A review on reactive oxygen species role in neurodegenerative disease

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***Abstract*—Neuroinflammation is a vital response to injury or disease in the central nervous system, acting as both a protective mechanism that aids in healing and repair, and a potential accelerator of neurodegenerative diseases when it becomes chronic or dysregulated. Reactive oxygen species (ROS) are highly reactive free radicals generated mainly from superoxide (O−2), which is mostly converted to hydrogen peroxide (H2O2) by superoxide dismutases (SOD) and can also lead to the formation of hydroperoxyl radicals (HO−2), with H2O2 further producing various ROS like hydroxyl radicals (OH), hydroxyl anions (HO−), singlet oxygen (1O2), and hypochlorite (ClO−), originating from several cellular sources, including mitochondria and NADPH oxidase. The brain's high metabolic activity results in significant energy consumption and the generation of reactive oxygen species (ROS), which are crucial in both healthy and pathological states as byproducts of processes like mitochondrial respiration and various enzymatic reactions. High levels of reactive oxygen species (ROS) can surpass a cell's capacity to eliminate them, resulting in oxidative stress and cellular damage, which is associated with various neurodegenerative diseases, including ALS, where ROS levels have been found to be elevated. Recent studies have shown that reactive oxygen species (ROS) influence mitochondrial dynamics, where elevated ROS levels lead to mitochondrial fragmentation and altered gene expression, while lower levels promote elongation.**

***Key word*—Apoptosis, Mitochondrial diseases, Mitochondrial DNA mutation, Neurodegenerative diseases,**

I. INTRODUCTION

That's a great description of neurodegenerative diseases. These conditions generally involve the gradual degeneration of the cells in the nervous system, leading to symptoms such as motor dysfunction, cognitive decline, and sensory impairments. The most well-known neurodegenerative diseases include Alzheimer's, Parkinson's, Amyotrophic Lateral Sclerosis (ALS), and multiple sclerosis (MS). Each of these diseases impacts different cell types—such as neurons or glial cells—in distinct ways, but the result is typically the same: progressive loss of function and, ultimately, death of affected cells. apoptosis plays a critical role in the degeneration of neuronal cells in many neurodegenerative diseases. Apoptosis is a form of programmed cell death that can be triggered by various internal or external signals. In the context of neurodegeneration, several factors—such as genetic mutations, environmental toxins, metabolic disturbances, and vascular issues—can activate apoptosis pathways in neurons.

- Genetic factors: Mutations in genes such as APP (amyloid precursor protein) in Alzheimer's disease or HTT in Huntington's disease can lead to abnormal protein accumulation or other molecular disruptions, triggering apoptosis.
- Toxic factors: Exposure to environmental toxins or oxidative stress can damage neurons, leading them to initiate apoptotic pathways as a defense mechanism.
- Metabolic factors: Disruptions in metabolic pathways, such as those seen in mitochondrial dysfunction, can lead to energy deficits in neurons, activating apoptosis.
- Vascular factors: Reduced blood flow to the brain, such as in stroke or vascular dementia, can cause neuronal injury and death through apoptosis.

Apoptosis is a highly regulated process that maintains cellular balance, and its dysregulation can contribute to both neurodegenerative diseases and cancer. In neurodegenerative diseases like Alzheimer’s, Parkinson’s, Huntington’s, and ALS, apoptosis is often upregulated, leading to excessive neuronal loss. This contributes to the progressive nature of these conditions. In these diseases, there's a failure to properly regulate the apoptotic pathways, leading to

premature or excessive neuronal death. For example:[1]

- Alzheimer's disease (AD): The accumulation of beta-amyloid plaques and tau tangles triggers apoptotic pathways, contributing to neuronal loss, particularly in regions involved in memory and cognition.
- Parkinson's disease (PD): The loss of dopaminergic neurons in the substantia nigra is thought to be driven by oxidative stress and mitochondrial dysfunction, which can activate apoptosis in these cells.
- Huntington's disease (HD): The mutation in the HTT gene leads to the production of a toxic protein that disrupts cellular function and induces apoptosis in neurons.
- Amyotrophic lateral sclerosis (ALS): Dysfunction of motor neurons, possibly triggered by excite toxicity, mitochondrial dysfunction, and inflammation, leads to their premature death via apoptosis.

