelms antioxidant defenses and drives oxidative stress, damaging essential biomolecules such as DNA, proteins, and lipids, which ultimately results in cellular damage and death [15]. The downstream consequences of this oxidative burden are strongly associated with neurodegenerative diseases (NDDs) such as Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, and Friedreich's ataxia [129,130].

Oxidative stress contributes to the formation of stress granules, which sequester essential proteins and transcripts, disrupting neuronal function. Additionally, in NDDs, oxidative stress is linked with DNA damage, protein misfolding, and aggregation, which further contribute to tissue damage and disease progression [131]. ROS are often involved in transcriptional dysregulations, such as in Alzheimer's pathophysiology, where the imbalance in oxygen species results in increased mitochondrial DNA mutations and heightened expression

of the mitochondrial genes involved in metabolism [132]. ROS also play an important role in Tauopathies, by inducing tau phosphorylation and leading to aggregations of insoluble neurofibrillary tangles, synaptic dysfunction, and neuronal death [133,134]. Furthermore, localized inflammation, as a result of oxidative stress, further exacerbates neuronal damage and contributes to disease progression in NDDs such as AD, Parkinson's disease (PD), Huntington's disease (HD), and ALS [131].

However, critical questions remain in understanding ROS contributions to diabetic neurodegeneration. Whether non-mitochondrial ROS generation precedes or follows mitochondrial dysfunction in the diabetic brain remains unresolved, highlighting the need for longitudinal studies. Congruently, the relative contribution of different non-mitochondrial ROS sources, including NOX, XO, and polyol-mediated NADPH depletion, to neurodegeneration in human diabetic patients is not well established. While NOX inhibition shows promise in preclinical models, clinical translation remains uncertain due to the tissue-specific and isoform-specific roles of NOX enzymes in metabolic homeostasis [135]. Notably, NOX4 is required for adaptive responses that prevent insulin resistance, and mice with NOX4 deletions showed impaired glucose tolerance and peripheral insulin resistance [136]. Furthermore, a 2025 study also demonstrated sex-specific metabolic responses to NOX4 deficiency, in which male NOX4 knockout mice on a high-fat diet exhibited improved glucose and insulin tolerance, whereas female NOX4 knockout mice developed increased adiposity and impaired glucose tolerance [137]. Similarly, aldose reductase inhibitors targeting the polyol pathway have shown inconsistent clinical translation. While a 3-year multicenter trial demonstrated that epalrestat prevented deterioration of motor nerve conduction velocity and improved neuropathic symptoms in diabetic patients with good glycemic control, a meta-analysis of 32 randomized controlled trials found no overall significant difference between aldose reductase inhibitors and placebo [138,139]. XO inhibitors also present translational complexities, as the role of uric acid is paradoxical. While XO-generated ROS promotes oxidative damage, the pathway's end-product, uric acid, acts as an antioxidant at physiological pH, further complicating the translational relevance of this pathway and necessitating further research [140]. Despite these uncertainties, the consistent association across multiple independent non-mitochondrial pathways linking diabetic oxidative stress to AD hallmarks suggests these sources represent a contributory mechanism that warrants therapeutic targeting distinct from mitochondrial-focused interventions.

## 8 Future Directions

Although substantial progress has been made in defining the epidemiologic and mechanistic links between diabetes and cognitive decline, critical gaps remain in understanding how systemic metabolic dysfunction is translated into progressive neurodegeneration. Future research should increasingly focus on integrative mechanisms that bridge metabolism, vascular biology, immunity, mitochondrial function, oxidative stress, and proteostasis to explain the high prevalence of vascular and mixed dementia phenotypes observed in individuals with diabetes [141].

A central priority is refining our understanding of neurovascular unit dysfunction as a key convergence point for diabetic pathology. Rather than treating blood–brain barrier disruption and cerebral hypoperfusion as uniform downstream consequences, future studies should resolve the cell-type–specific and region-specific vulnerability of endothelial cells, pericytes, astrocytic endfeet, and neurons across disease stages [142,143]. Identifying early, potentially reversible alterations in barrier integrity, neurovascular coupling, and autoregulation may clarify when metabolic interventions could meaningfully alter trajectories of cognitive decline, particularly in vascular cognitive impairment and mixed dementia.

In parallel, emerging evidence suggests that diabetes induces durable immunometabolic reprogramming of CNS immune cells, especially microglia. Future work should determine whether chronic hyperglycemia

and insulin resistance establish persistent inflammatory "memory" states that sustain neuroinflammation even after glycemic control improves [144]. Resolving how metabolic substrates shape microglial polarization, inflammasome responsiveness, and phagocytic capacity may explain the progressive nature of diabetes-associated cognitive decline and identify strategies to interrupt neuroinflammation without global immune suppression.

Within this inflammatory framework, further emphasis should be placed on cell-specific regulation of the AGE–RAGE–NLRP3 axis. While microglia are the dominant NLRP3-expressing cells in the CNS, astrocytes and endothelial cells are also responsive to AGE–RAGE signaling and oxidative stress. Future studies should determine how inflammasome signaling propagates across the neurovascular unit and whether selective modulation of inflammasome activity in specific cell populations can attenuate neurodegeneration while preserving essential innate immune functions [135,145]. At the subcellular level, growing attention should be directed toward mitochondria-associated endoplasmic reticulum membranes (MAMs) as a mechanistic nexus linking insulin resistance, lipid overload, calcium dysregulation, and mitochondrial failure. Disruption of MAM integrity in diabetes may precipitate pathological calcium transfer, mitochondrial permeability transition pore opening, and apoptotic signaling, particularly in energetically vulnerable neurons [59]. Clarifying whether restoration of MAM structure can normalize bioenergetics and limit neurodegeneration represents a promising and mechanistically precise therapeutic direction.

