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Neuroinflammation in diabetes: from pathophysiological mechanisms to therapeutic opportunities

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Abstract

Diabetes is increasingly recognized as a systemic metabolic disease with significant consequences beyond glycemic dysregulation, including a growing impact on brain structure and function. Among the mechanisms involved in this process, neuroinflammation has emerged as a central biological axis that links chronic metabolic stress with neuronal injury, cognitive decline, and broader nervous system dysfunction. Rather than representing an isolated consequence of hyperglycemia, diabetes-associated neuroinflammation reflects the convergence of blood–brain barrier disruption, glial activation, innate immune signaling, oxidative stress, mitochondrial dysfunction, and inflammasome activation. These interconnected processes reinforce each other and contribute to the transition from adaptive neuroimmune responses to chronic pathogenic inflammation. In this review, we synthesize current evidence on cellular and molecular mechanisms that connect diabetes with neuroinflammatory signaling, highlighting key pathophysiological processes and their therapeutic implications. We also analyze current and emerging therapeutic approaches, including conventional pharmacological agents and natural compounds with anti-inflammatory and neuroprotective potential. Taken together, the available evidence supports the view that diabetes-associated neuroinflammation is a multidimensional and therapeutically relevant process that should be studied further to provide opportunities in identifying new biomarkers related to the mechanistic stratification of the process, and designing new neuroprotective interventions, which could also contribute significantly to healthy aging.

Keywords: Diabetes mellitus, neuroinflammation, blood–brain barrier, microglia, oxidative stress

Introduction

Neuroinflammation is broadly defined as a highly regulated immunobiological response within the central and peripheral nervous systems, triggered by infection, injury, metabolic dysregulation, or other disturbances in tissue homeostasis and mediated by complex interactions among glial cells, resident immune components, and soluble inflammatory factors [1, 2]. While transient neuroinflammatory signaling is considered an adaptive and protective response, persistent or dysregulated responses are increasingly recognized as important contributors to neuronal dysfunction, structural damage, and the pathophysiology of various neurological and metabolic disorders.

Astrocytes and microglia are key cellular mediators of neuroinflammatory responses [3]. Microglia, the resident immune cells of the nervous system, constitute the first line of surveillance and respond rapidly to tissue damage, pathogens, and metabolic disturbances through changes in morphology, proliferation, phagocytosis, and cytokine release [4]. Astrocytes, in turn, actively modulate the inflammatory environment by responding to microglial signals, releasing cytokines and chemokines, regulating glutamate uptake, and contributing to the blood–brain barrier (BBB) maintenance [5]. Under chronic or dysregulated conditions, reactive astrocytes and activated microglia can establish a self-perpetuating inflammatory cycle that exacerbates oxidative stress, synaptic dysfunction, and neuronal damage [6, 7].

These neuroinflammatory mechanisms are particularly

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relevant in the context of diabetes, a metabolic disorder characterized not only by chronic hyperglycemia but also by systemic low-grade inflammation, oxidative stress, and vascular dysfunction, whose incidence increases with age [8, 9]. Increasing evidence indicates that diabetic conditions can promote microglial activation and astrocytic reactivity through multiple interconnected pathways, including advanced glycation end products (AGEs), mitochondrial dysfunction, insulin resistance, and impaired BBB integrity [7, 10]. As a result, diabetes can trigger and sustain neuroinflammatory responses, thereby contributing to neuronal damage and increasing susceptibility to cognitive decline and other nervous system complications. Collectively, these observations underscore the intricate and bidirectional relationship between metabolic dysregulation and neuroinflammatory signaling in diabetes. Rather than representing a mere consequence of chronic hyperglycemia, diabetes-related neural injury appears to arise from the interaction of interdependent inflammatory, oxidative, vascular, and glial mechanisms that progressively disrupt nervous system homeostasis, and which can trigger severe cognitive impairment when there is a prolonged diabetic state in elderly subjects [11, 12]. Therefore, elucidating the molecular and cellular basis of this interaction is essential for a more comprehensive understanding of the processes underlying neurological complications in diabetes and brain aging.

Crucially, diabetes-associated neuroinflammation does not merely represent a localized metabolic complication but rather functions as a potent driver of accelerated brain aging [8, 9]. Chronic exposure to hyperglycemia and AGEs triggers a state of premature senescence in microglia and astrocytes, closely mimicking the low-grade systemic inflammatory state known as 'inflammaging' [10, 13]. This sustained glial activation shifts cells toward a senescence-associated secretory phenotype, characterized by the chronic release of pro-inflammatory cytokines and reactive oxygen species (ROS) [7, 14, 15]. Consequently, the pathological convergence of diabetes and neuroinflammation exacerbates synaptic pruning deficits and neuronal apoptosis, effectively lowering the threshold for age-related cognitive decline and neurodegenerative diseases [11, 12, 16].

In this context, the present review provides a conceptually integrative synthesis of the biological mechanisms linking diabetes and neuroinflammation, with particular emphasis on BBB dysfunction, glial activation, downstream inflammatory signaling, and emerging therapeutic strategies relevant to diabetes-associated neural damage. It is based primarily on evidence generated over the past six years, thereby capturing the most recent advances in the field. More importantly, unlike previous reviews that have largely examined isolated inflammatory pathways or single mechanistic domains, this review brings together neurovascular dysfunction, glial crosstalk, innate immune signaling, inflammasome activation, oxidative and mitochondrial stress, and therapeutic perspectives into a single unified framework. By articulating these interdependent processes within the same pathophysiological landscape, this review offers a broader and more mechanistically cohesive perspective on diabetes-associated neuroinflammation than is currently available in the literature.

Diabetes as a systemic condition that predisposes to neuroinflammation

Diabetes should be understood not only as a disorder of glucose homeostasis, but also as a multisystemic condition capable of reshaping immune, vascular, and metabolic function throughout the body. A defining characteristic of diabetes, particularly type 2 diabetes, is chronic low-grade systemic inflammation [13], characterized by persistent increases in inflammatory mediators derived from adipose tissue, immune cells, the vasculature, and metabolically stressed organs. This inflammatory-metabolic environment is further reinforced by oxidative imbalance, altered lipid handling, endothelial dysfunction, AGEs, free fatty acids, and danger-associated molecular patterns (DAMPs), all of which can act on distant tissues, including the central nervous system (CNS), and can worsen with aging [10, 17]. From this perspective, neuroinflammation may be viewed not merely as a local brain process, but also as a downstream consequence of a broader systemic pathological state that progressively compromises neural homeostasis.

