Review

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[1] Sir Salimullah Medical College Hospital, Mitford Rd, Dhaka 1100, Bangladesh

[2] Department of Endocrinology, Diabetes & Metabolism; Jacobs School of Medicine and Biomedical Sciences, The State University of New York, 705 Maple Road, Williamsville, NY 14221, USA

[3] Department of Foundations of Medicine, NYU Grossman Long Island School of Medicine, 101 Mineola Blvd, Mineola, NY 11501, USA

[4] Department of Pharmaceutical Sciences, North South University, Dhaka 1229, Bangladesh

[5] Department of Health Informatics, Harrisburg University of Science and Technology, Harrisburg, PA 17101, USA

[6] Medical City Fort Worth, HCA Healthcare, 900 8th Ave, Fort Worth, TX 76104, USA

[7] Julius Bernstein Institute of Physiology, Medical School, Martin Luther University of Halle-Wittenberg, Magdeburger Straße 6, 06112 Halle, Germany

[*] Correspondence: Mohib_nsu007@yahoo.com (M.M.M.); mohammad.uddin@northsouth.edu (M.B.U.); Tel.: 16 +880-2-55668200 (ext. 6273)

Abstract

Diabetes mellitus casts a long shadow over the nervous system, driving a spectrum of complications that extend far beyond glycemic control. Diabetic peripheral neuropathy and diabetes-associated cognitive decline—long viewed as separate clinical entities—are now recognized as intertwined expressions of a multi-organ, multi-pathway disease process. At the molecular core, hyperglycemia, oxidative stress, mitochondrial injury, immune activation, and vascular dysfunction converge with insulin resistance to erode neuronal and glial integrity. These events are amplified by gut dysbiosis, which reshapes immune tone, disrupts neurovascular homeostasis, and fuels neurodegeneration via the gut–brain–nerve axis. Recent advances reveal that neuroinflammation, microvascular rarefaction, metabolic inflexibility, and lipid-mediated toxicity act not in isolation but as a self-reinforcing network linking peripheral and central injury. Yet, progress toward disease-modifying therapy remains slow, hindered by knowledge gaps in longitudinal human phenotyping, incomplete animal models, underdeveloped biomarkers, and neglected dimensions such as epigenetic memory, circadian disruption, and sex-specific biology. This Review integrates emerging mechanistic insights—from endothelial dysfunction and mitochondrial permeability transition to short-chain fatty acid signaling and ceramide neurotoxicity—with an urgent call for precision medicine approaches. By aligning metabolic, vascular, immune, and microbial interventions within longitudinal, biomarker-driven frameworks, the field stands poised to shift from symptom management to strategies that can slow, halt, or even reverse the neurological toll of diabetes.

Keywords: diabetic neuropathy; cognitive decline; neuroinflammation; gut–brain axis; oxidative stress; insulin resistance; microvascular dysfunction

1. Introduction

Diabetes mellitus (DM), particularly type 2 diabetes (T2DM), is not solely a disorder of chronic hyperglycemia, it is a systemic condition that progressively compromises neural integrity and function. Beyond the well-characterized vascular, renal, and ocular complications, diabetes exerts substantial yet often underrecognized effects on the nervous system—both peripheral and central—leading to diminished quality of life, increased healthcare utilization, and adverse long-term outcomes [1]. Diabetic peripheral neuropathy (DPN) is the most prevalent neurological complication, affecting up to 50% of individuals with long-standing diabetes. Clinically, DPN encompasses small- and large-fiber neuropathies, painful neuropathy, and autonomic dysfunction, which frequently progress insidiously until neurological deficits become irreversible [2]. In parallel, diabetes is increasingly linked to central nervous system (CNS) complications, including mild cognitive impairment, accelerated brain aging, Alzheimer's disease (AD)-like neurodegeneration, and mood disorders such as depression and anxiety. This constellation of findings has led to the broader concept of diabetes-associated neurodegeneration, with some investigators using the term "type 3 diabetes" to emphasize its neuropathological parallels with AD [3,4].

At the mechanistic level, hyperglycemia initiates multiple maladaptive biochemical pathways: activation of the polyol pathway, accumulation of advanced glycation end-products (AGEs), overactivation of protein kinase C (PKC), and increased flux through the hexosamine biosynthetic pathway. These processes converge to induce oxidative stress, mitochondrial dysfunction, endothelial injury, and impaired axonal transport [5]. Insulin resistance within neural tissue further exacerbates pathology by disrupting IRS–PI3K–Akt signaling, impairing synaptic plasticity, reducing neuronal survival, and imposing metabolic inflexibility—thereby rendering neurons more susceptible to injury and accelerating neurodegenerative changes [6,7].

Neuroinflammation serves as a critical amplifier of this injury. Chronic metabolic stress and immune dysregulation lead to activation of glial cells, infiltration of peripheral immune cells, and increased expression of proinflammatory cytokines such as TNF-α, IL-6, and IL-1β, which collectively exacerbate neural damage. The gut–brain axis emerges as another key contributor: diabetes-induced dysbiosis reduces beneficial taxa and microbial metabolites (e.g., short-chain fatty acids, indole derivatives), increases intestinal permeability, and promotes metabolic endotoxemia—thereby fueling systemic and neuroinflammation. Simultaneously, blood–brain barrier (BBB) integrity is compromised, particularly in hippocampal and cortical regions, allowing peripheral inflammatory mediators to access CNS compartments [8–11].

Current diagnostic modalities—such as nerve conduction studies, quantitative sensory testing, and standard neuroimaging—often detect damage only after it is well established [12]. Emerging biomarkers and tools, including neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) as blood-based indicators of neuroaxonal and astroglial injury [13–17], corneal confocal microscopy for early small-fiber loss [18,19], and novel mitochondrial stress markers such as GDF15, FGF21, and circulating mitochondrial DNA [20,21], hold promise for earlier detection and risk stratification.

Therapeutic strategies remain largely palliative, focused on glycemic control and symptomatic management of neuropathic pain. However, a shift toward disease-modifying interventions is underway. Promising avenues include antioxidants and neurotrophic agents; incretin-based therapies such as GLP-1 receptor agonists with anti-inflammatory and neuroprotective effects; AMPK-activating compounds to enhance neuronal bioenergetics; and microbiota-targeted therapies to restore gut–brain axis homeostasis. When integrated with lifestyle-based interventions—structured exercise programs, cognitive training, and dietary modulation—these approaches may extend beyond symptom control to altering disease trajectory [1,14,22,23].

This review therefore begins with the clinical spectrum of diabetic neuropathies—including DPN, autonomic neuropathy, and CNS complications—before examining the underlying cellular and molecular mechanisms (oxidative stress, mitochondrial dysfunction, neuroinflammation, insulin resistance). It further explores the gut–brain axis as an integrator of systemic and neural pathology,

and concludes with emerging diagnostic and therapeutic strategies. By integrating insights from endocrinology, neurology, immunology, and microbiome science, we aim to inform precision approaches that can transition diabetes-related neurodegeneration management from late-stage intervention to early, disease-modifying prevention [1,2].

2. Classification of Diabetes-Induced Neurological Disorders

Diabetes-induced neurological disorders encompass a diverse array of syndromes that can be broadly categorized based on the anatomical regions they affect: the peripheral nervous system (PNS) and the central nervous system (CNS). These disorders often overlap in pathogenesis but differ in their clinical manifestations, progression, and impact on functional outcomes. This section delineates the primary neurological complications of diabetes, including diabetic peripheral neuropathy (DPN), autonomic neuropathy, and central nervous system disorders, with a focus on their clinical classification and diagnostic features [24,25].

2.1. Diabetic Peripheral Neuropathy (DPN)

Diabetic peripheral neuropathy (DPN) is the most common neurological complication of diabetes, affecting ~50% of individuals with long-standing disease, particularly in the presence of poor glycemic control and cardiometabolic risk factors. Classically, it manifests as a length-dependent, symmetrical sensorimotor neuropathy—progressing in a "stocking–glove" distribution and predisposing to foot ulceration, infection, falls, and amputation [26].

The predominant form, distal symmetric polyneuropathy (DSPN), involves sensory, motor, and autonomic fibers, with sensory loss preceding motor deficits. Reduced ankle reflexes, impaired proprioception, and intrinsic foot muscle weakness are common, and electrophysiology typically reveals a mixed axonal–demyelinating pattern [26]. Small-fiber neuropathy—often an early stage—selectively affects Aδ and C fibers, producing burning pain, allodynia, hyperalgesia, and autonomic symptoms despite normal nerve conduction studies. Diagnosis relies on quantitative sensory testing, corneal confocal microscopy, and skin biopsy for intraepidermal nerve fiber density [27]. Large-fiber neuropathy impairs vibration and joint position sense, with gait instability and characteristic conduction slowing [26]. Less common focal and multifocal neuropathies include cranial mononeuropathies (oculomotor with pupil sparing), thoracolumbar radiculopathies, and entrapment syndromes. Diabetic amyotrophy presents with asymmetric proximal pain, weakness, and weight loss, typically improving over months to years [28]. Painful DPN (PDN), driven by both peripheral injury and central sensitization, manifests as burning, stabbing, or electric shock–like pain, often nocturnal and refractory to standard analgesics [26].

Diagnosis integrates symptom/sign assessment with nerve conduction studies, guided by validated tools such as the Michigan Neuropathy Screening Instrument and Toronto Clinical Neuropathy Score. For small-fiber disease, skin biopsy, corneal confocal microscopy, and laser-evoked potentials are recommended [27]. The ADA advises screening at T2DM diagnosis, 5 years after T1DM onset, and annually thereafter. Subtype identification informs prognosis and management [26].

2.2. Diabetic Autonomic Neuropathy (DAN)

Diabetic autonomic neuropathy (DAN) is a serious and underrecognized complication of both type 1 and type 2 diabetes, arising from chronic metabolic injury to autonomic nerve fibers. It impairs cardiovascular, gastrointestinal, genitourinary, and sudomotor regulation, and is associated with increased morbidity and mortality [29]. Risk increases with longer diabetes duration, poor glycemic control, and coexisting microvascular complications, and DAN may precede distal symmetric polyneuropathy in onset and pathophysiology.

Cardiovascular autonomic neuropathy (CAN) is the most prognostically severe manifestation, linked to sudden cardiac death, silent myocardial ischemia, and arrhythmias [30]. Clinical features

include resting tachycardia, reduced heart rate variability (HRV), exercise intolerance, and orthostatic hypotension. Diagnosis relies on HRV analysis during deep breathing, the Valsalva maneuver, postural changes, and occasionally baroreflex sensitivity testing—yet early disease is often asymptomatic, necessitating proactive screening.

Gastrointestinal involvement reflects enteric and vagal neuropathy. Gastroparesis delays gastric emptying, causing nausea, vomiting, bloating, and early satiety; colonic dysmotility results in constipation, diarrhea, or fecal incontinence. Gastric scintigraphy remains the diagnostic gold standard, with wireless motility capsules and 13C-octanoic acid breath tests emerging as alternatives [31–34].

Genitourinary dysfunction includes erectile dysfunction, retrograde ejaculation, and reduced libido in men, and decreased lubrication, sexual dysfunction, and urinary incontinence in women [35]. Diabetic cystopathy presents with diminished bladder sensation, impaired detrusor contractility, and increased post-void residual volume, predisposing to retention and infection. Urodynamic testing and residual urine measurement aid diagnosis [36–38].

Sudomotor failure arises from degeneration of sympathetic cholinergic fibers, producing anhidrosis, hyperhidrosis, or patchy sweating, most pronounced in the feet [39]. Resultant xerosis increases the risk of ulcers, and impaired thermoregulation compounds systemic vulnerability. Quantitative sudomotor axon reflex testing (QSART), thermoregulatory sweat testing, and electrochemical skin conductance can detect early small-fiber autonomic damage [40–42].

Diagnosis incorporates standardized symptom questionnaires (e.g., COMPASS-31), Ewing's battery, HRV testing, and autonomic reflex assessment [29]. Given its prognostic significance, routine autonomic evaluation should be integrated into diabetes care to enable early recognition, targeted intervention, and prevention of progression.

2.3. Central Nervous System (CNS) Complications of Diabetes

T2DM exerts a substantial yet often under-recognized impact on the central nervous system (CNS), spanning mild cognitive impairment, major depressive disorder, and increased Alzheimer's disease (AD) risk. These complications often develop insidiously, remain asymptomatic for years, and ultimately impair quality of life, increase morbidity, and raise mortality [43–45].

Cognitive impairment is the most frequent CNS manifestation. Longitudinal studies, including ACCORD-MIND, Rotterdam, and Framingham Offspring, consistently report deficits in executive function, attention, processing speed, and memory in individuals with diabetes compared with non-diabetic peers [45]. Decline accelerates with longer disease duration, poor glycemic control, and vascular comorbidities. Mechanistically, brain insulin resistance disrupts neuronal survival signaling, synaptic plasticity, and energy metabolism; microvascular disease drives hypoperfusion, white-matter injury, and impaired neurogenesis; and microglial and astrocytic activation fuels chronic neuroinflammation [43–47]. The association between T2DM and AD is particularly strong, with epidemiological data indicating a ~50–100% higher risk of AD in T2DM[48]. This has prompted the term "type 3 diabetes" to describe insulin-resistant states within the brain. AD neuropathology includes reduced insulin and insulin-receptor signaling, impaired amyloid-β clearance due to insulin-degrading enzyme (IDE) competition, and GSK3β-mediated tau hyperphosphorylation—all amplified by oxidative stress and mitochondrial dysfunction [45,48–50].

Depression is another major comorbidity, with meta-analyses and prospective studies showing a two- to three-fold increased risk in diabetes. The relationship is bidirectional: depression worsens glycemic control and self-management, while diabetes promotes depression via HPA-axis dysregulation, elevated IL-6 and TNF-α, and reduced monoaminergic tone. Structural neuroimaging reveals overlapping reductions in hippocampal and prefrontal volumes in both conditions [51,52].

Neuroimaging across MRI, PET, and diffusion tensor modalities shows consistent diabetes-related changes: hippocampal and cortical atrophy correlating with memory deficits; white-matter hyperintensities and tract injury indicative of small-vessel ischemia; and reduced cerebral glucose metabolism and hypoperfusion, especially in temporoparietal and frontal regions. These

abnormalities intensify with poorer glycemic control, greater glycemic variability, and longer disease duration [43,50,53]. Despite the prevalence and impact of CNS involvement, routine diabetes care rarely incorporates cognitive or mood screening, and patients may underreport symptoms. Brief, validated tools—Montreal Cognitive Assessment (MoCA) for cognition [54], Mini-Mental State Examination (MMSE) for global status [55], and Patient Health Questionnaire-9 (PHQ-9) for depression, enable rapid detection [56].

Overall, the CNS effects of diabetes reflect an interplay of metabolic, vascular, inflammatory, and neurodegenerative mechanisms. The clustering of cognitive decline, depression, and elevated AD risk highlights a systemic neural vulnerability likely to grow more clinically relevant as life expectancy increases in diabetes. Proactive, multidisciplinary care—linking neurology, endocrinology, and mental health—together with routine cognitive and mood screening, offers the best opportunity for early intervention [44,51].

3. Pathophysiological Mechanisms

3.1. Hyperglycemia and Glucotoxicity

Chronic hyperglycemia is the fundamental driver of diabetes-related complications and plays a pivotal role in the onset and progression of diabetic neuropathy and central nervous system (CNS) dysfunction. Sustained elevations in blood glucose initiate a cascade of maladaptive biochemical processes, collectively referred to as "glucotoxicity." These processes are particularly detrimental to neurons and glial cells, which are highly metabolically active and vulnerable to oxidative stress [57–59]. Among the most studied pathways involved in hyperglycemia-induced neural damage are the polyol pathway, advanced glycation end-products (AGE)–receptor for AGE (RAGE) axis, the hexosamine biosynthetic pathway, and protein kinase C (PKC) activation. Each contributes uniquely to cellular dysfunction, inflammation, oxidative stress, and ultimately neurodegeneration [60,61].

3.1.1. Polyol Pathway Activation

The polyol pathway is a central contributor to hyperglycemia-induced injury in insulin-independent tissues such as peripheral nerves, retina, renal glomeruli, and the lens. Under euglycemic conditions, it accounts for minimal glucose metabolism; in chronic hyperglycemia, it becomes a major metabolic route, strongly implicated in diabetic peripheral neuropathy (DPN) and other microvascular complications [62–64].

Glucose flux through this pathway is catalyzed by two key enzymes. Aldose reductase reduces glucose to sorbitol using NADPH, followed by sorbitol dehydrogenase oxidation of sorbitol to fructose with NAD^+ reduction to NADH [62,64]. While physiologically innocuous at low flux, hyperglycemia drives excessive sorbitol accumulation—particularly in Schwann cells and neurons, where membrane permeability to sorbitol is limited. This induces osmotic stress, leading to cell swelling, membrane instability, cytoskeletal disruption, and ultimately neurodegeneration [62,65,66].

Polyol pathway activation also perturbs cellular redox homeostasis. Aldose reductase activity depletes NADPH, impairing glutathione regeneration, while sorbitol dehydrogenase increases the $NADH/NAD^+$ ratio, shifting redox balance and worsening mitochondrial dysfunction [64,65]. Furthermore, excessive glucose flux depletes myo-inositol, reducing phosphoinositide synthesis and impairing Na^+/K^+-ATPase activity—disturbances that alter membrane potentials, slow nerve conduction, and increase excitability risk. Classical studies demonstrated that aldose-reductase inhibition or myo-inositol supplementation restored Na^+/K^+-ATPase activity and conduction velocity [67–70]. In experimental models, heightened aldose-reductase activity correlates with early axonal swelling, segmental demyelination, and fiber loss, particularly in long peripheral nerves with high metabolic demand [66]. Aldose-reductase inhibitors such as epalrestat and ranirestat have shown partial clinical efficacy, especially when initiated early in the disease [71–73].

