Review

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Oxidative Stress, Neuroinflammation, and Microvascular Damage in Neurodegenerative Diseases: Mechanistic Insights and Therapeutic Approaches

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Oxidative Stress, Neuroinflammation, and Microvascular Damage in Neurodegenerative Diseases: Mechanistic Insights and Therapeutic Approaches

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Abstract

Neurodegenerative diseases such as Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis share common molecular mechanisms involving oxidative stress, neuroinflammation, and microvascular dysfunction. These interrelated processes form a self-perpetuating cycle that accelerates neuronal loss and cognitive decline. Oxidative stress triggers mitochondrial impairment and lipid peroxidation, while chronic glial activation amplifies the inflammatory milieu through cytokine release and reactive oxygen species generation. Concurrently, endothelial and pericytic injury disrupts the blood–brain barrier (BBB), compromising neurovascular coupling and metabolic homeostasis. This review summarizes the mechanistic crosstalk between oxidative, inflammatory, and vascular pathways in neurodegeneration, highlighting recent advances in antioxidant, anti-inflammatory, and vasoprotective strategies. We further discuss emerging therapeutic approaches such as nanocarrier-based delivery systems, multitarget drugs, and genetic modulation aimed at restoring redox balance and microvascular integrity. Understanding the molecular intersections of these mechanisms may provide new insights into disease-modifying interventions for neurodegenerative disorders.

Keywords: oxidative stress; neuroinflammation; microvascular damage; neurodegeneration; blood–brain barrier; mitochondria; therapeutic approaches

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1. Introduction

Neurodegenerative diseases (NDs) such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) represent a major global health burden characterized by progressive neuronal loss, cognitive decline, and functional disability [1,2]. Despite the heterogeneity of their clinical manifestations, these disorders share fundamental pathophysiological mechanisms involving oxidative stress, neuroinflammation, and microvascular dysfunction [3–5]. The convergence of these processes underlies a self-perpetuating cycle that disrupts neuronal homeostasis, impairs synaptic plasticity, and compromises the blood–brain barrier (BBB), ultimately contributing to neurodegeneration [6–9].

Oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) generation and antioxidant defense systems, induces lipid peroxidation, mitochondrial dysfunction, and DNA damage [10–12]. Chronic activation of glial cells—particularly microglia and astrocytes—drives a sustained neuroinflammatory response, releasing cytokines, chemokines, and reactive nitrogen species that amplify neuronal injury [13–16]. Simultaneously, endothelial dysfunction, pericyte loss, and tight-junction disruption contribute to BBB breakdown and cerebral hypoperfusion, creating a permissive environment for neurotoxic cascades [17–20].

In recent years, the neurovascular unit (NVU) has emerged as a central integrative framework for understanding how redox imbalance and inflammation converge at the microvascular level to accelerate neurodegenerative processes [21–23]. Growing evidence suggests that restoring vascular integrity, modulating glial activation, and re-establishing redox homeostasis may hold promise as disease-modifying strategies [24–27].

This review provides a comprehensive synthesis of current mechanistic insights into the oxidative–inflammatory–vascular triad in neurodegeneration and highlights emerging therapeutic interventions targeting these interconnected pathways [28–30]. Understanding their crosstalk offers novel opportunities for early intervention and neuroprotection in aging and disease contexts [31–33].

2. Molecular Basis of Oxidative Stress in Neurodegeneration

Oxidative stress is a major pathological hallmark across neurodegenerative diseases, arising from an imbalance between reactive oxygen species (ROS) production and the antioxidant defense mechanisms that maintain redox homeostasis [1–3]. In the central nervous system (CNS), neurons are particularly vulnerable to oxidative damage due to their high oxygen consumption, abundant polyunsaturated lipids, and limited regenerative capacity [4,5]. Mitochondria, NADPH oxidases, and peroxisomes are the primary sources of ROS, while antioxidant enzymes such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), and peroxiredoxins act as the main defensive systems [6–8].

In neurodegenerative conditions like Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), excessive ROS and reactive nitrogen species (RNS) lead to protein oxidation, lipid peroxidation, and nucleic acid damage, ultimately compromising neuronal survival [9–12]. Mitochondrial dysfunction—particularly in complex I and complex IV of the electron transport chain—results in increased superoxide anion generation and reduced ATP synthesis [13,14]. The accumulation of oxidized mitochondrial DNA (mtDNA) further triggers apoptotic signaling via cytochrome c release and caspase activation [15,16].

Beyond the mitochondria, aberrant activation of NADPH oxidase (NOX) isoforms, particularly NOX2 and NOX4, has been implicated in microglial ROS production and synaptic injury [17,18]. Elevated NOX activity amplifies oxidative stress through a feed-forward loop that activates NF-κB and other pro-inflammatory transcription factors, linking redox imbalance directly to neuroinflammation [19–21]. Moreover, lipid peroxidation products such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA) form adducts with neuronal proteins, altering their structure and function, and serving as biomarkers of oxidative injury [22,23].

Dysregulation of antioxidant defenses further exacerbates neuronal vulnerability [24]. Reduced glutathione (GSH) levels and decreased activity of GPx and SOD have been consistently observed in both brain tissue and cerebrospinal fluid of patients with AD and PD [25–27]. Additionally, impairment of the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway—a master regulator of antioxidant gene expression—has been shown to aggravate oxidative damage and mitochondrial failure [28–30]. Restoration of Nrf2 signaling has therefore become a promising therapeutic strategy, with agents such as sulforaphane, dimethyl fumarate, and curcumin demonstrating neuroprotective effects through activation of Nrf2–ARE (antioxidant response element)–dependent transcription [31–34].

Recent studies emphasize the bidirectional relationship between oxidative stress and protein aggregation [35]. In AD, oxidative modification of amyloid precursor protein (APP) and tau accelerates plaque and tangle formation, while in PD, oxidation of α-synuclein promotes its misfolding into toxic oligomers [36–38]. Conversely, these aggregates further disrupt mitochondrial function and calcium homeostasis, intensifying oxidative injury [39,40]. Thus, oxidative stress is not

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merely a byproduct but a central driver of neurodegenerative cascades, interwoven with inflammation and vascular dysfunction within the neurovascular unit (NVU) [41–43].

Collectively, these findings underscore oxidative stress as a unifying molecular mechanism in neurodegeneration [44,45]. Targeting mitochondrial resilience, NOX inhibition, and Nrf2 activation represents a triad of potential interventions to restore redox balance and attenuate disease progression [46–48].

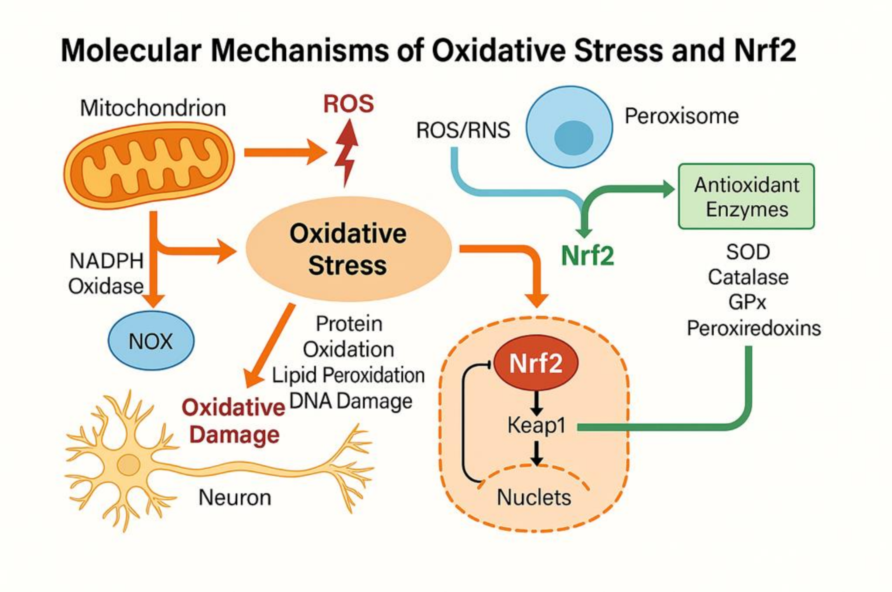

Figure 1. Molecular Mechanisms of Oxidative Stress and Nrf2 Pathway in Neurodegeneration.

The figure illustrates the main sources and regulatory pathways of oxidative stress in neuronal cells. Mitochondrial dysfunction and NADPH oxidase (NOX) activity generate reactive oxygen species (ROS), leading to protein oxidation, lipid peroxidation, and DNA damage. Under oxidative stress, nuclear factor erythroid 2–related factor 2 (Nrf2) dissociates from its repressor Keap1, translocates into the nucleus, and activates antioxidant response element (ARE)-dependent transcription of detoxifying enzymes, including superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), and heme oxygenase-1 (HO-1), which restore redox balance and protect neurons from oxidative injury.

3. Neuroinflammatory Pathways and Glial Crosstalk

Neuroinflammation constitutes a second major pathological axis in neurodegenerative deseases (NDs), orchestrated primarily by glial cells—microglia and astrocytes—that serve as the immune sentinels of the central nervous system (CNS) [49–51]. While acute inflammatory responses can promote neuroprotection and tissue repair, chronic activation of these glial populations leads to persistent release of pro-inflammatory mediators, oxidative radicals, and excitotoxins that amplify neuronal damage [52,53].

Microglial activation represents the earliest and most dynamic component of neuroinflammation [54]. Under physiological conditions, microglia maintain homeostasis through synaptic pruning, phagocytosis of cellular debris, and neurotrophic factor release [55]. However, in response to chronic stressors such as misfolded proteins (amyloid-β, α-synuclein, or mutant huntingtin), mitochondrial dysfunction, and damaged neurons, microglia shift from a surveillant to an activated phenotype [56–58]. This activation involves the engagement of pattern recognition receptors (PRRs), including toll-like receptors (TLR2, TLR4) and NOD-like receptors (NLRP3 inflammasome) [59,60]. The downstream signaling cascade activates NF-κB and MAPK pathways, leading to the transcription of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, as well as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) [61,62].

Persistent activation of microglia results in a "cytokine storm" that sustains oxidative and nitrosative stress [63]. The release of nitric oxide (NO) and superoxide anions generates peroxynitrite ($ONOO^-$), a potent oxidant capable of inducing lipid peroxidation, protein nitration, and mitochondrial injury [64,65]. Moreover, activated microglia express NADPH oxidase (NOX2), contributing directly to the ROS pool and reinforcing a feed-forward loop between inflammation and oxidative stress [66,67].

Astrocytes, which normally maintain extracellular ion balance, neurotransmitter recycling, and BBB integrity, also undergo reactive transformation (astrogliosis) in response to chronic inflammation [68]. Reactive astrocytes upregulate glial fibrillary acidic protein (GFAP), release cytokines and complement components (C3, C1q), and exhibit altered glutamate uptake through decreased expression of the excitatory amino acid transporter EAAT2 [69,70]. This dysregulation increases extracellular glutamate levels, promoting excitotoxicity and neuronal death [71]. Additionally, astrocyte–microglia communication via cytokines (IL-33, CXCL10, TGF-β) creates a paracrine network that sustains neuroinflammatory signaling [72,73].

Crosstalk between glial cells and endothelial components of the neurovascular unit (NVU) further exacerbates pathology [74]. Inflammatory cytokines disrupt tight-junction proteins such as claudin-5, occludin, and ZO-1, increasing BBB permeability and facilitating infiltration of peripheral immune cells [75]. These infiltrating leukocytes amplify the inflammatory milieu by releasing proteases, ROS, and matrix metalloproteinases (MMP-2, MMP-9), leading to vascular leakage and microvascular degeneration [76,77].

Recent evidence highlights the existence of dual glial phenotypes, with M1-like microglia and A1 astrocytes exhibiting pro-inflammatory, neurotoxic profiles, whereas M2-like microglia and A2 astrocytes promote tissue repair, phagocytosis, and release of anti-inflammatory mediators (IL-10, TGF-β) [78,79]. However, in neurodegeneration, the equilibrium between these phenotypes shifts toward the M1/A1 axis, reinforcing a state of chronic neuroinflammation [80]. Therapeutic modulation of glial polarization—through agents targeting TLR4, PPAR-γ, or Nrf2 pathways—has shown promising neuroprotective outcomes in preclinical studies [81–83].