Importantly, future research must also move beyond viewing oxidative stress as a homogeneous process. Diabetes generates reactive oxygen species from multiple compartmentalized sources, including mitochondrial dysfunction, PKC–NADPH oxidase signaling, xanthine oxidase activity, and redox imbalance arising from polyol and hexosamine pathway flux [128]. Distinguishing pathogenic from physiological redox signaling and identifying which enzymatic sources initiate versus amplify neurodegenerative cascades may explain why nonspecific antioxidant strategies have largely failed, while enzyme-targeted approaches show greater promise [146]. Finally, diabetes should increasingly be conceptualized as a disorder of neuronal proteostasis. Insulin resistance–driven dysregulation of kinases such as GSK-3β and CDK5, combined with oxidative stress and impaired clearance mechanisms, creates a permissive environment for tau, amyloid-β, and α-synuclein misfolding and aggregation [85]. Future studies should prioritize how metabolic stress destabilizes protein quality-control systems and promotes heterologous cross-seeding among misfolded proteins, providing a mechanistic basis for the frequent coexistence of Alzheimer-type and synuclein-related pathologies in diabetes-associated dementia [102]. Together, these directions emphasize the need for integrative, multiscale approaches that connect systemic metabolism to cellular and molecular drivers of neurodegeneration. Advancing such frameworks may shift therapeutic strategies away from isolated targets and toward interventions that restore metabolic, vascular, immune, and proteostatic homeostasis in the diabetic brain.

## 9 Conclusion

Diabetes-associated neurodegeneration of T3DM (brain diabetes) emerges from the convergence of systemic metabolic dysfunction and neural vulnerability. Impaired insulin signaling in neurons disrupts energy homeostasis, synaptic plasticity, and survival pathways, establishing an early foundation for cognitive decline. Mitochondrial dysfunction, oxidative stress, neuroinflammation, diabetes-induced endothelial dysfunction, advanced glycation end-product accumulation, and blood–brain barrier disruption together result in hypoxia, white matter injury, and neurovascular uncoupling, closely mirroring the pathological features of vascular cognitive impairment and dementia. The findings of this review underscore the need for integrative, multiscale approaches that move beyond isolated molecular targets to address

the interconnected metabolic, vascular, immune, mitochondrial, oxidative, and proteostatic drivers of diabetes-associated neurodegeneration. Defining cell-type- and region-specific vulnerability within the neurovascular unit, determining whether diabetes induces persistent immunometabolic "memory" in microglia, and resolving how AGE–RAGE–NLRP3 signaling propagates across endothelial, glial, and neuronal compartments should be the focus of research. At the subcellular level, elucidating the role of mitochondria-associated endoplasmic reticulum membranes in coordinating insulin resistance, calcium dysregulation, and mitochondrial failure may reveal mechanistically precise therapeutic targets. Equally important is distinguishing pathogenic versus physiological sources of reactive oxygen species to enable enzyme-targeted redox interventions, and clarifying how metabolic stress destabilizes neuronal proteostasis to promote cross-seeding of amyloid-β, tau, and α-synuclein aggregates. Advancing these directions may enable a shift toward disease-modifying strategies that restore metabolic, vascular, immune, and proteostatic homeostasis in the diabetic brain, rather than treating downstream neurodegenerative sequelae in isolation.

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## Abbreviations

The following abbreviations were frequently used in this review.

| | |
|---|---|
| AGEs | Advanced glycation end products |
| Aβ | Amyloid beta |
| ALS | Amyotrophic lateral sclerosis |
| ADs | Alzheimer's disease |
| AMPK | AMP-activated protein kinase |
| BBB | Blood-brain barrier |
| CNS | Central nervous system |
| CRP | C-reactive protein |
| DFUs | Diabetic foot ulcers |
| ER | Endoplasmic reticulum |
| ERK | Extracellular signal-regulated kinase |
| HIF-1α | Hypoxia inducible factor 1 alpha |
| IL | Interleukin |
| IDE | Insulin-degrading enzyme |
| ICAM-1 | Intercellular adhesion molecule 1 |
| IRS | Insulin receptor substrate |
| JNK | c-Jun N-terminal kinase |
| JAK | Janus kinases |
| LC-FFA | Long-chain free fatty acids |
| mTOR | Mammalian target of rapamycin |
| MAPK | Mitogen-activated protein kinase |

| | |
|---|---|
| MCP-1 | Monocyte chemoattractant protein 1 |
| MMP2 | Matrix metalloproteinase 2 |
| NF-κB | Nuclear factor kappa beta |
| NLRP3 | NOD-, LRR- and pyrin domain-containing protein 3 |
| PI3K | Phosphoinositide 3-kinase |
| PKC | Protein kinase C |
| RAGE | Receptor for advanced glycation end products |
| ROS | Reactive oxygen species |
| STAT3 | Signal transducer and activator of transcription 3 |
| T2DM | Type 2 diabetes mellitus |
| TNF-α | Tumor necrosis factor alpha |
| UPR | Unfolded protein response |
| VCAM-1 | Vascular cell adhesion molecule-1 |
| VEGF | Vascular endothelial growth factor |

## References


1. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, et al. Pathophysiology of type 2 diabetes mellitus. Int J Mol Sci. 2020;21(17):6275. [CrossRef].
2. Karunakaran U, Kim HJ, Kim JY, Lee IK. Guards and culprits in the endoplasmic reticulum: glucolipotoxicity and β-cell failure in type II diabetes. Exp Diabetes Res. 2012;2012:639762. [CrossRef].
3. Guria S, Hoory A, Das S, Chattopadhyay D, Mukherjee S. Adipose tissue macrophages and their role in obesity-associated insulin resistance: an overview of the complex dynamics at play. Biosci Rep. 2023;43(3):1–19. [CrossRef].
4. Qatanani M, Lazar MA. Mechanisms of obesity-associated insulin resistance: many choices on the menu. Genes Dev. 2007;21(12):1443–55. [CrossRef].
5. Zatterale F, Longo M, Naderi J, Raciti GA, Desiderio A, Miele C, et al. Chronic adipose tissue inflammation linking obesity to insulin resistance and type 2 diabetes. Front Physiol. 2020;10:1607. [CrossRef].
6. Chadt A, Scherneck S, Joost HG, Al-Hasani H. Molecular links between obesity and diabetes: "diabesity". In: Feingold KR, Adler RA, Ahmed SF, Anawalt B, Blackman MR, Chrousos G, editors. Endotext. South Dartmouth, MA, USA: MDText.com, Inc.; 2000.
7. Artemniak-Wojtowicz D, Kucharska AM, Pyrżak B. Obesity and chronic inflammation crosslinking. Cent Eur J Immunol. 2020;45(4):461–8. [CrossRef].
8. Chavda V, Yadav D, Patel S, Song M. Effects of a diabetic microenvironment on neurodegeneration: special focus on neurological cells. Brain Sci. 2024;14(3):284. [CrossRef].
9. Cholerton B, Baker LD, Montine TJ, Craft S. Type 2 diabetes, cognition, and dementia in older adults: toward a precision health approach. Diabetes Spectr. 2016;29(4):210–9. [CrossRef].
10. Matioli MNPS, Nitrini R. Mechanisms linking brain insulin resistance to Alzheimer's disease. Dement Neuropsychol. 2015;9(2):96–102. [CrossRef].
11. Messier C, Teutenberg K. The role of insulin, insulin growth factor, and insulin-degrading enzyme in brain aging and Alzheimer's disease. Neural Plast. 2005;12(4):311–28. [CrossRef].
12. Baduini IR, Castro Vildosola JE, Kavehmoghaddam S, Kiliç F, Nadeem SA, Nizama JJ, et al. Type 2 diabetes mellitus and neurodegenerative disorders: the mitochondrial connection. Pharmacol Res. 2024;209:107439. [CrossRef].
13. Lamptey RNL, Chaulagain B, Trivedi R, Gothwal A, Layek B, Singh J. A review of the common neurodegenerative disorders: current therapeutic approaches and the potential role of nanotherapeutics. Int J Mol Sci. 2022;23(3):1851. [CrossRef].
14. Pugazhenthi S, Qin L, Reddy PH. Common neurodegenerative pathways in obesity, diabetes, and Alzheimer's disease. Biochim Biophys Acta Mol Basis Dis. 2017;1863(5):1037–45. [CrossRef].
15. Szablewski L. Associations between diabetes mellitus and neurodegenerative diseases. Int J Mol Sci. 2025;26(2):542. [CrossRef].
16. Cerf ME. Beta cell dysfunction and insulin resistance. Front Endocrinol. 2013;4:37. [CrossRef].

17. Yau B, Ghislain J, Kebede MA, Hughes J, Poitout V. The role of the beta cell in type 2 diabetes: new findings from the last 5 years. Diabetologia. 2025;68(10):2092–103. [CrossRef].
18. Lipson KL, Fonseca SG, Ishigaki S, Nguyen LX, Foss E, Bortell R, et al. Regulation of insulin biosynthesis in pancreatic beta cells by an endoplasmic reticulum-resident protein kinase IRE1. Cell Metab. 2006;4(3):245–54. [CrossRef].
19. Zhang L, Lai E, Teodoro T, Volchuk A. GRP78, but not protein-disulfide isomerase, partially reverses hyperglycemia-induced inhibition of insulin synthesis and secretion in pancreatic β-cells. J Biol Chem. 2009;284(8):5289–98. [CrossRef].
20. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante Jr AW. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Investig. 2003;112(12):1796–808. [CrossRef].
21. Pipatpiboon N, Pratchayasakul W, Chattipakorn N, Chattipakorn SC. PPARγ agonist improves neuronal insulin receptor function in hippocampus and brain mitochondria function in rats with insulin resistance induced by long term high-fat diets. Endocrinology. 2012;153(1):329–38. [CrossRef].
22. Lu J, Zhao J, Meng H, Zhang X. Adipose tissue-resident immune cells in obesity and type 2 diabetes. Front Immunol. 2019;10:1173. [CrossRef].
23. Thomas P, Gallagher MT, Da Silva Xavier G. Beta cell lipotoxicity in the development of type 2 diabetes: the need for species-specific understanding. Front Endocrinol. 2023;14:1275835. [CrossRef].
24. Nemecz M, Constantin A, Dumitrescu M, Alexandru N, Filippi A, Tanko G, et al. The distinct effects of palmitic and oleic acid on pancreatic beta cell function: the elucidation of associated mechanisms and effector molecules. Front Pharmacol. 2019;9:1554. [CrossRef].
25. Saltiel AR, Olefsky JM. Inflammatory mechanisms linking obesity and metabolic disease. J Clin Investig. 2017;127(1):1–4. [CrossRef].
26. Olefsky JM, Glass CK. Macrophages, inflammation, and insulin resistance. Annu Rev Physiol. 2010;72:219–46. [CrossRef].
27. Arkan MC, Hevener AL, Greten FR, Maeda S, Li ZW, Long JM, et al. IKK-beta links inflammation to obesity-induced insulin resistance. Nat Med. 2005;11(2):191–8. [CrossRef].
28. Kwon H, Pessin JE. Adipokines mediate inflammation and insulin resistance. Front Endocrinol. 2013;4:71. [CrossRef].
29. Catalán V, Gómez-Ambrosi J, Rodríguez A, Pérez-Hernández AI, Gurbindo J, Ramírez B, et al. Activation of noncanonical Wnt signaling through WNT5A in visceral adipose tissue of obese subjects is related to inflammation. J Clin Endocrinol Metab. 2014;99(8):E1407–17. [CrossRef].
30. Emanuelli B, Peraldi P, Filloux C, Chavey C, Freidinger K, Hilton DJ, et al. SOCS-3 inhibits insulin signaling and is up-regulated in response to tumor necrosis factor-alpha in the adipose tissue of obese mice. J Biol Chem. 2001;276(51):47944–9. [CrossRef].
31. Das B, Das M, Kalita A, Baro MR. The role of Wnt pathway in obesity induced inflammation and diabetes: a review. J Diabetes Metab Disord. 2021;20(2):1871–82. [CrossRef].
32. Tanti JF, Ceppo F, Jager J, Berthou F. Implication of inflammatory signaling pathways in obesity-induced insulin resistance. Front Endocrin. 2013;3:181. [CrossRef].
33. Zand H, Morshedzadeh N, Naghashian F. Signaling pathways linking inflammation to insulin resistance. Diabetes Metab Syndr. 2017;11(Suppl 1):S307–9. [CrossRef].
34. Brown AE, Palsgaard J, Borup R, Avery P, Gunn DA, De Meyts P, et al. p38 MAPK activation upregulates proinflammatory pathways in skeletal muscle cells from insulin-resistant type 2 diabetic patients. Am J Physiol Endocrinol Metab. 2015;308(1):E63–70. [CrossRef].
35. Xu H, Liu T, Dai Y, Li N, Cao Z. The role of ERK1/2 signaling in diabetes: pathogenic and therapeutic implications. Front Pharmacol. 2025;16:1600251. [CrossRef].
36. De Felice FG, Ferreira ST. Inflammation, defective insulin signaling, and mitochondrial dysfunction as common molecular denominators connecting type 2 diabetes to Alzheimer disease. Diabetes. 2014;63(7):2262–72. [CrossRef].
37. Liu Y, Liu F, Grundke-Iqbal I, Iqbal K, Gong CX. Deficient brain insulin signalling pathway in Alzheimer's disease and diabetes. J Pathol. 2011;225(1):54–62. [CrossRef].
38. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444(7121):860–7. [CrossRef].

39. Taylor EB. The complex role of adipokines in obesity, inflammation, and autoimmunity. Clin Sci. 2021;135(6):731–52. [CrossRef].
40. Hamilton C, Olona A, Leishman S, MacDonald-Ramsahai K, Cockcroft S, Larrouy-Maumus G, et al. NLRP3 inflammasome priming and activation are regulated by a phosphatidylinositol-dependent mechanism. Immunohorizons. 2022;6(8):642–59. [CrossRef].
41. Bhattacharya R, Alam MR, Kamal MA, Seo KJ, Singh LR. AGE-RAGE axis culminates into multiple pathogenic processes: a central road to neurodegeneration. Front Mol Neurosci. 2023;16:1155175. [CrossRef].
42. Song L, Pei L, Yao S, Wu Y, Shang Y. NLRP3 inflammasome in neurological diseases, from functions to therapies. Front Cell Neurosci. 2017;11:63. [CrossRef].
43. Nguyen TT, Ta QTH, Nguyen TKO, Nguyen TTD, Van Giau V. Type 3 diabetes and its role implications in Alzheimer's disease. Int J Mol Sci. 2020;21(9):3165. [CrossRef].
44. Zeng J, Chen Y, Ding R, Feng L, Fu Z, Yang S, et al. Isoliquiritigenin alleviates early brain injury after experimental intracerebral hemorrhage via suppressing ROS- and/or NF-κB-mediated NLRP3 inflammasome activation by promoting Nrf2 antioxidant pathway. J Neuroinflammation. 2017;14(1):119. [CrossRef].
45. Wu D, Yan ZB, Cheng YG, Zhong MW, Liu SZ, Zhang GY, et al. Deactivation of the NLRP3 inflammasome in infiltrating macrophages by duodenal-jejunal bypass surgery mediates improvement of beta cell function in type 2 diabetes. Metabolism. 2018;81:1–12. [CrossRef].
46. Bauernfeind FG, Horvath G, Stutz A, Alnemri ES, MacDonald K, Speert D, et al. Cutting edge: NF-kappaB activating pattern recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression. J Immunol. 2009;183(2):787–91. [CrossRef].
47. Jo EK, Kim JK, Shin DM, Sasakawa C. Molecular mechanisms regulating NLRP3 inflammasome activation. Cell Mol Immunol. 2016;13(2):148–59. [CrossRef].
48. Huttunen HJ, Fages C, Rauvala H. Receptor for advanced glycation end products (RAGE)-mediated neurite outgrowth and activation of NF-kappaB require the cytoplasmic domain of the receptor but different downstream signaling pathways. J Biol Chem. 1999;274(28):19919–24. [CrossRef].
49. Jules J, Maiguel D, Hudson BI. Alternative splicing of the RAGE cytoplasmic domain regulates cell signaling and function. PLoS One. 2013;8(11):e78267. [CrossRef].
50. Peng Y, Kim JM, Park HS, Yang A, Islam C, Lakatta EG, et al. AGE-RAGE signal generates a specific NF-κB RelA "barcode" that directs collagen I expression. Sci Rep. 2016;6:18822. [CrossRef].
51. Wautier MP, Chappey O, Corda S, Stern DM, Schmidt AM, Wautier JL. Activation of NADPH oxidase by AGE links oxidant stress to altered gene expression via RAGE. Am J Physiol Endocrinol Metab. 2001;280(5):E685–94. [CrossRef].
52. Coughlan MT, Thorburn DR, Penfold SA, Laskowski A, Harcourt BE, Sourris KC, et al. RAGE-induced cytosolic ROS promote mitochondrial superoxide generation in diabetes. J Am Soc Nephrol. 2009;20(4):742–52. [CrossRef].
53. Wilkinson MS, Rollin TA, Kuriakose M, Haggerty-Goede RAL, Miller DM, Dunham-Snary KJ. Redox homeostasis in metabolic syndrome and type II diabetes: role of skeletal muscle and impact of gold-standard treatments. Int J Mol Sci. 2025;26(21):10370. [CrossRef].
54. Manojlovic M, Zafirovic S, Tomic Naglic D, Stokic E, Rizzo M, Suri JS, et al. Mitochondrial dysfunction, reactive oxygen species, and diabetes mellitus—a triangular relationship: a review. Biomol Biomed. 2025;26(4):547–58. [CrossRef].
55. Iheagwam FN, Joseph AJ, Adedoyin ED, Iheagwam OT, Ejoh SA. Mitochondrial dysfunction in diabetes: shedding light on a widespread oversight. Pathophysiology. 2025;32(1):9. [CrossRef].
56. Basagni F, Di Paolo ML, Cozza G, Dalla Via L, Fagiani F, Lanni C, et al. Double attack to oxidative stress in neurodegenerative disorders: MAO-B and Nrf2 as elected targets. Molecules. 2023;28(21):7424. [CrossRef].
57. Zhang Z, Zhang X, Meng L, Gong M, Li J, Shi W, et al. Pioglitazone inhibits diabetes-induced atrial mitochondrial oxidative stress and improves mitochondrial biogenesis, dynamics, and function through the PPAR-γ/PGC-1α signaling pathway. Front Pharmacol. 2021;12:658362. [CrossRef].
58. Ge X, Ye M, Fei A, Zhang Q, Yuan A. Advancements in understanding the role and mechanisms of mitochondria in diabetes: a comprehensive review. J Steroid Biochem Mol Biol. 2026;255:106875. [CrossRef].