Collectively, these data position the polyol pathway as a pivotal mediator of glucose-induced neurotoxicity in diabetes. Its overactivation integrates osmotic imbalance, cofactor depletion, redox

shifts, and ion-transport dysfunction into a unified pathogenic cascade, making it an enduring target for therapeutic intervention to prevent or slow the progression of DPN [62,64,74].

3.1.2. AGE–RAGE Signaling

Advanced glycation end-products (AGEs) are chemically stable adducts formed via the Maillard reaction—non-enzymatic glycation and oxidation of proteins, lipids, and nucleic acids—accelerated by chronic hyperglycemia and oxidative stress. Long-lived structural proteins, such as collagen and laminin in neural basement membranes and myelin-associated proteins, are preferential substrates, making neural and vascular tissues major depots of AGE accumulation [75–77].

AGEs profoundly alter tissue mechanics through covalent cross-linking, which stiffens extracellular matrices, thickens basal laminae, narrows capillary lumens, and reduces elasticity. In the peripheral nervous system (PNS), these changes disrupt the endoneurial microenvironment required for axonal conduction and regeneration, while glycation of myelin components compromises Schwann cell support and myelin stability, accelerating demyelination and axonal loss [76,77]. AGE-modified laminin and fibronectin impair neurite outgrowth in vitro, mechanistically linking matrix glycation to axonal failure [76] . The receptor for AGEs (RAGE) amplifies this injury. Expressed on neurons, Schwann cells, glia, and endothelium, RAGE is upregulated in diabetic peripheral nerves and dorsal root ganglia. AGE–RAGE engagement activates NF-κB, inducing TNF-α, IL-1β, and IL-6, and triggers MAPK signaling (ERK1/2, JNK, p38), establishing a self-reinforcing inflammatory loop [78–80]. Parallel activation of NADPH oxidase and mitochondrial ROS production promotes lipid peroxidation, DNA damage, and mitochondrial dysfunction [79,81,82].

Diabetic vasculopathy intersects with these pathways. AGE–RAGE signaling reduces nitric oxide bioavailability, upregulates endothelial adhesion molecules (ICAM-1, VCAM-1), and increases permeability, compromising both the blood–nerve barrier (BNB) and blood–brain barrier (BBB) [83,84]. In brain microvascular endothelium and pericytes, AGEs downregulate tight junction proteins (claudin-5, occludin) via VEGF/MMP-2 and TGF-β autocrine signaling, while inducing basement membrane hypertrophy—changes that mirror BBB leakage in diabetic models [85,86]. At the BNB, similar processes promote endoneurial ischemia and hypoxia [85]. In the CNS, endothelial RAGE also facilitates amyloid-β transport across the BBB, linking diabetes to Alzheimer's disease pathology [87].

Preclinical studies confirm causality: RAGE deletion or antagonism attenuates neural inflammation, preserves myelinated fiber density, improves conduction velocity, and enhances axonal regeneration in diabetic models [85,88]. At the organelle level, blocking AGE–RAGE signaling reduces ROS and protects mitochondrial function [81]. Clinically, circulating and tissue AGE levels correlate with neuropathy severity, while skin autofluorescence, a non-invasive marker of AGE burden, associates with large- and small-fiber deficits in type 2 diabetes. Higher AGE load correlates with slower conduction velocity, and longitudinal data link elevated AGE levels to faster cognitive decline, bridging glycation to both peripheral and central neurodegeneration [89–91].

Collectively, AGE–RAGE signaling represents a convergence point for hyperglycemia, oxidative stress, and inflammation in diabetic neurodegeneration. By remodeling extracellular matrices, driving glial and neuronal stress responses, and compromising neurovascular barriers, this pathway fuels both PNS injury and CNS pathology. Therapies targeting AGE formation, RAGE activation, or cross-link cleavage offer rational, mechanism-based strategies to modify disease trajectory [79,92].

3.1.3. Hexosamine Biosynthetic Pathway (HBP)

The hexosamine biosynthetic pathway (HBP) is a minor branch of glycolysis that exerts outsized regulatory influence. Under physiological conditions, only ~2–5% of intracellular glucose enters this pathway to generate UDP-N-acetylglucosamine (UDP-GlcNAc)—the donor substrate for O-GlcNAcylation, a dynamic post-translational modification of nuclear and cytosolic proteins [93,94]. In diabetes, excess glucose flux elevates UDP-GlcNAc levels, driving widespread hyper-O-GlcNAcylation and altering transcriptional, signaling, and metabolic programs [95].

O-GlcNAcylation modifies transcription factors such as Sp1 and NF-κB, enhancing DNA binding and promoting pro-inflammatory gene expression [96,97]. In neurons and glia, O-GlcNAcylation of insulin signaling intermediates—including IRS-1 and Akt—impairs phosphorylation dynamics, thereby attenuating downstream signaling [95]. Within the hippocampus, a key locus for memory processing, O-GlcNAcylation regulates vesicle trafficking, dendritic spine structure, and AMPA receptor function, with consequences for synaptic plasticity and cognitive performance [98,99]. Beyond transcriptional and synaptic effects, hyper-O-GlcNAcylation impacts mitochondrial function. Modification of electron transport chain subunits reduces ATP production and disrupts mitochondrial biogenesis, fission–fusion dynamics, and mitophagy, collectively impairing energy supply to long axons and compromising neuronal resilience [95,100]. Importantly, experimental modulation of O-GlcNAc cycling can reverse these deficits. Genetic or pharmacological manipulation of O-GlcNAc transferase (OGT) and O-GlcNAcase (OGA) alters hippocampal long-term potentiation (LTP) and memory in rodents [98,99]. In diabetic mice, preventing hyper-O-GlcNAcylation of the circadian regulator Bmal1 restores dendritic architecture and rescues cognitive function [101].

Thus, in the diabetic nervous system, the HBP functions as a nutrient sensor turned pathogenic effector, linking nutrient excess to impaired insulin signaling, mitochondrial dysfunction, disrupted neuroplasticity, and chronic inflammation. Targeting dysregulated O-GlcNAcylation represents a promising therapeutic avenue to restore neuronal function and cognitive health [93,95].

3.1.4. Protein Kinase C (PKC) Activation

Protein kinase C (PKC) is a family of serine/threonine kinases—conventional (α, βI, βII, γ) and novel (δ, ε, η, θ)—that regulate vascular tone, permeability, extracellular matrix turnover, and gene transcription. In diabetes, chronic hyperglycemia increases diacylglycerol (DAG) levels, persistently activating PKC isoforms and coupling metabolic stress to vascular and neural injury [102–104].

Within the vasa nervorum, PKC activation suppresses endothelial nitric oxide synthase (eNOS), reducing nitric oxide bioavailability and impairing vasodilation, while upregulating endothelin-1, a potent vasoconstrictor. The resulting ischemia diminishes endoneurial perfusion and oxygen delivery [105–107]. In parallel, PKC-driven induction of VEGF and other permeability mediators disrupts blood–nerve and blood–brain barrier integrity, facilitating plasma protein leakage, immune cell infiltration, neural edema, and glial activation [108–113]. PKC signaling also orchestrates pro-inflammatory transcriptional programs, activating NF-κB and AP-1 to upregulate TNF-α, IL-6, chemokines, and endothelial adhesion molecules [114–117]. This inflammatory milieu compounds axonal stress. Moreover, PKC impairs neurotrophic signaling—including NGF and BDNF pathways—and disrupts retrograde axonal transport, compromising neuronal survival and Schwann cell function [118–121]. Among PKC isoforms, PKCβ is most extensively implicated in diabetic microvascular complications. Pharmacological inhibition improves endothelial and neurovascular function in experimental models and early clinical studies. However, large randomized trials in diabetic neuropathy—such as those with ruboxistaurin—demonstrated safety and some subgroup benefit but failed to achieve consistent primary endpoint success [122–125]. PKC does not act in isolation. It intersects with the polyol pathway, AGE–RAGE axis, and hexosamine biosynthetic pathway, synergistically amplifying inflammation, oxidative stress, and mitochondrial dysfunction. Together, these interactions drive progressive injury to neurons, Schwann cells, endothelial cells, and glia, transitioning the neurovascular unit from metabolic imbalance to structural breakdown [102,126].