In summary, the interplay between microglia, astrocytes, and endothelial cells defines the inflammatory landscape of neurodegenerative diseases [84]. Persistent glial activation transforms the NVU from a neuroprotective barrier into a source of oxidative and inflammatory stress, thereby bridging neuroinflammation with vascular dysfunction and neuronal loss [85–87].

4. Microvascular Dysfunction and Blood–Brain Barrier Breakdown

The integrity of the cerebral microvasculature is essential for maintaining neural homeostasis. The blood–brain barrier (BBB), composed of endothelial cells, pericytes, astrocytic endfeet, and basement membrane, ensures selective permeability and protects the brain from peripheral insults [73–75]. However, in neurodegenerative diseases (NDs), chronic oxidative stress and inflammation lead to progressive microvascular dysfunction, compromising BBB structure and function [76–78].

Endothelial dysfunction is one of the earliest manifestations of vascular compromise [79]. Cerebral endothelial cells are highly sensitive to oxidative and inflammatory stimuli, which impair nitric oxide (NO) bioavailability, induce mitochondrial injury, and up-regulate adhesion molecules such as ICAM-1, VCAM-1, and E-selectin [80,81]. These alterations promote leukocyte adhesion and trans-endothelial migration, triggering local inflammation and microvascular obstruction [82]. Furthermore, ROS-mediated oxidation of tight-junction proteins (claudin-5, occludin, ZO-1) disrupts intercellular cohesion, increasing BBB permeability and facilitating neurotoxic molecule entry from the circulation [83,84].

Pericyte degeneration represents a critical event linking vascular and neuronal pathology [85,86]. Pericytes regulate capillary tone, endothelial proliferation, and BBB stability through PDGFR-β and Ang/Tie2 signaling [87]. In Alzheimer's disease and other NDs, pericyte loss has been

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demonstrated in both animal models and human autopsy studies, correlating with cerebral hypoperfusion, micro-aneurysm formation, and accumulation of plasma proteins such as fibrinogen and albumin in the parenchyma [88,89]. These extravasated proteins further exacerbate neuroinflammation by activating astrocytes and microglia, thereby amplifying tissue injury [90].

Astrocytic and glial contributions to BBB disruption are increasingly recognized [91]. Under oxidative and inflammatory stress, astrocytic endfeet retract and lose aquaporin-4 (AQP4) polarization, impairing water and ion homeostasis [92]. This alteration compromises the glymphatic system, a recently described clearance pathway essential for removing metabolic waste and amyloid aggregates [93]. Dysfunctional glymphatic flow leads to toxic metabolite accumulation, perpetuating oxidative stress and neuronal degeneration [94,95].

Senescence of endothelial and glial cells adds a further layer of complexity [96]. Senescent cells exhibit a pro-inflammatory secretory phenotype (SASP) characterized by cytokine and MMP release, which deteriorates the extracellular matrix and basement membrane [97]. This process weakens capillary walls and reduces cerebral blood-flow regulation, promoting micro-infarcts and white-matter lesions observed in aging and dementia [98].

Additionally, vascular rarefaction and hypoxia emerge as key pathological features [99]. Chronic hypoperfusion decreases oxygen and nutrient supply to neurons, activates hypoxia-inducible factor-1α (HIF-1α), and shifts metabolism toward glycolysis [100]. Although initially adaptive, sustained HIF-1α activation induces VEGF over-expression, leading to abnormal angiogenesis and leaky, immature vessels that further compromise BBB integrity [100].

In summary, microvascular dysfunction in neurodegenerative diseases results from the synergistic impact of oxidative stress, endothelial injury, pericyte degeneration, astrocytic dysregulation, and cellular senescence [99,100]. These events collectively transform the BBB from a neuroprotective interface into a source of neurotoxicity. Preservation of microvascular health and BBB stability is therefore central to halting the cascade of neurodegeneration and represents a crucial therapeutic target for future interventions [100].

5. Interconnection Between Oxidative Stress, Neuroinflammation, and Microvascular Damage

The interplay between oxidative stress, neuroinflammation, and microvascular dysfunction forms a self-amplifying pathogenic triad that drives the progression of neurodegenerative diseases (NDs) [85–87]. These processes do not act in isolation; rather, they are mechanistically and temporally interconnected through reciprocal signaling within the neurovascular unit (NVU), ultimately leading to neuronal death and cognitive decline [88,89].