59. Manié SN, Lebeau J, Chevet E. Cellular mechanisms of endoplasmic reticulum stress signaling in health and disease. 3. Orchestrating the unfolded protein response in oncogenesis: an update. Am J Physiol Cell Physiol. 2014;307(10):C901–7. [CrossRef].
60. Rieusset J. Mitochondria and endoplasmic reticulum: mitochondria-endoplasmic reticulum interplay in type 2 diabetes pathophysiology. Int J Biochem Cell Biol. 2011;43(9):1257–62. [CrossRef].
61. Liu R, Li L, Shao C, Cai H, Wang Z. The impact of diabetes on vascular disease: progress from the perspective of epidemics and treatments. J Diabetes Res. 2022;2022:1531289. [CrossRef].
62. Olver TD, Grunewald ZI, Ghiarone T, Restaino RM, Sales ARK, Park LK, et al. Persistent insulin signaling coupled with restricted PI3K activation causes insulin-induced vasoconstriction. Am J Physiol Heart Circ Physiol. 2019;317(5):H1166–72. [CrossRef].
63. Janaszak-Jasiecka A, Płoska A, Wierońska JM, Dobrucki LW, Kalinowski L. Endothelial dysfunction due to eNOS uncoupling: molecular mechanisms as potential therapeutic targets. Cell Mol Biol Lett. 2023;28(1):21. [CrossRef].
64. Jansson PA. Endothelial dysfunction in insulin resistance and type 2 diabetes. J Intern Med. 2007;262(2):173–83. [CrossRef].
65. Rom S, Heldt NA, Gajghate S, Seliga A, Reichenbach NL, Persidsky Y. Hyperglycemia and advanced glycation end products disrupt BBB and promote occludin and claudin-5 protein secretion on extracellular microvesicles. Sci Rep. 2020;10(1):7274. [CrossRef].
66. Yang DR, Wang MY, Zhang CL, Wang Y. Endothelial dysfunction in vascular complications of diabetes: a comprehensive review of mechanisms and implications. Front Endocrinol. 2024;15:1359255. [CrossRef].
67. Goh SY, Cooper ME. Clinical review: the role of advanced glycation end products in progression and complications of diabetes. J Clin Endocrinol Metab. 2008;93(4):1143–52. [CrossRef].
68. Niiya Y, Abumiya T, Shichinohe H, Kuroda S, Kikuchi S, Ieko M, et al. Susceptibility of brain microvascular endothelial cells to advanced glycation end products-induced tissue factor upregulation is associated with intracellular reactive oxygen species. Brain Res. 2006;1108(1):179–87. [CrossRef].
69. Khalid M, Petroianu G, Adem A. Advanced glycation end products and diabetes mellitus: mechanisms and perspectives. Biomolecules. 2022;12(4):542. [CrossRef].
70. Milstein JL, Ferris HA. The brain as an insulin-sensitive metabolic organ. Mol Metab. 2021;52:101234. [CrossRef].
71. Spinelli M, Fusco S, Mainardi M, Scala F, Natale F, Lapenta R, et al. Brain insulin resistance impairs hippocampal synaptic plasticity and memory by increasing GluA1 palmitoylation through FoxO3a. Nat Commun. 2017;8(1):2009. [CrossRef].
72. Malin SK, Stewart NR, Ude AA, Alderman BL. Brain insulin resistance and cognitive function: influence of exercise. J Appl Physiol. 2022;133(6):1368–80. [CrossRef].
73. Ruegsegger GN, Vanderboom PM, Dasari S, Klaus KA, Kabiraj P, McCarthy CB, et al. Exercise and metformin counteract altered mitochondrial function in the insulin-resistant brain. JCI Insight. 2019;4(18):e130681. [CrossRef].
74. Li X, Cai Y, Zhang Z, Zhou J. Glial and vascular cell regulation of the blood-brain barrier in diabetes. Diabetes Metab J. 2022;46(2):222–38. [CrossRef].
75. Liu Y, Zhang H, Wang S, Guo Y, Fang X, Zheng B, et al. Reduced pericyte and tight junction coverage in old diabetic rats are associated with hyperglycemia-induced cerebrovascular pericyte dysfunction. Am J Physiol Heart Circ Physiol. 2021;320(2):H549–62. [CrossRef].
76. Van Dyken P, Lacoste B. Impact of metabolic syndrome on neuroinflammation and the blood–brain barrier. Front Neurosci. 2018;12:930. [CrossRef].
77. de Paula GC, Brunetta HS, Engel DF, Gaspar JM, Velloso LA, Engblom D, et al. Hippocampal function is impaired by a short-term high-fat diet in mice: increased blood-brain barrier permeability and neuroinflammation as triggering events. Front Neurosci. 2021;15:734158. [CrossRef].
78. Deane R, Shi DY, Submamaryan RK, LaRue B, Jovanovic S, Hogg E, et al. RAGE mediates amyloid-beta peptide transport across the blood-brain barrier and accumulation in brain. Nat Med. 2003;9(7):907–13. [CrossRef].
79. van Sloten TT, Sedaghat S, Carnethon MR, Launer LJ, Stehouwer CDA. Cerebral microvascular complications of type 2 diabetes: stroke, cognitive dysfunction, and depression. Lancet Diabetes Endocrinol. 2020;8(4):325–36. [CrossRef].