In summary, PKC hyperactivation is a central mediator of vascular dysfunction, inflammation, and neurovascular injury in diabetic neuropathy—and likely in diabetes-associated cognitive decline. While single-target PKC inhibition has yielded mixed results, multi-targeted therapeutic strategies addressing PKC alongside other pathogenic pathways remain a compelling avenue for disease modification [102–104].
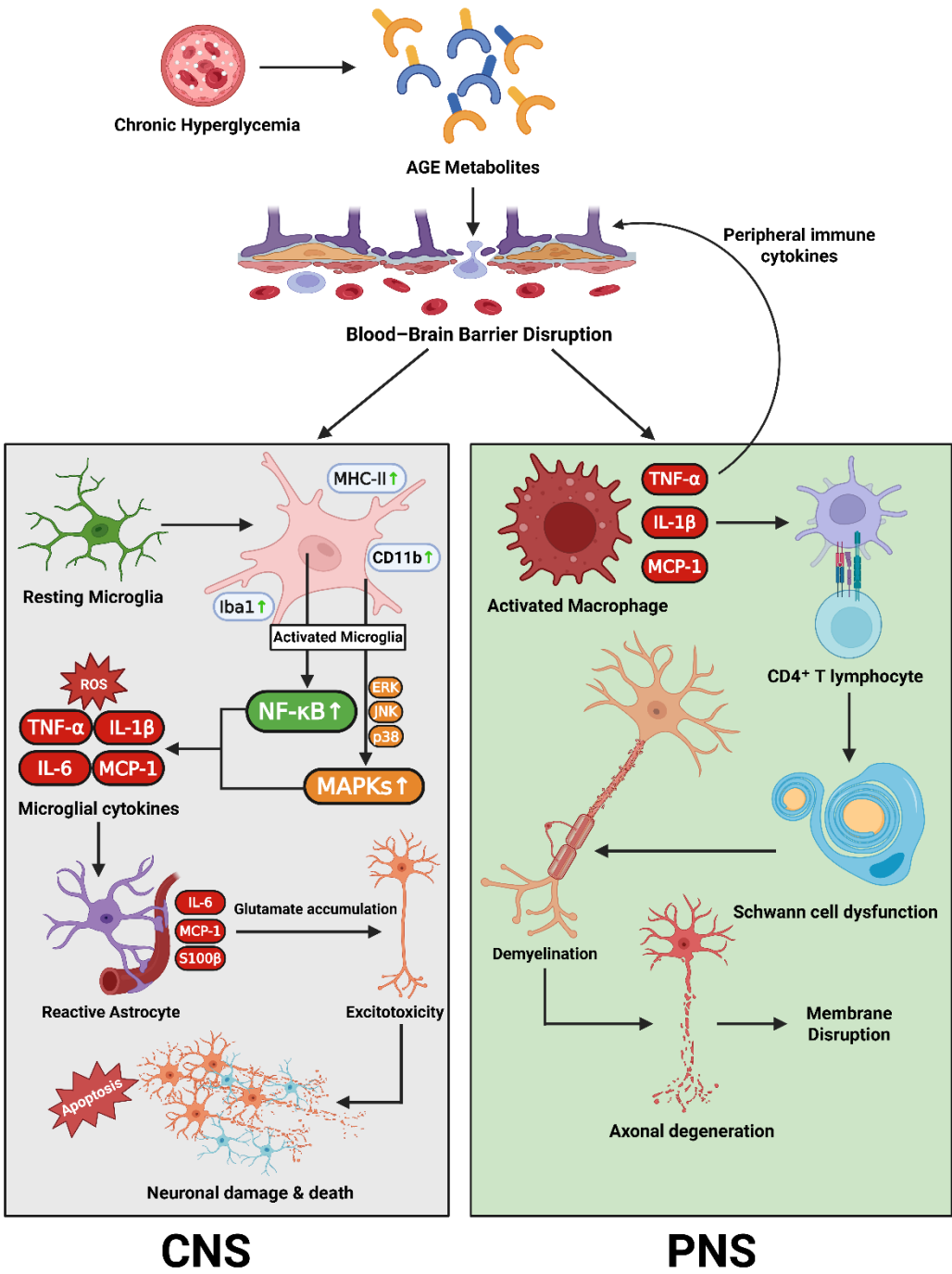
Figure 1. Chronic hyperglycemia-driven neuroinflammation and neurodegeneration in the CNS and PNS. Chronic hyperglycemia induces advanced glycation end-products (AGEs), disrupting the blood–brain barrier (BBB) and enabling peripheral cytokine infiltration. In the CNS, oxidative stress and AGEs activate microglia (↑MHC-II, CD11b, Iba1) via NF-κB and MAPK signaling, triggering TNF-α, IL-1β, IL-6, and MCP-1 release. These cytokines stimulate reactive astrocytes to produce IL-6, MCP-1, and S100B, causing glutamate accumulation, excitotoxicity, and neuronal apoptosis. In the PNS, activated macrophages release TNF-α, IL-1β, and MCP-1, recruiting CD4^{+} T lymphocytes, which impair Schwann cells, induce demyelination, and promote axonal degeneration. Together, these processes mediate diabetes-associated neuroinflammation, demyelination, and neuronal loss.

3.2. Mitochondrial Dysfunction and Oxidative Stress

Mitochondria serve as the primary energy-generating organelles in neurons and glial cells, supplying ATP through oxidative phosphorylation and regulating calcium homeostasis, redox balance, and apoptosis [127,128]. Neurons are especially dependent on proper mitochondrial function due to their high metabolic demand and long axons, which require energy-intensive maintenance and repair [128]. In diabetes, chronic hyperglycemia and lipid overload lead to mitochondrial perturbations that initiate and sustain oxidative stress, bioenergetic failure, and ultimately, neurodegeneration [129].

3.2.1. Reactive Oxygen Species (ROS) Generation in Neurons and Glia

Hyperglycemia-driven mitochondrial dysfunction is a central initiating event in diabetic neurodegeneration. Excess glucose flux increases electron transport chain (ETC) activity, hyperpolarizing the mitochondrial membrane and promoting electron leakage from complexes I and III, generating superoxide anion ($O_2^-\cdot$). Manganese superoxide dismutase (MnSOD) rapidly converts superoxide to hydrogen peroxide (H_2O_2), which, in the presence of iron, undergoes Fenton chemistry to yield hydroxyl radicals. This reactive oxygen species (ROS) cascade damages lipids, proteins, and DNA—marked by 8-oxo-deoxyguanosine (8-oxo-dG)—and activates NF-κB and MAPK signaling, as well as NLRP3 inflammasome assembly in microglia and astrocytes, triggering release of IL-1β, IL-6, and TNF-α [130–134]. In axons, ROS destabilizes microtubules and impairs motor proteins, stalling organelle transport; in Schwann cells, oxidative injury disrupts myelin maintenance and neurotrophic support. Endogenous antioxidant defenses—glutathione (GSH), SOD, and catalase—are overwhelmed, perpetuating oxidative injury.

Chronic oxidative stress also impairs mitochondrial biogenesis, which PGC-1α orchestrates in cooperation with NRF1/NRF2 to induce TFAM and mitochondrial DNA transcription [135,136]. Pro-inflammatory cytokines and reduced AMPK activity suppress this program, decreasing mitochondrial content and ATP supply at energy-demanding sites such as synaptic terminals and distal axons [137,138]. Mitochondrial dynamics shift toward fission (DRP1) at the expense of fusion (MFN1/2, OPA1), producing fragmented, bioenergetically compromised organelles with diminished oxidative phosphorylation (OXPHOS) capacity, impaired calcium buffering, and heightened ROS output [138–142]. Mitophagy, the PINK1/Parkin-dependent clearance of damaged mitochondria, is likewise impaired in diabetes. Reduced PINK1/Parkin signaling, lysosomal dysfunction secondary to AGE and lipid toxicity, and defective autophagic flux allow dysfunctional mitochondria to persist, amplifying ROS production and precipitating apoptosis or necroptosis. Restoration of the FoxO3a–PINK1–Parkin axis in experimental painful diabetic neuropathy (PDN) improves mitophagy, reduces allodynia, and attenuates inflammasome activation; conversely, mitophagy failure exacerbates neuroinflammation [143–145]. Mitochondrial ROS is not only a direct effector of injury but also a master upstream trigger for multiple hyperglycemia-induced pathways, including the hexosamine biosynthetic pathway, PKC activation, and the AGE–RAGE axis, as well as inflammatory circuits that impair axonal transport and Schwann cell homeostasis [130,131].

Therapeutic targeting of mitochondrial dysfunction shows translational promise. AMPK activators (e.g., metformin) and interventions that upregulate PGC-1α can restore mitochondrial biogenesis and attenuate ROS production. Modulation of mitochondrial dynamics—such as DRP1 inhibition with mdivi-1—rescues fragmentation and improves neurovascular outcomes in diabetic models, though potential adverse effects from over-suppressed fission (including hippocampal dysfunction) necessitate caution. Redox-active agents such as melatonin and SIRT3 activators suppress excessive fission and restore FoxO3a–PINK1–Parkin-mediated mitophagy, alleviating neuropathic hypersensitivity in preclinical models [139,142,143,146].

### 3.2.2. Antioxidant Depletion and Redox Imbalance

Neurons and glia maintain high metabolic rates and rely on a robust antioxidant defense network to balance reactive oxygen species (ROS)—inevitable byproducts of mitochondrial respiration and cellular metabolism [147]. Key enzymatic systems include glutathione (GSH) and its partner glutathione peroxidase (GPx), superoxide dismutases (SODs), catalase, peroxiredoxins, and the thioredoxin (Trx) system, which sequentially detoxify superoxide ($O_2^-\cdot$) to hydrogen peroxide (H_2O_2) and then to water, thereby preserving DNA, protein, and lipid integrity [148,149].

In diabetes, this protective network is compromised at multiple levels. Hyperglycemia diverts glucose into the polyol pathway, where aldose reductase consumes NADPH, and concurrently activates NADPH oxidases (NOX2/NOX4), which also deplete NADPH while producing superoxide. NADPH scarcity limits regeneration of reduced GSH and Trx, increases oxidized glutathione (GSSG), and shifts the intracellular redox state toward pro-oxidative stress [62,65,150–154].

The master transcriptional regulator Nrf2, which normally translocates to the nucleus under stress to induce antioxidant genes such as SOD2, GPx, HO-1, and NQO1, is suppressed by chronic hyperglycemia and inflammation. This blunted activation limits inducible antioxidant capacity precisely when cytoprotective reinforcement is required [155–157]. Additionally, antioxidant enzymes themselves are susceptible to non-enzymatic glycation and dicarbonyl (e.g., methylglyoxal) modification, impairing their catalytic function and, in some cases, antigenicity—changes documented in tissues vulnerable to diabetic complications, including retinal microvasculature [158–161]. Within mitochondria, oxidative stress damages mtDNA, disrupts electron transport chain assembly, and promotes opening of the mitochondrial permeability transition pore (mPTP). The resulting loss of membrane potential ($\Delta\psi$m), swelling, and cytochrome c release initiate caspase-dependent apoptosis in neurons and glia, affecting both the peripheral and central nervous systems [162–165].

This progressive depletion of antioxidant reserves marks a transition from reversible metabolic dysfunction to entrenched neurodegeneration. Experimental interventions that restore redox balance—such as α-lipoic acid (ALA), coenzyme Q10 (CoQ10), N-acetylcysteine (NAC), or mitochondria-targeted antioxidants (e.g., mitoTEMPO)—reduce ROS, preserve mitochondrial integrity, and improve nerve conduction in preclinical models [166–171]. Clinical trials report symptomatic and conduction improvements, though effects are generally modest, variable, and short-lived, often limited by study design.

Therapeutic strategies that preserve NADPH (e.g., limiting polyol pathway flux) and reactivate Nrf2-driven transcription offer compelling adjunctive approaches to protect neuronal and glial redox homeostasis in diabetes [156,172].
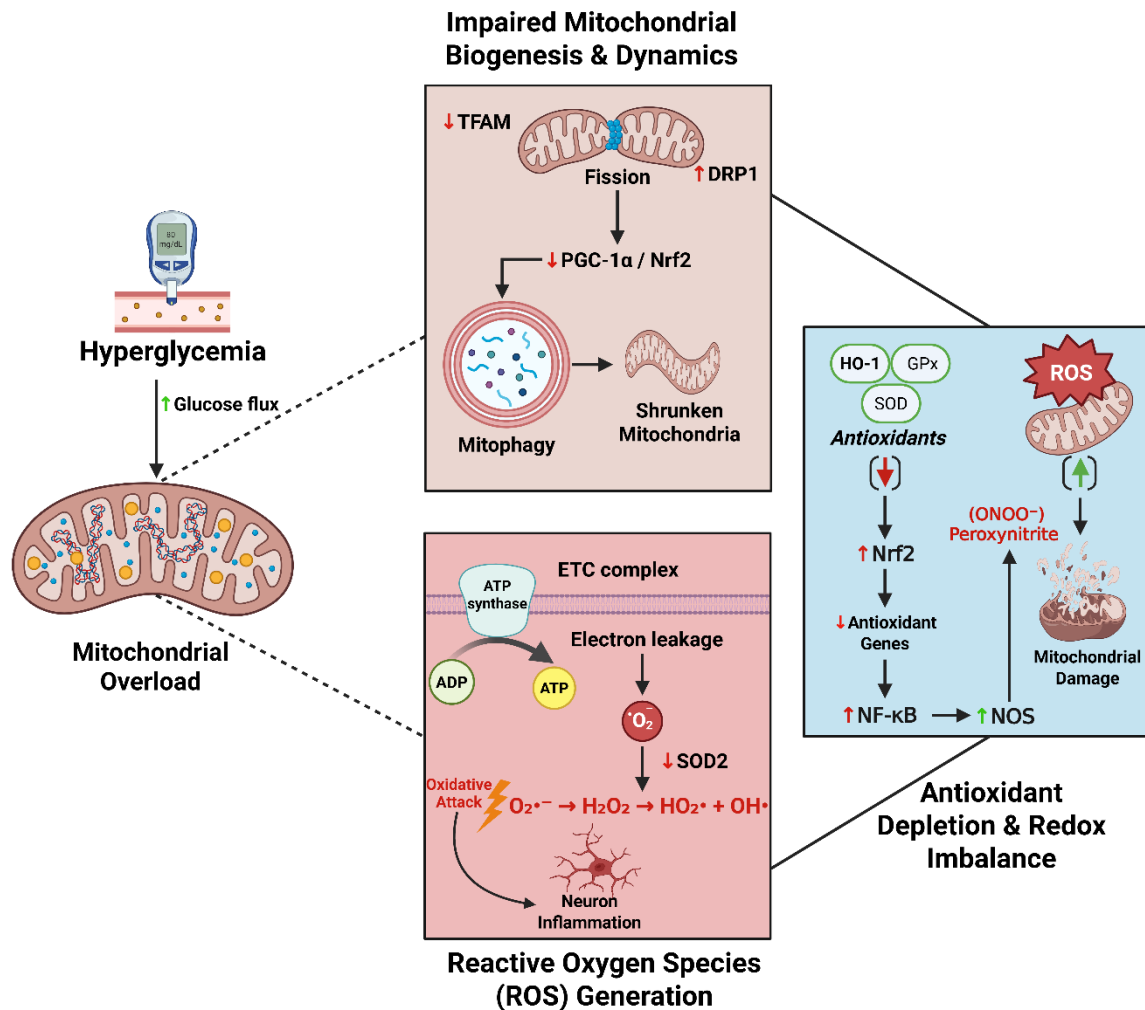
Figure 2. Hyperglycemia-driven mitochondrial overload, oxidative stress, and redox failure. Chronic hyperglycemia increases glucose flux into mitochondria (left), over-reducing the electron transport chain (ETC). The heightened reducing pressure promotes electron leak to O_2 (bottom), generating superoxide ($O_2\bullet-$), which is converted to H_2O_2 and $\bullet OH$; diminished SOD2 activity limits detoxification, amplifying oxidative damage and provoking neuronal inflammation. In parallel, mitochondrial quality control is impaired (top): ↓ TFAM and ↓ PGC-1α/Nrf2 suppress biogenesis; ↑ DRP1-mediated fission with mitophagy yields a fragmented, shrunken mitochondrial pool with reduced capacity. Antioxidant defenses are concurrently depleted (right): ↓ Nrf2-dependent genes (HO-1, SOD, GPx) weaken redox buffering, while ↑ NF-κB and ↑ NOS favor peroxynitrite (ONOO–) formation, further escalating ROS and mitochondrial injury. Together, these processes form a self-reinforcing cycle of oxidative stress, mitochondrial dysfunction, and inflammation.

3.3. Neuroinflammation and Immune Dysregulation

Neuroinflammation is a key amplifier of neural injury in diabetes, linking metabolic stress to progressive degeneration in both the central (CNS) and peripheral nervous system (PNS). Chronic hyperglycemia and oxidative stress activate microglia, the brain's resident immune sentinels, via pattern-recognition receptors including TLR4 and the receptor for advanced glycation end-products (RAGE). Activated microglia adopt amoeboid morphology, express CD11b, Iba1, and MHC-II, and initiate NF-κB and MAPK signaling, producing pro-inflammatory cytokines TNF-α, IL-1β, and IL-6. These mediators impair synaptic plasticity, suppress neurogenesis, and weaken the blood–brain barrier (BBB), facilitating peripheral immune cell entry [173,174].

Astrocytes, which normally regulate ion balance, clear glutamate, and support the BBB, undergo reactive gliosis marked by elevated GFAP. In diabetes, impaired glucose handling and reduced GLT-1 expression in hippocampal astrocytes compromise glutamate clearance, increasing excitotoxic risk

and potentially contributing to cognitive decline. Insulin treatment can partially restore astrocytic function in experimental models [175–177].

