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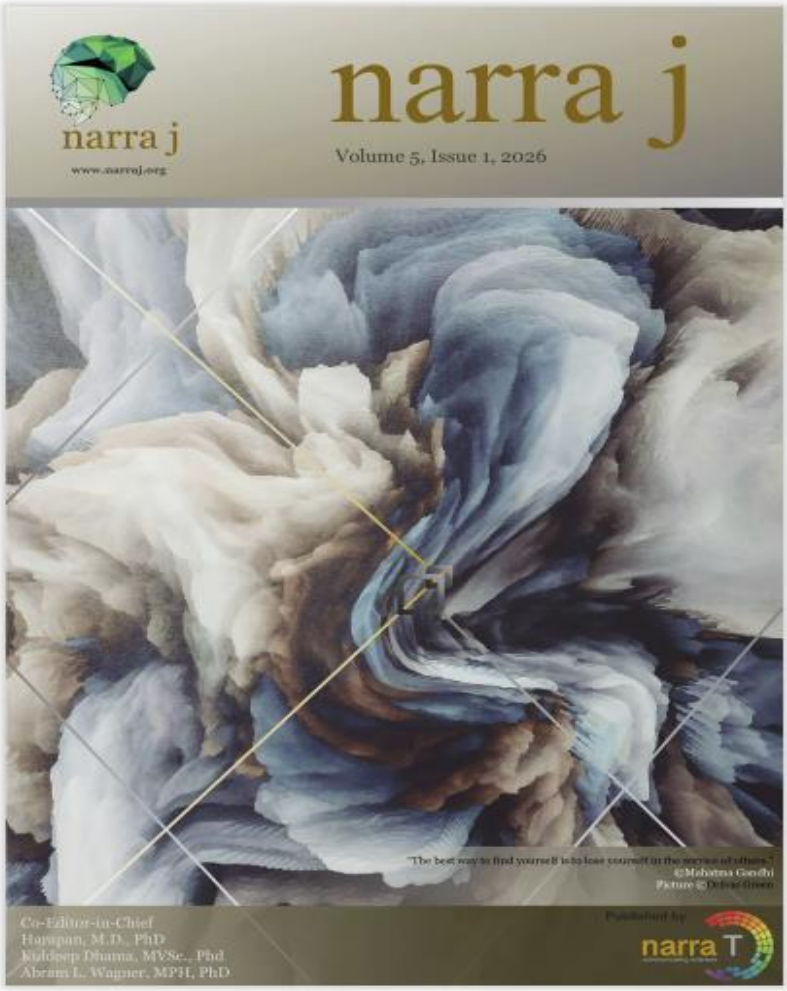

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Oxidative stress_review article

by Meutia Faradilla

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Oxidative stress as a converging mechanism of aging and neurodegeneration: From molecular pathways to therapeutic targets

Introduction

The unprecedented expansion of the elderly demographic worldwide has been paralleled by a dramatic rise in neurodegenerative disorders (NDDs), most notably Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) (1). Although these conditions present with distinct clinical manifestations and hallmark protein signatures, they converge upon a common and arguably central risk factor that is biological aging (2). Oxidative stress represents a fundamental biological process that becomes progressively dysregulated with aging, driving neuronal vulnerability and neurodegenerative disease progression. This observation suggests that the molecular processes governing senescence do not serve merely as a passive backdrop, but rather act as active drivers of neuronal vulnerability and decline. Within the network of aging-related mechanisms, Oxidative stress functions as a central converging mechanism linking normal physiological aging to pathological neurodegeneration (3). Rather than being a mere by-product of metabolic activity, oxidative stress represents a failure of redox homeostasis, a state in which the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) overwhelms the capacity of cellular detoxification and repair systems (4). Crucially, while basal ROS levels play indispensable roles in signal transduction and cellular adaptation, chronic elevations beyond physiological thresholds instigate cumulative structural damage to DNA, membrane lipids, and functional proteins (5).

Classical theories, such as Harman's Free Radical Theory of Aging, have historically attributed aging to random accumulation of oxidative damage. However, contemporary research has refined this perspective to emphasize that oxidative stress disrupts regulated redox-sensitive signaling pathways, thereby destabilizing fundamental processes essential for neuronal survival (6). The Central Nervous System (CNS) is uniquely susceptible to this form of dysregulation. Although the brain constitutes only about 2% of total body mass, it consumes roughly 20% of basal oxygen, reflecting a metabolic intensity that predisposes it to disproportionate oxidative burden. At the heart of this vulnerability lies the mitochondrion (7). As the primary source of intracellular ROS generation, mitochondria are paradoxically both the generators and principal victims of oxidative insult. In the aging brain, progressive mitochondrial compromise precipitates a bioenergetic crisis, impairing neuronal capacity to sustain ionic gradients, neurotransmission, and synaptic plasticity. Moreover, damaged electron transport chains become leakier, generating excessive ROS that further tax dwindling antioxidant defenses(8).

This bioenergetic imbalance is intimately linked to the collapse of proteostasis, the constellation of cellular systems that govern protein folding, trafficking, and degradation. Oxidative modifications such as carbonylation and nitration render proteins prone to misfolding while simultaneously inhibiting the ubiquitin proteasome system and autophagy lysosomal pathways responsible for their clearance (9). The resultant molecular gridlock fosters the accumulation of neurotoxic aggregates, including amyloid β in AD and alpha-synuclein in PD. In turn, these aggregates destabilize redox balance, creating a synergistic feedback loop in which protein aggregation exacerbates oxidative stress, and oxidative stress accelerates aggregation (10). This review integrates molecular, cellular, and translational evidence to explain how oxidative stress links biological aging to neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. We dissect the molecular origins of ROS, the age associated erosion of antioxidant defenses, and the convergence of these pathways on protein aggregation and neuronal loss. Furthermore, we explore the historical pitfalls of broad-spectrum antioxidant therapies and advocate for a paradigm shift toward targeted modulation of redox-sensitive circuits rather than non-specific scavenging. Although oxidative stress has been widely implicated in aging and neurodegeneration, existing literature often examines these mechanisms independently. Few reviews integrate mitochondrial dysfunction, proteostatic collapse, neuroinflammation, and redox signaling into a unified framework. Although oxidative stress has

been widely implicated in aging and neurodegeneration, existing literature often examines these mechanisms independently. Few reviews integrate mitochondrial dysfunction, proteostatic collapse, neuroinflammation, and redox signaling into a unified framework. This article addresses this gap by synthesizing multi-level evidence to clarify how redox imbalance acts as a converging driver of neuronal decline.

Molecular mechanisms of oxidative stress

Global population aging has been accompanied by a marked increase in neurodegenerative diseases, including AD, PD and ALS. Although these disorders are clinically distinct, they share biological aging as a common risk factor, indicating that age-related cellular processes actively contribute to neuronal degeneration(11). Among the molecular pathways involved, oxidative stress has emerged as a central converging mechanism linking physiological aging with neurodegenerative pathology(12). Oxidative stress arises when the production of reactive oxygen and nitrogen species exceeds the capacity of cellular defense systems, leading to damage of DNA, lipids, and proteins. While low levels of reactive species are essential for normal cellular signaling, sustained elevations disrupt redox homeostasis and impair neuronal function(3)(8). The central nervous system is particularly susceptible to oxidative injury due to its high metabolic demand and disproportionate oxygen consumption, making oxidative stress a critical driver of age-related neurodegeneration(13).

Molecular origins of reactive species

ROS are primarily generated as metabolic byproducts of aerobic respiration, with the mitochondrial electron transport chain (ETC) serving as the principal intracellular source. During oxidative phosphorylation, electron leakage occurs most notably at Complex I (NADH dehydrogenase) and Complex III (ubiquinone–cytochrome c reductase). This leakage results in the partial reduction of molecular oxygen (O_2), forming the superoxide anion ($O_2^{\cdot -}$), as described by the reaction(14):

$$O_2 + e^- \rightarrow O_2^{\cdot -}$$

Superoxide is rapidly dismutated into the more stable hydrogen peroxide (H_2O_2), which can diffuse across cellular membranes and function as a signaling molecule. However, the pathogenic potential of oxidative stress markedly increases in the presence of transition metals. Through the Fenton reaction, hydrogen peroxide reacts with ferrous iron (Fe^{2+}) or cuprous copper (Cu^{+}), generating the highly reactive and destructive hydroxyl radical (·OH) (15):

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {\cdot}OH + OH^-$$

The oxidative burden within the brain is not exclusively of mitochondrial origin. Several enzymatic systems contribute significantly to intracellular ROS production, including the NADPH oxidase (NOX) family, peroxisomes, and cytochrome P450 enzymes. In the context of neurodegeneration, the activation of NOX enzymes in microglia is recognized as a major driver of neuroinflammation. This process creates a toxic synergy between oxidative stress and immune activation, amplifying neuronal damage and accelerating neurodegenerative progression(16)(17).

Mitochondrial ROS Generation

Mitochondria are central to cellular energy production through oxidative phosphorylation, but they are also the primary source of reactive oxygen species (ROS). During oxidative phosphorylation, electrons are transferred through the mitochondrial electron transport chain, and some electrons leak at Complex I and Complex III. This leakage leads to the partial reduction of molecular oxygen, producing superoxide anions ($O_2^{\cdot -}$). These superoxides are then converted into hydrogen peroxide (H_2O_2), which, in turn, can form hydroxyl radicals (·OH) through Fenton reactions, further amplifying oxidative stress(18). This ROS production becomes self-perpetuating in aging and neurodegenerative diseases, as damaged mitochondria generate more ROS, worsening mitochondrial dysfunction. This creates a vicious cycle where oxidative damage to cellular structures such as lipids, proteins, and DNA intensifies cellular dysfunction, accelerating the progression of diseases like Alzheimer's and Parkinson's. Moreover, mitochondrial damage can reduce ATP production, impeding cellular functions and contributing to neuronal degeneration(5).

Lipid Peroxidation and Membrane Vulnerability

Oxidative stress also leads to lipid peroxidation, a process in which ROS attack the polyunsaturated fatty acids in cellular membranes. Lipid peroxidation generates highly reactive secondary products such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA), which can diffuse across the cell and interact with other cellular components. These lipid peroxidation products disrupt the structural integrity of neuronal membranes, impairing the fluidity and function of the lipid bilayer(19). This damage compromises membrane-bound proteins, receptors, and ion channels, leading to disturbances in cellular signaling, neurotransmission, and overall neuronal efficiency. In neurodegenerative diseases, this membrane vulnerability accelerates neuronal damage and contributes to synaptic dysfunction. For instance, in Alzheimer's disease, lipid peroxidation can facilitate the aggregation of amyloid-beta (Aβ), further exacerbating the pathological cycle. The lipid-rich membranes of neurons make them particularly susceptible to oxidative damage, reinforcing the progression of diseases like AD and PD(20).

Proteostasis Collapse

Proteostasis is essential for maintaining cellular homeostasis by regulating protein synthesis, folding, and degradation. However, oxidative stress disrupts proteostasis, leading to the accumulation of damaged and misfolded proteins. ROS can induce oxidative modifications such as carbonylation and nitration on proteins, altering their structure and function. These misfolded proteins are typically targeted for degradation by the proteasome or autophagy pathways. However, oxidative stress impairs these systems, leading to the accumulation of toxic protein aggregates. In neurodegenerative diseases like Alzheimer's and Parkinson's, this collapse of proteostasis is particularly detrimental. For example, in Alzheimer's disease, amyloid-beta (Aβ) accumulates and forms plaques, while in Parkinson's disease, α-synuclein forms Lewy bodies. These protein aggregates not only disrupt cellular function but also impair synaptic plasticity, damage mitochondria, and promote neuroinflammation. The accumulation of misfolded proteins creates a positive feedback loop that exacerbates oxidative stress, mitochondrial dysfunction, and cellular damage**(21).**

Redox Inflammatory Crosstalk

Oxidative stress and neuroinflammation are intimately connected, with ROS playing a crucial role in activating redox-sensitive transcription factors like NF-κB. NF-κB, once activated by ROS, translocates to the nucleus and initiates the expression of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α. These cytokines activate microglia, the resident immune cells of the brain, which further increase ROS production and promote inflammation. Chronic neuroinflammation exacerbates neuronal damage by impairing synaptic function, disrupting calcium homeostasis, and sensitizing neurons to excitotoxicity. This inflammatory response becomes self-perpetuating under conditions of sustained oxidative stress, where proinflammatory cytokines further exacerbate ROS production, leading to a cycle of oxidative injury and inflammation. This crosstalk between oxidative stress and inflammation is a critical driver of neurodegenerative diseases like Alzheimer's and Parkinson's, where inflammation amplifies the damage caused by ROS, leading to progressive neuronal death and dysfunction (22).

Autophagy and Mitophagy Failure

Autophagy and mitophagy are vital cellular processes for maintaining cellular integrity by degrading damaged proteins and organelles. In neurons, where turnover is limited due to the lack of cell division, the efficient functioning of autophagic pathways is critical for long-term survival. However, oxidative stress compromises the integrity of these pathways. ROS can damage the lysosomal system, which is responsible for the final stages of autophagic degradation, impairing its function(23). As a result, damaged proteins and dysfunctional organelles accumulate within neurons, further exacerbating cellular stress. In particular, mitophagy, the selective removal of damaged mitochondria, is essential to protect cells from oxidative damage. However, oxidative stress impairs mitophagy by disrupting the PINK1/Parkin pathway, which is responsible for marking damaged mitochondria for degradation. The failure to clear dysfunctional mitochondria allows them to persist

and continue generating ROS, perpetuating mitochondrial dysfunction and oxidative stress. This accumulation of damaged mitochondria, often referred to as "zombie mitochondria," further disrupts cellular function, leading to energy depletion and contributing to the neurodegenerative processes observed in diseases like Parkinson's(24).

Antioxidant defense

Enzymatic vanguard: The first line of redox control

The first layer of cellular antioxidant defense is formed by a tightly coordinated system of enzymatic antioxidants that operate in a sequential and highly regulated manner. Superoxide dismutases (SODs) act as primary responders by rapidly neutralizing superoxide radicals, which are predominantly produced through electron leakage from the mitochondrial respiratory chain(25). Because superoxide is highly reactive and short lived, its rapid conversion into hydrogen peroxide constitutes a crucial protective mechanism rather than a simple chemical reaction. However, hydrogen peroxide occupies a dual role within neuronal physiology(26). At low concentrations, it functions as a diffusible second messenger involved in synaptic plasticity and signal transduction. Yet, when allowed to accumulate, it becomes a latent threat, particularly in metal-rich neural environments where iron and copper are abundant. To prevent this transition from signaling molecule to cytotoxic precursor, downstream enzymes such as catalase (CAT) and glutathione peroxidase (GPx) assume decisive roles (27)(28). By decomposing hydrogen peroxide into water and molecular oxygen, these enzymes effectively terminate the oxidative cascade before it can culminate in hydroxyl radical formation a species widely regarded as the most destructive ROS due to its indiscriminate reactivity (16). This enzymatic cascade is not simply redundant; instead, it represents an evolutionarily refined system built to maintain redox stability under stress. When any component of this network is compromised whether due to genetic variation, post-translational alterations, or age-related functional decline the balance of redox control can be disrupted. As a result, neurons become particularly vulnerable to oxidative damage(29).

Non-enzymatic buffers and thiol-based redox modulation

Alongside enzymatic antioxidants, cells rely on a broad network of non-enzymatic redox buffers, with glutathione (GSH) playing a central and indispensable role. As the most abundant intracellular thiol antioxidant, glutathione functions as a dynamic redox reservoir that buffers oxidative fluctuations beyond the capacity of enzymatic systems. By donating electrons, GSH neutralizes reactive species and is converted into its oxidized form, glutathione disulfide (GSSG). Consequently, the balance between reduced and oxidized glutathione (the GSH/GSSG ratio) serves as a sensitive marker of cellular redox status. In neurons, which possess limited tolerance to oxidative stress, even subtle changes in this ratio may indicate early metabolic strain (30). Evidence from aging studies consistently shows a gradual decline in glutathione levels, suggesting that neurodegeneration is preceded by a slow weakening of intrinsic redox buffering rather than an abrupt oxidative event. Beyond direct antioxidant activity, glutathione supports detoxification processes and modulates redox-sensitive protein thiols, thereby influencing gene regulation, mitochondrial stability, and synaptic function. Loss of glutathione therefore reflects not only diminished antioxidant protection but a broader breakdown in redox regulation (31).

Regulatory control and the Nrf2 axis

The effectiveness of antioxidant defenses within the CNS is ultimately governed at the transcriptional level. Central to this regulation is the nuclear factor erythroid 2–related factor 2 (Nrf2), a master regulator of cellular stress responses. Under basal conditions, Nrf2 is sequestered in the cytoplasm; however, in the presence of oxidative stress, it translocates to the nucleus and initiates the expression of a broad repertoire of antioxidant and cytoprotective genes, including those encoding SOD, GPx, catalase, and glutathione synthesis enzymes. In youthful and healthy neural tissue, this inducible system provides a remarkable degree of plasticity, enabling neurons to adapt rapidly to fluctuating redox demands**(32)**. With advancing age, however, the responsiveness of the Nrf2 pathway becomes progressively attenuated. This decline does not necessarily reflect a complete loss of function, but rather a diminished sensitivity to oxidative

cues. As a result, the antioxidant response becomes delayed or insufficient, allowing ROS production to outpace detoxification. This age-associated regulatory failure creates what can be described as a "redox vulnerability gap," wherein neurons persist under conditions of chronic, low-grade oxidative stress. Over time, this imbalance promotes cumulative macromolecular damage, mitochondrial dysfunction, and inflammatory signaling hallmarks that converge to drive the initiation and progression of neurodegenerative disorders(33).

Oxidative stress in aging: The "hardwiring" of senescence

The modified free radical theory of aging

Harman's Free Radical Theory of Aging, introduced in 1956, initially proposed that aging results from the gradual accumulation of oxidative damage to essential biomolecules caused by reactive oxygen species (ROS). While this concept laid the foundation for modern aging research, it has since evolved beyond the idea of random and irreversible molecular injury (34). Current perspectives recognize ROS not only as damaging agents but also as critical regulators of physiological redox signaling. In young and healthy cells, redox balance is tightly controlled(35). However, this regulatory capacity declines with age, leading to a state of chronic, low-grade oxidative stress. This persistent redox imbalance subtly disrupts cellular signaling pathways and promotes a pro-inflammatory milieu, commonly referred to as inflammaging. In this framework, oxidative stress contributes to aging not merely through direct macromolecular damage, but by driving immune dysregulation and sustained inflammatory signaling. The modified Free Radical Theory therefore reframes aging as a systemic failure of redox homeostasis, in which oxidative stress and inflammation interact to accelerate functional decline (36).

Accumulation of macromolecular damage in the aging brain

The aging brain is particularly susceptible to oxidative damage due to its high oxygen consumption, lipid-rich composition, and limited regenerative capacity. Over time, an imbalance between reactive oxygen species (ROS) production and antioxidant defenses leads to the gradual accumulation of damage to lipids, proteins, and nucleic acids, ultimately compromising neuronal structure and function(37). Lipid peroxidation represents an early and amplifying form of oxidative injury in neurons. Neuronal membranes are rich in polyunsaturated fatty acids, which are highly vulnerable to oxidative attack. This process generates reactive secondary products such as 4-hydroxynonenal and malondialdehyde, which persist longer than primary radicals and diffuse across cellular compartments. These byproducts disrupt membrane integrity, impair receptor signaling, and interfere with synaptic transmission, thereby reducing neuronal efficiency (38).

Proteins are also major targets of oxidative stress. Oxidative modifications promote protein misfolding and aggregation, a process that is especially harmful in post-mitotic neurons. With aging, the efficiency of proteostatic systems, including the ubiquitin–proteasome pathway and autophagy, progressively declines. As a result, damaged proteins accumulate and form insoluble aggregates that disrupt intracellular transport and synaptic maintenance, further exacerbating cellular stress (21). Oxidative damage to DNA, particularly mitochondrial DNA, adds another layer of vulnerability. Located near the electron transport chain and lacking robust protective and repair mechanisms, mitochondrial DNA is highly prone to oxidative lesions such as 8-hydroxy-2′-deoxyguanosine. These mutations impair mitochondrial gene expression and energy production, increasing electron leakage and ROS generation. This establishes a self-perpetuating cycle in which oxidative damage and mitochondrial dysfunction reinforce one another, accelerating neuronal aging and degeneration (39).

Oxidative stress in neurodegenerative diseases

Alzheimer's disease: Oxidative stress as a self-reinforcing pathological loop

In Alzheimer's disease, oxidative stress is no longer viewed as a secondary consequence of neuronal damage but rather as a central driver of disease progression. It operates through interconnected, self-reinforcing loops that involve amyloid-beta (Aβ) accumulation, mitochondrial dysfunction, and Tau pathology. Soluble Aβ oligomers display redox-active properties and readily interact with neuronal membranes and redox-active metals such as iron and copper, triggering localized production of reactive oxygen species (ROS). This pro-oxidative microenvironment damages surrounding cellular components while simultaneously promoting further Aβ aggregation, creating a bidirectional interaction between amyloid pathology and oxidative stress that contributes to early synaptic impairment (40). As shown in figure 1, the pathological process begins with the accumulation of Aβ within neuronal mitochondria further intensifies oxidative injury by disrupting the electron transport chain, particularly cytochrome c oxidase, resulting in reduced ATP synthesis and increased electron leakage. These changes enhance mitochondrial ROS generation, induce mitochondrial DNA damage, and progressively compromise cellular energy balance. In parallel, oxidative stress modulates Tau pathology by activating stress-responsive kinases that promote Tau hyperphosphorylation, leading to microtubule destabilization and impaired axonal transport. Aggregated Tau subsequently worsens mitochondrial dysfunction and oxidative imbalance. Together, these interdependent mechanisms place oxidative stress at the center of a pathological network that links amyloid toxicity, bioenergetic failure, and cytoskeletal disruption in Alzheimer's disease(41).

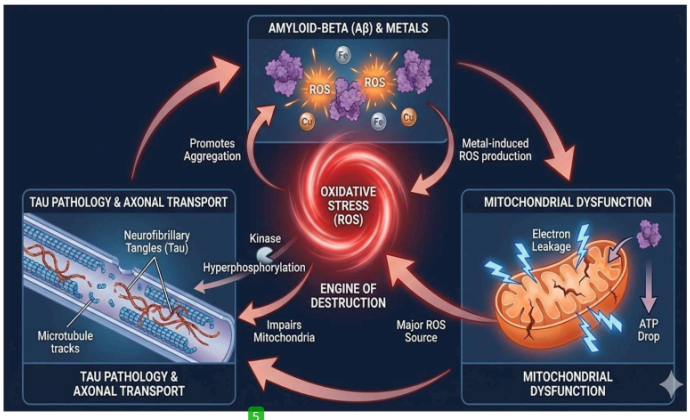

Figure 1. The self-reinforcing cycle of oxidative stress and mitochondrial dysfunction, illustrating the roles of amyloid-beta, metals, tau pathology, and mitochondrial dysfunction in Alzheimer's disease. The illustration was generated using BioRender, which was used to visualize the key mechanisms of oxidative stress and neuronal damage in AD pathology.

Parkinson's disease: Selective vulnerability to oxidative stress

Parkinson's disease illustrates how intrinsic metabolic characteristics render specific neuronal populations highly vulnerable to oxidative stress. Degeneration of dopaminergic neurons in the substantia nigra pars compacta arises from the convergence of dopamine metabolism, mitochondrial dysfunction, and impaired antioxidant defenses. Dopamine itself contributes to oxidative burden through enzymatic degradation by monoamine oxidase B, which generates hydrogen peroxide, as well as through spontaneous auto-oxidation that produces reactive quinones capable of damaging proteins and mitochondrial enzymes. This persistent oxidative environment selectively stresses dopaminergic neurons(42).

As shown in figure 2, the pathological process of parkinson's disease begins with mitochondrial dysfunction, which further amplifies oxidative injury. Genes implicated in familial PD, including PINK1, Parkin, and DJ-1, play critical roles in mitochondrial quality control and redox regulation. Under normal conditions, damaged mitochondria are removed via PINK1–Parkin–mediated mitophagy, limiting excessive reactive oxygen species production. Disruption of this system allows dysfunctional, ROS-generating mitochondria to accumulate, intensifying oxidative stress(43). Loss of DJ-1–mediated redox sensing further reduces neuronal resilience. Together, these mechanisms establish a self-reinforcing cycle in which oxidative stress and mitochondrial failure drive selective dopaminergic neurodegeneration in Parkinson's disease [36].

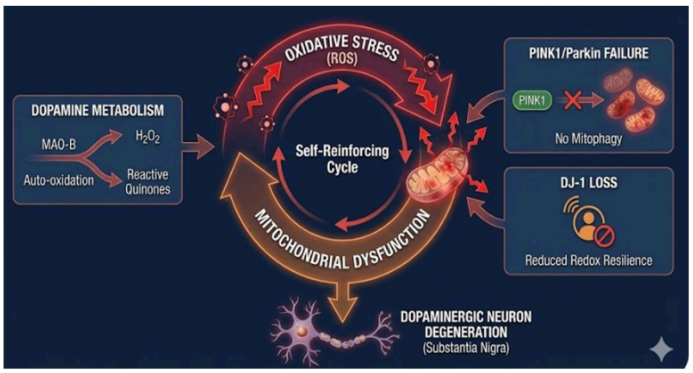

Figure 2. The self-reinforcing cycle of oxidative stress and mitochondrial dysfunction in Parkinson's disease, illustrating how dopamine metabolism, PINK1/Parkin failure, and DJ-1 loss contribute to dopaminergic neuron degeneration in the substantia nigra. The illustration was generated using BioRender to visualize the key mechanisms of oxidative stress and mitochondrial impairment in Parkinson's pathology

The converging pathways: Inflammation and autophagy

Oxidative stress represents an early destabilizing force in neuronal homeostasis, yet its most destructive effects emerge through its capacity to activate downstream pathological pathways (45). Rather than acting as an isolated insult, sustained redox imbalance orchestrates a broader cellular collapse by engaging neuroinflammatory signaling and disrupting intracellular quality-control mechanisms. Among these, chronic inflammation and autophagy impairment stand out as convergent pathways that transform transient oxidative disturbances into irreversible neurodegenerative trajectories (46).

The oxidative inflammatory axis: From redox imbalance to neurotoxicity

In the central nervous system, oxidative stress and inflammation are intimately intertwined, forming a self-amplifying pathological circuit. Microglia, the brain's resident immune cells, are uniquely positioned at the interface between neuronal metabolism and immune surveillance. Under physiological conditions, microglia maintain synaptic integrity and respond transiently to injury. However, persistent oxidative stress alters this homeostatic role, pushing microglia toward a chronically activated, proinflammatory phenotype (47).

ROS-mediated activation of proinflammatory signaling

Reactive oxygen species function as potent second messengers capable of activating redox-sensitive transcription factors. Among these, nuclear factor kappa-light-chain-enhancer of

activated B cells (NF-κB) plays a central role in translating oxidative cues into inflammatory gene expression. Elevated ROS levels promote the dissociation of NF-κB from its cytoplasmic inhibitors, allowing its translocation into the nucleus. Once activated, NF-κB drives the transcription of a broad spectrum of proinflammatory mediators, including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). These cytokines exert pleiotropic effects within the neural microenvironment. Beyond recruiting additional immune responses, they directly impair synaptic function, disrupt neuronal calcium homeostasis, and sensitize neurons to excitotoxic injury. Importantly, this inflammatory signaling is not a short-lived response but becomes sustained under conditions of chronic oxidative stress, reshaping the neural milieu into one that favors degeneration rather than repair (48).

Self-perpetuating cycle of ROS and inflammation

Once neuroinflammation is established, it further amplifies oxidative stress through the activation of enzymatic sources of reactive oxygen species. Proinflammatory cytokines promote the activation of microglial NADPH oxidase 2 (NOX2), an enzyme complex specifically dedicated to regulated ROS generation. Unlike mitochondrial ROS, which are produced as byproducts of cellular metabolism, NOX2-derived ROS are intentionally generated as part of immune signaling. Under conditions of sustained activation, however, this response becomes maladaptive. Elevated ROS levels inflict additional damage on neuronal membranes, proteins, and mitochondria, leading to the release of danger-associated molecular patterns that further stimulate microglial activation. This feedback loop establishes a self-perpetuating cycle in which oxidative stress and inflammation reinforce one another, progressively spreading neuronal injury and contributing to the chronic and progressive nature of neurodegenerative disorders(49).

Autophagy and mitophagy failure: Breakdown of cellular quality control

While inflammation accelerates extracellular and intercellular damage, oxidative stress simultaneously undermines the intracellular systems responsible for maintaining neuronal integrity. Autophagy, the primary pathway for degrading aggregated proteins and dysfunctional organelles, is particularly vulnerable to redox dysregulation. In post-mitotic cells such as neurons, where damaged components cannot be diluted through cell division, the integrity of autophagic flux is essential for long-term survival(50).

Lysosomal dysfunction and autophagic arrest

Effective autophagy depends on intact lysosomal function. However, oxidative stress generates lipid peroxidation products such as 4-hydroxynonenal (4-HNE) that covalently modify lysosomal membranes and hydrolytic enzymes. These modifications compromise lysosomal acidity and enzymatic efficiency, impairing the final stages of autophagic degradation. As autophagic flux slows, damaged proteins and organelles accumulate within neurons, placing additional stress on already compromised cellular systems. This accumulation not only disrupts intracellular trafficking and synaptic maintenance but also amplifies oxidative stress by allowing ROS-generating structures to persist. Thus, lysosomal dysfunction represents a critical bottleneck where oxidative damage translates into widespread cellular failure(24).

Mitophagy failure and energetic collapse

Among autophagic processes, the selective removal of damaged mitochondria, known as mitophagy. is of particular importance in neurodegeneration. Mitochondria are both the primary producers and principal targets of ROS. Under normal conditions, the PINK1/Parkin pathway identifies dysfunctional mitochondria and targets them for autophagic clearance, preventing excessive ROS leakage. Oxidative stress, however, disrupts this quality-control system. Damage to PINK1/Parkin signaling impairs mitochondrial tagging and clearance, allowing dysfunctional mitochondria to accumulate. These organelles, often described as “zombie mitochondria,” remain metabolically active enough to generate ROS but fail to produce adequate ATP. The persistence of such mitochondria exacerbates oxidative stress while simultaneously precipitating cellular energy failure. As ATP levels decline, energy-dependent processes including ion homeostasis, axonal transport, and synaptic transmission become unsustainable. Ultimately, this convergence

of oxidative damage, autophagy impairment, and bioenergetic collapse pushes neurons toward apoptotic or necrotic death(51). Figure 3 illustrate the central role of oxidative stress in neurodegenerative diseases such as Alzheimer's and Parkinson's. It highlights key mechanisms including mitochondrial ROS generation, proteostasis collapse, neuroinflammation, and defective autophagy, all contributing to cellular damage. The figure 3 below shows how oxidative stress promotes synaptic dysfunction and cognitive decline by driving the accumulation of toxic proteins like amyloid-β and tau in Alzheimer's and neuronal loss in Parkinson's. Additionally, it emphasizes therapeutic targets, such as Nrf2 activators (e.g., dimethyl fumarate), mitochondria-targeted antioxidants (e.g., MitoQ), and proteostasis and autophagy enhancers (e.g., rapamycin, SS-31, Urolithin A), which aim to mitigate oxidative damage and restore cellular function.

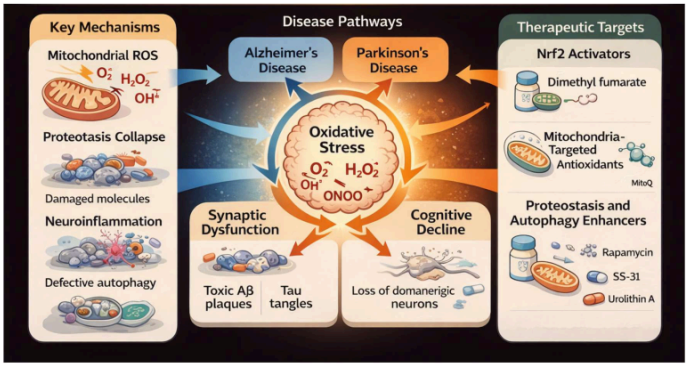

Figure 3. The journey from molecular origins (ROS) through cellular damage (mitochondria/inflammation) to clinical disease (AD/PD), while proposing a shift toward precision medicine and targeted therapies. The illustration was generated using BioRender.

Therapeutic targets and clinical implications

The recognition of oxidative stress as a central driver of neurodegeneration has naturally positioned antioxidant-based strategies as attractive therapeutic candidates. However, decades of clinical experience have revealed the limitations of simplistic antioxidant supplementation. The emerging consensus is that effective intervention requires a shift away from indiscriminate radical scavenging toward targeted modulation of endogenous defense pathways, mitochondrial resilience, and adaptive stress responses. In this context, oxidative stress is no longer viewed merely as a pathological burden to be neutralized, but as a dysregulated signaling state that must be recalibrated(52).

Nrf2 pathway activation: Reinforcing endogenous redox resilience

Nuclear factor erythroid 2–related factor 2 (Nrf2) serves as a central regulator of cellular antioxidant defense by coordinating a broad transcriptional program that maintains redox homeostasis and cytoprotection. Under physiological conditions, Nrf2 is sequestered in the cytoplasm by Kelch-like ECH-associated protein 1 (KEAP1) and targeted for proteasomal degradation. Oxidative or electrophilic stress modifies key cysteine residues on KEAP1, allowing Nrf2 to escape degradation and translocate into the nucleus. There, Nrf2 binds antioxidant response elements and induces the expression of genes involved in antioxidant defense and detoxification, including heme oxygenase-1, NAD(P)H quinone oxidoreductase 1, and enzymes regulating glutathione metabolism. Rather than simply scavenging reactive oxygen species, Nrf2 activation enhances intrinsic redox resilience by strengthening the cell's capacity to respond to future oxidative challenges(32). While Nrf2 activation is beneficial in protecting against oxidative stress, chronic activation can have limitations. Continuous Nrf2 activation may inadvertently

promote tumorigenesis by aiding the survival of damaged cells, which may facilitate cancer progression. The activation of the pathway in non-cancerous tissues should, therefore, be carefully regulated. In terms of activating Nrf2, there are two primary categories: electrophilic and non-electrophilic activators. Electrophilic activators, such as sulforaphane, directly modify KEAP1, leading to the activation of Nrf2. However, these compounds can cause unintended damage due to their reactivity, potentially affecting cellular structures beyond their target. On the other hand, non-electrophilic activators, such as bardoxolone methyl, activate Nrf2 without directly altering KEAP1, which offers a safer profile with fewer side effects but may have lower potency.

Conventional antioxidants have shown limited efficacy in neurodegenerative

Conventional antioxidant therapies have demonstrated limited benefit in neurodegenerative diseases, largely because they fail to adequately target mitochondria, the main intracellular source of neuronal reactive oxygen species (ROS). This shortcoming has driven the development of mitochondria-targeted antioxidants that preferentially accumulate within the mitochondrial matrix by utilizing the mitochondrial membrane potential. MitoQ, for example, couples a ubiquinone moiety to a triphenylphosphonium cation, enabling direct scavenging of mitochondrial ROS and protection of mitochondrial lipids, proteins, and DNA. Similarly, SS-31 (elamipretide) exerts its effects by stabilizing cardiolipin in the inner mitochondrial membrane, thereby preserving electron transport efficiency and limiting ROS production at its origin. Collectively, these strategies reflect a paradigm shift from broad-spectrum antioxidant use toward targeted modulation of mitochondrial redox homeostasis(53). Table 1 compares MitoQ and SS-31, both targeting mitochondria. MitoQ accumulates via membrane potential to scavenge ROS, while SS-31 stabilizes cardiolipin to prevent ROS. Both show preclinical efficacy in neurodegenerative diseases. MitoQ failed in Parkinson's trials but is used for vascular health, while SS-31 is FDA-approved for Barth Syndrome but failed in heart failure trials.(54–60)

Table 1. Comparative Summary of MitoQ and SS-31 (54–60)

Feature	MitoQ (Mitoquinone Mesylate)	SS-31 (Elamipretide)
Primary Mechanism	Electrophoretic accumulation driven by mitochondrial membrane potential.	Potential-independent uptake; targets and stabilizes cardiolipin in the inner membrane.
Antioxidant Action	Redox-active ubiquinone moiety directly scavenges radicals and is regenerated by Complex II.	Structural stabilization of cristae/supercomplexes to prevent electron leakage and ROS formation.
Physical Impact	Can cause mitochondrial swelling and depolarization at high concentrations due to its alkyl chain.	Acts as "mitochondrial armor," protecting against membrane fragmentation and structural decay.
Preclinical Evidence	Robust protection in Alzheimer's (3xTg-AD), Parkinson's (MPTP), and Huntington's disease (HD) models.	Consistent success in AD, PD, HD, and brain injury models, improving dynamics and synaptic health.
Clinical Status	Failed PD trials (no clinical effect on UPDRS). Currently used as a dietary supplement for vascular health.	FDA Approved (Sept 2025) for Barth Syndrome. Failed trials in heart failure and primary mitochondrial myopathy.

Lifestyle interventions and hormetic redox adaptation

Lifestyle interventions, such as physical exercise and caloric restriction, activate endogenous antioxidant defenses through a process known as hormesis. Hormesis refers to the phenomenon where low-level, transient oxidative stress triggers adaptive protective responses within cells. When applied in moderation, physical exercise and mild caloric restriction induce controlled oxidative stress that enhances cellular resilience**(61)**. These interventions improve mitochondrial efficiency by promoting better ATP production and reducing the production of excess ROS, stimulate autophagy for the clearance of damaged proteins and organelles, and upregulate antioxidant signaling pathways such as the Nrf2 pathway, which enhances the cell's ability to combat oxidative damage. Additionally, they boost the secretion of neurotrophic factors like brain-derived neurotrophic factor (BDNF), which support neuronal growth, survival, and synaptic plasticity, playing a crucial role in brain health**(62)**.

However, it is important to note that the beneficial effects of hormesis are dose-dependent. When physical exercise or caloric restriction exceeds a certain threshold, it can shift from an adaptive to a maladaptive stress response. Prolonged or excessive exercise, for example, can lead to chronic oxidative stress, resulting in mitochondrial dysfunction, muscle damage, and an increase in inflammatory markers. Similarly, prolonged caloric restriction may impair cellular homeostasis, weaken the immune system, and exacerbate metabolic dysfunction. These maladaptive responses may overwhelm the body's protective mechanisms, leading to cellular damage rather than the intended health benefits. Therefore, while moderate exercise and caloric restriction can enhance redox balance and improve health outcomes, extreme or prolonged levels of these stressors may cause harm, highlighting the importance of balance in these lifestyle interventions(63).

Therapeutic potential and clinical translation

Pharmacological activation of Nrf2 has therefore emerged as a promising therapeutic strategy in neurodegenerative disorders. Dimethyl fumarate, an approved treatment for multiple sclerosis, represents a clinically validated example of this approach. By inducing mild electrophilic stress, it activates Nrf2 signaling and confers neuroprotective and anti-inflammatory effects. Beyond fumarates, synthetic triterpenoids and other Nrf2 activators are under investigation for their ability to restore redox homeostasis in aging and neurodegeneration. Nevertheless, clinical translation requires careful calibration. Chronic or excessive Nrf2 activation may disrupt physiological redox signaling or promote maladaptive metabolic states. Thus, the therapeutic challenge lies not in maximal activation, but in restoring dynamic responsiveness to oxidative stress(32).

Challenges and future directions

Despite an increasingly robust molecular framework linking oxidative stress to neurodegenerative disease, clinical translation of antioxidant-based therapies in Alzheimer's disease (AD) and Parkinson's disease (PD) has been largely underwhelming. Numerous trials, particularly those relying on conventional antioxidant supplementation, have failed to demonstrate consistent or meaningful clinical benefit. This disconnects between compelling preclinical data and disappointing clinical outcomes highlights a critical "translational gap" that extends beyond simple issues of drug efficacy. Rather than invalidating the role of oxidative stress in neurodegeneration, these failures underscore the complexity of redox biology in the human brain and reveal fundamental limitations in how antioxidant strategies have been conceptualized and implemented.

Table 2. Comparative Summary between Mechanisms of oxidative stress, Their roles in AD vs. PD and Potential therapeutic interventions
(1,1,1,3,3,11,19,24,33,42,42–44,46,46,52,52)

Mechanisms of Oxidative Stress	Role in Alzheimer's Disease (AD)	Role in Parkinson's Disease (PD)	Potential Therapeutic Interventions
Mitochondrial Dysfunction	Mitochondrial dysfunction leads to bioenergetic failure, impairing synaptic plasticity and contributing to neuronal damage.	Mitochondrial dysfunction in dopaminergic neurons accelerates ROS production and contributes to neuronal loss.	Mitochondria-targeted antioxidants (e.g., MitoQ, SS31) that help reduce ROS and restore mitochondrial function.
Lipid Peroxidation	Oxidative damage to membrane lipids leads to neuronal damage and loss of synaptic function.	Lipid peroxidation exacerbates dopaminergic neuron death and disrupts membrane integrity.	Use of lipid antioxidants like alpha-lipoic acid or other peroxyl scavengers to prevent oxidative damage.
Proteostasis Collapse	Proteostasis collapse contributes to the accumulation of amyloid β and tau, which disrupt neuronal function.	Accumulation of misfolded proteins, such as α-synuclein, leads to dopaminergic dysfunction.	Proteostasis regulators, such as proteasome activators or autophagy enhancers (e.g., rapamycin, spermidine).
Neuroinflammation	Chronic neuroinflammation amplifies the amyloid plaque formation and accelerates disease progression.	Neuroinflammation in microglia worsens dopaminergic neuron death and amplifies ROS production.	Anti-inflammatory agents targeting NF-κB or microglial activation (e.g., minocycline, curcumin).
Redox-Imbalance (ROS and RNS)	ROS accumulation damages cellular structures (DNA, lipids, proteins) and triggers apoptosis.	ROS generation through dopamine metabolism leads to neuronal damage and contributes to cell death.	Nrf2 activators (e.g., dimethyl fumarate), which boost cellular antioxidant defenses and help restore redox homeostasis.
Autophagy and Mitophagy Failure	Impaired autophagy leads to the accumulation of damaged proteins, exacerbating neurodegeneration.	Deficient mitophagy results in the accumulation of dysfunctional mitochondria, contributing to neurodegeneration.	Autophagy enhancers (e.g., rapamycin) and mitophagy activators (e.g., Urolithin A, PINK1 activators) to clear damaged organelles.

Temporal mismatch: Treating too late in the disease course

One of the most significant challenges lies in the timing of therapeutic intervention. Neurodegenerative diseases are characterized by long preclinical phases, during which molecular and cellular damage accumulates silently over years or even decades. By the time clinical symptoms emerge and patients are enrolled in trials, substantial neuronal loss and synaptic disintegration have already occurred. At this advanced stage, oxidative stress is no longer a primary driver but rather a downstream consequence of irreversible structural damage. Antioxidant therapy administered under these conditions is therefore unlikely to restore lost neurons or reverse established network failure. This temporal mismatch suggests that antioxidant interventions may be more effective as preventive or early-stage strategies, rather

than as treatments for symptomatic disease. Future clinical trials must therefore prioritize early diagnosis and intervention, potentially targeting individuals with prodromal disease or those identified as high-risk based on genetic, metabolic, or biomarker profiles(64).

Bioavailability and blood brain barrier limitations

Another major obstacle is the limited bioavailability of many antioxidant compounds within the central nervous system. The blood–brain barrier (BBB), while essential for protecting neural tissue, poses a formidable challenge for drug delivery. Many antioxidants exhibit poor lipophilicity, rapid systemic clearance, or extensive peripheral metabolism, resulting in insufficient concentrations reaching neuronal targets(65). Even when compounds successfully cross the BBB, their intracellular distribution is often non-specific, failing to reach subcellular compartments such as mitochondria, where oxidative stress is most pronounced. This pharmacokinetic mismatch further diminishes therapeutic efficacy and helps explain the failure of broad-spectrum antioxidants in clinical trials. Advances in drug delivery such as nanoparticle-based carriers, mitochondria-targeted molecules, and ligand-mediated transport systems represent promising avenues for overcoming these limitations. However, their clinical translation will require rigorous evaluation of safety, specificity, and long-term effects(66).

The paradox of reductive stress

A less intuitive, yet increasingly recognized challenge is the phenomenon of reductive stress. While oxidative stress reflects an excess of reactive species, excessive antioxidant supplementation can shift the redox balance in the opposite direction, suppressing physiological ROS signaling. Reactive oxygen species are not inherently pathological; at controlled levels, they play essential roles in synaptic plasticity, immune defense, and cellular adaptation. Overzealous scavenging of ROS can therefore impair normal signaling pathways, disrupt mitochondrial function, and paradoxically exacerbate cellular dysfunction. This concept challenges the simplistic view that “more antioxidants are better” and highlights the need for precision in redox modulation. Therapeutic strategies must aim to restore redox homeostasis rather than eliminate ROS indiscriminately. This requires a nuanced understanding of individual redox states and the context-dependent roles of oxidative signaling in health and disease(67).

The need for redox biomarkers and patient stratification

Perhaps the most critical gap in current clinical approaches is the lack of reliable biomarkers to assess oxidative status in vivo. Neurodegenerative diseases are heterogeneous, and not all patients exhibit the same degree or pattern of redox dysregulation. Without biomarkers to stratify patients, antioxidant therapies are applied indiscriminately, diluting potential benefits within responsive subgroups. Future research must therefore focus on developing and validating biomarkers that reflect systemic and brain-specific oxidative stress, antioxidant capacity, and mitochondrial function. These may include circulating redox markers, imaging-based indicators of oxidative metabolism, or genetic and epigenetic signatures linked to redox regulation. Such biomarkers would enable precision medicine approaches, identifying individuals most likely to benefit from antioxidant or redox-modulating interventions and allowing therapies to be tailored in terms of timing, dosage, and mechanism(68).

Toward a systems-level therapeutic strategy

Looking forward, the field must move beyond reductionist strategies that target oxidative stress in isolation. Neurodegeneration arises from the convergence of redox imbalance, mitochondrial dysfunction, neuroinflammation, impaired autophagy, and synaptic failure. Effective therapies will likely need to engage multiple nodes within this network, either through combination treatments or through interventions that restore upstream regulatory control, such as Nrf2 signaling or mitochondrial quality control pathways(69). In this context, antioxidant therapy should be reframed not as a standalone solution, but as one component of an integrated disease-modifying strategy. Bridging the translational gap will require early intervention, targeted delivery, biomarker-guided patient selection, and a deeper appreciation of redox biology as a dynamic and context-dependent system(70).

Conclusion

This review demonstrates that oxidative stress serves as a central, unifying mechanism linking biological aging to neurodegenerative disorders. Through sustained redox imbalance, ROS drive mitochondrial dysfunction, proteostatic failure, neuroinflammation, and impaired autophagy, collectively undermining neuronal integrity. The limited success of conventional antioxidants highlights the need for targeted redox modulation rather than indiscriminate radical scavenging. Strategies that enhance endogenous defenses, restore mitochondrial quality control, and activate adaptive pathways such as Nrf2 offer promising avenues for delaying neurodegenerative progression and extending neural healthspan.

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Declaration of artificial intelligence use

During the preparation of this manuscript, the authors made limited use of artificial intelligence–based tools as a supporting aid for language editing and improvement of sentence clarity. These tools were used only to assist in refining grammar and readability. All scientific content, interpretations, critical analyses, and conclusions presented in this manuscript were developed, reviewed, and finalized by the authors. The use of AI did not influence the scientific substance of the work and does not replace the authors' intellectual contribution or responsibility.

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Review Article

Oxidative stress as a converging mechanism of aging and neurodegeneration: From molecular pathways to therapeutic targets

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Abstract

Aging is the primary risk factor for major neurodegenerative disorders, yet the precise molecular links between biological aging and progressive neuronal loss remain complex. Oxidative stress, defined as an imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses, has emerged as a central converging mechanism driving both processes. This review aims to synthesize current evidence demonstrating how chronic redox imbalance drives cellular senescence and neuronal vulnerability through mitochondrial dysfunction, lipid peroxidation, and oxidative protein damage. These insights underscore how sustained oxidative insults promote the misfolding and aggregation of disease-defining proteins, including amyloid-beta in Alzheimer's disease and α-synuclein in Parkinson's disease, thereby amplifying neuroinflammation, synaptic dysfunction, and bioenergetic failure. Furthermore, antioxidant-based therapeutic strategies are critically reassessed, highlighting a paradigm shift from non-specific radical scavenging toward targeted modulation of endogenous defense systems, particularly NRF2 signaling and mitochondria-directed antioxidants. By integrating molecular mechanisms with translational perspectives, this review integrates molecular, cellular, and translational evidence to explain how oxidative stress links biological aging to neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.

Keywords: Oxidative stress, aging, neurodegeneration, mitochondria, reactive oxygen species

Introduction

The unprecedented expansion of the elderly demographic worldwide has been paralleled by a dramatic rise in neurodegenerative disorders, most notably Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) [1]. Although these conditions present with distinct clinical manifestations and hallmark protein signatures, they converge upon a common and arguably central risk factor that is biological aging [2]. Oxidative stress represents a fundamental biological process that becomes progressively dysregulated with aging, driving neuronal vulnerability and neurodegenerative disease progression. This observation suggests that the molecular processes governing senescence do not serve merely as a passive backdrop, but rather act as active drivers of neuronal vulnerability and decline. Within the network of aging-related mechanisms, oxidative stress functions as a central converging mechanism linking normal physiological aging to pathological neurodegeneration [3]. Rather than being a mere byproduct

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of metabolic activity, oxidative stress represents a failure of redox homeostasis, a state in which the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) overwhelms the capacity of cellular detoxification and repair systems [4]. Crucially, while basal ROS levels play indispensable roles in signal transduction and cellular adaptation, chronic elevations beyond physiological thresholds instigate cumulative structural damage to DNA, membrane lipids, and functional proteins [5].

Classical theories, such as Harman's Free Radical Theory of Aging [6], have historically attributed aging to the random accumulation of oxidative damage. However, contemporary research has refined this perspective to emphasize that oxidative stress disrupts regulated redox-sensitive signaling pathways, thereby destabilizing fundamental processes essential for neuronal survival [7]. The central nervous system is uniquely susceptible to this form of dysregulation. Although the brain constitutes only about 2% of total body mass, it consumes roughly 20% of basal oxygen, reflecting a metabolic intensity that predisposes it to disproportionate oxidative burden [8]. At the heart of this vulnerability lies the mitochondrion [9]. As the primary source of intracellular ROS generation, mitochondria are paradoxically both the generators and principal victims of oxidative insult. In the aging brain, progressive mitochondrial compromise precipitates a bioenergetic crisis, impairing neuronal capacity to sustain ionic gradients, neurotransmission, and synaptic plasticity. Moreover, damaged electron transport chains become leakier, generating excessive ROS that further tax dwindling antioxidant defenses [10].

This bioenergetic imbalance is intimately linked to the collapse of proteostasis, the constellation of cellular systems that govern protein folding, trafficking, and degradation. Oxidative modifications such as carbonylation and nitration render proteins prone to misfolding while simultaneously inhibiting the ubiquitin proteasome system and autophagy lysosomal pathways responsible for their clearance [11]. The resultant molecular gridlock fosters the accumulation of neurotoxic aggregates, including amyloid-beta in AD and alpha-synuclein in PD. In turn, these aggregates destabilize redox balance, creating a synergistic feedback loop in which protein aggregation exacerbates oxidative stress, and oxidative stress accelerates aggregation [12]. Although oxidative stress is widely recognized as a hallmark of biological aging and neurodegeneration, existing literature frequently addresses mitochondrial dysfunction, proteostatic failure, neuroinflammation, and redox signaling in isolation. This review addresses this gap by integrating molecular, cellular, and translational evidence to clarify how redox imbalance functions as a convergent driver of neuronal dysfunction and loss in Alzheimer's and Parkinson's diseases. The molecular sources of reactive oxygen species, age-related declines in antioxidant capacity, and the convergence of these processes on protein aggregation and neurodegeneration are synthesized. Finally, the limitations of broad-spectrum antioxidant strategies are discussed, and a conceptual shift toward targeted modulation of redox-sensitive pathways, rather than non-specific scavenging, is proposed.

Molecular mechanisms of oxidative stress

Global population aging has been accompanied by a marked increase in neurodegenerative diseases, including AD, PD, and ALS. Although these disorders are clinically distinct, they share biological aging as a common risk factor, indicating that age-related cellular processes actively contribute to neuronal degeneration [13]. Among the molecular pathways involved, oxidative stress has emerged as a central converging mechanism linking physiological aging with neurodegenerative pathology [14]. Oxidative stress arises when the production of reactive oxygen and nitrogen species exceeds the capacity of cellular defense systems, leading to damage to DNA, lipids, and proteins. While low levels of reactive species are essential for normal cellular signaling, sustained elevations disrupt redox homeostasis and impair neuronal function [8]. The central nervous system is particularly susceptible to oxidative injury due to its high metabolic demand and disproportionate oxygen consumption, making oxidative stress a critical driver of age-related neurodegeneration [15].

Molecular origins of reactive species

ROS are primarily generated as metabolic byproducts of aerobic respiration, with the mitochondrial electron transport chain (ETC) serving as the principal intracellular source. During

oxidative phosphorylation, electron leakage occurs most notably at Complex I (nicotinamide adenine dinucleotide reduced (NADH) dehydrogenase) and Complex III (ubiquinone–cytochrome c reductase). This leakage results in the partial reduction of molecular oxygen (O_2), forming the superoxide anion ($O_2^{\cdot -}$), as described by the reaction $O_2 + e^- \rightarrow O_2^{\cdot -}$ [16].

Superoxide is rapidly dismutated into the more stable hydrogen peroxide (H_2O_2), which can diffuse across cellular membranes and function as a signaling molecule. However, the pathogenic potential of oxidative stress markedly increases in the presence of transition metals. Through the Fenton reaction, hydrogen peroxide reacts with ferrous iron (Fe^{2+}) or cuprous copper (Cu^+), generating the highly reactive and destructive hydroxyl radical (·OH): $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \cdot OH + OH^-$ [17].

The oxidative burden within the brain is not exclusively of mitochondrial origin. Several enzymatic systems contribute significantly to intracellular ROS production, including the NADPH oxidase (NOX) family, peroxisomes, and cytochrome P450 enzymes. In the context of neurodegeneration, the activation of NOX enzymes in microglia is recognized as a major driver of neuroinflammation. This process creates a toxic synergy between oxidative stress and immune activation, amplifying neuronal damage and accelerating neurodegenerative progression [18].

Mitochondrial ROS generation

Mitochondria are central to cellular energy production through oxidative phosphorylation, but they are also the primary source of ROS. During oxidative phosphorylation, electrons are transferred through the mitochondrial electron transport chain, and some electrons leak at Complex I and Complex III. This leakage leads to the partial reduction of molecular oxygen, producing superoxide anions ($O_2^{\cdot -}$). These superoxides are then converted into hydrogen peroxide, which, in turn, can form hydroxyl radicals (·OH) through Fenton reactions, further amplifying oxidative stress [19]. This ROS production becomes self-perpetuating in aging and neurodegenerative diseases, as damaged mitochondria generate more ROS, worsening mitochondrial dysfunction. This creates a vicious cycle where oxidative damage to cellular structures such as lipids, proteins, and DNA intensifies cellular dysfunction, accelerating the progression of diseases like AD and PD. Moreover, mitochondrial damage can reduce ATP production, impeding cellular functions and contributing to neuronal degeneration [5].

Lipid peroxidation and membrane vulnerability

Oxidative stress also leads to lipid peroxidation, a process in which ROS attack the polyunsaturated fatty acids in cellular membranes. Lipid peroxidation generates highly reactive secondary products such as 4-hydroxynonenal and malondialdehyde, which can diffuse across the cells and interact with other cellular components [20]. These lipid peroxidation products disrupt the structural integrity of neuronal membranes, impairing the fluidity and function of the lipid bilayer [21]. This damage compromises membrane-bound proteins, receptors, and ion channels, leading to disturbances in cellular signaling, neurotransmission, and overall neuronal efficiency. In neurodegenerative diseases, this membrane vulnerability accelerates neuronal damage and contributes to synaptic dysfunction. For instance, in AD, lipid peroxidation can facilitate the aggregation of amyloid-beta, further exacerbating the pathological cycle [20]. The lipid-rich membranes of neurons make them particularly susceptible to oxidative damage, reinforcing the progression of diseases like AD and PD [20].

Proteostasis collapse

Proteostasis is essential for maintaining cellular homeostasis by regulating protein synthesis, folding, and degradation. However, oxidative stress disrupts proteostasis, leading to the accumulation of damaged and misfolded proteins. ROS can induce oxidative modifications such as carbonylation and nitration on proteins, altering their structure and function [22]. These misfolded proteins are typically targeted for degradation by the proteasome or autophagy pathways. However, oxidative stress impairs these systems, leading to the accumulation of toxic protein aggregates [23]. In neurodegenerative diseases like AD and PD, this collapse of proteostasis is particularly detrimental. For example, in AD, amyloid-beta accumulates and forms plaques, while in PD, α-synuclein forms Lewy bodies. These protein aggregates not only disrupt cellular function but also impair synaptic plasticity, damage mitochondria, and promote

neuroinflammation [23]. The accumulation of misfolded proteins creates a positive feedback loop that exacerbates oxidative stress, mitochondrial dysfunction, and cellular damage [11]].

Redox inflammatory crosstalk

Oxidative stress and neuroinflammation are intimately connected, with ROS playing a crucial role in activating redox-sensitive transcription factors like nuclear factor kappa B (NF-κB). NF-κB, once activated by ROS, translocates to the nucleus and initiates the expression of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α [24]. These cytokines activate microglia, the resident immune cells of the brain, which further increase ROS production and promote inflammation [25]. Chronic neuroinflammation exacerbates neuronal damage by impairing synaptic function, disrupting calcium homeostasis, and sensitizing neurons to excitotoxicity. This inflammatory response becomes self-perpetuating under conditions of sustained oxidative stress, where proinflammatory cytokines further exacerbate ROS production, leading to a cycle of oxidative injury and inflammation [24]. This crosstalk between oxidative stress and inflammation is a critical driver of neurodegenerative diseases like AD and PD, where inflammation amplifies the damage caused by ROS, leading to progressive neuronal death and dysfunction [24].

Autophagy and mitophagy failure

Autophagy and mitophagy are vital cellular processes for maintaining cellular integrity by degrading damaged proteins and organelles. In neurons, where turnover is limited due to the lack of cell division, the efficient functioning of autophagic pathways is critical for long-term survival. However, oxidative stress compromises the integrity of these pathways. ROS can damage the lysosomal system, which is responsible for the final stages of autophagic degradation, impairing its function [26]. As a result, damaged proteins and dysfunctional organelles accumulate within neurons, further exacerbating cellular stress. In particular, mitophagy, the selective removal of damaged mitochondria, is essential to protect cells from oxidative damage. However, oxidative stress impairs mitophagy by disrupting the PINK1/Parkin pathway, which is responsible for marking damaged mitochondria for degradation [27]. The failure to clear dysfunctional mitochondria allows them to persist and continue generating ROS, perpetuating mitochondrial dysfunction and oxidative stress. This accumulation of damaged mitochondria, often referred to as “zombie mitochondria,” further disrupts cellular function, leading to energy depletion and contributing to the neurodegenerative processes observed in diseases like PA [27].

Antioxidant defense

Enzymatic vanguard: The first line of redox control

The first layer of cellular antioxidant defense is formed by a tightly coordinated system of enzymatic antioxidants that operate in a sequential and highly regulated manner. Superoxide dismutases (SODs) act as primary responders by rapidly neutralizing superoxide radicals, which are predominantly produced through electron leakage from the mitochondrial respiratory chain [28]. Because superoxide is highly reactive and short-lived, its rapid conversion into hydrogen peroxide constitutes a crucial protective mechanism rather than a simple chemical reaction. However, hydrogen peroxide occupies a dual role within neuronal physiology [29]. At low concentrations, it functions as a diffusible second messenger involved in synaptic plasticity and signal transduction. Yet, when allowed to accumulate, it becomes a latent threat, particularly in metal-rich neural environments where iron and copper are abundant. To prevent this transition from signaling molecule to cytotoxic precursor, downstream enzymes such as catalase (CAT) and glutathione peroxidase assume decisive roles [30,31]. By decomposing hydrogen peroxide into water and molecular oxygen, these enzymes effectively terminate the oxidative cascade before it can culminate in hydroxyl radical formation, a species widely regarded as the most destructive ROS due to its indiscriminate reactivity [18]. This enzymatic cascade is not simply redundant; instead, it represents an evolutionarily refined system built to maintain redox stability under stress. When any component of this network is compromised, whether due to genetic variation,

post-translational alterations, or age-related functional decline, the balance of redox control can be disrupted. As a result, neurons become particularly vulnerable to oxidative damage [32].

Non-enzymatic buffers and thiol-based redox modulation

Alongside enzymatic antioxidants, cells rely on a broad network of non-enzymatic redox buffers, with glutathione playing a central and indispensable role. As the most abundant intracellular thiol antioxidant, glutathione functions as a dynamic redox reservoir that buffers oxidative fluctuations beyond the capacity of enzymatic systems. By donating electrons, glutathione neutralizes reactive species and is converted into its oxidized form, glutathione disulfide. Consequently, the balance between reduced and oxidized glutathione (the ratio of glutathione to glutathione disulfide) serves as a sensitive marker of cellular redox status. In neurons, which possess limited tolerance to oxidative stress, even subtle changes in this ratio may indicate early metabolic strain [33]. Evidence consistently shows a gradual decline in glutathione levels, suggesting that neurodegeneration is preceded by a slow weakening of intrinsic redox buffering rather than an abrupt oxidative event [34]. Beyond direct antioxidant activity, glutathione supports detoxification processes and modulates redox-sensitive protein thiols, thereby influencing gene regulation, mitochondrial stability, and synaptic function [24]. Loss of glutathione therefore reflects not only diminished antioxidant protection but a broader breakdown in redox regulation [35].

Regulatory control and the NRF2 axis

The effectiveness of antioxidant defenses within the central nervous system is ultimately governed at the transcriptional level. Central to this regulation is the nuclear factor erythroid 2–related factor 2 (NRF2), a master regulator of cellular stress responses. Under basal conditions, NRF2 is sequestered in the cytoplasm; however, in the presence of oxidative stress, it translocates to the nucleus and initiates the expression of a broad repertoire of antioxidant and cytoprotective genes, including those encoding superoxide dismutases, glutathione peroxidase, catalase, and glutathione synthesis enzymes. In youthful and healthy neural tissue, this inducible system provides a remarkable degree of plasticity, enabling neurons to adapt rapidly to fluctuating redox demands [36]. With advancing age, however, the responsiveness of the NRF2 pathway becomes progressively attenuated. This decline does not necessarily reflect a complete loss of function, but rather a diminished sensitivity to oxidative cues. As a result, the antioxidant response becomes delayed or insufficient, allowing ROS production to outpace detoxification. This age-associated regulatory failure creates what can be described as a “redox vulnerability gap”, wherein neurons persist under conditions of chronic, low-grade oxidative stress. Over time, this imbalance promotes cumulative macromolecular damage, mitochondrial dysfunction, and inflammatory signaling hallmarks that converge to drive the initiation and progression of neurodegenerative disorders [37].

Oxidative stress in aging: Molecular mechanism of senescence

The modified free radical theory of aging

Harman’s Free Radical Theory of Aging, introduced in 1956, initially proposed that aging results from the gradual accumulation of oxidative damage to essential biomolecules caused by ROS [38]. While this concept laid the foundation for modern aging research, it has since evolved beyond the idea of random and irreversible molecular injury [39]. Current perspectives recognize ROS not only as damaging agents but also as critical regulators of physiological redox signaling. In young and healthy cells, redox balance is tightly controlled [40]. However, this regulatory capacity declines with age, leading to a state of chronic, low-grade oxidative stress. This persistent redox imbalance subtly disrupts cellular signaling pathways and promotes a pro-inflammatory milieu, commonly referred to as inflammaging. In this framework, oxidative stress contributes to aging not merely through direct macromolecular damage, but by driving immune dysregulation and sustained inflammatory signaling. The modified Free Radical Theory therefore reframes

aging as a systemic failure of redox homeostasis, in which oxidative stress and inflammation interact to accelerate functional decline [41].

Accumulation of macromolecular damage in the aging brain

The aging brain is particularly susceptible to oxidative damage due to its high oxygen consumption, lipid-rich composition, and limited regenerative capacity. Over time, an imbalance between ROS production and antioxidant defenses leads to the gradual accumulation of damage to lipids, proteins, and nucleic acids, ultimately compromising neuronal structure and function [42]. Lipid peroxidation represents an early and amplifying form of oxidative injury in neurons. Neuronal membranes are rich in polyunsaturated fatty acids, which are highly vulnerable to oxidative attack. This process generates reactive secondary products such as 4-hydroxynonenal and malondialdehyde, which persist longer than primary radicals and diffuse across cellular compartments. These byproducts disrupt membrane integrity, impair receptor signaling, and interfere with synaptic transmission, thereby reducing neuronal efficiency [43].

Proteins are also major targets of oxidative stress. Oxidative modifications promote protein misfolding and aggregation, a process that is especially harmful in post-mitotic neurons. With aging, the efficiency of proteostatic systems, including the ubiquitin–proteasome pathway and autophagy, progressively declines. As a result, damaged proteins accumulate and form insoluble aggregates that disrupt intracellular transport and synaptic maintenance, further exacerbating cellular stress [22]. Oxidative damage to DNA, particularly mitochondrial DNA, adds another layer of vulnerability. Located near the electron transport chain and lacking robust protective and repair mechanisms, mitochondrial DNA is highly prone to oxidative lesions such as 8-hydroxy-2′-deoxyguanosine. These mutations impair mitochondrial gene expression and energy production, increasing electron leakage and ROS generation. This establishes a self-perpetuating cycle in which oxidative damage and mitochondrial dysfunction reinforce one another, accelerating neuronal aging and degeneration [44].

Oxidative stress in neurodegenerative diseases

Alzheimer's disease (AD): Oxidative stress as a self-reinforcing pathological loop

In AD, oxidative stress is no longer viewed as a secondary consequence of neuronal damage but rather as a central driver of disease progression. It operates through interconnected, self-reinforcing loops that involve amyloid-beta accumulation, mitochondrial dysfunction, and Tau pathology (**Figure 1**). Soluble amyloid-beta oligomers have redox-active properties and readily interact with neuronal membranes and redox-active metals such as iron and copper, triggering localized production of ROS [13]. This pro-oxidative microenvironment damages surrounding cellular components while simultaneously promoting further amyloid-beta aggregation, creating a bidirectional interaction between amyloid pathology and oxidative stress that contributes to early synaptic impairment [45]. As shown in **Figure 1**, the pathological process begins with the accumulation of amyloid-beta within neuronal mitochondria, which further intensifies oxidative injury by disrupting the electron transport chain, particularly cytochrome c oxidase, resulting in reduced ATP synthesis and increased electron leakage. These changes enhance mitochondrial ROS generation, induce mitochondrial DNA damage, and progressively compromise cellular energy balance [10]. In parallel, oxidative stress modulates Tau pathology by activating stress-responsive kinases that promote Tau hyperphosphorylation, leading to microtubule destabilization and impaired axonal transport [1]. Aggregated Tau subsequently worsens mitochondrial dysfunction and oxidative imbalance. Together, these interdependent mechanisms place oxidative stress at the center of a pathological network that links amyloid toxicity, bioenergetic failure, and cytoskeletal disruption in AD [46].

Parkinson's disease (PA): Selective vulnerability to oxidative stress

PA illustrates how intrinsic metabolic characteristics render specific neuronal populations highly vulnerable to oxidative stress. Degeneration of dopaminergic neurons in the substantia nigra pars compacta arises from the convergence of dopamine metabolism, mitochondrial dysfunction, and

impaired antioxidant defenses. Dopamine itself contributes to oxidative burden through enzymatic degradation by monoamine oxidase B, which generates hydrogen peroxide, as well as through spontaneous auto-oxidation that produces reactive quinones capable of damaging proteins and mitochondrial enzymes. This persistent oxidative environment selectively stresses dopaminergic neurons [47].

As shown in **Figure 2**, the pathological process of PA begins with mitochondrial dysfunction, which further amplifies oxidative injury. Genes implicated in familial PD, including PINK1, Parkin, and DJ-1, play critical roles in mitochondrial quality control and redox regulation. Under normal conditions, damaged mitochondria are removed via PINK1–Parkin–mediated mitophagy, limiting excessive reactive oxygen species production. Disruption of this system allows dysfunctional, ROS-generating mitochondria to accumulate, intensifying oxidative stress [48]. Loss of DJ-1–mediated redox sensing further reduces neuronal resilience. Together, these mechanisms establish a self-reinforcing cycle in which oxidative stress and mitochondrial failure drive selective dopaminergic neurodegeneration in PD [36].

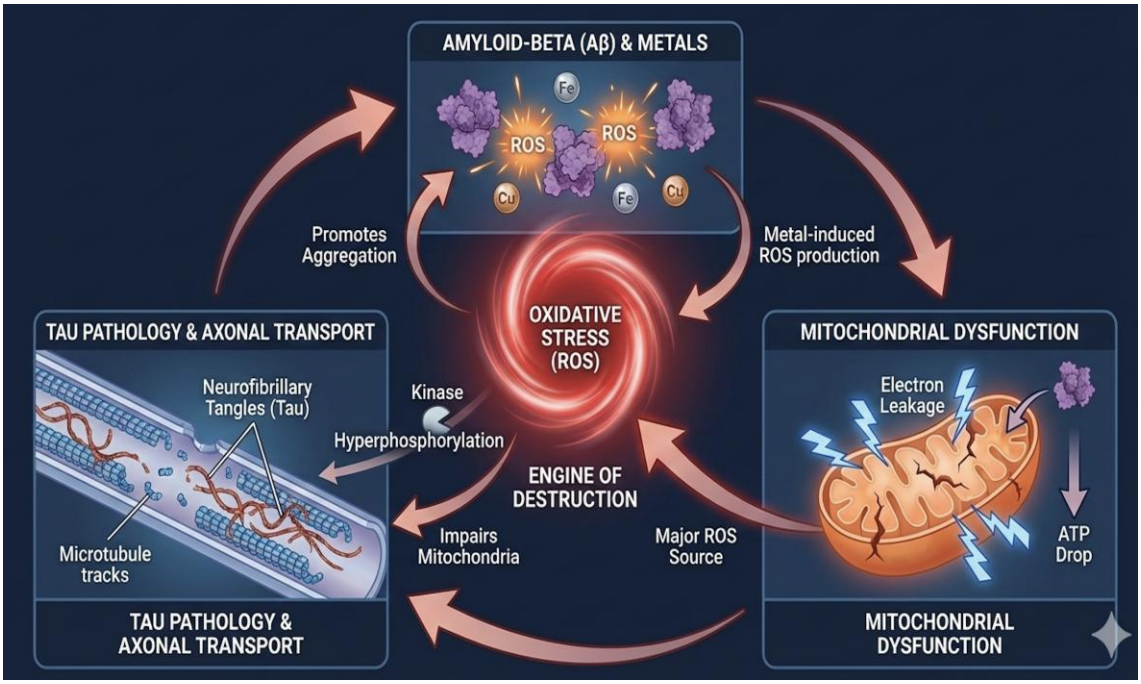

Figure 1. Key mechanisms of oxidative stress and neuronal damage in Alzheimer's disease (AD) pathology. Self-reinforcing cycle of oxidative stress and mitochondrial dysfunction, illustrating the roles of amyloid-beta, metals, tau pathology, and mitochondrial dysfunction in AD. The figure is generated using BioRender.

Self-perpetuating cycle of ROS and inflammation

Once neuroinflammation is established, it further amplifies oxidative stress through the activation of enzymatic sources of reactive oxygen species. Proinflammatory cytokines promote the activation of microglial NADPH oxidase 2 (NOX2), an enzyme complex specifically dedicated to regulated ROS generation. Unlike mitochondrial ROS, which are produced as byproducts of cellular metabolism, NOX2-derived ROS are intentionally generated as part of immune signaling. Under conditions of sustained activation, however, this response becomes maladaptive. Elevated ROS levels inflict additional damage on neuronal membranes, proteins, and mitochondria, leading to the release of danger-associated molecular patterns that further stimulate microglial activation [50]. This feedback loop establishes a self-perpetuating cycle in which oxidative stress and inflammation reinforce one another, progressively spreading neuronal injury and contributing to the chronic and progressive nature of neurodegenerative disorders [50].

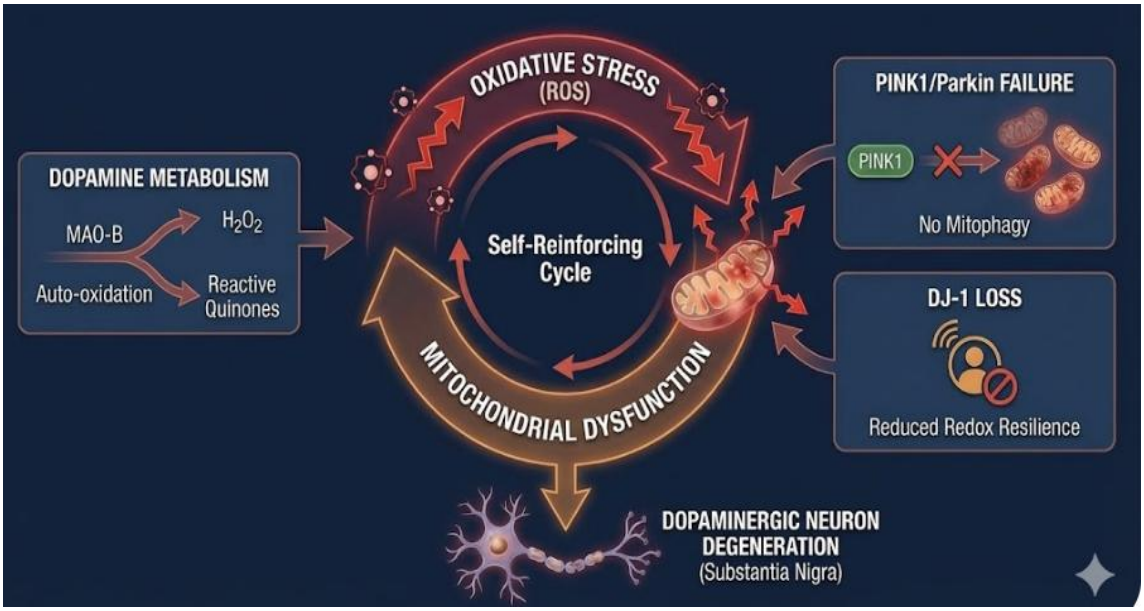

Figure 2. Key mechanisms of oxidative stress and mitochondrial impairment in Parkinson's disease (PD) pathology. The self-reinforcing cycle of oxidative stress and mitochondrial dysfunction in PD, illustrating how dopamine metabolism, PINK1/Parkin failure, and DJ-1 loss contribute to dopaminergic neuron degeneration in the substantia nigra. The figure is generated using BioRender.

Autophagy and mitophagy failure: Breakdown of cellular quality control

While inflammation accelerates extracellular and intercellular damage, oxidative stress simultaneously undermines the intracellular systems responsible for maintaining neuronal integrity. Autophagy, the primary pathway for degrading aggregated proteins and dysfunctional organelles, is particularly vulnerable to redox dysregulation. In post-mitotic cells such as neurons, where damaged components cannot be diluted through cell division, the integrity of autophagic flux is essential for long-term survival [51].

Lysosomal dysfunction and autophagic arrest

Effective autophagy depends on intact lysosomal function. However, oxidative stress generates lipid peroxidation products such as 4-hydroxynonenal that covalently modify lysosomal membranes and hydrolytic enzymes. These modifications compromise lysosomal acidity and enzymatic efficiency, impairing the final stages of autophagic degradation. As autophagic flux slows, damaged proteins and organelles accumulate within neurons, placing additional stress on already compromised cellular systems. This accumulation not only disrupts intracellular trafficking and synaptic maintenance but also amplifies oxidative stress by allowing ROS-generating structures to persist. Thus, lysosomal dysfunction represents a critical bottleneck where oxidative damage translates into widespread cellular failure [27].

Mitophagy failure and energetic collapse

Among autophagic processes, the selective removal of damaged mitochondria is known as mitophagy. It is of particular importance in neurodegeneration. Mitochondria are both the primary producers and principal targets of ROS. Under normal conditions, the PINK1/Parkin pathway identifies dysfunctional mitochondria and targets them for autophagic clearance, preventing excessive ROS leakage [3]. Oxidative stress, however, disrupts this quality-control system. Damage to PINK1/Parkin signaling impairs mitochondrial tagging and clearance, allowing dysfunctional mitochondria to accumulate. These organelles, often described as "zombie mitochondria," remain metabolically active enough to generate ROS but fail to produce adequate ATP. The persistence of such mitochondria exacerbates oxidative stress while simultaneously precipitating cellular energy failure [52]. As ATP levels decline, energy-dependent processes, including ion homeostasis, axonal transport, and synaptic transmission, become unsustainable. Ultimately, this convergence of oxidative damage, autophagy impairment, and bioenergetic

collapse pushes neurons toward apoptotic or necrotic death [53]. The central roles of oxidative stress in neurodegenerative diseases such as AD and PD are illustrated in **Figure 3**. It highlights key mechanisms, including mitochondrial ROS generation, proteostasis collapse, neuroinflammation, and defective autophagy, all contributing to cellular damage. **Figure 3** also shows how oxidative stress promotes synaptic dysfunction and cognitive decline by driving the accumulation of toxic proteins like amyloid-beta and tau in AD and neuronal loss in PD. Additionally, it emphasizes therapeutic targets, such as NRF2 activators (e.g., dimethyl fumarate), mitochondria-targeted antioxidants (e.g., MitoQ), and proteostasis and autophagy enhancers (e.g., rapamycin, SS-31, Urolithin A), which aim to mitigate oxidative damage and restore cellular function.

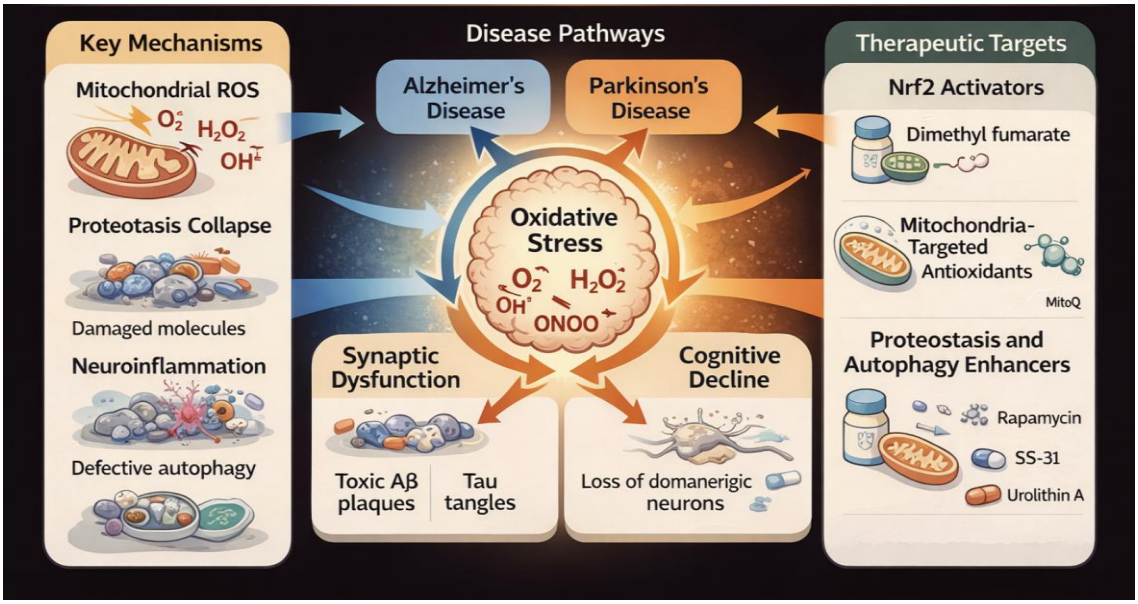

Figure 3. Schematic overview illustrating the continuum from the molecular origins of reactive oxygen species (ROS) through cellular damage—encompassing mitochondrial dysfunction and neuroinflammation—to clinical manifestations of neurodegenerative disorders, including Alzheimer's disease and Parkinson's disease. The figure also highlights the emerging shift toward precision medicine and targeted therapeutic strategies. The illustration was created using BioRender.

Therapeutic targets and clinical implications

The recognition of oxidative stress as a central driver of neurodegeneration has naturally positioned antioxidant-based strategies as attractive therapeutic candidates. However, decades of clinical experience have revealed the limitations of simplistic antioxidant supplementation. The emerging consensus is that effective intervention requires a shift away from indiscriminate radical scavenging toward targeted modulation of endogenous defense pathways, mitochondrial resilience, and adaptive stress responses. In this context, oxidative stress is no longer viewed merely as a pathological burden to be neutralized, but as a dysregulated signaling state that must be recalibrated [31].

NRF2 pathway activation: Reinforcing endogenous redox resilience

NRF2 serves as a central regulator of cellular antioxidant defense by coordinating a broad transcriptional program that maintains redox homeostasis and cytoprotection. Under physiological conditions, NRF2 is sequestered in the cytoplasm by Kelch-like ECH-associated protein 1 (KEAP1) and targeted for proteasomal degradation [37]. Oxidative or electrophilic stress modifies key cysteine residues on KEAP1, allowing NRF2 to escape degradation and translocate into the nucleus. There, NRF2 binds antioxidant response elements and induces the expression of genes involved in antioxidant defense and detoxification, including heme oxygenase-1, NAD(P)H quinone oxidoreductase 1, and enzymes regulating glutathione metabolism. Rather than simply scavenging reactive oxygen species, NRF2 activation enhances intrinsic redox

resilience by strengthening the cell's capacity to respond to future oxidative challenges [36]. While NRF2 activation is beneficial in protecting against oxidative stress, chronic activation can have limitations. Continuous NRF2 activation may inadvertently promote tumorigenesis by aiding the survival of damaged cells, which may facilitate cancer progression. The activation of the pathway in non-cancerous tissues should, therefore, be carefully regulated. In terms of activating NRF2, activators can be classified into two primary categories, which include electrophilic and non-electrophilic types. Electrophilic activators, such as sulforaphane, directly modify KEAP1, leading to the activation of NRF2 [53]. However, these compounds can cause unintended damage due to their reactivity, potentially affecting cellular structures beyond their target. On the other hand, non-electrophilic activators, such as bardoxolone methyl, activate NRF2 without directly altering KEAP1, which offers a safer profile with fewer side effects but may have lower potency[37].

Conventional antioxidants have shown limited efficacy in neurodegenerative

Conventional antioxidant therapies have demonstrated limited benefit in neurodegenerative diseases, largely because they fail to adequately target mitochondria, the main intracellular source of neuronal ROS. This shortcoming has driven the development of mitochondria-targeted antioxidants that preferentially accumulate within the mitochondrial matrix by utilizing the mitochondrial membrane potential. MitoQ, for example, couples a ubiquinone moiety to a triphenylphosphonium cation, enabling direct scavenging of mitochondrial ROS and protection of mitochondrial lipids, proteins, and DNA. Similarly, elamipretide (SS-31) exerts its effects by stabilizing cardiolipin in the inner mitochondrial membrane, thereby preserving electron transport efficiency and limiting ROS production at its origin. Collectively, these strategies reflect a paradigm shift from broad-spectrum antioxidant use toward targeted modulation of mitochondrial redox homeostasis [54]. Comparison of mitochondria-targeted antioxidants MitoQ and SS-31 is summarized in Table 1 [25,55–60].

Table 1. Comparative summary of mitochondria-targeted antioxidants MitoQ and SS-31

Feature	Mitoquinone mesylate (MitoQ)	Elamipretide (SS-31)
Primary mechanism	Electrophoretic accumulation driven by mitochondrial membrane potential.	Potential-independent uptake; targets and stabilizes cardiolipin in the inner membrane.
Antioxidant action	Redox-active ubiquinone moiety directly scavenges radicals and is regenerated by Complex II.	Structural stabilization of cristae/supercomplexes to prevent electron leakage and ROS formation.
Physical impact	It can cause mitochondrial swelling and depolarization at high concentrations due to its alkyl chain.	Acts as "mitochondrial armor," protecting against membrane fragmentation and structural decay.
Preclinical evidence	Robust protection in Alzheimer's, Parkinson's, and Huntington's disease models.	Consistent success in Alzheimer's, Parkinson's, Huntington's disease, and brain injury models, improving dynamics and synaptic health.
Clinical status	Failed PD trials (no clinical effect on UPDRS). Currently used as a dietary supplement for vascular health.	FDA approved (Sept 2025) for Barth syndrome. Failed trials in heart failure and primary mitochondrial myopathy.

Lifestyle interventions and hormetic redox adaptation

Lifestyle interventions, such as physical exercise and caloric restriction, activate endogenous antioxidant defenses through a process known as hormesis. Hormesis refers to the phenomenon where low-level, transient oxidative stress triggers adaptive protective responses within cells. When applied in moderation, physical exercise and mild caloric restriction induce controlled oxidative stress that enhances cellular resilience [61]. These interventions improve mitochondrial efficiency by promoting better ATP production and reducing the production of excess ROS, stimulate autophagy for the clearance of damaged proteins and organelles, and upregulate antioxidant signaling pathways such as the Nrf2 pathway, which enhances the cell's ability to combat oxidative damage. Additionally, they boost the secretion of neurotrophic factors like brain-derived neurotrophic factor (BDNF), which support neuronal growth, survival, and synaptic plasticity, playing a crucial role in brain health [62].

However, it is important to note that the beneficial effects of hormesis are dose-dependent. When physical exercise or caloric restriction exceeds a certain threshold, it can shift from an adaptive to a maladaptive stress response. Prolonged or excessive exercise, for example, can lead to chronic oxidative stress, resulting in mitochondrial dysfunction, muscle damage, and an increase in inflammatory markers. Similarly, prolonged caloric restriction may impair cellular homeostasis, weaken the immune system, and exacerbate metabolic dysfunction. These maladaptive responses may overwhelm the body's protective mechanisms, leading to cellular damage rather than the intended health benefits. Therefore, while moderate exercise and caloric restriction can enhance redox balance and improve health outcomes, extreme or prolonged levels of these stressors may cause harm, highlighting the importance of balance in these lifestyle interventions [63].

Therapeutic potential and clinical translation

Pharmacological activation of NRF2 has therefore emerged as a promising therapeutic strategy in neurodegenerative disorders. Dimethyl fumarate, an approved treatment for multiple sclerosis, represents a clinically validated example of this approach [64]. By inducing mild electrophilic stress, it activates NRF2 signaling and confers neuroprotective and anti-inflammatory effects. Beyond fumarates, synthetic triterpenoids and other NRF2 activators are under investigation for their ability to restore redox homeostasis in aging and neurodegeneration. Nevertheless, clinical translation requires careful calibration. Chronic or excessive NRF2 activation may disrupt physiological redox signaling or promote maladaptive metabolic states. Thus, the therapeutic challenge lies not in maximal activation, but in restoring dynamic responsiveness to oxidative stress [36].

Challenges and future directions

Despite an increasingly robust molecular framework linking oxidative stress to neurodegenerative disease, clinical translation of antioxidant-based therapies in AD and PD has been largely underwhelming. Numerous trials, particularly those relying on conventional antioxidant supplementation, have failed to demonstrate consistent or meaningful clinical benefit. This disconnect between compelling preclinical data and disappointing clinical outcomes highlights a critical “translational gap” that extends beyond simple issues of drug efficacy. Rather than invalidating the role of oxidative stress in neurodegeneration, these failures underscore the complexity of redox biology in the human brain and reveal fundamental limitations in how antioxidant strategies have been conceptualized and implemented.

Table 2. Comparative summary between mechanisms of oxidative stress, their roles in Alzheimer's disease (AD) vs. Parkinson's disease (PD) and potential therapeutic interventions

Mechanisms of oxidative stress	Role in Alzheimer's disease (AD)	Role in Parkinson's disease (PD)	Potential therapeutic interventions
Mitochondrial dysfunction	Mitochondrial dysfunction leads to bioenergetic failure, impairing synaptic plasticity and contributing to neuronal damage.	Mitochondrial dysfunction in dopaminergic neurons accelerates ROS production and contributes to neuronal loss.	Mitochondria-targeted antioxidants (e.g., MitoQ, SS31) that help reduce ROS and restore mitochondrial function.
Lipid peroxidation	Oxidative damage to membrane lipids leads to neuronal damage and loss of synaptic function.	Lipid peroxidation exacerbates dopaminergic neuron death and disrupts membrane integrity.	Use of lipid antioxidants like alpha-lipoic acid or other peroxyl scavengers to prevent oxidative damage.
Proteostasis collapse	Proteostasis collapse contributes to the accumulation of amyloid-beta and tau, which disrupt neuronal function.	Accumulation of misfolded proteins, such as α-synuclein, leads to dopaminergic dysfunction.	Proteostasis regulators, such as proteasome activators or autophagy enhancers (e.g., rapamycin, spermidine).

Mechanisms of oxidative stress	Role in Alzheimer's disease (AD)	Role in Parkinson's disease (PD)	Potential therapeutic interventions
Neuroinflammation	Chronic neuroinflammation amplifies the amyloid plaque formation and accelerates disease progression.	Neuroinflammation in microglia worsens dopaminergic neuron death and amplifies ROS production.	Anti-inflammatory agents targeting NF-κB or microglial activation (e.g., minocycline, curcumin).
Redox-Imbalance (ROS and RNS)	ROS accumulation damages cellular structures (DNA, lipids, proteins) and triggers apoptosis.	ROS generation through dopamine metabolism leads to neuronal damage and contributes to cell death.	Nrf2 activators (e.g., dimethyl fumarate), which boost cellular antioxidant defences and help restore redox homeostasis.
Autophagy and mitophagy failure	Impaired autophagy leads to the accumulation of damaged proteins, exacerbating neurodegeneration.	Deficient mitophagy results in the accumulation of dysfunctional mitochondria, contributing to neurodegeneration.	Autophagy enhancers (e.g., rapamycin) and mitophagy activators (e.g., Urolithin A, PINK1 activators) to clear damaged organelles.

Temporal mismatch: Treating too late in the disease course

One of the most significant challenges lies in the timing of therapeutic intervention. Neurodegenerative diseases are characterized by long preclinical phases, during which molecular and cellular damage accumulates silently over years or even decades. By the time clinical symptoms emerge and patients are enrolled in trials, substantial neuronal loss and synaptic disintegration have already occurred [66,67]. At this advanced stage, oxidative stress is no longer a primary driver but rather a downstream consequence of irreversible structural damage. Antioxidant therapy administered under these conditions is therefore unlikely to restore lost neurons or reverse established network failure [68]. This temporal mismatch suggests that antioxidant interventions may be more effective as preventive or early-stage strategies, rather than as treatments for symptomatic disease. Future clinical trials must therefore prioritize early diagnosis and intervention, potentially targeting individuals with prodromal disease or those identified as high-risk based on genetic, metabolic, or biomarker profiles [69].

Bioavailability and blood-brain barrier limitations

Another major obstacle is the limited bioavailability of many antioxidant compounds within the central nervous system. The blood-brain barrier, while essential for protecting neural tissue, poses a formidable challenge for drug delivery. Many antioxidants exhibit poor lipophilicity, rapid systemic clearance, or extensive peripheral metabolism, resulting in insufficient concentrations reaching neuronal targets [70]. Even when compounds successfully cross the blood–brain barrier, their intracellular distribution is often non-specific, failing to reach subcellular compartments such as mitochondria, where oxidative stress is most pronounced. This pharmacokinetic mismatch further diminishes therapeutic efficacy and helps explain the failure of broad-spectrum antioxidants in clinical trials. Advances in drug delivery, such as nanoparticle-based carriers, mitochondria-targeted molecules, and ligand-mediated transport systems, represent promising avenues for overcoming these limitations. However, their clinical translation will require rigorous evaluation of safety, specificity, and long-term effects [71].

Paradox of reductive stress

A less intuitive, yet increasingly recognized challenge is the phenomenon of reductive stress. While oxidative stress reflects an excess of reactive species, excessive antioxidant supplementation can shift the redox balance in the opposite direction, suppressing physiological ROS signaling. ROS are not inherently pathological; at controlled levels, they play essential roles in synaptic plasticity, immune defense, and cellular adaptation. Overzealous scavenging of ROS can therefore impair normal signaling pathways, disrupt mitochondrial function, and paradoxically exacerbate cellular dysfunction [23]. This concept challenges the simplistic view that “more antioxidants are better” and highlights the need for precision in redox modulation. Therapeutic strategies must aim to restore redox homeostasis rather than eliminate ROS

indiscriminately. This requires a nuanced understanding of individual redox states and the context-dependent roles of oxidative signaling in health and disease [72].

Need for redox biomarkers and patient stratification

Perhaps the most critical gap in current clinical approaches is the lack of reliable biomarkers to assess oxidative status in vivo. Neurodegenerative diseases are heterogeneous, and not all patients exhibit the same degree or pattern of redox dysregulation. Without biomarkers to stratify patients, antioxidant therapies are applied indiscriminately, diluting potential benefits within responsive subgroups. Future research must therefore focus on developing and validating biomarkers that reflect systemic and brain-specific oxidative stress, antioxidant capacity, and mitochondrial function. These may include circulating redox markers, imaging-based indicators of oxidative metabolism, or genetic and epigenetic signatures linked to redox regulation. Such biomarkers would enable precision medicine approaches, identifying individuals most likely to benefit from antioxidant or redox-modulating interventions and allowing therapies to be tailored in terms of timing, dosage, and mechanism [73].

Toward a systems-level therapeutic strategy

Looking forward, the field must move beyond reductionist strategies that target oxidative stress in isolation. Neurodegeneration arises from the convergence of redox imbalance, mitochondrial dysfunction, neuroinflammation, impaired autophagy, and synaptic failure. Effective therapies will likely need to engage multiple nodes within this network, either through combination treatments or through interventions that restore upstream regulatory control, such as Nrf2 signaling or mitochondrial quality control pathways [74]. In this context, antioxidant therapy should be reframed not as a standalone solution, but as one component of an integrated disease-modifying strategy. Bridging the translational gap will require early intervention, targeted delivery, biomarker-guided patient selection, and a deeper appreciation of redox biology as a dynamic and context-dependent system [75].

Conclusion

This review demonstrates that oxidative stress serves as a central, unifying mechanism linking biological aging to neurodegenerative disorders. Through sustained redox imbalance, ROS drive mitochondrial dysfunction, proteostatic failure, neuroinflammation, and impaired autophagy, collectively undermining neuronal integrity. The limited success of conventional antioxidants highlights the need for targeted redox modulation rather than indiscriminate radical scavenging. Strategies that enhance endogenous defenses, restore mitochondrial quality control, and activate adaptive pathways such as Nrf2 offer promising avenues for delaying neurodegenerative progression and extending neural healthspan.

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Competing interests

All authors declare that there are no conflicts of interest related to this work.

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Underlying data

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declaration of artificial intelligence use

This study employed the artificial intelligence (AI) tools Gemini Pro and ChatGPT to support manuscript writing, including language refinement (improving grammar, sentence structure, and overall readability) and technical writing assistance (providing suggestions for structuring complex technical descriptions more effectively). All AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were made solely by the authors.

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