Several mechanisms underline this systemic-neural transition in diabetes. Persistent peripheral inflammation, metabolic dysregulation, and oxidative stress can disrupt the functional interface between the systemic circulation and CNS by progressively compromising the neurovascular unit and BBB [18]. In this context, circulating cytokines, chemokines, AGEs, and lipid-derived inflammatory mediators do not necessarily need to enter the brain directly to influence neuroimmune responses. Instead, they may act on, or signal through, endothelial and neurovascular pathways that promote BBB dysfunction, facilitate abnormal peripheral-central communication, and contribute to the amplification of neuroinflammation [19, 20]. This process provides a mechanistic link between systemic metabolic inflammation and CNS alterations, which are examined in greater detail at the molecular level in the section "BBB dysfunction".

From adaptive neuroinflammation to chronic diabetic dysfunction

Currently, neuroinflammation is understood as a context-dependent immune response within the nervous system involving resident glial cells, soluble inflammatory mediators, vascular components, and, under specific conditions, peripheral immune signals [21, 22]. In physiological conditions, low-level inflammatory signaling contributes to immune surveillance, synaptic remodeling, and the maintenance of CNS homeostasis. However, when these responses become excessive, prolonged, or maladaptively regulated, they may shift toward a pathogenic state char-

acterized by sustained cytokine production, altered glial reactivity, synaptic dysfunction, and neuronal vulnerability [16, 23]. Defining the factors that govern this transition remains an important conceptual challenge in this field and is particularly relevant for understanding how metabolic disease converts adaptive neuroimmune signaling into chronic neural pathology.

A critical distinction in the study of neuroinflammation lies in the difference between acute and chronic neuroinflammatory responses. Acute neuroinflammation is usually induced by infection, trauma, ischemia, or transient metabolic stress and is generally characterized by a rapid but coordinated activation of glial cells and inflammatory pathways, the aim of which is to limit tissue damage and restore local homeostasis [24-26]. In this context, inflammatory mediators can promote phagocytosis, eliminate damaged cellular components, and contribute to tissue remodeling and repairing. Conversely, chronic neuroinflammation reflects a persistent and dysregulated inflammatory state in which glial activation is sustained over time, and homeostatic resolution fails to occur. This chronic condition is commonly associated with continuous production of pro-inflammatory cytokines, oxidative stress, mitochondrial dysfunction, and progressive disturbances in neuronal communication [27-29]. The transition from an adaptive acute response to a chronic maladaptive process represents a key pathophysiological turning point in multiple neurological and metabolic disorders.

Cellular and molecular mechanisms linking diabetes to neuroinflammation

BBB dysfunction

The BBB is a highly specialized interface that regulates the exchange of oxygen, nutrients, ions, and signaling molecules between the circulation and CNS. Its integrity depends on the coordinated interaction of endothelial cells, pericytes, astrocytic end-feet, and tight junction proteins, such as occludin and claudins, which together restrict the uncontrolled entry of toxins, pathogens, circulating immune cells, and other blood-borne factors into neural tissue [11]. In diabetes, increased BBB permeability or disruption is considered a key event in the development of neuroinflammation, partly driven by circulating AGEs, and cytokines and chemokines that are overproduced by immune cells, dysfunctional adipocytes and stressed organs in response to diabetic hyperglycemia [13]. These mediators can influence the CNS without extensively crossing the BBB. By binding to their cognate receptors on endothelial cells, they trigger intracellular inflammatory programs that compromise barrier function, increase reactivity, and stimulate the release of chemokines, adhesion molecules, and other inflammatory mediators [14]. This interaction also promotes ROS production, AGE accumulation, and inflammasome activation within the endothelium, thereby facilitating downstream signaling toward the brain parenchyma [16, 17]. Chemokines like C-C motif chemokine ligand 2 (CCL2) amplify this process by activating endothelial cells and recruiting leukocytes to the neurovascular unit [18]. In parallel, peripheral AGEs interact with the receptor for advanced glycation end-products (RAGE) on brain endothelial cells, driving NF-κB-dependent inflammation that links systemic metabolic stress to the CNS [19, 20]. These convergent signals progressively disrupt the neurovascular unit through endothelial dysfunction, tight junction degradation, and altered expression of adhesion molecules (vascular cell adhesion molecule-1 [VCAM-1] and intercellular adhesion molecule-1 [ICAM-1]) [21-23]. At the cellular level, these changes lead to astrocyte end-feet retraction, tight junction breakdown, mitochondrial damage, and vacuolization [23-25], facilitating the entry of peripheral cells and mediators into the brain parenchyma.

Evidence of BBB disruption has also been reported in humans. Dynamic contrast-enhanced magnetic resonance imaging (MRI) studies have shown that diabetic patients with cognitive impairment exhibit increased permeability signals in the basal ganglia and hippocampus, suggesting that BBB dysfunction may contribute to deficits in memory and executive function in the clinical setting [26]. Collectively, these alterations increase BBB permeability, strengthen the signaling impact of circulating inflammatory mediators, and facilitate maladaptive communication between the periphery and the CNS.

Notably, in diabetic mice with BBB dysfunction—characterized by increased angiogenesis, reduced pericyte coverage and greater vascular permeability—treatment with the dipeptidyl peptidase-4 (DPP-4) inhibitor linagliptin or the sulfonylurea glimepiride has been reported to partially reverse barrier leakage and normalize capillary pericyte coverage [25].

Because the BBB is not a static structure but a responsive neurovascular interface, its progressive dysfunction may help explain how metabolic stress, vascular alterations, inflammatory signaling, and glial activation converge to promote neuronal vulnerability and cognitive decline. Therefore, a more detailed characterization of BBB remodeling in diabetes can provide an important framework for elucidating disease mechanisms, identifying early biomarkers of neural damage, and developing strategies aimed at preserving neurovascular integrity before irreversible brain dysfunction becomes established.

Glial activation and neuroimmune crosstalk in diabetes

Microglia are the resident innate immune cells of the CNS and play essential roles in immune surveillance and maintenance of tissue homeostasis [27]. However, under BBB dysfunction triggered by diabetic conditions, the pathological combination of chronic hyperglycemia, insulin resistance, high AGEs concentration, oxidative stress, and circulating inflammatory mediators promotes persistent microglial activation, leading to increased production of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), ROS, and reactive nitrogen species (RNS) [28-30]. Rather than representing a transient protective response, sustained diabetic stress shifts microglia

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toward maladaptive phenotypes that perpetuate neuroinflammation, synaptic dysfunction, and neuronal injury in the brain [4, 28, 31].

Astrocytes are equally important regulators of neural homeostasis through their roles in metabolic support, neurotransmitter recycling, and maintenance of BBB integrity [32]. In diabetes, prolonged exposure to hyperglycemia, inflammatory cytokines, AGEs, and oxidative stress induces astrocytic reactivity, characterized by increased secretion of cytokines, chemokines, and complement components, together with impaired glutamate uptake, altered potassium homeostasis, and disruption of metabolic coupling with neurons [28, 30, 33]. These alterations increase excitotoxic stress, compromise neuronal resilience, and further reinforce the inflammatory microenvironment [34-36].

Experimental evidence consistently supports the involvement of both glial cell populations in diabetes-associated neuroinflammation. Rodent models of streptozotocin-induced diabetes, high-fat diet-induced diabetes, and db/db mice exhibit increased ionized calcium-binding adapter molecule 1 (Iba-1) and glial fibrillary acidic protein (GFAP) immunoreactivity in several brain regions, including the hippocampus and cerebral cortex, together with elevated expression of TNF-α, IL-1β, IL-6, and components of the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome [24, 28, 37-41]. These glial alterations correlate with oxidative stress, synaptic dysfunction, and cognitive impairment, supporting the concept that glial activation represents one of the principal mechanisms linking metabolic dysregulation to neuronal damage in diabetes [28, 29].

Bidirectional communication between microglia and astrocytes can initially help contain tissue damage and restore local balance; however, under persistent diabetic conditions this interaction evolves into a self-sustaining inflammatory circuit. Microglia-derived cytokines, particularly TNF-α and IL-1β, promote astrocytic activation, whereas reactive astrocytes release additional cytokines, chemokines, complement factors, and inflammatory mediators that further stimulate microglia [7, 28]. Hyperglycemia, oxidative stress, AGEs accumulation, and BBB dysfunction continuously reinforce this reciprocal activation, maintaining chronic neuroinflammation even in the absence of acute insults [10, 28, 29]. Consequently, glial crosstalk constitutes a central pathological mechanism underlying diabetes-associated neuronal dysfunction and represents an attractive therapeutic target for interrupting the self-reinforcing cycle of chronic neuroinflammation [30, 42].

Downstream inflammatory signaling and metabolic stress pathways

Pattern recognition receptors in diabetes

Pattern recognition receptors (PRRs) provide a crucial link between cellular stress and innate immune activation in neural tissue [43]. These host receptors exist either as membrane-bound proteins or as cytosolic sensors and are specialized in detecting pathogen-associated molecular patterns (PAMPs) and DAMPs released during tissue stress, injury, or infection. In diabetes, metabolic imbalance promotes the accumulation of DAMP-like signals and other inflammatory stimuli, thus creating conditions that favor persistent PRR activation [44, 45].

Among the PRRs expressed in brain cells, the most studied receptors in relation to diabetes include Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs), although increasing attention has also been directed toward retinoic acid-inducible gene I (RIG-I)-like receptors and several chemokine receptors. In all these families, receptor activation in diabetic conditions initiates intracellular signaling cascades that converge on inflammatory transcription factors, cytokine production, and inflammasome priming [30, 46, 47].

TLRs are transmembrane receptors located on the cell surface, where they primarily detect lipid and protein components, or in endosomal compartments, where they recognize nucleic acids. Structurally, they contain an extracellular domain involved in PAMPs and DAMPs recognition, a transmembrane region, and a cytoplasmic Toll/interleukin-1 receptor (TIR) domain that initiates downstream signaling [47]. In neural tissue, TLR activation promotes inflammation, structural alterations, and apoptosis mainly through canonical NF-κB signaling, which in turn stimulates the production of pro-inflammatory cytokines [48-50].

NLRs are intracellular PRRs that also recognize PAMPs and DAMPs and play a central role in inflammasome assembly and caspase activation [51, 52]. These receptors are structurally composed of a core nucleotide-binding domain (NBD), a C-terminal ligand-sensing region, and a N-terminal interaction domain whose identity determines the major receptor subfamilies [53]. Among them, NLRP3 has been the most researched due to its functional interaction with TLR signaling and its prominent role in metabolic inflammation [54].

Several markers associated with NLR activation are elevated in diabetic patients and in experimental models of diabetes, in peripheral tissues [55], in the CNS, and *in vivo* and *in vitro* settings [37, 38]. Consistent with this observation, pharmacological or experimental inhibition of NLRP3 has been reported to reduce excessive ROS production, attenuate glial inflammatory responses, and improve diabetes-associated cognitive dysfunction [30, 40, 41].

RIG-I-like receptors are also intracellular sensors, classically involved in the recognition of viral nucleic acids and the induction of antiviral immune responses [52, 56]. Their structure includes N-terminal signaling domains, a central helicase/ATPase region, and a C-terminal regulatory domain [53]. Emerging evidence suggests that some metabolic features of diabetes, including intestinal dysbiosis and changes in tryptophan-related microbial metabolites, may activate inflammatory pathways linked to these receptors [57-60].

NF-κB, MAPK, and JAK/STAT signaling in diabetes

Several intracellular pathways activated downstream of

the receptors described above shape the transcriptional and functional profile of the neuroinflammatory response in diabetes. Among these, NF-κB, MAPK, and JAK/STAT stand out as key signaling hubs, integrating stress, inflammation, and damage signals into coordinated transcriptional programs. NF-κB regulates the expression of numerous cytokines, chemokines, adhesion molecules, and enzymes involved in oxidative and nitrosative stress [61] and is consistently activated in experimental models of neuroinflammation, where it is often regarded as a hallmark of neuroinflammatory status [62-65].

MAPK signaling, which includes the ERK, JNK, and p38 branches, modulates glial activation, inflammatory gene expression, processes related to apoptosis, and cellular adaptation to diabetic stress [66-68]. In parallel, the JAK/STAT pathway converts extracellular cytokine signals into transcriptional programs that influence astrocytic reactivity, microglial polarization, and broader neuroimmune remodeling [69]. Together, these pathways form a central signaling layer that coordinates communication among microglia, astrocytes, neurons, and endothelial cells by promoting the expression of inflammatory mediators such as IL-1β, IL-6, TNF-α, cyclooxygenase 2 (COX-2), inducible nitric oxide synthase (iNOS), chemokines including CCL2 and CXCL10, adhesion molecules such as ICAM-1 and VCAM-1, and genes related to survival and apoptosis, such as Bcl-2, Bax, and caspases. Their dynamic interaction helps determine whether inflammation remains adaptive or progresses toward chronic pathogenic signaling in diabetic neural tissue.

Cytokines and chemokines in diabetes-associated neuroinflammation

Consistent evidence from experimental models of diabetes identifies TNF-α, IL-1β, and IL-6 as key markers of neuroinflammation. These mediators are closely related to dysregulation of glial and endothelial function, as well as cognitive impairment in diabetes [70-75]. In parallel, several chemokine receptors have also been implicated in diabetes-associated neuroinflammation. These G protein-coupled receptors regulate the behavior of immune cells in the brain through ligand-dependent signaling, and receptors such as CX3CR1, CXCR3, CXCR4, CCR2, and CCR5 have been particularly associated with microglial activity in CNS lesions [76, 77]. In this sense, some chemokines, including CXCL9, CXCL8, and CXCL10, are altered in diabetic patients [78, 79]. While their direct contribution to diabetes-induced neuroinflammatory signaling is not yet fully defined, they are known to facilitate the spread of inflammation by promoting cellular recruitment, modulating glial migration, and amplifying local immune communication [80]. In diabetic complications, the activation of some of these pathways has even been linked to neuroprotective effects, which underlies the functional complexity of chemokine signaling in this context [81-83].

Activation of NLRP3 inflammasome in diabetes

Inflammasomes are cytosolic multiprotein complexes activated in response to diverse danger signals, such as mitochondrial damage, reactive oxygen species, lysosomal destabilization, ionic imbalance, and metabolic stress. Among them, the NLRP3 inflammasome occupies a particularly relevant position as an amplifier of neuroinflammation in diabetes [37, 39, 84]. Accordingly, its modulation has become an increasing focus of research in metabolic syndrome and diabetic conditions, using drugs and compounds that act as inhibitors of this protein assembly, both in the brain [24, 85] and in peripheral organs [86].

Inflammasome activation typically requires a priming step, often mediated by PRR and NF-κB signaling, followed by an assembly step that leads to caspase-1 activation [87-89]. Active caspase-1 cleaves pro-IL-1β and pro-IL-18 into their mature forms and can also trigger pyroptotic cell death through gasdermin-mediated membrane disruption [90-92]. In neural tissue, excessive inflammasome activation enhances glial reactivity, increases cytokine release, and contributes to synaptic damage and neuronal loss [93-95]. Therefore, NLRP3 should be considered an integrative inflammatory hub that connects cellular stress sensing with potent downstream effector cascades and pathological neuroinflammation.

Oxidative stress and mitochondrial dysfunction as amplifiers of diabetic neuroinflammation

Oxidative stress and mitochondrial dysfunction are both consequences and amplifiers of neuroinflammatory signaling. Activated glial cells generate reactive oxygen and nitrogen species as part of the inflammatory response: microglia mainly through the NADPH oxidase/NOX2 pathway, and astrocytes through disturbances in mitochondrial redox regulation and mechanisms related to nitric oxide synthase [96, 97]. Excessive accumulation of these reactive molecules damages lipids, proteins, and nucleic acids, thereby compromising both neuronal and glial function.

Mitochondria are among the main sources of ROS because some of the oxygen processed by the respiratory chain is released as partially reduced intermediates [98]. At the same time, mitochondria are especially vulnerable to ROS-induced damage, which can manifest as impaired ATP production, poor calcium buffering, increased ROS generation, and the release of mitochondrial danger signals that stimulate innate immune pathways [99]. These abnormalities reinforce cytokine production, facilitate inflammasome activation, and lower the threshold for persistent glial reactivity. The result is a self-perpetuating cycle in which redox imbalance and impaired mitochondrial homeostasis maintain inflammatory signaling and accelerate neural damage. Therefore, oxidative stress and mitochondrial dysfunction should be considered mechanistic amplifiers that consolidate the transition from transient neuroimmune activation to chronic pathological inflammation. Figure 1 integrates the general mechanisms presented in the previous sections.

Integrated sequence of events linking diabetes to neuroinflammation

The mechanisms in the above sections represent an interdependent, overlapping cascade rather than a linear sequence, which can be divided into distinct modules. The

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first module encompasses concurrent chronic hyperglycemia, insulin resistance, dyslipidemia, AGE accumulation, elevated free fatty acids, oxidative stress, and low-grade systemic inflammation, which collectively drive a peripheral metabolic-inflammatory state affecting the neurovascular unit. Therapeutics including metformin, adamantane derivatives, and GIP/GLP-1 receptor agonists have shown efficacy in mitigating aspects of this phase [100-110]. According to the International Diabetes Federation, this step is still largely reversible, with hyperglycemia and its immediate systemic effects responding well to lifestyle modifications [9].

A second closely related module centers on the BBB, where circulating cytokines, chemokines, AGEs, and lipid-derived signals activate endothelial receptors and stress-sensitive pathways [17]. This triggers oxidative stress, adhesion molecule expression, tight junction breakdown, pericyte loss, astrocyte end-feet retraction, and BBB hyperpermeability. Together, these alterations intensify aberrant peripheral-to-central signaling, fostering

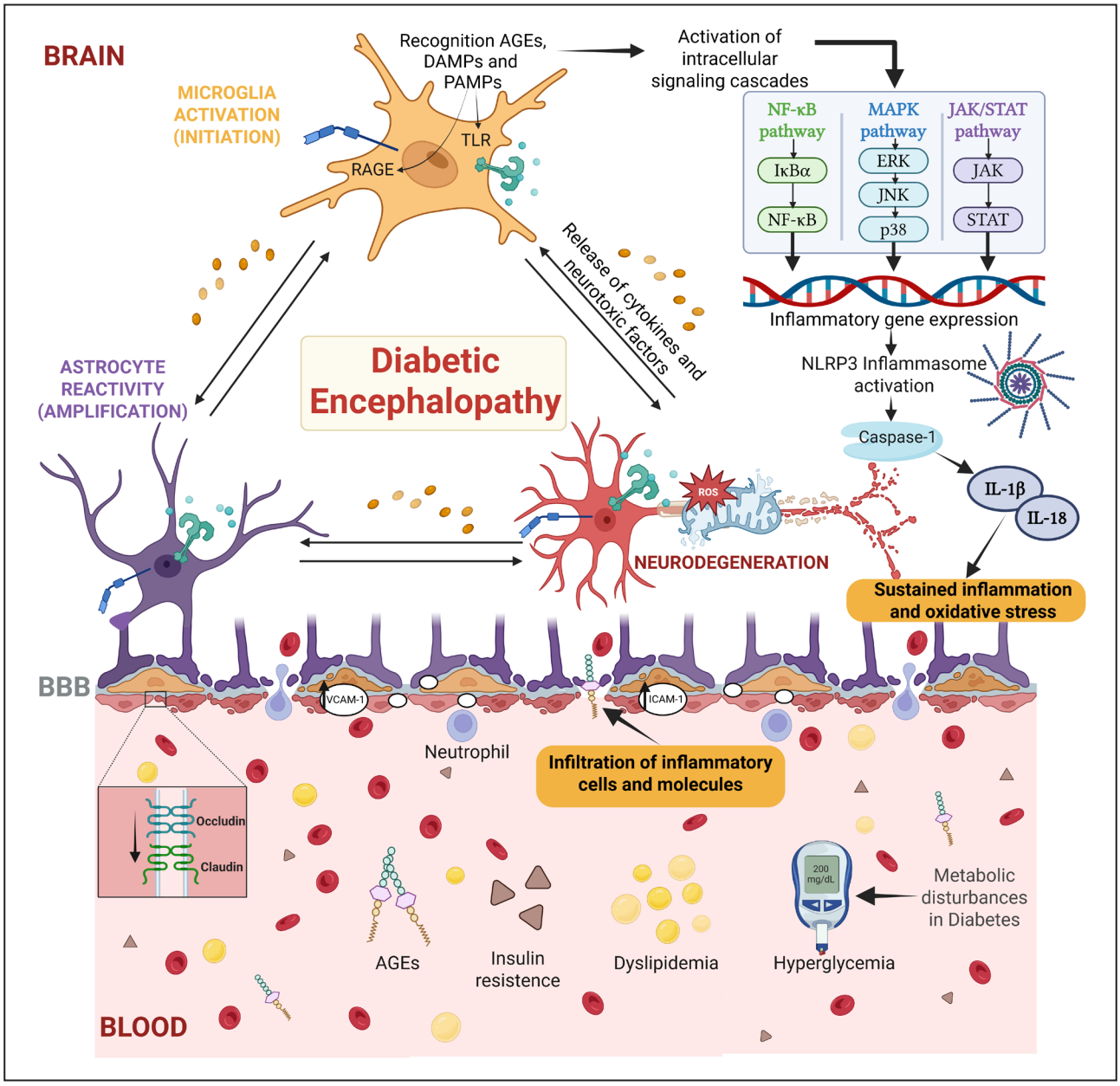


Figure 1. Proposed mechanisms linking metabolic disturbances to neuroinflammation and neurodegeneration in diabetes. Chronic metabolic alterations associated with diabetes, including hyperglycemia, insulin resistance, dyslipidemia, and the accumulation of AGEs, contribute to blood–brain barrier (BBB) dysfunction through endothelial activation, loss of tight junction integrity (↓), and increased expression of adhesion molecules such as ICAM-1 and VCAM-1 (↑). BBB disruption facilitates the infiltration of peripheral inflammatory cells and circulating inflammatory mediators into the brain parenchyma. These signals activate microglia through pattern recognition receptors, including TLRs and the receptor for AGEs, triggering intracellular signaling pathways such as NF-κB, MAPK, and JAK/STAT. The activation of these pathways promotes inflammatory gene expression, production of pro-inflammatory cytokines and neurotoxic mediators, and priming of the NLRP3 inflammasome. Activated microglia and reactive astrocytes engage in bidirectional crosstalk that amplifies neuroinflammatory responses and oxidative stress. Subsequent NLRP3 inflammasome activation leads to caspase-1 activation and maturation of IL-1β and IL-18, further sustaining chronic inflammation. Persistent neuroinflammation and oxidative stress contribute to neuronal dysfunction, synaptic impairment, neurodegeneration, and cognitive decline, ultimately promoting the development of diabetic encephalopathy.

a microenvironment for glial activation prior to marked cellular infiltration. Therapeutics such as sodium-glucose cotransporter-2 (SGLT2) inhibitors, GLP-1 receptor agonists, and various natural products have been shown to preserve BBB integrity across preclinical and clinical models [17, 111, 112].

In a third module, microglia and astrocytes respond to endothelial, metabolic, and inflammatory signals by adopting reactive phenotypes characterized by increased production of cytokines, chemokines, ROS, RNS, and complement-related mediators. This glial response overlaps with the activation of PRRs, including TLRs, RAGE-related pathways, and NLR sensors, which converge on NF-κB, MAPK, and JAK/STAT signaling to sustain inflammatory gene expression and amplify the production of TNF-α, IL-1β, IL-6, CCL2, CXCL10, ICAM-1, VCAM-1, COX-2, and iNOS [28].