Oxidative stress as the initiator: Reactive oxygen and nitrogen species (ROS/RNS) generated by mitochondrial dysfunction, NADPH oxidases, and activated glia initiate redox imbalance [90,91]. Oxidative stress acts as a potent trigger for microglial activation through redox-sensitive transcription factors such as NF-κB and AP-1 [92,93]. The resulting cytokine release (IL-1β, TNF-α, IL-6) recruits additional immune cells and amplifies the inflammatory cascade [94]. Furthermore, ROS directly impair endothelial cell function by oxidizing membrane lipids and disrupting nitric-oxide signaling, thereby contributing to vasoconstriction and BBB permeability [95,96].

Neuroinflammation as the amplifier: Once initiated, the inflammatory response perpetuates oxidative stress through feed-forward mechanisms [97,98]. Activated microglia and astrocytes release large amounts of superoxide, NO, and hydrogen peroxide, overwhelming antioxidant defenses [99]. Cytokines such as IL-1β and TNF-α activate iNOS and NOX enzymes, establishing a vicious cycle that sustains redox imbalance [100]. The chronic presence of these mediators promotes endothelial activation, up-regulating adhesion molecules and metalloproteinases that degrade tight-junction proteins [94–96].

Microvascular dysfunction as the facilitator: The breakdown of the BBB and microvascular integrity permits peripheral immune-cell infiltration, introducing additional ROS and inflammatory mediators from the circulation [89,97]. This extravasation exacerbates oxidative and inflammatory signaling within the CNS, creating a bidirectional feedback loop between systemic and central processes [98]. Loss of pericytes and endothelial senescence further impair cerebrovascular autoregulation, resulting in hypoxia and nutrient deprivation, which intensify mitochondrial dysfunction and oxidative injury [99,100].

Cellular and molecular crosstalk within the NVU: Endothelial cells, astrocytes, microglia, and neurons engage in complex intercellular communication mediated by cytokines, chemokines, and oxidative metabolites [92,93]. For example, microglial-derived ROS activate endothelial NF-κB signaling, while endothelial IL-6 and MCP-1 further activate microglia, forming a sustained inflammatory loop [94,95]. Astrocytes, in turn, sense oxidative stress and release glutamate and ATP, propagating excitotoxicity and calcium dysregulation in neurons [96–98]. This integrated failure of the NVU transforms a local redox disturbance into widespread neurovascular dysfunction [99,100].

Emerging conceptual model: Current evidence supports the notion that these three mechanisms—oxidative stress, inflammation, and vascular injury—converge into a unified neurodegenerative pathway [90,94,99]. Early oxidative imbalance sets the stage for glial activation, while neuroinflammation accelerates endothelial deterioration and BBB leakage [95,96]. Vascular dysfunction, in turn, fuels hypoxia and metabolic distress, perpetuating redox imbalance [97–100]. This cyclic interdependence accounts for the progressive and irreversible nature of neuronal loss observed in disorders such as Alzheimer's, Parkinson's, and ALS [88–90].

Understanding this triadic interplay offers a paradigm shift in neurodegeneration research [91,92]. It suggests that effective therapeutic strategies should adopt multimodal approaches that simultaneously target redox homeostasis, inflammatory modulation, and vascular protection, rather than treating these mechanisms independently [93–95].