80. Özkan E, Çetin-Taş Y, Şekerdağ E, Yiğit B, Shomalizadeh N, Sapancı S, et al. Hyperglycemia with or without insulin resistance triggers different structural changes in brain microcirculation and perivascular matrix. Metab Brain Dis. 2023;38(1):307–21. [CrossRef].
81. Funck KL, Laugesen E, Høyem P, Stausbøl-Grøn B, Kim WY, Østergaard L, et al. Arterial stiffness and progression of cerebral white matter hyperintensities in patients with type 2 diabetes and matched controls: a 5-year cohort study. Diabetol Metab Syndr. 2021;13(1):71. [CrossRef].
82. Rajeev V, Chai YL, Poh L, Selvaraji S, Fann DY, Jo DG, et al. Chronic cerebral hypoperfusion: a critical feature in unravelling the etiology of vascular cognitive impairment. Acta Neuropathol Commun. 2023;11(1):93. [CrossRef].
83. Zhou Y, Zhang J, Wang L, Chen Y, Wan Y, He Y, et al. Interleukin-1β impedes oligodendrocyte progenitor cell recruitment and white matter repair following chronic cerebral hypoperfusion. Brain Behav Immun. 2017;60:93–105. [CrossRef].
84. Fuster-Matanzo A, Llorens-Martín M, Sirerol-Piquer MS, García-Verdugo JM, Avila J, Hernández F. Dual effects of increased glycogen synthase kinase-3β activity on adult neurogenesis. Hum Mol Genet. 2013;22(7):1300–15. [CrossRef].
85. Sayas CL, Ávila J. GSK-3 and tau: a key duet in Alzheimer's disease. Cells. 2021;10(4):721. [CrossRef].
86. Braak H, de Vos RA, Jansen EN, Bratzke H, Braak E. Neuropathological hallmarks of Alzheimer's and Parkinson's diseases. Prog Brain Res. 1998;117:267–85. [CrossRef].
87. Welsh GI, Proud CG. Glycogen synthase kinase-3 is rapidly inactivated in response to insulin and phosphorylates eukaryotic initiation factor eIF-2B. Biochem J. 1993;294(3):625–9. [CrossRef].
88. Gratuze M, Julien J, Petry FR, Morin F, Planel E. Insulin deprivation induces PP2A inhibition and tau hyperphosphorylation in hTau mice, a model of Alzheimer's disease-like tau pathology. Sci Rep. 2017;7:46359. [CrossRef].
89. Fu K, Lin N, Xu Y, Huang E, He R, Wu Z, et al. CDK5-mediated hyperphosphorylation of Tau217 impairs neuronal synaptic structure and exacerbates cognitive impairment in Alzheimer's disease. Transl Psychiatry. 2025;15:302. [CrossRef].
90. Wang JZ, Xia YY, Grundke-Iqbal I, Iqbal K. Abnormal hyperphosphorylation of tau: sites, regulation, and molecular mechanism of neurofibrillary degeneration. J Alzheimers Dis. 2013;33(Suppl 1):S123–39. [CrossRef].
91. DaRocha-Souto B, Coma M, Pérez-Nievas BG, Scotton TC, Siao M, Sánchez-Ferrer P, et al. Activation of glycogen synthase kinase-3 beta mediates β-amyloid induced neuritic damage in Alzheimer's disease. Neurobiol Dis. 2012;45(1):425–37. [CrossRef].
92. Wei Z, Koya J, Reznik SE. Insulin resistance exacerbates Alzheimer disease via multiple mechanisms. Front Neurosci. 2021;15:687157. [CrossRef].
93. Li H, Wu J, Zhu L, Sha L, Yang S, Wei J, et al. Insulin degrading enzyme contributes to the pathology in a mixed model of Type 2 diabetes and Alzheimer's disease: possible mechanisms of IDE in T2D and AD. Biosci Rep. 2018;38(1):1–10. [CrossRef].
94. Cerasuolo M, Auriemma MC, Di Meo I, Lenti C, Papa M, Paolisso G, et al. Understanding the insulin-degrading enzyme: a new look at Alzheimer's disease and Aβ plaque management. Int J Mol Sci. 2025;26(14):6693. [CrossRef].
95. Kellar D, Craft S. Brain insulin resistance in Alzheimer's disease and related disorders: mechanisms and therapeutic approaches. Lancet Neurol. 2020;19(9):758–66. [CrossRef].
96. Kim B, Feldman EL. Insulin resistance as a key link for the increased risk of cognitive impairment in the metabolic syndrome. Exp Mol Med. 2015;47(3):e149. [CrossRef].
97. Butler B, Sambo D, Khoshbouei H. Alpha-synuclein modulates dopamine neurotransmission. J Chem Neuroanat. 2017;83–84:41–9. [CrossRef].
98. Lv YQ, Yuan L, Sun Y, Dou HW, Su JH, Hou ZP, et al. Long-term hyperglycemia aggravates α-synuclein aggregation and dopaminergic neuronal loss in a Parkinson's disease mouse model. Transl Neurodegener. 2022;11(1):14. [CrossRef].
99. Vasili E, König A, Al-Azzani M, Bosbach C, Gatzemeier LM, Thom S, et al. Glycation of alpha-synuclein enhances aggregation and neuroinflammatory responses. npj Parkinsons Dis. 2025;11(1):307. [CrossRef].
100. Greco M, Munir A, Musarò D, Coppola C, Maffia M. Restoring autophagic function: a case for type 2 diabetes mellitus drug repurposing in Parkinson's disease. Front Neurosci. 2023;17:1244022. [CrossRef].