In the PNS, disruption of the blood–nerve barrier (BNB) parallels CNS barrier breakdown. Diabetes reduces expression of the tight-junction protein claudin-1 in the perineurium, depletes vessel-associated macrophages, and increases permeability to small solutes—changes that sustain neuropathic pain [111,174]. Injured axons, Schwann cells, and endoneurial endothelial cells release monocyte chemoattractant protein-1 (MCP-1/CCL2), recruiting monocytes that differentiate into M1-polarized macrophages. These macrophages produce nitric oxide, ROS, TNF-α, and IL-1β, release matrix metalloproteinases, degrade myelin, and inhibit Schwann cell-mediated repair [111,178,179].

T-cell infiltration further shapes the inflammatory milieu. In human and experimental diabetic neuropathy, CD4$^+$ T cells show activation markers CD69 and CD25, with a Th1 bias marked by interferon-γ production. Regulatory T cells (Tregs) are numerically and functionally reduced in diabetes, tilting immune balance toward sustained inflammation [180,181].

Three cytokines dominate the effector landscape. TNF-α sensitizes nociceptors and promotes neuronal apoptosis via TNFR1; inhibition of TNF signaling improves conduction velocity and reduces pain in diabetic neuropathy models [182,183]. IL-1β, generated via inflammasomes such as NLRP3, disrupts barrier integrity and induces pyroptosis, exacerbating neuroinflammation and axonal injury [184,185]. IL-6, although pleiotropic, can impair neuronal and glial insulin signaling via SOCS3 induction, thereby disrupting energy metabolism and neurotrophic support [186,187]. Sustained activation of microglia, astrocytes, macrophages, and T cells creates a self-reinforcing inflammatory loop that inhibits neurogenesis, remyelination, and axonal regeneration—mirroring the systemic low-grade inflammation of diabetes.

Therapeutic approaches targeting this axis are under active investigation. Anti-cytokine strategies (e.g., TNF-α blockade) show structural and functional benefit in models of diabetic neuropathy [183]. Minocycline, a microglial inhibitor, reduces spinal microglial activation and alleviates pain behaviors in streptozotocin-diabetic rats [188]. Restoration of Treg function using low-dose IL-2 has been proposed to rebalance immunity without promoting effector T-cell activation [189].

In summary, while hyperglycemia and oxidative stress initiate neural injury, it is chronic, dysregulated immune activation—driven by CNS glia, PNS macrophages, T cells, and the cytokines TNF-α, IL-1β, and IL-6—that sustains and amplifies neurodegeneration in diabetes. Strategies that restore barrier integrity, resolve glial overactivation, and re-establish immune regulation offer promising routes toward disease modification [111,173,174,190].

3.4. Vascular and Endothelial Dysfunction

Neural integrity depends on its microvascular networks—the **vasa nervorum** in the periphery and the brain's capillary beds—delivering oxygen and glucose while clearing metabolic waste. In diabetes, these microvessels undergo structural and functional injury that precedes and accelerates both **diabetic peripheral neuropathy (DPN)** and **diabetes-associated cognitive decline** [191].

Peripheral microangiopathy is well documented in human sural nerve biopsies and experimental models, characterized by **basement membrane thickening**, **luminal narrowing**, **endothelial hyperplasia**, and perivascular support cell abnormalities [192–194]. These changes restrict blood flow and cause **endoneurial hypoxia**—confirmed by direct oxygen-tension measurements in diabetic nerves and by hypoxia markers such as **HIF-1α** induction [195–198]. Hypoxic axons exhibit impaired mitochondrial respiration and reduced ATP supply, compromising long, metabolically demanding fibers before overt axonal loss occurs.

Endothelial nitric oxide (NO) bioavailability is diminished in diabetes due to decreased **eNOS** expression and activation, accumulation of **asymmetric dimethylarginine (ADMA)**, and **eNOS uncoupling**, which shifts the enzyme toward superoxide generation [199,200]. In peripheral nerve microvessels, this results in blunted arteriolar vasodilation and reduced perfusion; in the

hippocampus, reduced NO impairs neurovascular coupling and contributes to early cognitive deficits [201–203].

In the CNS, **blood–brain barrier (BBB)** integrity is compromised. Diabetes downregulates **tight-junction proteins** (occludin, claudin-5, ZO-1) and increases barrier permeability, initially detected in hippocampal and cortical microvessels in diabetic rodents and confirmed in humans using dynamic contrast–enhanced MRI [9,204,205]. BBB breakdown allows entry of circulating cytokines, immune cells, and metabolites, propagating central inflammation and correlating with cognitive impairment [206].

Systemic endothelial activation further fuels neurovascular injury. High glucose increases endothelial expression of **ICAM-1**, **VCAM-1**, and selectins, promoting leukocyte adhesion, transendothelial migration, and impaired vascular repair—observed both in vitro and in people with type 2 diabetes [207,208]

Angiogenic imbalance is another hallmark. **VEGF** is often reduced in neuropathic target tissues, and exogenous VEGF delivery in experimental diabetes restores vasa nervorum density and improves nerve function [209,210]. Conversely, destabilizing signals such as **angiopoietin-2** and **thrombospondins** are elevated in diabetic microangiopathy, favoring capillary regression and rarefaction [211].

In summary, vascular injury precedes neural degeneration. **Vasa-nervorum ischemia** and **BBB disruption** set the stage for metabolic and inflammatory damage; **NO loss** impairs perfusion and neurovascular coupling; endothelial activation and skewed angiogenic signaling perpetuate a microenvironment hostile to axons and glia. These vascular pathologies are therefore not mere accomplices but **early, actionable targets** for interventions aimed at preventing or reversing DPN and diabetes-related cognitive decline [191].

3.5. Insulin Resistance and Metabolic Inflexibility in the Nervous System

Insulin signaling is essential for neural metabolism, synaptic function, and structural integrity. Neurons and glia express insulin receptors, and ligand binding activates the canonical IRS–PI3K–Akt cascade, promoting glucose uptake, inhibiting GSK3β, regulating mTOR activity, and supporting both synaptic plasticity and mitochondrial function [212,213]. In diabetes, chronic hyperinsulinemia and hyperglycemia induce brain and peripheral nerve insulin resistance, impairing metabolic flexibility—the ability to switch between fuel substrates in response to demand [212,214].

In the healthy CNS, insulin facilitates translocation of glucose transporters, activates pro-survival pathways, and enhances plasticity. Astrocytes adjust glycolysis and lactate shuttling to match neuronal needs, while oligodendrocytes, under the insulin/IGF axis, maintain myelin and lipid metabolism [215–218]. In diabetes, inflammatory cytokines TNF-α and IL-6 activate JNK and IKK, inducing serine phosphorylation of IRS-1, which blocks PI3K recruitment and diminishes Akt activity. Reduced Akt allows GSK3β hyperactivation, a tau kinase implicated in Alzheimer's disease–like pathology and neuronal loss [219–222]. Glucose transport is further compromised. Neuronal GLUT3—normally insulin-independent but responsive to stress—and astrocytic/BBB GLUT1 both decline in experimental diabetes, limiting glucose entry into neural tissue and producing cellular energy deficit despite systemic hyperglycemia [223,224]. Energy scarcity at axon terminals impairs vesicle cycling, ion pump activity, and axonal transport, slowing conduction and weakening synaptic transmission [225,226].

Dyslipidemia compounds these deficits. Insulin-resistant adipose tissue releases excess fatty acids that enter the CNS and PNS. Under mitochondrial stress, incomplete β-oxidation yields diacylglycerols (DAGs) and ceramides, bioactive lipids that activate PKC isoforms or PP2A, further suppressing Akt signaling, increasing ROS generation, promoting mitochondrial outer membrane permeabilization, and triggering caspase-dependent apoptosis [227–229]. Sphingolipid dysregulation, particularly ceramide accumulation, associates with neuropathic pain, myelin instability, and cognitive decline, linking insulin resistance to oxidative stress and inflammatory activation [230]. Therapeutic approaches to restore insulin sensitivity and metabolic flexibility show

emerging potential. Intranasal insulin and GLP-1 receptor agonists have demonstrated preliminary benefits for cognition and neural metabolism, although results are mixed and mechanisms remain multifactorial [231–235]. Strategies to preserve GLUT1/GLUT3 expression at the BBB and in astrocytes, and to limit DAG/ceramide synthesis or block PP2A/PKC-mediated Akt inhibition, are rational targets [223].