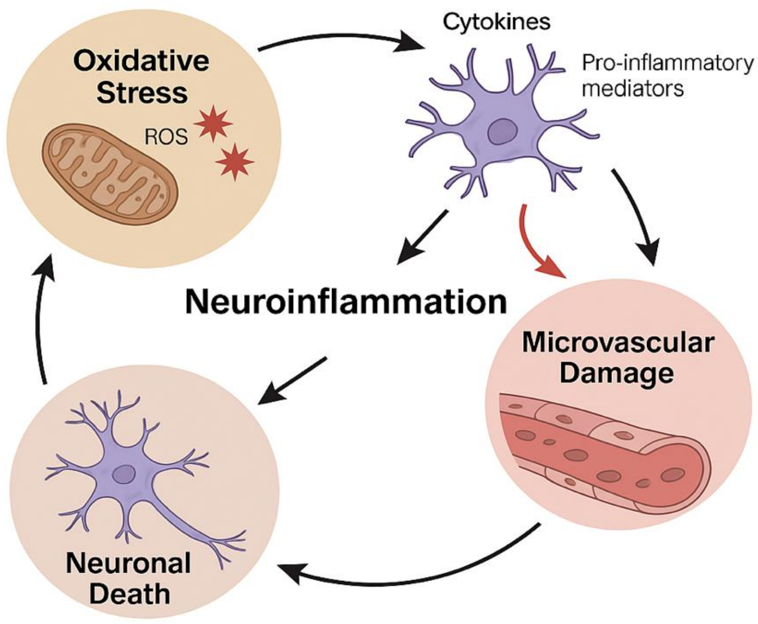

Figure 2. Oxidative Stress–Neuroinflammation–Microvascular Dysfunction Cycle.

The diagram illustrates the self-perpetuating cycle linking oxidative stress, neuroinflammation, and microvascular damage in neurodegenerative diseases. Excessive production of reactive oxygen species (ROS) promotes glial activation and the release of pro-inflammatory mediators, which in turn exacerbate endothelial dysfunction and blood–brain barrier breakdown. These events contribute to neuronal death and perpetuate the oxidative–inflammatory–vascular feedback loop within the neurovascular unit (NVU).

6. Therapeutic and Preventive Strategies

The intricate interdependence between oxidative stress, neuroinflammation, and microvascular dysfunction highlights the necessity for multitarget therapeutic approaches capable of restoring redox balance, modulating inflammatory signaling, and preserving neurovascular integrity [91–93]. Although no current pharmacological intervention fully halts neurodegeneration, numerous preclinical and clinical studies suggest that combined strategies acting on these interconnected mechanisms may significantly slow disease progression [94–96].

6.1. Antioxidant-Based Therapies

Restoration of redox equilibrium remains a cornerstone of neuroprotective strategies [97]. Traditional antioxidants such as vitamin E, vitamin C, and coenzyme Q10 have shown limited clinical efficacy due to poor bioavailability and inability to cross the BBB [98]. Consequently, research has shifted toward mitochondria-targeted antioxidants such as MitoQ, SkQ1, and SS-31 (elamipretide), which directly localize within mitochondria to prevent ROS overproduction and maintain ATP synthesis [99,100].

Polyphenolic compounds—including resveratrol, curcumin, quercetin, and epigallocatechin gallate (EGCG)—have demonstrated robust neuroprotective effects in experimental models [83,84]. Their mechanisms extend beyond direct ROS scavenging to activation of the Nrf2–ARE pathway, which enhances the expression of endogenous antioxidants (SOD, catalase, GPx, HO-1) [85,86]. Moreover, melatonin exhibits dual antioxidant and mitochondrial-protective functions, modulating Bcl-2 family proteins and preventing cytochrome c release [87].

6.2. Anti-Inflammatory and Glial-Modulating Approaches

Targeting chronic glial activation is critical for mitigating the inflammatory amplification loop [88]. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and indomethacin have shown partial protection in epidemiological studies but carry risks of systemic side effects [89]. Modern approaches aim to achieve selective immunomodulation without global suppression [90].

Agents such as minocycline and pioglitazone (a PPAR-γ agonist) have been shown to inhibit microglial activation, suppress NF-κB signaling, and shift microglia toward the anti-inflammatory M2 phenotype [91,92]. Similarly, dimethyl fumarate (approved for multiple sclerosis) exerts combined anti-inflammatory and antioxidant effects through activation of Nrf2 and inhibition of pro-inflammatory cytokines [93]. Novel small molecules targeting NLRP3 inflammasome assembly (e.g., MCC950) or TLR4 antagonists (e.g., TAK-242) show promise in restoring glial homeostasis [94–96].

Astrocyte-directed therapies are gaining attention as regulators of BBB integrity and excitotoxicity [97,98]. Ceftriaxone, an FDA-approved β-lactam antibiotic, upregulates the glutamate transporter EAAT2, reducing glutamate-induced neuronal injury [99]. Similarly, adenosine A2A receptor antagonists modulate astrocyte–microglia communication and have demonstrated cognitive benefits in early clinical trials for Parkinson's disease [100].

6.3. Vascular and BBB-Targeted Interventions

Protection and restoration of microvascular function represent a growing therapeutic frontier [95,96]. Angiotensin II receptor blockers (ARBs) and ACE inhibitors have demonstrated neurovascular protective effects independent of blood pressure regulation, partly by enhancing endothelial NO availability and reducing oxidative stress [97]. Statins, through pleiotropic antioxidant and anti-inflammatory properties, improve endothelial function and reduce amyloid-β deposition [98,99].

Experimental compounds that stabilize the tight-junction architecture (e.g., claudin-5 mimetics, MMP inhibitors) and enhance pericyte survival (via PDGF-BB or Tie2 agonists) have shown promise in preclinical neurodegeneration models [100]. Vasoprotective peptides, such as angiopoietin analogues and VEGF modulators, are under active investigation to repair BBB leakage while preventing aberrant angiogenesis [99,100].

6.4. Emerging and Multimodal Strategies

Given the multifactorial nature of neurodegeneration, combined or multitarget therapies are increasingly favored [93,94]. Nanocarrier-based delivery systems improve drug penetration across the BBB and allow co-delivery of antioxidants and anti-inflammatory agents [95,96]. Lipid nanoparticles, polymeric micelles, and exosome-based carriers are being engineered to transport Nrf2 activators, siRNAs, or mitochondria-protective compounds with enhanced precision [97,98].

Gene and cell-based therapies are also entering the translational stage [99]. Overexpression of antioxidant enzymes (e.g., SOD2, GPx1) via viral vectors reduces ROS burden and protects against neuronal loss [100]. Mesenchymal stem cell (MSC)-derived exosomes exert potent anti-inflammatory and vasoprotective effects by transferring microRNAs that regulate Nrf2 and NF-κB pathways [95–97].

Additionally, lifestyle and metabolic interventions—including physical exercise, caloric restriction, and ketogenic diets—modulate mitochondrial function and vascular health through activation of sirtuins and AMP-activated protein kinase (AMPK) [98,99]. These non-pharmacological strategies have demonstrated synergistic effects when combined with pharmacological treatments [100].

6.5. Integrative Perspective

Collectively, these therapeutic approaches underscore the importance of addressing neurodegeneration as a multisystem disorder encompassing oxidative, inflammatory, and vascular dimensions [99,100]. Future research should prioritize the development of multimodal therapies that integrate antioxidant and anti-inflammatory actions with microvascular protection, ideally delivered through advanced targeted systems capable of crossing the BBB [95,96]. Precision-medicine approaches—guided by patient-specific redox and vascular biomarkers—may enable early intervention and improved clinical outcomes in neurodegenerative disorders [99,100].

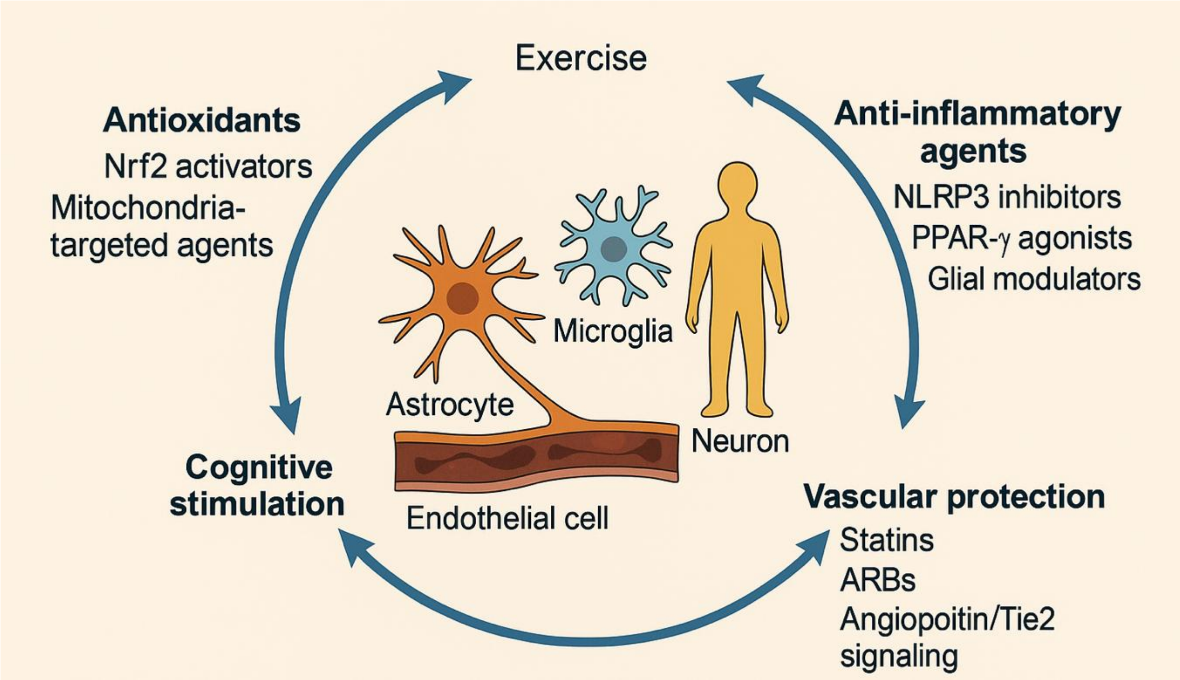

Figure 3. Multimodal Therapeutic Strategies Targeting the Oxidative–Inflammatory–Vascular Axis in Neurodegenerative Diseases.

The diagram summarizes integrative therapeutic approaches aimed at restoring redox and neurovascular homeostasis. Antioxidant therapies (e.g., Nrf2 activators, mitochondria-targeted agents) reduce oxidative stress; anti-inflammatory agents (PPAR-γ agonists, NLRP3 inhibitors, glial modulators) attenuate chronic neuroinflammation; and vascular-protective compounds (statins, ARBs, Angiopoietin/Tie2 signaling modulators) maintain endothelial and BBB integrity. Lifestyle interventions such as exercise, diet optimization, and cognitive stimulation further enhance neuroprotection and functional recovery.

7. Future Perspectives and Conclusions

The convergence of oxidative stress, neuroinflammation, and microvascular dysfunction represents a unified mechanistic framework underlying the onset and progression of neurodegenerative diseases [94–96]. Rather than independent pathological entities, these processes form an interdependent network that accelerates neuronal damage through reciprocal amplification [97,98]. Mitochondrial dysfunction, glial activation, and vascular breakdown together compromise the structural and functional integrity of the neurovascular unit (NVU), transforming a once-protective environment into a pro-degenerative niche [99,100].

Future research directions should focus on dissecting this triadic interplay at cellular and molecular levels using high-resolution imaging, multi-omics approaches, and integrative computational models [95–97]. Systems biology and single-cell transcriptomics are particularly promising for identifying novel biomarkers that capture the dynamic crosstalk between redox, inflammatory, and vascular pathways [98,99]. The discovery of early circulating biomarkers—such as oxidative metabolites, cytokine profiles, or endothelial-derived extracellular vesicles—could revolutionize diagnosis, enabling pre-symptomatic detection and therapeutic intervention at reversible stages [100].

Translationally, there is growing consensus that monotherapy approaches targeting a single mechanism have limited efficacy in complex disorders like Alzheimer's or Parkinson's disease [93–95]. Consequently, multimodal interventions that simultaneously modulate oxidative, inflammatory, and vascular targets are likely to yield more durable benefits [96–98]. Advances in nanomedicine, gene therapy, and stem cell-derived exosomes open new avenues for delivering neuroprotective agents across the BBB with higher specificity and safety [99,100]. Furthermore, the integration of lifestyle interventions—including exercise, diet modulation, and cognitive stimulation—may potentiate pharmacological treatments by enhancing mitochondrial resilience and vascular perfusion [97–99].

Clinically, the implementation of personalized therapeutic algorithms based on patient-specific molecular signatures will be pivotal [95,96]. Stratifying patients according to oxidative, inflammatory, and vascular biomarkers could improve treatment responsiveness and reduce heterogeneity in clinical outcomes [97,98].

In conclusion, the oxidative–inflammatory–vascular axis provides a comprehensive lens through which neurodegeneration can be reinterpreted not as an isolated neuronal disorder, but as a systemic failure of the neurovascular unit [99,100]. Targeting this triad holds transformative potential for developing disease-modifying therapies. Future efforts must bridge mechanistic insights with clinical translation, ensuring that therapeutic advances move from bench to bedside with precision and efficacy [99,100].

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