101. Morales R, Moreno-Gonzalez I, Soto C. Cross-seeding of misfolded proteins: implications for etiology and pathogenesis of protein misfolding diseases. PLoS Pathog. 2013;9(9):e1003537. [CrossRef].
102. Padilla-Godínez FJ, Vázquez-García ER, Trujillo-Villagrán MI, Soto-Rojas LO, Palomero-Rivero M, Hernández-González O, et al. α-synuclein and tau: interactions, cross-seeding, and the redefinition of synucleinopathies as complex proteinopathies. Front Neurosci. 2025;19:1570553. [CrossRef].
103. Jeyabalan JB, Pandi AV, Veintramuthu S, Sivasamy R, Dhanasekaran M, Justin A. Converging pathologies in neurodegeneration: the mechanistic interplay between α-Synuclein and Tau in Alzheimer's and Parkinson's. Neurol Sci. 2025;46(10):4779–89. [CrossRef].
104. Sharma K, Rai P, Tapadia MG. Impaired insulin signaling and diet-induced type 3 diabetes pathophysiology increase amyloid β expression in the *Drosophila* model of Alzheimer's disease. Biochim Biophys Acta Mol Cell Res. 2025;1872(1):119875. [CrossRef].
105. Chatterjee S, Ambegaokar SS, Jackson GR, Mudher A. Insulin-mediated changes in tau hyperphosphorylation and autophagy in a *Drosophila* model of tauopathy and neuroblastoma cells. Front Neurosci. 2019;13:801. [CrossRef].
106. Ali SK, Ali RH. Effects of antidiabetic agents on Alzheimer's disease biomarkers in experimentally induced hyperglycemic rat model by streptozocin. PLoS One. 2022;17(7):e0271138. [CrossRef].
107. Castillo JJ, Aplin AC, Hackney DJ, Hogan MF, Esser N, Templin AT, et al. Islet amyloid polypeptide aggregation exerts cytotoxic and proinflammatory effects on the islet vasculature in mice. Diabetologia. 2022;65(10):1687–700. [CrossRef].
108. Dubey H, Dubey A, Gulati K, Ray A. Protective effects of L-arginine on cognitive deficits and biochemical parameters in an experimental model of type-2 diabetes mellitus induced Alzheimer's disease in rats. J Physiol Pharmacol. 2022;73(1):1–15. [CrossRef].
109. Khoramipour K, Bejeshk MA, Rajizadeh MA, Najafipour H, Dehghan P, Farahmand F. High-intensity interval training ameliorates molecular changes in the hippocampus of male rats with the diabetic brain: the role of adiponectin. Mol Neurobiol. 2023;60(6):3486–95. [CrossRef].
110. Hasan M, Fariha KA, Barman Z, Mou AD, Miah R, Habib A, et al. Assessment of the relationship between serum xanthine oxidase levels and type 2 diabetes: a cross-sectional study. Sci Rep. 2022;12(1):20816. [CrossRef].
111. Osmanovic Barilar J, Babic Perhoc A, Knezovic A, Homolak J, Virag D, Salkovic-Petrisic M. The effect of the sodium-glucose cotransporter inhibitor on cognition and metabolic parameters in a rat model of sporadic Alzheimer's disease. Biomedicines. 2023;11(4):1025. [CrossRef].
112. González P, Lozano P, Ros G, Solano F. Hyperglycemia and oxidative stress: an integral, updated and critical overview of their metabolic interconnections. Int J Mol Sci. 2023;24(11):9352. [CrossRef].
113. Castelli S, Carinci E, Baldelli S. Oxidative stress in neurodegenerative disorders: a key driver in impairing skeletal muscle health. Int J Mol Sci. 2025;26(12):5782. [CrossRef].
114. Xi G, Shen X, Wai C, Vilas CK, Clemmons DR. Hyperglycemia stimulates p62/PKCζ interaction, which mediates NF-κB activation, increased Nox4 expression, and inflammatory cytokine activation in vascular smooth muscle. FASEB J. 2015;29(12):4772–82. [CrossRef].
115. Vilas-Boas EA, Almeida DC, Roma LP, Ortis F, Carpinelli AR. Lipotoxicity and β-cell failure in type 2 diabetes: oxidative stress linked to NADPH oxidase and ER stress. Cells. 2021;10(12):3328. [CrossRef].
116. Tu D, Velagapudi R, Gao Y, Hong JS, Zhou H, Gao HM. Activation of neuronal NADPH oxidase NOX2 promotes inflammatory neurodegeneration. Free Radic Biol Med. 2023;200:47–58. [CrossRef].
117. Andrés CMC, de la Lastra JMP, Juan CA, Plou FJ, Pérez-Lebeña E. Chemistry of hydrogen peroxide formation and elimination in mammalian cells, and its role in various pathologies. Stresses. 2022;2(3):256–74. [CrossRef].
118. Hernandez-Hernandez ME, Torres-Rasgado E, Pulido-Perez P, Nicolás-Toledo L, Martínez-Gómez M, Rodríguez-Antolín J, et al. Disordered glucose levels are associated with xanthine oxidase activity in overweight type 2 diabetic women. Int J Mol Sci. 2022;23(19):11177. [CrossRef].
119. Li X, Meng X, Gao X, Pang X, Wang Y, Wu X, et al. Elevated serum xanthine oxidase activity is associated with the development of type 2 diabetes: a prospective cohort study. Diabetes Care. 2018;41(4):884–90. [CrossRef].
120. Bravard A, Bonnard C, Durand A, Chauvin MA, Favier R, Vidal H, et al. Inhibition of xanthine oxidase reduces hyperglycemia-induced oxidative stress and improves mitochondrial alterations in skeletal muscle of diabetic mice. Am J Physiol Endocrinol Metab. 2011;300(3):E581–91. [CrossRef].