In summary, insulin resistance and metabolic inflexibility represent a central node linking synaptic dysfunction, axonal transport failure, and lipid-mediated injury in the diabetic nervous system. Preserving insulin signaling, maintaining glucose transporter function, and mitigating sphingolipid-driven Akt suppression may collectively protect neuronal and glial viability.
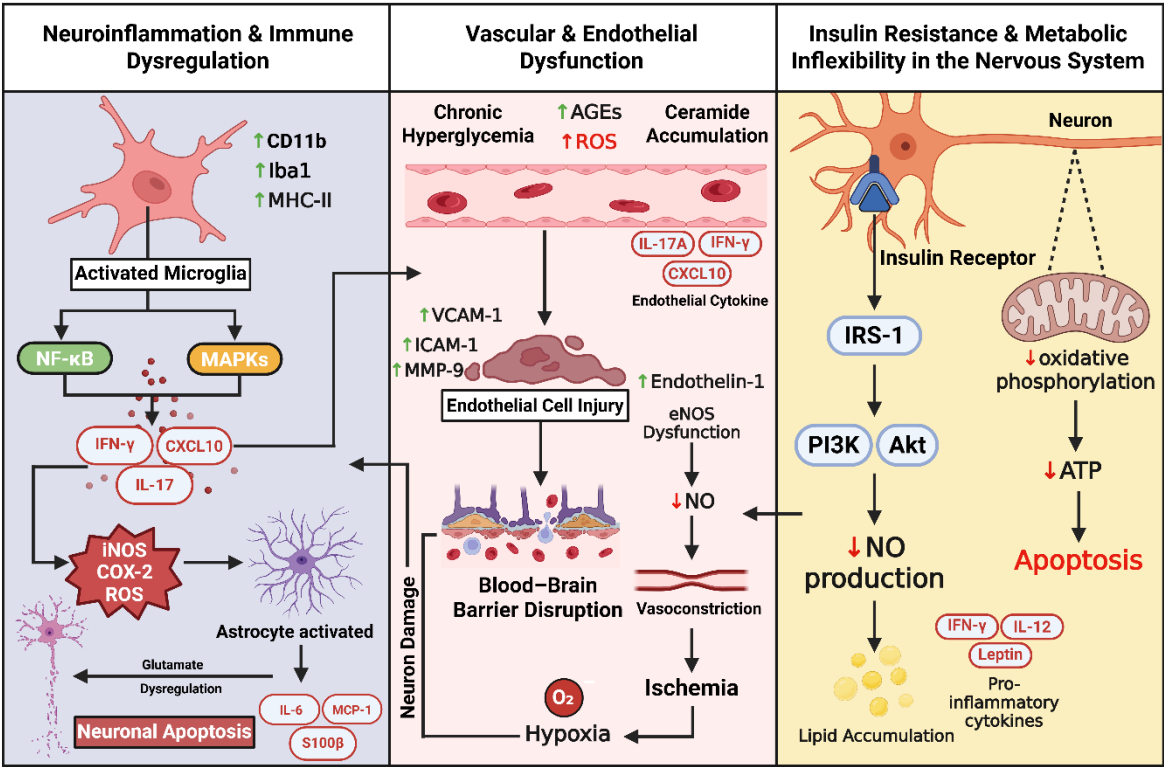
Figure 3. Hyperglycemia-induced neuroinflammation, vascular injury, and insulin resistance in the nervous system. Chronic hyperglycemia activates microglia (↑CD11b, ↑Iba1, ↑MHC-II), triggering NF-κB/MAPK signaling, release of IFN-γ, CXCL10, IL-17, and upregulation of iNOS, COX-2, and ROS. Astrocyte activation disrupts glutamate balance and releases IL-6, MCP-1, and S100β, driving excitotoxic neuronal apoptosis. Concurrently, AGEs, ROS, and ceramides increase VCAM-1, ICAM-1, and MMP-9, leading to endothelial injury, cytokine release (IL-17A, IFN-γ, CXCL10), upregulation of Endothelin-1, and eNOS dysfunction. Reduced NO promotes vasoconstriction, ischemia, and blood–brain barrier disruption, enabling inflammatory infiltration, hypoxia, and further neuron damage. In parallel, impaired IRS-1–PI3K–Akt signaling results in lower NO production, increased lipid accumulation, and the production of pro-inflammatory cytokines (IFN-γ, IL-12, and leptin), as well as reduced mitochondrial oxidative phosphorylation, leading to decreased ATP and neuronal apoptosis. Together, these mechanisms create a reinforcing cycle of oxidative stress, vascular dysfunction, inflammation, and neurodegeneration in diabetes.

3.6. The Gut–Brain Axis in Diabetes-Induced Neuropathy

The gut–brain–nerve axis is increasingly recognized as a modulator of diabetic neurodegeneration, with intestinal dysbiosis serving as an upstream driver of metabolic and neural injury. In diabetes, SCFA-producing taxa such as Faecalibacterium and Roseburia decline, while pro-inflammatory species including Ruminococcus gnavus and Bacteroides vulgatus expand [8,236–238]. Reduced butyrate availability compromises epithelial tight junctions, increases intestinal

permeability, and promotes metabolic endotoxemia, wherein lipopolysaccharide (LPS) activates TLR4 signaling to induce inflammatory cytokine cascades that propagate through neural and glial compartments [239].

SCFAs have direct neuroimmune significance. Microglia require SCFA signals for maturation and homeostatic regulation; depletion shifts them toward pro-inflammatory phenotypes, increasing synaptic remodeling and inflammatory signaling. Replenishing SCFAs or stimulating their receptors (FFAR2/3) restores microglial homeostasis, while SCFA-driven enteroendocrine signaling enhances GLP-1 release, indirectly supporting neural metabolism [240,241]. Microbial tryptophan metabolites, particularly indole-3-propionic acid (IPA), act via the aryl hydrocarbon receptor (AhR) to suppress NF-κB–mediated inflammatory programs in astrocytes. Human studies link higher IPA levels to reduced type 2 diabetes risk, and in vitro work demonstrates that IPA reduces LPS-induced cytokine production in human astrocytes, implicating indole restoration as a potential anti-inflammatory strategy within the CNS [242–244].

Bile acids, reshaped by microbial metabolism, also contribute to neuroimmune modulation. Through TGR5 and FXR signaling in neurons and glia, they can suppress neuroinflammation and, in preclinical models, alleviate neuropathic pain behaviors—suggesting that altered bile acid composition in diabetes may have direct neurological consequences [245,246]. The vagus nerve provides a direct neural conduit linking gut and brain. In diabetes, reduced vagal tone—reflected in diminished heart rate variability—weakens the cholinergic anti-inflammatory reflex, allowing gut-derived immune activation to propagate unchecked. Restoration of vagal tone therefore holds potential as both a cardiovascular and neuroimmune intervention [237,247].

Causality is supported by interventional studies. In rodent models, fecal microbiota transplantation (FMT) from lean donors or direct butyrate supplementation improves gut barrier integrity, lowers systemic cytokines, and normalizes mechanical and thermal nociceptive thresholds. Early clinical evidence suggests that FMT may ameliorate painful DPN, while in metabolic diabetes models it rebalances microbial composition, metabolite profiles, and systemic inflammation [248,249].

In summary, diabetes-associated dysbiosis reduces SCFAs, compromises epithelial integrity, and promotes LPS–TLR4-mediated inflammation. SCFA depletion disrupts microglial regulation and GLP-1–mediated metabolic support; loss of indole signals impairs astrocytic immune control; altered bile acid signaling skews neuroimmune balance; and diminished vagal tone removes an essential anti-inflammatory checkpoint. These gut-derived mechanisms are modifiable—microbiota restoration, targeted metabolite supplementation, and neural–microbial signaling enhancement represent promising strategies to prevent or mitigate diabetic neuropathy and cognitive decline, complementing but distinct from mitochondrial, vascular, inflammatory, or insulin-resistance–focused interventions.
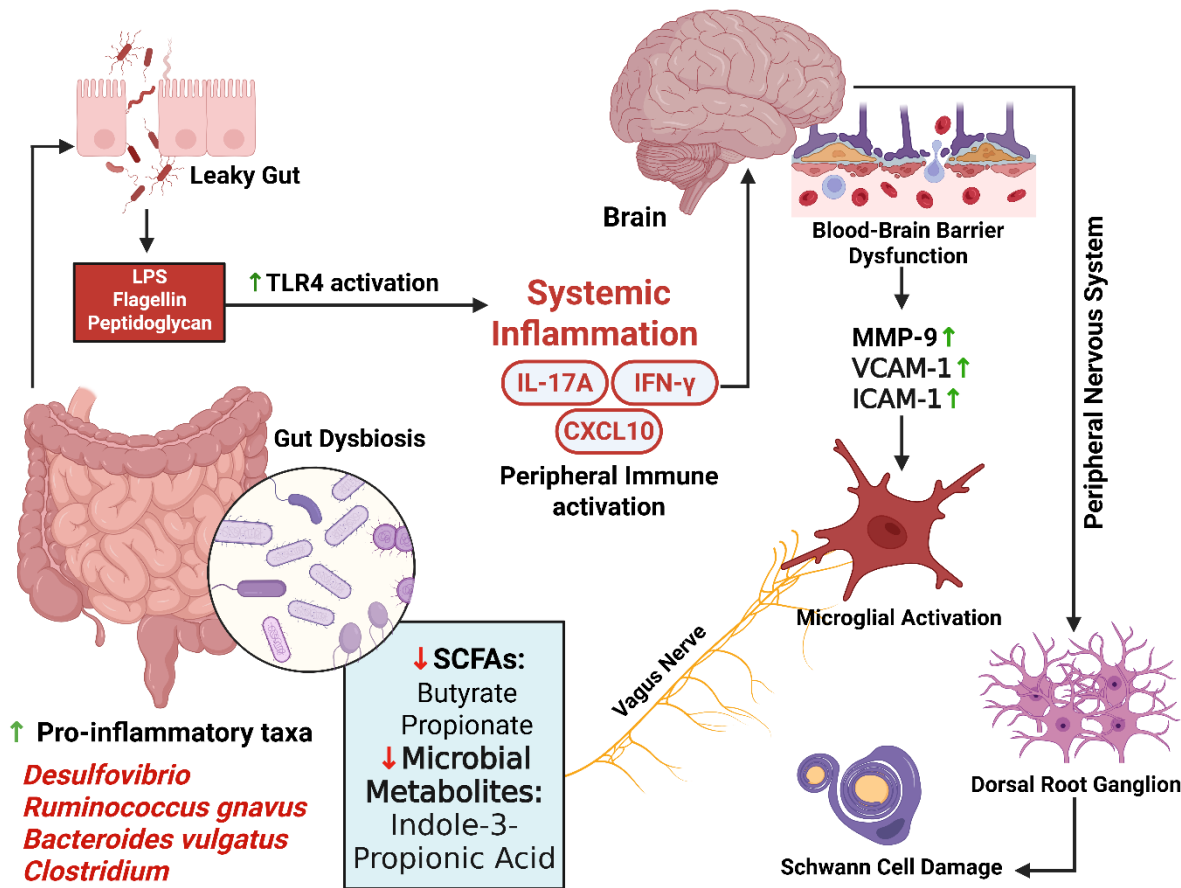
Figure 4. Gut dysbiosis–induced systemic inflammation and neuroimmune injury via the gut–brain axis. Pro-inflammatory gut taxa (Desulfovibrio, Ruminococcus gnavus, Bacteroides vulgatus, Clostridium) reduce beneficial SCFAs (butyrate, propionate) and neuroprotective metabolites (indole-3-propionic acid). Barrier disruption (leaky gut) allows bacterial components (LPS, flagellin, peptidoglycan) to activate TLR4, driving systemic inflammation with ↑IL-17A, IFN-γ, CXCL10. These mediators disrupt the blood–brain barrier (↑MMP-9, VCAM-1, ICAM-1), trigger microglial activation, and promote neuroinflammation. Parallel immune activation damages the peripheral nervous system, causing Schwann cell and dorsal root ganglion injury. The vagus nerve provides a bidirectional route for gut-derived signals to influence central and peripheral neuroimmune responses.