The fourth module centers on PRR- and NF-κB-dependent priming, mitochondrial dysfunction, ROS generation, ionic imbalance, and metabolic stress. Together, these drivers promote NLRP3 inflammasome activation, caspase-1 signaling, IL-1β/IL-18 maturation, and pyroptosis-driven inflammatory amplification [73, 86, 96]. Consequently, oxidative stress and mitochondrial injury act not as passive endpoints, but as active amplifiers throughout the cascade. Ultimately, the interplay among these modules establishes a vicious cycle wherein neurovascular impairment, neuroinflammation, redox imbalance, and synaptic dysfunction converge toward cognitive decline and diabetic brain pathology.

In general, animal studies have focused on palliative strategies targeting the mediator molecules of the third and fourth modules [100-110, 113-117]. However, because the mechanisms in these modules are self-sustaining and rooted in preceding chronic events, their modulation should be regarded as palliative—helping to prevent further, more pronounced deterioration—rather than as fully restorative or reversible. Figure 2 outlines these modular events.

Therapeutic perspectives in diabetes-associated neuroinflammation

Diabetes-associated neuroinflammation offers multiple therapeutic opportunities, as diabetic brain injury arises from the convergence of BBB dysfunction, glial reactivity, oxidative stress, and chronic inflammatory signaling. Consequently, current strategies increasingly focus on the pathways that perpetuate this self-reinforcing pathology, including TLR4, NF-κB, MAPK, JAK/STAT, and inflammasome-related signaling, with the aim of reducing cytokine production, oxidative damage, and synaptic dysfunction.

Beyond direct anti-inflammatory approaches, therapeutic strategies also target oxidative stress, mitochondrial dysfunction, AGEs-RAGE signaling, redox-sensitive pathways, NLRP3 activation, and modulators of glial phenotypes. Taken together, these interventions aim not only to suppress chronic pathogenic signaling but also to preserve physiological neuroimmune functions. It is worth noting that many of the proposed approaches involve naturally occurring compounds, reflecting growing interest in alternatives that may offer lower toxicity and greater suitability for long-term use.

Pharmacological approaches to diabetes

Metformin remains a first-line therapy for hyperglycemia and type 2 diabetes, but it has also shown relevant neuroprotective effects in experimental settings [100]. In aged male C57BL/6 mice with diet-induced hyperglycemia, metformin reduced markers of pro-inflammatory microglial phenotypes and decreased TNF-α levels in the motor and sensory cortices, supporting its ability to attenuate diabetes-associated neuroinflammation by modulating glial responses [101]. In addition, metformin increased antioxidant markers in the hippocampus, an effect that was potentiated when combined with an ethanolic purslane extract [102].

Other pharmacological strategies have also demonstrated anti-inflammatory and neuroprotective potential in diabetic models. Adamantine derivatives and antidiabetic agents containing the adamantane moiety, such as vildagliptin and saxagliptin, reduce the expression of IL-1β, IL-6, and TNF-α and help prevent diabetes-associated cognitive decline, suggesting a favorable profile for limiting neuroinflammatory damage [113]. Incretin-based therapies have also gained attention due to their combined metabolic actions and potential neuroprotective effects. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are intestinal hormones essential for metabolic regulation, and their receptors are also expressed in the brain. In this context, tirzepatide, a dual GIP/GLP-1 receptor agonist approved for the treatment of type 2 diabetes mellitus, has emerged as a promising candidate for modulating diabetes-associated neuroinflammation [114]. Experimental evidence indicates that tirzepatide improves spatial and recognition memory and reduces the cerebral expression of TNF-α, IL-6, IL-1β, and oxidative stress markers in diabetic rats [115].

Neurocognitive effects of antidiabetic agents

A growing body of clinical evidence—including one large randomized trial with a cognitive secondary endpoint, longitudinal cohort studies, and meta-analyses—suggests that several major classes of antidiabetic agents—specifically metformin, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and SGLT2 inhibitors—may have neuroprotective properties. These medications have been associated with slower rates of cognitive decline, better performance on standardized neurocognitive assessments, and a lower risk of incident dementia in patients with diabetes, although most of these data derive from exploratory analyses of cardiovascular outcome trials and observational cohorts rather than from cognition-primary randomized trials. Table 1 summarizes the clinical trials with published cognitive outcomes, as well as registered ongoing trials, evaluating the neurocognitive effects of antidiabetic agents.

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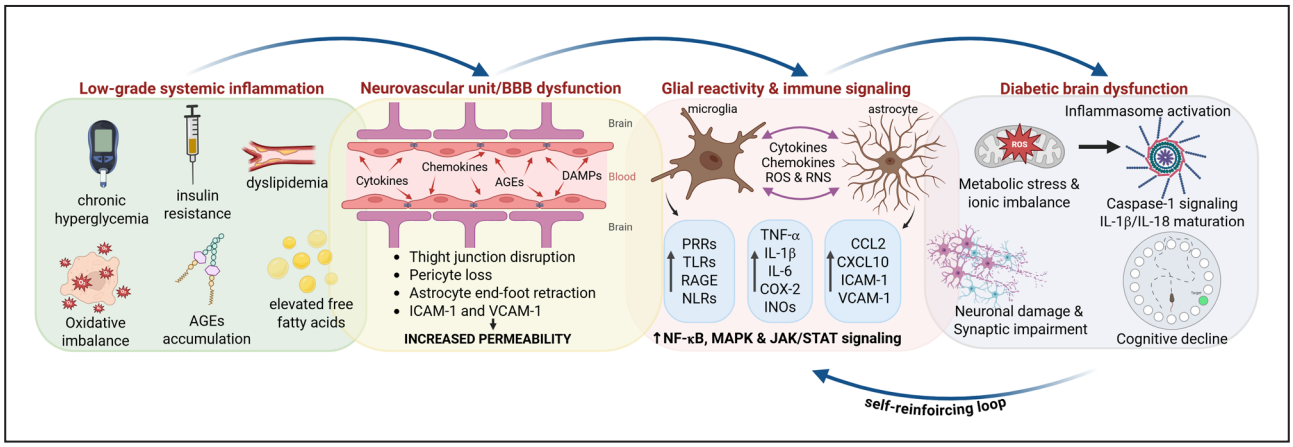