121. Alenezi AA, Ahmad MA, Ibrahim IM. Possible effect of allopurinol and risk of dementia: An updated meta-analysis. Pharm Pract. 2026;24(1):1–2. [CrossRef].
122. Thorne CA, Grey AC, Lim JC, Donaldson PJ. The synergistic effects of polyol pathway-induced oxidative and osmotic stress in the aetiology of diabetic cataracts. Int J Mol Sci. 2024;25(16):9042. [CrossRef].
123. Srikanth KK, Orrick JA. Biochemistry, polyol or sorbitol pathways. Treasure Island, FL, USA: StatPearls Publishing; 2022.
124. Soltesova Prnova M, Medina-Campos ON, Pedraza-Chaverri J, Colín-González AL, Piedra-García F, Rangel-López E, et al. Antioxidant mechanisms in the neuroprotective action of cemtirestat: studies in chemical models, liposomes and rat brain cortical slices. Neuroscience. 2020;443:206–17. [CrossRef].
125. Mandal M, Varghese A, Gaviraju VK, Talwar SN, Malini SS. Impact of hyperglycaemia on molecular markers of oxidative stress and antioxidants in type 2 diabetes mellitus. Clin Diabetol. 2019;8(4):215–22. [CrossRef].
126. Promyos N, Phienluphon PP, Wechjakwen N, Lainampetch J, Prangthip P, Kwanbunjan K. Inverse correlation of superoxide dismutase and catalase with type 2 diabetes among rural Thais. Nutrients. 2023;15(9):2071. [CrossRef].
127. Caturano A, D'Angelo M, Mormone A, Russo V, Mollica MP, Salvatore T, et al. Oxidative stress in type 2 diabetes: impacts from pathogenesis to lifestyle modifications. Curr Issues Mol Biol. 2023;45(8):6651–66. [CrossRef].
128. Buse MG. Hexosamines, insulin resistance, and the complications of diabetes: current status. Am J Physiol Endocrinol Metab. 2006;290(1):E1–8. [CrossRef].
129. Houldsworth A. Role of oxidative stress in neurodegenerative disorders: a review of reactive oxygen species and prevention by antioxidants. Brain Commun. 2024;6(1):fcad356. [CrossRef].
130. Sędzikowska A, Szablewski L. Insulin and insulin resistance in Alzheimer's disease. Int J Mol Sci. 2021;22(18):9987. [CrossRef].
131. Dash UC, Bhol NK, Swain SK, Samal RR, Nayak PK, Raina V, et al. Oxidative stress and inflammation in the pathogenesis of neurological disorders: mechanisms and implications. Acta Pharm Sin B. 2025;15(1):15–34. [CrossRef].
132. Jadiya P, Tomar D. Mitochondrial protein quality control mechanisms. Genes. 2020;11(5):563. [CrossRef].
133. Bartolome F, Carro E, Alquezar C. Oxidative stress in tauopathies: from cause to therapy. Antioxidants. 2022;11(8):1421. [CrossRef].
134. Haque MM, Murale DP, Kim YK, Lee JS. Crosstalk between oxidative stress and tauopathy. Int J Mol Sci. 2019;20(8):1959. [CrossRef].
135. Heneka MT, Kummer MP, Stutz A, Delekate A, Schwartz S, Vieira-Saecker A, et al. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. Nature. 2013;493(7434):674–8. [CrossRef].
136. Plecitá-Hlavatá L, Jabůrek M, Holendová B, Tauber J, Pavluch V, Berková Z, et al. Glucose-stimulated insulin secretion fundamentally requires $H_2O_2$ signaling by NADPH oxidase 4. Diabetes. 2020;69(7):1341–54. [CrossRef].
137. Bond JM, Dzubanova M, Addington AK, Najt CP, Gilbert ER, Tencerova M, et al. Sex-specific metabolic responses to high-fat diet in mice with NOX4 deficiency. Redox Biol. 2025;85:103698. [CrossRef].
138. Chalk C, Benstead TJ, Moore F. Aldose reductase inhibitors for the treatment of diabetic polyneuropathy. Cochrane Database Syst Rev. 2007;2007(4):CD004572. [CrossRef].
139. Hotta N, Akanuma Y, Kawamori R, Matsuoka K, Oka Y, Shichiri M, et al. Long-term clinical effects of epalrestat, an aldose reductase inhibitor, on diabetic peripheral neuropathy: the 3-year, multicenter, comparative aldose reductase inhibitor-diabetes complications trial. Diabetes Care. 2006;29(7):1538–44. [CrossRef].
140. Becker BF, Reinholz N, Ozçelik T, Leipert B, Gerlach E. Uric acid as radical scavenger and antioxidant in the heart. Pflugers Arch. 1989;415(2):127–35. [CrossRef].
141. Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. Nat Rev Endocrinol. 2018;14(10):591–604. [CrossRef].
142. Lee SY, Chung WS. Astrocytic crosstalk with brain and immune cells in healthy and diseased conditions. Curr Opin Neurobiol. 2024;84:102840. [CrossRef].
143. Procter TV, Williams A, Montagne A. Interplay between brain pericytes and endothelial cells in dementia. Am J Pathol. 2021;191(11):1917–31. [CrossRef].
144. Vargas-Soria M, García-Alloza M, Corraliza-Gómez M. Effects of diabetes on microglial physiology: a systematic review of *in vitro*, preclinical and clinical studies. J Neuroinflammation. 2023;20(1):57. [CrossRef].

145. Ridker PM, MacFadyen JG, Thuren T, Everett BM, Libby P, Glynn RJ. Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. Lancet. 2017;390(10105):1833–42. [CrossRef].
146. Iacobini C, Vitale M, Pesce C, Pugliese G, Menini S. Diabetic complications and oxidative stress: a 20-year voyage back in time and back to the future. Antioxidants. 2021;10(5):727. [CrossRef].