Linking Mechanisms to Clinical Phenotypes in Diabetic Neurodegeneration

Pathogenic Mechanism	Mechanism	Clinical Phenotypes	Key References
Polyol Pathway Overdrive	AR-mediated glucose-to-sorbitol conversion consuming NADPH, causing osmotic and redox stress (myo-inositol depletion; Na^+/K^+-ATPase impairment)	Length-dependent DPN; early small-fiber symptoms; slowed conduction	[64,65]
AGE–RAGE Axis	Tissue glycation, ECM stiffening, RAGE-mediated NF-κB/MAPK activation and oxidative stress	DPN (axonal/demyelination); painful DPN; cognitive decline	[250]

PKC Activation (via DAG)	Impaired eNOS/NO, elevated endothelin-1, VEGF-induced permeability	Ischemic DPN; microvascular dysfunction; autonomic neuropathy	[104]
Oxidative Stress & Mitochondrial Dysfunction	ETC superoxide generation; imbalance of mitochondrial fission/fusion; impaired biogenesis	Axonal transport impairment; PDN; cognitive slowing	[133]
Compromised Antioxidant Defenses	Nrf2 suppression, enzyme glycation (SOD, catalase, GPx), NADPH depletion	Accelerated DPN progression; CNS vulnerability	[155,251,252]
Neuroinflammation (Microglia/Astrocytes, Cytokines)	TLR4/RAGE induction; astrocytic GLT-1 downregulation; release of TNF-α, IL-1β, IL-6	Painful DPN; cognitive impairment; barrier dysfunction	[173]
Neurovascular Dysfunction (vasa nervorum & BBB)	Microangiopathy; reduced eNOS/mitigated NO; BBB tight-junction breakdown	DPN ischemia; cognitive decline	[191,204]
Insulin Resistance & Metabolic Inflexibility	IRS-1 Ser-phosphorylation; GLUT1/GLUT3 downregulation; lipotoxic DAG/ceramide accumulation	Cognitive decline; synaptic fatigue; DPN progression	[212]
Gut–Brain–Nerve Axis (Dysbiosis)	Loss of SCFA-producing species; LPS-TLR4 endotoxemia; impaired SCFA/indole/bile signaling; vagal dysfunction	PDN; cognitive symptoms; systemic inflammation	[236,242]
Small-Fiber Predominant Pathology	Early Aδ/C-fiber involvement; autonomic sudomotor fiber loss	Painful DPN; autonomic features	[18]
Large-Fiber Predominant Pathology	Axonal degeneration ± demyelination	Numbness, gait instability	[26]
CNS Cognitive/Affective Manifestations	BBB leak; insulin resistance; neuroinflammation	MCI; depression/anxiety	[54]
Autonomic Neuropathy (CAN & GI Dysmotility)	Autonomic fiber loss; impaired vagal signaling; enteric dysfunction	Orthostatic hypotension; gastroparesis	[253]

4. Knowledge Gaps and Future Directions

Diabetes-induced neurological disorders arise from a convergence of mechanistic insults that act in concert across the peripheral and central nervous systems. Hyperglycemia and oxidative stress initiate a cascade that activates microglia via AGE–RAGE and TLR4 signaling, triggering NF-κB and

MAPK pathways and releasing pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) that impair synaptic plasticity, weaken the blood–brain barrier, and promote neurodegeneration [173,174]. Astrocytic gliosis further disrupts glutamate clearance and barrier integrity, while in the periphery, blood–nerve barrier leakage and macrophage recruitment amplify demyelination and axonal injury [111,181].

Vascular pathology compounds this injury. Microangiopathy of the vasa nervorum, reduced nitric oxide bioavailability, and capillary rarefaction generate chronic endoneurial hypoxia, mirrored in the brain by impaired neurovascular coupling and BBB breakdown [191]. Concurrent insulin resistance within neurons and glia disrupts PI3K–Akt signaling, reduces GLUT1/GLUT3-mediated glucose transport, and drives lipid-mediated toxicity through diacylglycerol and ceramide accumulation [212,254].

The gut–brain–nerve axis adds another layer: dysbiosis diminishes the production of short-chain fatty acids, such as butyrate, weakening microglial maturation and anti-inflammatory tone, while reduced microbial indole metabolites destabilize astrocytic homeostasis [236,242]. Altered bile acid signaling through TGR5/FXR and diminished vagal tone further skew neuroimmune balance [237,245]. These interconnected systems form a multiorgan network of degeneration, where vascular, metabolic, immune, and microbial pathways amplify one another over time.

Yet critical knowledge gaps persist. Few longitudinal human studies track individuals from pre-symptomatic metabolic dysfunction to overt neuropathy or cognitive decline with integrated multimodal measures—combining neuroimaging, electrophysiology, omics profiling, and microbiome analysis [255,256]. Commonly used rodent models incompletely recapitulate the chronic, low-grade inflammation and gradual sensory-cognitive decline of human disease, underscoring the need for standardized phenotyping and humanized microbiota platforms [257–259].

Biomarker development is another frontier. Circulating neurofilament light (NfL) and GFAP show potential for early detection and monitoring, while corneal nerve fiber metrics offer a window into small-fiber pathology and regeneration [260,261]. These should be validated across ancestries and combined with cytokine, endothelial, and metabolic signatures for patient stratification. Mechanistic gaps also include the underexplored roles of epigenetic programming ("metabolic memory") and circadian disruption in neural vulnerability [262,263], as well as sex-specific differences in immune tone, pain processing, and mitochondrial function—factors too often ignored in study design [264].

Toward Precision-Based, Multi-Targeted Therapy

Addressing these gaps will require interdisciplinary convergence—linking endocrinology, neurology, immunology, microbiology, and systems biology. Precision medicine can integrate advanced biomarkers, neuroimaging, and microbiome profiling with metabolic, vascular, and neuroimmune interventions. Lifestyle-based strategies—structured exercise, dietary modulation, cognitive training—should be systematically combined with pharmacologic approaches, including GLP-1 receptor agonists, intranasal insulin, anti-inflammatory agents, and microbiota-modulating therapies.

The field must also invest in longitudinal, stratified cohorts that sample brain, nerve, blood, and gut over time; in preclinical models that reflect human chronicity and complexity; and in mechanistic mapping of inter-organ networks linking gut, liver, vasculature, and nervous tissue. Only by aligning these strands—metabolism and immunity, vasculature and mitochondria, gut and brain—can the goal shift from symptomatic control toward slowing, halting, or reversing the neurodegenerative trajectory in people living with diabetes.

Conflicts of Interest: The authors declare no conflict of interest.

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