Figure 2. Integrated modular cascade linking diabetes-associated metabolic dysfunction to chronic neuroinflammation and neural impairment. Chronic hyperglycemia, insulin resistance, dyslipidemia, AGEs accumulation, oxidative imbalance, and low-grade systemic inflammation generate a peripheral inflammatory-metabolic state that compromises the neurovascular unit and promotes BBB dysfunction. Increased BBB permeability and endothelial activation facilitate abnormal peripheral-to-central signaling, favoring microglial and astrocytic reactivity. In parallel, activation of pattern recognition receptors, including TLRs, RAGE-related pathways, and NLR sensors, converges on NF-κB, MAPK, and JAK/STAT signaling, amplifying cytokine, chemokine, ROS/RNS, COX-2, and iNOS production. Mitochondrial dysfunction and redox imbalance further promote NLRP3 inflammasome activation, caspase-1 signaling, IL-1β/IL-18 maturation, and pyroptosis-related amplification. These interdependent modules establish a self-reinforcing loop in which neurovascular dysfunction, glial crosstalk, innate immune signaling, inflammasome activation, oxidative stress, synaptic impairment, and neuronal vulnerability converge toward cognitive decline and diabetic brain dysfunction.

The cognitive preservation offered by these antidiabetic agents is driven by pleiotropic mechanisms that extend beyond simple glycemic control. At the cellular level, these therapies mitigate chronic neuroinflammation by suppressing microglial activation and downregulating systemic pro-inflammatory cytokines. Additionally, they attenuate central neurodegenerative pathology by reducing the accumulation of beta-amyloid plaques and hyperphosphorylated tau, while concurrently improving mitochondrial energy metabolism, enhancing cerebral blood flow, and preserving BBB integrity [111, 112].

Furthermore, while some clinical data suggest a promising neuroprotective signal for the antidiabetic therapies described above, the current body of evidence remains inherently limited and methodologically restricted [112, 120, 122, 123]. Therefore, much of the existing data comes from exploratory secondary analyses or post-hoc endpoints incorporated into large cardiovascular outcome trials, such as the REWIND trial, rather than studies specifically designed to assess cognitive performance [118]. Moreover, targeted intervention trials have yielded mixed results. For example, large-scale phase 3 trials such as EVOKE and EVOKE+, which evaluated oral semaglutide in early Alzheimer's disease, failed to meet their primary cognitive endpoint on the Clinical Dementia Rating Scale-Sum of Scores (CDR-SB) [124]. This discrepancy highlights that reducing epidemiological risk does not automatically translate into disease modification or clinical reversal of established neurodegeneration. These challenges are compounded by the relatively short duration of trials—typically lasting only 12 to 36 months—which prevents the capture of neurodegenerative processes that evolve over decades, as well as by the significant heterogeneity of the psychometric assessment tools used across trials [125]. Additionally, clinicians face a key mechanistic dilemma: it remains difficult to determine whether the observed cognitive preservation is due to direct CNS actions, such as reduced neuroinflammation, or to secondary systemic benefits, such as improved microvascular health and glycemic control [111]. To address these limitations and move toward definitive clinical translation, future research should focus on large-scale, prospective, randomized, phase 3 controlled trials where cognitive preservation and dementia incidence serve as primary endpoints. These studies should incorporate direct comparisons between multiple drug classes and systematically integrate fluid biomarkers, such as plasma and cerebrospinal fluid levels of neurofilament light chain (NfL), GFAP, and hyperphosphorylated tau protein (p-tau181/217), along with structural MRI and positron emission tomography (PET) imaging to objectively monitor neuronal preservation [121, 126]. Furthermore, a precision medicine strategy will be essential to stratify patient subpopulations according to genetic risk factors such as *APOE* gene status, baseline insulin resistance, and specific underlying etiology, such as distinguishing between vascular cognitive impairment and Alzheimer's disease pathology [112]. Finally, research into new multi-agonist molecules (such as dual GLP-1/GIP agonists) designed for better penetration of the BBB, along with long-term follow-up periods of five to ten years, will clarify the true therapeutic potential of antidiabetic agents to delay or prevent cognitive decline.

Natural compounds as complementary strategies to diabetes

A wide range of plant extracts, phytochemical derivatives, and compounds of animal origin have been assessed in experimental *in vivo* and *in vitro* non-diabetic neuroinflammation models relevant to mechanisms. These agents are of particular interest because they can provide anti-inflammatory, antioxidant, and metabolic benefits with potentially lower toxicity and fewer side effects than conventional synthetic drugs. Consequently, they are increasingly being explored as adjuvant or complementary strategies to

Table 1. Published and ongoing clinical trials evaluating the neurocognitive effects of antidiabetic agents.

Drug class & pharmaceutical intervention	Trial name, NCT registration & phase	Sample size (*N*)	Primary endpoints	Key cognitive findings
GLP-1 RA (Dulaglutide) [118]	REWIND Trial NCT01394952 Phase 3	*N* = 8,828 (Cognitive cohort)	Time to occurrence of substantial cognitive impairment (decrease > 1.5 SD on MoCA or DSST score)	Reduced hazard of cognitive impairment by 14% compared to placebo (HR = 0.86, 95% CI: 0.79–0.95, *P* = 0.0018)
GLP-1 RA (Liraglutide) [119]	ELAD Trial NCT01843075 Phase 2b	*N* = 204	Change in cerebral glucose metabolic rate (FDG-PET) and ADAS-Cog/MoCA battery scores over 12 months	Attenuated brain volume loss (temporal/parietal cortex) and significantly slowed cognitive decline compared to placebo
Biguanide (Metformin XR)	MetMemory Trial NCT04511416 Phase 2	*N* = 242	3-year change in cognitive domain Z-scores (memory, executive function) and hippocampal volume on MRI	Ongoing—endpoints: 3-year change in global cognitive function and hippocampal atrophy on MRI; results not yet published
SGLT2 Inhibitor (Dapagliflozin)	DECIST Trial NCT05565976 Phase 4	*N* = 270	Change in global cognitive function (MoCA) and vascular risk markers at 12 months post-ischemic event	Ongoing—endpoints: change in MoCA, blood biomarkers (NfL, GFAP, p-tau), and MRI parameters at 12 months after ischemic stroke; results not yet published
SGLT2 Inhibitor (Empagliflozin)	COG-EMPA NCT04708704 Phase 4	*N* = 160	Mean change in MoCA and MMSE composite scores from baseline to Week 36	Ongoing—endpoints: change in MoCA and MMSE scores at 36 weeks; results not yet published