neuroinflammation is indeed a critical aspect of the response to injury or disease within the central nervous system (CNS), and it plays a dual role in neurodegenerative diseases. On one hand, inflammation is a natural defense mechanism that helps protect and repair the brain by promoting tissue healing, removing debris, and supporting cellular repair processes. On the other hand, when neuroinflammation becomes chronic or dysregulated, it can exacerbate neuronal damage and contribute to the progression of neurodegenerative diseases.[2] reactive oxygen species (ROS) play a critical role in both the beneficial and harmful aspects of the immune response, particularly in the context of neurodegenerative diseases. ROS, like superoxide, hydrogen peroxide, and hydroxyl radicals, are generated during normal cellular metabolism, especially during the mitochondrial production of ATP. In small, controlled amounts, they can be part of essential signaling pathways that regulate neuronal function and development. For instance, ROS help in processes like synaptic plasticity and memory formation.However, when produced in excess—whether due to mitochondrial dysfunction, oxidative stress, or prolonged inflammation—ROS can overwhelm the body's natural antioxidant defenses. This leads to oxidative damage, which affects various cellular components, such as lipids, proteins, and DNA. In neurons, this damage can impair normal function, trigger apoptosis, and contribute to the pathogenesis of several neurodegenerative diseases.[3.4]

REACTIVE OXYGEN SPECIES: Reactive oxygen species (ROS) are highly reactive small free radicals derived primarily from superoxide (O−2), which is mostly converted to hydrogen peroxide (H2O2) by superoxide dismutases (SOD) but can also form hydroperoxyl radicals (HO−2), and H2O2 can further generate various other ROS like hydroxyl radicals (OH), hydroxyl anions (HO−), singlet oxygen (1O2), and hypochlorite (ClO−), with several cellular sources including mitochondria and NADPH oxidase. [5] Discussing ROS inevitably leads to the topic of clearance, as cells have various antioxidant defenses to combat oxidative stress, with superoxide being a particularly harmful, membrane-impermeable molecule that is swiftly converted to H2O2 by specific superoxide dismutases in different cellular compartments.[6]

Endogenous production and physiological/ pathophysiological role of ROS

The brain's metabolic demands and the important role reactive oxygen species (ROS) play in both healthy and pathological conditions. The brain is indeed a metabolically active organ, and its high energy consumption leads to a considerable production of ROS, which are byproducts of cellular processes like mitochondrial respiration and other enzymatic reactions[7.8.9.10]

Let’s break down some of the key points:

Sources of ROS in the Brain:

1. Mitochondria: The mitochondria are the primary source of ROS in neurons, as they generate energy through oxidative phosphorylation. While generating ATP, mitochondria can produce byproducts like superoxide (O2•-) and hydrogen peroxide (H2O2), which are typical ROS. These ROS can, in turn, damage cellular components if not properly regulated. Given the brain's reliance on mitochondrial activity, this is a major source of ROS in the brain.
2. NADPH oxidase: This enzyme complex, found in various brain cells like microglia and neurons, also generates ROS. It's particularly involved in the brain's immune response, as it can produce superoxide to help defend against pathogens. However, its activity can lead to excessive ROS

production if not regulated, contributing to neuroinflammation and neurodegeneration.

3. Enzymes such as xanthine oxidase: Xanthine oxidase is another enzyme that produces ROS as part of purine metabolism. While its role is typically associated with tissue damage and inflammatory responses, it can contribute to ROS generation in the brain during pathological conditions.
4. Peroxisomes: These organelles also contribute to ROS production as they metabolize lipids and other molecules. Peroxisomal ROS can interact with other oxidative pathways in the cell, further increasing the oxidative load.

ROS in Normal Brain Function:
As you mentioned, ROS are not always harmful; they play an essential role in several physiological functions:

- Synaptic plasticity and learning: ROS are involved in signaling pathways that promote synaptic plasticity, which is vital for learning and memory. Low levels of ROS help in the activation of certain transcription factors like NF-kB, which are involved in strengthening synaptic connections.
- Immune response: ROS generated by microglia (the brain's resident immune cells) are part of the brain's defense mechanism against pathogens. ROS can help kill invading microorganisms and facilitate the clearing of cellular debris, a process known as phagocytosis.
- Neurogenesis: ROS play a role in the generation of new neurons, particularly in regions like the hippocampus, which is important for memory formation and cognitive function.

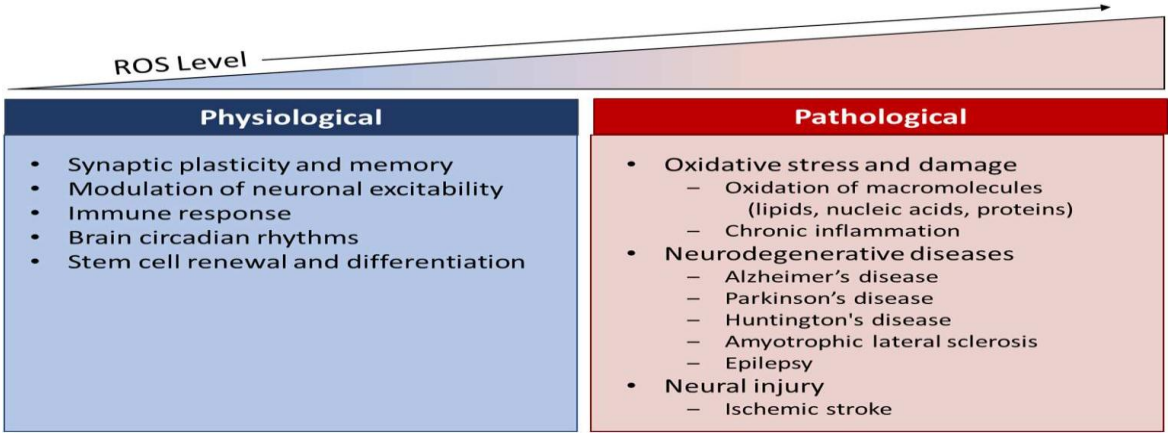

Figure 1: *Physiological importance of ROS in the brain, and its pathological effects when unregulated.*

ROS AS SIGNALING MOLECULES: While high levels of ROS can harm lipids, proteins, and DNA, substantial evidence supports the physiological significance of low to moderate ROS concentrations.[11]. NADPH oxidases, especially in phagocytes and cardiovascular tissue, are crucial enzyme complexes that generate reactive oxygen species (ROS) like superoxide, playing a significant role in cell signaling and immune defense.[12] the role of reactive oxygen species (ROS) in cellular signaling and the activation of antioxidant defenses. Indeed, ROS are not just by-products of cellular metabolism but also play a key role in regulating various cellular processes. One critical pathway that gets activated in response to oxidative stress is the Nrf2 pathway.When ROS levels rise, Nrf2 (nuclear factor erythroid 2-related factor 2) is activated and translocates to the nucleus. There, it binds to antioxidant response elements (AREs) in the promoter regions of target genes, promoting the expression of various antioxidant proteins, such as superoxide dismutase (SOD), peroxiredoxins (Prxs), glutathione peroxidases (GPXs), and heme oxygenases (HO-1). These proteins help to neutralize ROS, protect cells from oxidative damage, and restore redox balance.This pathway is crucial for maintaining cellular homeostasis, especially in tissues exposed to high oxidative stress, like the liver, brain, and lungs. However, dysregulation of Nrf2 or its target genes can contribute to various diseases, including cancer, neurodegenerative disorders, and cardiovascular diseases.Do you have a specific focus on how Nrf2 activation impacts certain conditions or are you looking to explore its broader role in cellular defense.[13]

ROS IN NEURODEGENERATIVE DISEASES: Excessively high levels of reactive oxygen species

(ROS) can overwhelm the cell's ability to clear them, leading to oxidative stress, mitochondrial dysfunction, cell damage, and often cell death, with evidence linking this oxidative stress to various neurodegenerative diseases, including ALS where increased ROS levels have been observed[14] Dysfunctional SOD1 not only increases oxidative stress in various ALS animal models but also leads to the formation of toxic aggregates in mitochondria.[15] The increased generation of reactive oxygen species (ROS) in familial amyotrophic lateral sclerosis (FALS) likely arises from a combination of depleted antioxidant defenses and the buildup of toxic SOD1 aggregates, with mitochondrial damage frequently contributing to this process alongside other neurodegenerative disease mechanisms.[16] The initial indication of reactive oxygen species (ROS) involvement in Parkinson's disease (PD) emerged from findings of mitochondrial dysfunction and oxidative damage in the brains of PD patients, notably in regions like the substantia nigra, which was corroborated by the discovery of several PD-related genes linked to mitochondrial function, including PINK1, Parkin, and DJ-1[17] PINK1 and Parkin play a crucial role in clearing damaged mitochondria, thereby reducing reactive oxygen species (ROS), which are also associated with the complex relationship between protein aggregates and neurodegenerative diseases, as seen with the toxic effects of mutant α-synuclein in Parkinson's disease that exacerbate mitochondrial dysfunction and cell death.[18] In Alzheimer's disease, the accumulation of amyloid-β plaques is associated with mitochondrial dysfunction, oxidative stress, energy failures, synaptic impairment, and ultimately, neuronal loss.[19] Aβ may influence ROS production by disrupting mitochondrial dynamics, causing fragmentation of the highly dynamic mitochondrial network.[20] The role of Aβ in Alzheimer's disease is still contentious, with other factors like tau hyperphosphorylation and accumulation being significant in the disease's progression, while also noting the interplay where protein aggregates can induce ROS production, which may, in turn, lead to the buildup of these neurotoxic aggregates, including Aβ.[21] Mitochondrial dysfunction may occur early in the process leading to protein aggregation, but it's important to remember that this dysfunction could also result from changes in other pathways, such as deregulated calcium homeostasis in Alzheimer's disease, which may contribute to reactive oxygen species (ROS) generation, amyloid-beta (Aβ) aggregation, and mitochondrial damage.[22] Oxidative stress is increasingly recognized as a key factor in neurodegeneration, driven by diminished mitochondrial antioxidants, heightened protein aggregation, and mitochondrial dysfunction that elevate ROS production, emphasizing the importance of eliminating dysfunctional mitochondria through autophagy to mitigate further damage.[23]

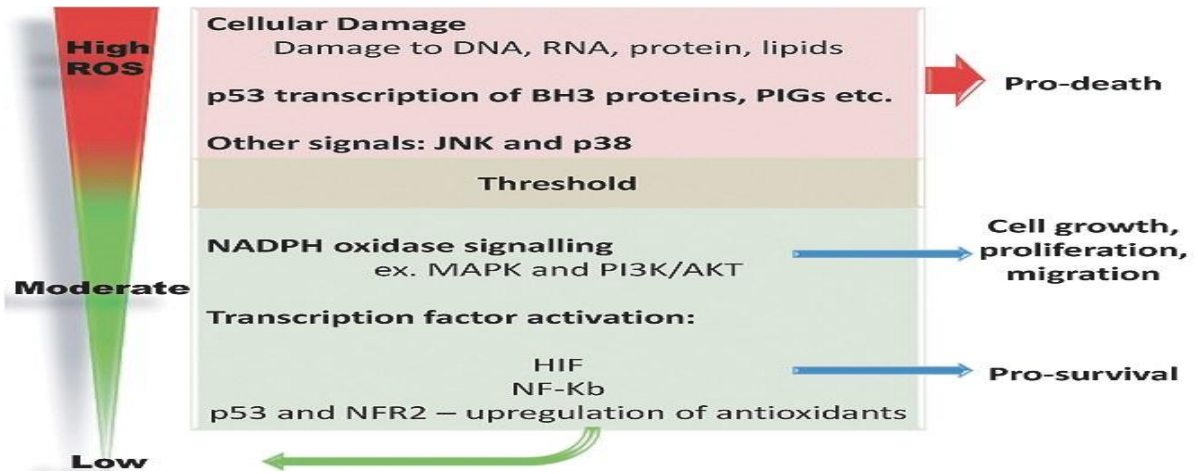

Fig. 2. Model of ROS levels moderating pro-survival and pro-death signaling. Moderate increases in ROS lead to activation of various cell signaling events that are generally pro-survival pathways. Moreover, activation of p53 and NRF2 are important to return the cell to a lower oxidative state by regulating the transcription of antioxidants. When ROS production exceeds a specific threshold (cell and stimulus specific), the cellular response shifts to promote cell death

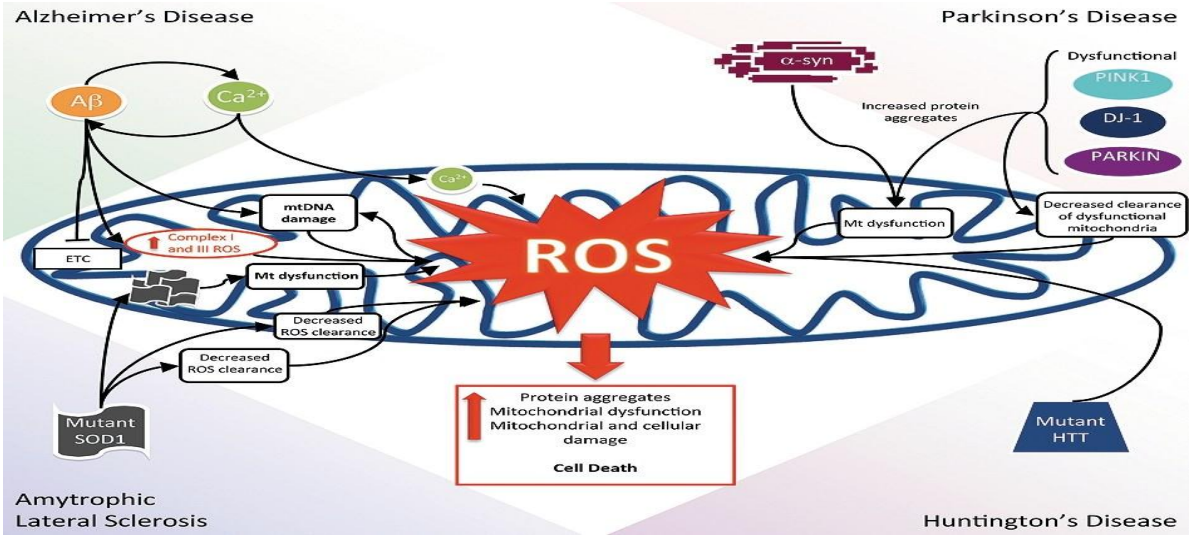

Fig. 3 Schematic of factors affecting mtROS in neurodegenerative diseases. Multiple pathways in neurodegenerative disease converge on the mitochondria to induce the production of mtROS. In the case of AD, Aβ accumulation is toxic to mitochondrial respiration and increases mtDNA damage and mtROS. In addition, deregulated Ca^{2+} levels are also detrimental to proper mitochondrial function. These two components are not mutually exclusive in that Aβ accumulation can deregulate Ca^{2+} levels and vice versa. Mutations in PD-related genes cause protein aggregation leading to mitochondrial dysfunction and oxidative stress. In addition, dysfunctional mitochondria are not appropriately disposed of by mitophagy, further increasing mtROS production. