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Review Article

Impact of Aging on Brain Redox Balance: Mechanistic Links to Synaptic Dysfunction and Neurodegenerative Disease

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ABSTRACT

Aging remains the most significant risk factor driving the development and progression of neurodegenerative diseases, as it reflects the gradual accumulation of molecular and cellular changes over time. Disturbance of redox balance has been recognized among these changes as a primary mechanism that links aging to synaptic decline. The imbalance favoring the production of reactive oxygen species over the capability of the antioxidant systems to neutralize them results in oxidative stress, which selectively disrupts synaptic morphology and function. In this context, mitochondrial dysfunction is a significant factor since it not only raises oxidative stress but also reduces the energy supply necessary for standard cellular activity. At the same time, the decline of the endogenous antioxidant system due to aging further weakens neuronal defence. Oxidative modification of synaptic proteins changes their composition and roles, thereby reducing neurotransmission and plasticity. These interconnected processes underlie the pathological basis of major neurodegenerative diseases, such as Parkinson's and Alzheimer's. The complexity of the involved systems restricts the success of redox-balance-restoring therapeutic strategies, although they have a high potential. Hence, further work is necessary to enhance redox-based therapies and facilitate their translation for neurodegeneration in aging.

Keywords: Redox Homeostasis; Oxidative Stress; Brain Aging; Synaptic Dysfunction; Neurodegenerative Diseases; Reactive Oxygen Species

Introduction

Brain aging remains the main risk factor for neurodegenerative disease and is defined by the steady deterioration of the central nervous system's structural and functional integrity. One of the main mechanisms connecting cellular dysfunction to synaptic and neuronal loss among the molecular changes linked to aging is the disruption of redox homeostasis [1]. Redox homeostasis is the carefully controlled equilibrium between the generation of reactive oxygen species [ROS] and antioxidant defense mechanisms that maintain metabolic stability and physiological communication. This equilibrium gradually deteriorates with age, increasing oxidative stress and decreasing neural resilience [2].

Neurones are particularly susceptible to redox imbalance due to their limited capacity for regeneration, high metabolic demand, reliance on mitochondrial oxidative phosphorylation, and abundance of oxidation-sensitive polyunsaturated fatty acids [3]. ROS are crucial signalling molecules involved in synaptic plasticity, neurotransmission, and adaptive stress responses, despite their conventional association with cellular destruction. Enzymatic and non-enzymatic antioxidant systems normally regulate redox signalling; however, aging causes mitochondrial malfunction, reduced antioxidant capacity, and persistent inflammatory activation that interfere with this coordination [4].

Synaptic dysfunction is one of the first effects of redox dysregulation and often occurs before overt neuronal death in neurodegenerative diseases. Long before irreversible neurodegeneration occurs, oxidative alterations in synaptic communication, calcium homeostasis, and structural plasticity impair neuronal function [5]. Thus, there is growing evidence that neurodegeneration is a result of both excessive oxidative stress and the gradual disintegration of coordinated redox signalling networks that preserve synaptic integrity. With a focus on the underlying processes and new therapeutic approaches, this review investigates how aging-associated breakdown of redox homeostasis contributes to synaptic dysfunction and neurodegenerative diseases [6].

Redox Homeostasis in the Healthy Brain

Physiological ROS Signalling

Reactive oxygen species are typically regarded as detrimental metabolic byproducts, yet there is growing evidence that they serve as vital signalling molecules in a healthy brain [7]. Reactive oxygen species are produced under physiological conditions at low and strictly controlled concentrations, mainly by nicotinamide adenine dinucleotide phosphate oxidases, mitochondrial oxidative phosphorylation, and other enzymatic activities related to cellular metabolism. These brief oxidative signals contribute to the control of neural communication, synaptic plasticity, and adaptive cellular responses rather than producing random molecular damage [8].

Neurotransmission and activity-dependent plasticity are directly influenced by localised redox signalling at synapses. Redox-sensitive cysteine residues on ion channels, receptors, and signalling proteins can be reversibly altered by mild increases in reactive oxygen species, which can affect neuronal excitability and synaptic strength [9]. The significance of oxidative signalling in learning and memory formation is highlighted by the fact that processes driving long-term potentiation and long-term depression are especially dependent on strictly regulated redox modulation. In this situation, reactive oxygen species serve as vital regulators of intracellular signalling networks rather than just being harmful agents [10].

The concentration, duration, and cellular location of reactive oxygen species all have a significant impact on their physiological consequences. Normal neural adaptation is supported by controlled and compartmentalised production, while excessive or protracted accumulation causes redox signalling to shift toward pathological oxidative stress [11]. Therefore, in order to maintain signalling integrity while avoiding molecular damage, redox homeostasis maintenance necessitates exact coordination between reactive species formation and antioxidant defence systems [12].

Crucially, physiological redox signalling in the brain microenvironment is further refined by interactions between neurones and glial cells [13]. Astrocytes play a major role in sustaining metabolic support and extracellular antioxidant equilibrium, which enables neurones to meet high energy and synaptic demands without experiencing an excessive oxidative burden. This coordinated regulation highlights the fact that physiological redox signalling is not just a byproduct of aerobic metabolism but rather an active and closely integrated part of normal brain function [14].

Antioxidant Systems

Redox processes in the brain are not characterized by the absence of oxidative species but by a carefully regulated balance. As natural by-products of aerobic metabolism, especially within mitochondria,

reactive oxygen species are produced constantly [15]. However, at low levels that are controlled, they perform important signalling roles. These molecules not only act as harmful agents; rather, they also help in regulating synaptic function and neuronal communication[16].

Reactive oxygen species have an important role in facilitating synaptic plasticity. Short and highly localised changes in redox signalling participate in the regulation of long-term potentiation, which is the cellular basis of learning and memory [17]. These molecules bring about reversible oxidative modifications to signalling proteins, thereby influencing receptor activity, ion channel functioning, and kinase cascades. In this capacity, they precisely modulate synaptic strength rather than cause damage [18].

The brain relies on a robust network of antioxidant defenses to keep its signalling environment accurately controlled. These systems ensure the redox balance by stopping the accumulation of reactive oxygen species to a harmful level [19].

The enzymatic antioxidant defenses include principal systems such as superoxide dismutase, which transforms superoxide radicals into hydrogen peroxide; catalase, which then splits hydrogen peroxide into water and oxygen; and glutathione peroxidase, which removes peroxides by using reducing equivalents supplied by glutathione [20]. Altogether, these enzymes form a protective network that not only limits oxidative stress but also preserves the redox state required for proper cellular signalling [21].

Besides, non-enzymatic antioxidants provide additional layers of protection. Glutathione, the major intracellular redox buffer, is not only critical for maintaining thiol balance but also for removing reactive species [22]. The intake of antioxidants from the diet, like the vitamins E and C, enhances the overall robustness of the cell by safeguarding the membranes and regenerating the redox-active moleculesm[23].

Cellular Compartments and Metabolic Cooperation

Functional specialisation among various cell types also influences redox homeostasis in the brain. Astrocytes and neurones work in tandem to preserve oxidative equilibrium[24]. Reactive oxygen species are mostly produced in neurones due to their high metabolic demand, while astrocytes play a more significant role in metabolic regulation and antioxidant support [25].

Maintaining this equilibrium requires astrocyte neurone metabolic coupling. Astrocytes buffer the oxidative burden on neurones by providing metabolic substrates, controlling the availability of extracellular glutathione, and helping to detoxify reactive substances [26]. Neurones can maintain elevated levels of electrical and synaptic activity without suffering oxidative damage due to this synergistic interaction [27].

Overall, rather than the total removal of oxidative molecules, redox homeostasis in the healthy brain depends on a dynamic equilibrium between the generation of reactive oxygen species and antioxidant defence. This equilibrium is crucial for regulating synaptic function, facilitating plasticity, and ensuring long-term neuronal integrity [12].

Aging-Associated Disruption of Redox Balance

Mitochondrial Dysfunction

With aging comes a gradual disruption in the balance of cell redox processes indicating less efficiency of antioxidant defense alongside more generation of oxidants. This change in the balance redox does not only mean an increase in the level of reactive oxygen species but also includes a coordinated loss of several regulatory systems that are usually responsible for maintaining redox balance [28]. These changes vary from one tissue to another and their effects are not always directly proportional to time; however, combined they result in the accumulation of molecular damage and decline in functional capabilities [29]. Recent findings imply that redox imbalance during aging is a breakdown at the level of the whole system, where different pathways of mitochondrial function, antioxidant levels, metal homeostasis, and protein quality control that are interlinked become increasingly dysfunctional [30].

Mitochondria play a pivotal role in redox biology, acting both as a major source of reactive oxygen species and as key regulators of cellular energy production. As aging progresses, mitochondrial efficiency declines, particularly within oxidative phosphorylation. The electron transport chain becomes less efficiently coupled, resulting in incomplete reduction of oxygen and increased electron leakage. This process promotes the generation of superoxide and other reactive species [31]. Concurrently, mitochondrial DNA is highly susceptible to oxidative damage due to its close proximity to the electron transport chain and its relatively limited repair mechanisms. The accumulation of mitochondrial DNA mutations further compromises respiratory function, establishing a self-perpetuating cycle of mitochondrial dysfunction and oxidative stress [32].

Crucially, aging-related changes to the mitochondria go beyond merely accumulating damage.

The endurance of malfunctioning organelles is influenced by modifications in mitochondrial dynamics, such as fusion, fission, and mitophagy[33]. The primary function of mitochondria in age-related redox imbalance is reinforced by the ineffective removal of damaged mitochondria, which increases oxidative burden and interferes with metabolic signalling [34].

Decline in Antioxidant Capacity

Aging increases neuronal susceptibility to oxidative stress by gradually impairing the cellular antioxidant systems in charge of preserving redox balance [35]. As individuals age, their enzymatic and non-enzymatic antioxidant defences deteriorate, which makes it harder for the brain to effectively neutralise reactive oxygen species. Even slight losses in antioxidant protection can significantly reduce cellular resilience since neurones have high metabolic needs and little ability for regeneration [5].

Depletion of glutathione, the main intracellular antioxidant and redox buffer, is one of the biggest alterations. In addition to reducing intracellular glutathione levels, ageing also hinders its ability to regenerate from the oxidised state, which limits its capacity to detoxify reactive species and preserve thiol equilibrium [36]. Simultaneously, oxidative defence mechanisms are further weakened by the gradual dysregulation of important antioxidant enzyme activities, such as glutathione peroxidase, catalase, and superoxide dismutase [37].

Impaired activation of protective signalling pathways is also associated with the decrease in antioxidant capacity. Nuclear factor erythroid 2-related factor 2 [Nrf2], a crucial regulator of antioxidant and detoxifying gene expression, has declined reactivity with ageing[38]. The stimulation of cytoprotective enzymes involved in glutathione production, peroxide detoxification, and cellular stress adaption is restricted by decreased Nrf2 signalling. As a result, ageing cells are less able to react to oxidative stressors [39].

Crucially, decreased antioxidant defence interacts intimately with mitochondrial dysfunction, inflammation, and compromised proteostasis rather than just increasing oxidative damage on its own. This linked decline significantly increases synaptic dysfunction and neuronal death throughout ageing, while also promoting chronic redox imbalance [40].

Metal Dyshomeostasis

As cells get older, their antioxidant mechanisms undergo both quantitative and qualitative changes that result in a decrease in their capability to protect themselves against ROS [41]. The main intracellular antioxidant glutathione in particular, is gradually losing its reduced form, which makes cells less capable of maintaining redox balance. However, this decline in glutathione is often accompanied by its poor regeneration from the oxidised form therefore significantly limiting its cycling between the two redox states [42].

The transcription factor, nuclear factor erythroid 2-related factor 2, which is responsible for the expression of a wide variety of detoxifying and antioxidant enzymes is a key player in the regulation of cellular antioxidant defense [43]. Unfortunately, the ability of this pathway to respond declines as one gets older. When there is a lack of activation of this signalling pathway, induction of redox homeostasis-related genes is limited, and therefore, cells become less capable of dealing with oxidative stress. This malfunction further contributes to the general decrease in redox tolerance by engaging with other stress pathways and mitochondrial dysfunction [44].

Transition metals like iron and copper are vital for biological functions and are necessary for functioning normally. Nonetheless, their redox properties can render them detrimental if their concentrations are not adequately regulated [37]. With aging, disruptions in metal homeostasis often cause certain tissues to accumulate redox-active metals. Excess iron is the primary factor that can initiate the Fenton reaction, resulting in the production of extremely reactive hydroxyl radicals that may cause significant damage on lipids, proteins, and nucleic acids.

This disruption is attributable to the failure of metal handling proteins regulation, including those responsible for export, transport, and storage. Also, metals localization can be altered as a result of the aging of cells, thereby exposing them to harmful effects [46]. Although redox imbalance is predominantly associated with the formation of reactive oxygen species, disruptions in metal homeostasis are also significantly influential. The interplay of metal excess and oxidative stress facilitates the generation of highly reactive radicals, hence intensifying cellular damage [47].

Impaired Proteostasis

Cellular work relies heavily on the maintenance of protein homeostasis, a very complex system that is greatly susceptible to oxidative stress. Reactive species can modify side chains of amino acids, promote protein misfolding, and facilitate the formation of aggregates [48]. In young organisms, the proteasome is capable of detecting and degrading defective proteins with high efficiency, or autophagic mechanisms get rid of them. However, these quality control systems become less effective as we grow older [49].

Decreased autophagic flow is often associated with reduced proteasomal function, partly due to oxidative modifications of its components. The accumulation of oxidatively damaged proteins that further impair cellular processes leads to a feedback loop that intensifies proteostatic stress [50]. Besides, since damaged proteins can disrupt metabolic and signalling pathways, this decrease in protein quality control not only indicates redox imbalance but also contributes to its propagation [51].

Critical Perspective

Collectively, these processes demonstrate that redox imbalance in aging cannot be traced to a single origin or pathway. Instead, it arises from the gradual breakdown of an interconnected network encompassing energy metabolism, antioxidant defenses, metal homeostasis, and protein maintenance systems [52]. Each of these components is interdependent, such that dysfunction in one area can spread and disrupt the others. Interpreting aging through this integrative perspective moves the emphasis away from isolated molecular damage toward a broader loss of regulatory coordination, providing a more comprehensive understanding of how redox biology contributes to age-related decline [53].

Mechanisms of Redox-Induced Synaptic Dysfunction

Synaptic integrity relies heavily on precisely regulated redox signalling, reflecting the high energy demands and molecular accuracy required for effective neurotransmission [54]. Neurons, particularly at synaptic terminals, function within a limited biochemical range in which even minor disturbances in redox balance can interfere with communication. In contrast to other cellular regions, synapses are specialized for rapid signalling, which increases their susceptibility to oxidative perturbations [55]. Growing evidence suggests the synapse is not merely a passive target of oxidative damage but a central site of redox susceptibility, where various interacting pathways converge to impair neuronal function[56].

Oxidative Modification of Synaptic Proteins

Proteins that play a role in synaptic transmission are highly susceptible to oxidative modification as they possess flexible structures and are continuously exposed to reactive species. Soluble N-ethylmaleimide-sensitive factor attachment protein receptor [SNARE] proteins are among the most critical mediators of synaptic transmission, regulating the docking and fusion of synaptic vesicles [57]. Oxidative modifications can break down their structural stability and reduce their ability to carry out vesicle exocytosis. Disruptions in the SNARE complex, even if minimal, can significantly hamper neurotransmitter release and lead to a decrease in synaptic efficiency [58].

Redox-dependent changes influence both the gating properties and trafficking of ionotropic glutamate receptors, including N-methyl-D-aspartate [NMDA] and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA] receptors. At the synaptic membrane, oxidative changes to receptor subunits might change channel conductance or lead to a lower number of receptors [59]. These alterations not only degrade synapses but also disrupt activity-dependent plasticity, which is vital for memory and learning. The decline in synaptic response is the result of both structural and functional degradation [60].

Lipid Peroxidation

Polyunsaturated fatty acids, which are more susceptible to oxidative damage, are abundant in synaptic membranes [61]. The structural organization of the lipid bilayer is disrupted by lipid peroxidation, which results in reduced membrane fluidity and changed membrane curvature. Since membrane characteristics are essential for vesicle fusion and receptor mobility, these alterations directly affect synaptic function [62].

Lipid peroxidation at the presynaptic terminal may hinder the fusion of synaptic vesicles with the plasma membrane. Both physical changes in membrane dynamics and subsequent impacts on membrane-associated proteins cause this deficiency [63]. Moreover, proteins can form adducts with lipid peroxidation byproducts like reactive aldehydes, which can intensify molecular damage after the initial oxidative event. Reduced membrane fluidity can impede receptor clustering and signalling effectiveness at the postsynaptic location. The fundamental basis of synaptic transmission is jeopardised by these modifications taken together [56].

Calcium Dysregulation

Calcium signalling, primarily regulates processes ranging from neurotransmitter release to synaptic plasticity, is crucial for synaptic function. There are several ways that redox imbalance disrupts calcium homeostasis [64]. Reactive oxygen species can change the permeability and responsiveness of ligand-gated receptors and voltage-gated calcium channels. Increased calcium influx from these changes frequently overwhelms cellular buffering mechanisms [65].

High levels of intracellular calcium induces a range of detrimental activities, including the activation of lipases, endonucleases, and proteases. This condition, referred to as excitotoxicity, impairs the

construction and function of synapses [66]. Moreover, oxidative stress can impede the function of calcium exchangers and pumps, thereby diminishing the cell's ability to restore normal calcium levels. Synaptic signalling is further destabilised by subsequent dysregulation, which perpetuates a cycle of oxidative stress and calcium overload [67].

Mitochondria at Synapses

Synaptic terminal mitochondria are essential for maintaining neurotransmission because they supply ATP and control calcium dynamics [68]. These organelles meet the substantial requirements of synaptic activity due to their strategic positioning. Nonetheless, they are more susceptible to oxidative stress due to their proximity to regions of increased metabolic activity [69].

Presynaptic terminals generate less ATP due to mitochondrial dysfunction induced by ageing and stress. This energy shortfall has a direct effect on ATP-dependent functions such vesicle loading, docking, and recycling [70]. Moreover, calcium dysregulation is exacerbated by compromised local calcium buffering due to decreased mitochondrial action. Before overt neuronal degeneration, synapse failure occurs due to the inability to sustain enough energy supply and ionic equilibrium. Importantly, damaged mitochondria can generate reactive oxygen species, thereby sustaining the cycle of oxidative damage [71].

Neuroinflammation

Redox-induced synaptic dysfunction is largely caused by neuroinflammatory mechanisms. Oxidative stress and neuronal damage cause the central nervous system's resident immune cells, microglia, to become activated [19]. A variety of pro-inflammatory cytokines and reactive species, such as superoxide and nitric oxide, are released by activated microglia. Chronic stimulation results in persistent inflammatory signalling that is harmful to synaptic integrity, even if these reactions may initially have beneficial purposes [72].

The reciprocal link between oxidative stress and inflammation is a crucial aspect of this process. While cytokines can promote the generation of more reactive species, reactive oxygen species can activate inflammatory pathways [73]. Synaptic damage is encouraged and cellular stress is increased by this feedback loop. By modifying receptor expression and interfering with synaptic plasticity pathways, inflammatory mediators can also have a direct impact on synaptic function. This ongoing inflammatory milieu eventually leads to synapse loss and compromised neuronal transmission [74].

Analytical Perspective

The idea that the synapse is a focal point of redox vulnerability is highlighted by the confluence of these mechanisms. Synaptic dysfunction results from the interplay of protein oxidation, lipid degradation, calcium imbalance, mitochondrial failure, and inflammatory signalling rather than from separate molecular events [75]. Each of these processes influences the others, resulting in a network of dysfunction that jeopardises synaptic integrity. Viewing the synapse through this integrated framework underscores its vital role in the initial stages of neurodegenerative disorders and emphasises the importance of preserving redox balance for the maintenance of neuronal transmission [76]. The major mechanisms linking aging-associated redox imbalance to synaptic dysfunction and neurodegeneration are summarized in Figure 1.

Figure 1. Impact of Aging on Brain Redox Balance; Mechanistic Links to Synaptic Dysfunction and Neurogenerative Diseases

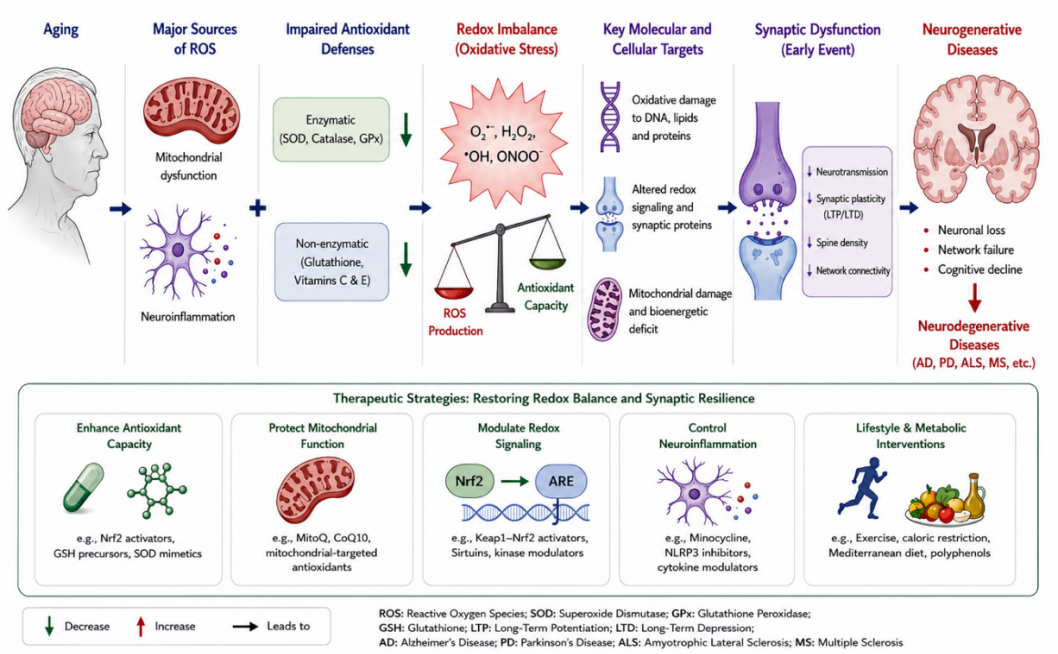

Figure 1 illustrates the mechanistic pathway through which aging disrupts brain redox homeostasis and promotes neurodegeneration. Aging is associated with increased production of reactive oxygen species arising from mitochondrial dysfunction and neuroinflammatory processes, together with a decline in both enzymatic and non-enzymatic antioxidant defenses. The resulting redox imbalance leads to oxidative damage of cellular macromolecules, altered redox signalling, and mitochondrial bioenergetic deficits. These molecular alterations impair synaptic transmission, plasticity, spine density, and network connectivity, thereby contributing to progressive neuronal dysfunction. Ultimately, the cumulative effects of oxidative stress and synaptic failure increase susceptibility to major neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis. The figure also highlights potential therapeutic strategies aimed at restoring redox balance, preserving mitochondrial function, modulating neuroinflammation, and enhancing synaptic resilience.

Source: Created by the author

Redox Dysregulation in Neurodegenerative Diseases

A key characteristic of numerous neurodegenerative diseases is redox imbalance, which promotes disease initiation, progression, and cellular damage. The disturbance of oxidative balance and its association with protein aggregation, mitochondrial malfunction, and synaptic failure is a consistent theme, although each condition possesses distinct clinical features [77]. Crucially, redox dysregulation is not a stand-alone phenomenon. It creates a self-propagating cycle of neuronal damage by both amplifying and being reinforced by disease-specific molecular events. A common paradigm for interpreting various neurodegenerative manifestations is provided by comprehending this interaction [78].

Alzheimer's Disease

Oxidative stress and the build-up of amyloid-β peptides, which are essential to the pathophysiology of Alzheimer's disease, are intimately related. Through interactions with redox-active metals, amyloid-β can directly produce reactive oxygen species, which can lead to oxidative damage to proteins, lipids, and nucleic acids [79]. Oxidative stress also increases the synthesis of amyloid-β by enhancing the amyloidogenic processing of amyloid precursor protein. A reinforcing loop is created by this reciprocal interaction, hastening the development of pathology [80].

Redox imbalance is further intensified by tau pathology, characterised by the abnormal hyperphosphorylation and aggregation of the microtubule-associated protein tau. Hyperphosphorylated tau destabilises microtubules and disrupts intracellular transport, particularly mitochondrial trafficking along axons [77]. At synaptic locations, this results in increased oxidative stress and localised energy deficits. In addition to decreasing ATP synthesis and increasing the formation of reactive species, mitochondrial dysfunction linked to tau pathology exacerbates neuronal vulnerability [81].

Synaptic loss is one of the first signs of Alzheimer's disease, occurring before overt neuronal death. This process is greatly aided by redox imbalance, which damages synaptic proteins, modifies receptor function, and reduces neurotransmission. Amyloid poisoning, tau malfunction, and oxidative stress come together to cause gradual cognitive deterioration [82].

Parkinson's Disease

Oxidative stress is closely associated with the selective destruction of dopaminergic neurones in the substantia nigra, which is a hallmark of Parkinson's disease. Since dopamine can undergo auto-oxidation to produce reactive quinones and hydrogen peroxide, dopamine metabolism itself is a major source of reactive species. These compounds make neurones more vulnerable to oxidative stress and degeneration [83].

Parkinson's disease is characterised by mitochondrial malfunction, especially at the level of complex I of the electron transport chain [84]. Reactive oxygen species are more likely to develop when complex I activity is compromised because it decreases ATP synthesis and increases electron leakage. Environmental pollutants and genetic abnormalities that impact mitochondrial quality control systems worsen this mitochondrial deficiency [83].

Aggregation of α-synuclein into Lewy bodies is another important aspect of Parkinson's disease. Aggregated forms of α-synuclein can impair mitochondrial function and intensify oxidative stress, while misfolding and aggregation of the protein are encouraged by oxidative stress [86]. Neuronal loss is caused by a cycle of protein aggregation and redox imbalance, which is facilitated by this reciprocal connection [84].

Amyotrophic Lateral Sclerosis

Progressive motor neurone degeneration is a hallmark of amyotrophic lateral sclerosis, and oxidative stress is a key factor in the pathophysiology of the disease. One of the most well-established genetic causes of the disease is mutations in the gene encoding superoxide dismutase 1. Mutant forms of this enzyme can develop toxic properties that promote oxidative

damage instead of mitigating it, despite the enzyme's typical antioxidant role [87].

Due to their high metabolic requirement and restricted ability for regeneration, motor neurones are especially susceptible to oxidative stress. Proteins, lipids, and DNA are among the cellular components that are impacted by oxidative damage in the context of amyotrophic lateral sclerosis. This damage is exacerbated by mitochondrial dysfunction, which increases the production of reactive species and impairs energy consumption [88].

Astrocytes and microglia are examples of non-neuronal cells that contribute to oxidative stress in amyotrophic lateral sclerosis in addition to intrinsic neuronal causes. These cells have the ability to generate inflammatory mediators and reactive substances that worsen damage to motor neurones [89]. Disease progression is fuelled by a complex milieu of redox dysregulation created by the combined actions of inflammatory processes, mitochondrial dysfunction, and genetic alterations [90].

Comparative Analysis

Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis share a number of basic pathways based on redox imbalance, although having different clinical and pathological characteristics. One prevalent factor is mitochondrial dysfunction, which impairs energy production and increases the creation of reactive species [91]. Another common characteristic is protein aggregation, where cellular stress and dysfunction are caused by misfolded proteins such amyloid-β, tau, α-synuclein, and mutant SOD1. In addition to being the product of oxidative damage, these aggregates also encourage more redox imbalance, which accelerates the course of the disease [92].

At the same time, each disorder has distinct triggers that determine its own course. Amyloid-β and tau pathology dominate the oxidative damage landscape in Alzheimer's disease. Dopamine metabolism and α-synuclein aggregation are important factors in Parkinson's disease [93]. The pattern of deterioration in amyotrophic lateral sclerosis is defined by selective motor neurone vulnerability and genetic alterations. These differences emphasise how crucial context is in determining how redox dysregulation appears in various neuronal groups [94].

When combined, these findings provide credence to the theory that neurodegenerative diseases result from the convergence of common pathogenic processes that are influenced by disease-specific variables [95]. Redox imbalance links disparate chemical events and shapes the distinctive characteristics of each disease by acting as both a unifying mechanism and a point of divergence [96].

Table 1. Comparative Overview of Redox Mechanisms in Major Neurodegenerative Diseases

Disease	Primary Redox Driver	Major Cellular Consequence	Characteristic Pathology
Alzheimer's disease	Amyloid-β-associated oxidative stress and metal-mediated ROS generation	Synaptic dysfunction, mitochondrial impairment, and reduced neurotransmission	Amyloid-β plaques and hyperphosphorylated tau accumulation
Parkinson's disease	Dopamine auto-oxidation and mitochondrial complex I dysfunction	Oxidative injury to dopaminergic neurons and impaired energy metabolism	α-synuclein aggregation and Lewy body formation
Amyotrophic lateral sclerosis	Mutant SOD1-associated oxidative stress and neuroinflammation	Motor neuron degeneration and impaired proteostasis	Progressive upper and lower motor neuron loss

Therapeutic Strategies Targeting Redox Imbalance

Numerous therapeutic approaches have been developed in an attempt to address redox imbalance in neurodegenerative diseases, but there has been little clinical success. This disparity highlights a basic problem in redox biology [97]. Reactive oxygen species are vital signalling molecules in addition to being harmful agents. Therefore, restoring equilibrium without impairing physiological redox processes is necessary for effective therapies. Current strategies include pathway-based modulation, mitochondria-targeted drugs, traditional antioxidants, and lifestyle modifications, each having unique benefits and drawbacks [98].

Antioxidants

Conventional antioxidant approaches, especially those involving vitamins such as vitamin C and vitamin E, were among the first strategies investigated. While these compounds can neutralize free radicals and reduce oxidative damage in experimental settings, their clinical outcomes have been inconsistent. A major limitation is their lack of specificity [99]. These antioxidants act in a broad, non-targeted manner and do not directly address the main

intracellular sources of reactive species. Consequently, they may not effectively reach critical regions such as mitochondria or synaptic compartments, where oxidative stress is most significant [11].

A further limitation is that excessive antioxidant supplementation can interfere with normal redox signalling. Physiological levels of reactive oxygen species are essential for processes such as synaptic plasticity and cellular adaptation to stress [47]. Broad, non-specific suppression of these signals may therefore produce unintended effects. Together, these issues help explain why vitamin-based interventions often fail to translate effectively from experimental models to meaningful clinical outcomes [41].

Mitochondria-Targeted Therapies

Targeted strategies have drawn more attention because of the crucial role mitochondria play in redox control. By taking use of membrane potential, substances like MitoQ are made to build up inside mitochondria and deliver antioxidant effects straight to a significant source of reactive oxygen species. Elamipretide and other SS peptides interact with mitochondrial membranes to stabilise electron transport and lower oxidative leakage [100].

These therapies offer greater selectivity than conventional antioxidants and have shown promise in preclinical studies. However, achieving consistent clinical outcomes remains challenging. Variations in tissue distribution, disease stage, and long-term safety continue to limit their widespread usage [101].

Nrf2 Pathway Activation

Instead of directly scavenging reactive species, a different approach concentrates on strengthening endogenous antioxidant defences[102]. Nrf2 pathway activation increases the transcription of genes related to redox homeostasis, glutathione production, and detoxification. This strategy enables cells to mount a coordinated defence against oxidative stress, possibly offering longer-lasting protection [103].

Experimental models of neurodegeneration have shown protective effects from pharmacological activators of this system. Concerns about off-target consequences and the possibility of changing regular cellular signalling are raised by persistent activation, though. The difficulty is in attaining regulated activation that improves resilience without upsetting homeostatic equilibrium [104].

Lifestyle Interventions

Modulating redox balance is another major function of non-pharmacological methods. It has been demonstrated that regular exercise increases endogenous antioxidant systems and enhances mitochondrial efficiency. Calorie restriction can also improve cellular repair processes and lessen metabolic stress [105].

Instead of directly suppressing reactive species, these therapies work through adaptive responses. They trigger pathways that gradually increase redox regulation by causing mild, temporary stress. They provide a low-risk and long-lasting way to boost cellular resilience, even if their effects are typically less pronounced than those of pharmaceutical drugs [12].

Critical Analysis

The limited effectiveness of antioxidant-based treatments draws attention to a number of crucial factors. Interventions that are started after substantial neuronal damage may not have much of an effect on the course of the disease, therefore timing is crucial[99]. Moreover, numerous medicines exhibit reduced efficacy in critical areas of oxidative stress due to their lack of specificity. The indiscriminate suppression of reactive oxygen species may severely impede their physiological activities in cellular signalling [98].

Targeted and context-dependent techniques that restore redox balance without compromising vital signalling processes will probably be necessary for a more successful treatment paradigm [106]. This viewpoint, which reflects a better understanding of oxidative biology in disease and health, changes the objective from straightforward antioxidant supplementation to specific manipulation of redox networks [107].

Challenges in Clinical Translation

Redox-targeted medicines have not yet been successfully translated into clinical practice, despite strong evidence connecting redox imbalance to neurodegenerative disease [108]. The intricacy of redox biology presents a significant obstacle since reactive oxygen species are not only dangerous substances but also crucial modulators of intracellular signalling, neuronal plasticity, and adaptive stress responses. Therefore, broad antioxidant methods may restrict treatment effectiveness by interfering with physiological signalling pathways necessary for normal brain function [22].

The timing of the intervention is another significant constraint. Significant brain damage may already be irreversible at diagnosis since oxidative stress and synaptic dysfunction may build progressively before overt clinical symptoms manifest [27]. The absence of reliable biomarkers to accurately monitor dynamic redox alterations in the brain hinders therapy development, particularly given the variability of oxidative stress among different brain regions, cell types, and stages of disease [109].

Inconsistent clinical results are also a result of disease heterogeneity. Treatment response and

vulnerability to oxidative damage are influenced by aging-related variability, environmental exposure, metabolic condition, and genetic background [110]. Differences in antioxidant capacity, inflammatory signalling, and mitochondrial function indicate that future treatments will probably need more individualised and context-dependent strategies rather than widespread antioxidant supplementation [111].

Ultimately, disparities between clinical diseases and experimental models remain a substantial obstacle. Inadequate clinical translation arises from the failure of numerous preclinical models to emulate the complexity and prolonged progression of neurodegenerative disorders in individuals [112]. Consequently, improved disease models, reliable biomarkers, and targeted therapy strategies that may re-establish redox balance while preserving essential signalling functions will be crucial for future advancements [113].

Emerging Concepts and Future Directions

Reactive oxygen species are now seen as crucial signalling molecules involved in synaptic plasticity, metabolic adaptation, and cellular resilience rather than just hazardous byproducts due to our expanding knowledge of redox biology [114]. Differentiating between pathological oxidative stress and healthy redox signalling is becoming more important since neuronal dysfunction can result from both excessive ROS generation and disturbance of the temporal and spatial regulation of redox networks. Because indiscriminate suppression of reactive species may disrupt essential signalling pathways necessary for normal brain function, this distinction has significant therapeutic implications [115].

The study of oxidative biology in neurodegeneration is changing as a result of developments in single-cell analysis, spatial transcriptomics, redox proteomics, and metabolomics. These technologies allow for the identification of cell-specific and compartment-specific redox changes in synapses, axons, mitochondria, and glial populations, in contrast to traditional bulk tissue methods [116]. Redox imbalance varies by cellular identity, anatomical location, and illness stage, according to new data. Systems biology and artificial intelligence methodologies are concurrently developing as valuable tools for simulating complex redox interactions and predicting disease progression through the integration of multi-omics datasets [117].

The discovery of dependable biomarkers for the early detection and monitoring of neurodegenerative diseases remains a significant research focus. Current oxidative stress indicators, such as lipid peroxidation products and oxidatively modified proteins, frequently offer indirect assessments of disease activity and may exhibit inadequate sensitivity and specificity for routine clinical application [118]. Consequently, dynamic biomarkers capable of detecting early redox alterations before irreversible brain injury are the emphasis of next research. The early identification and tracking of treatment in neurodegenerative illnesses may be improved through the integration of proteomic, metabolomic, and imaging methodologies [119].

In addition, precision medicine approaches targeting redox dysregulation are also gaining prominence. Factors associated with ageing, environmental exposure, metabolic state, and genetic predisposition all influence treatment efficacy and vulnerability to oxidative damage. Metabolic inefficiency associated with Apolipoprotein E [APOE] may heighten brain vulnerability to oxidative stress [111]. Therefore, in order to restore redox balance while maintaining physiological signalling pathways, future therapies will probably need patient-specific techniques. Together, these developments provide a more sophisticated framework for comprehending and treating neurodegenerative disease by facilitating the shift from generalised antioxidant therapy to focused manipulation of redox networks [120].

Conclusion

Aging gradually destabilizes redox homeostasis, initiating a cascade of molecular and cellular changes that ultimately lead to synaptic dysfunction. Evidence from both experimental models and human studies suggests that synaptic impairment is not a late-stage outcome of neurodegeneration but an early and critical event that occurs before noticeable neuronal loss. This temporal pattern challenges traditional perspectives that emphasize cell death as the primary endpoint, instead highlighting the synapse as the principal site of vulnerability.

In neurodegenerative disorders, redox imbalance appears as a unifying mechanism that connects several clinical characteristics such as protein aggregation, mitochondrial dysfunction, and neuroinflammation. However, it also serves as a regulator of activities that, when dysregulated, propel the advancement of disease. This dichotomy highlights

the drawbacks of strategies that depend on widespread suppression of reactive species.

Future advancements in redox-based treatments will probably depend on the creation of sensitive biomarkers that can identify early oxidative dysfunction in synapses before irreversible neuronal death takes place. Combining precision medicine techniques with biomarker-guided intervention may increase clinical efficacy and therapeutic specificity.

Therefore, targeted, stage-specific, and mechanistically informed therapeutic strategies must replace generalised antioxidant therapies. The objective of interventions should be to preserve key signalling pathways while re-establishing redox balance within particular cellular environments, particularly at the synapse. Such a shift is essential for translating advances in redox biology into meaningful clinical benefits.

Collectively, the evidence reviewed in this article suggests that maintaining redox homeostasis may be an effective strategy for preserving synaptic integrity, delaying neurodegenerative progression, and reducing the burden of age-related neurodegenerative diseases.

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