Notes: Trial registrations: MetMemory, ClinicalTrials.gov, NCT04511416; DECIST, ClinicalTrials.gov, NCT05565976; COG-EMPA, ClinicalTrials.gov, NCT04708704. GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose cotransporter-2 inhibitor; XR, extended release; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; DSST, Digit Symbol Substitution Test; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; CI, confidence interval; HR, hazard ratio; N, number of participants; NCT, National Clinical Trial registration identifier; SD, standard deviation; FDG-PET, fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging; NfL, neurofilament light chain; GFAP, glial fibrillary acidic protein; p-tau, hyperphosphorylated tau.

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Table 2. Pharmacological strategies and natural compounds evaluated against diabetes-associated neuroinflammation.

Strategy	Study model	Key mechanisms and effects
Conventional drugs		
Metformin	Aged male C57BL/6 mice with diet-induced hyperglycemia [101]; HFD- and STZ-induced diabetic rats [102]	↓ Markers of pro-inflammatory microglial phenotypes; ↓ TNF-α levels in motor and sensory cortices; ↑ antioxidant markers in the hippocampus (effect enhanced when combined with purslane extract)
Adamantane derivatives (vildagliptin, saxagliptin)	Diabetic mice with cognitive impairment [113]	↓ IL-1β, IL-6, and TNF-α expression; prevents diabetes-associated cognitive decline
Tirzepatide (dual GIP/GLP-1 receptor agonist)	Diabetic rats [115]	Improves spatial and recognition memory; ↓ cerebral expression of TNF-α, IL-6, IL-1β, and oxidative stress markers
Natural compounds		
Nattokinase (alkaline serine protease)	Diabetic retinopathy models [71]	Rescues endothelial dysfunction and pericyte loss; ↓ inflammation and neurodegeneration by modulating microglial signaling
Melissa officinalis (lemon balm, phytocomplex rich in rosmarinic acid)	BV2 microglial cells exposed to high glucose [116]	Prevents CD11b increase, NF-κB activation, and iNOS expression; inhibits ERK1/2 phosphorylation and IL-6 expression, while restoring SIRT1 levels
Tiliacora triandra (medicinal plant)	Models with LPS-induced memory deficits and sickness behavior [117]	Significantly ameliorates memory deficits and sickness behavior; ↓ TNF-α, IL-1β levels, and glial activation markers
Polyherbal extract (*Citrullus colocynthis, Curcuma longa,* and *Myristica fragrans*)	STZ-induced diabetic rats [103]	↓ Fasting blood glucose; lipid balance restored; ↑ antioxidant defenses; behavioral and histological outcomes improved
Cornulaca monacantha (extract rich in flavonoids and phenolic compounds)	Neuro-2a mouse neuroblastoma cells [104]	↓ inflammatory biomarkers; actively modulates the Nrf2 pathway
Hydrolea zeylanica (flavonoid-rich plant)	Rats with diabetic encephalopathy [105]	Optimizes learning and memory; ↓ glucose, ↑ insulin, and ↓ oxidative and inflammatory markers; improves cortical histology
Dietary combinations (grape, bilberry, saffron, and omega-3 as nutritional strategy)	Response to LPS-induced neuroinflammation in the hippocampus [106]	Selectively increase pro-resolving mediators; improve overall antioxidant status within the hippocampus
Anthocyanin-rich extract (aqueous extract of *Hibiscus sabdariffa*)	STZ-induced diabetic rats [107]	↓ Blood glucose levels; notably optimize short-term memory performance
Bee venom (alone or combined with metformin)	Diabetic and hyperlipidemic mice [108, 109] and rats [110]	↓ Systemic levels of glucose, insulin, TNF-α, and IL-6 and oxidative stress markers; pancreatic and cardiac histological improvements reported. Effects on neuroinflammation have not been directly assessed in these models.

Notes: CD11b, cluster of differentiation 11b; ERK1/2, extracellular signal-regulated kinase 1/2; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HFD, high-fat diet; IL-1β, interleukin-1β; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; NF-κB, nuclear factor kappa-B; Nrf2, nuclear factor erythroid 2-related factor 2; SIRT1, sirtuin 1; STZ, streptozotocin; TNF-α, tumor necrosis factor-α.

standard pharmacological treatment. Table 2 systematizes the fundamental experimental models, molecular targets, and therapeutic results of both conventional pharmacological agents and new natural compounds targeting diabetes-induced neuroinflammation.

Taken together, these findings suggest that natural compounds could offer a valuable complementary approach to limiting diabetes-associated neuroinflammation. Their ability to modulate oxidative stress, inflammatory mediators, glial activation and metabolic dysfunction supports their potential integration into long-term therapeutic strategies, although stronger clinical and translational evidence is still required before their adjunctive use can be recommended.

Conclusions and future directions

In summary, diabetes-associated neuroinflammation should be considered a multidimensional pathological process arising from the convergence of metabolic stress, glial dysregulation, vascular impairment, oxidative damage, and sustained inflammatory signaling. This integrative framework helps explain why diabetes promotes progressive neural dysfunction rather than isolated metabolic injury and underscores the need to move beyond glucose-centric interpretations of diabetic complications.

Future research should prioritize mechanistic stratification among diabetes phenotypes, the identification of early and reliable biomarkers of neurovascular and glial dysfunction, and the development of targeted interventions capable of attenuating chronic pathogenic signaling while preserving adaptive neuroimmune functions across the lifespan, thereby promoting healthy brain aging. Greater integration of experimental, imaging, and clinical evidence will be essential to elucidate causal pathways, enhance translational relevance, and identify therapeutic windows before irreversible neural damage is established.

Declarations

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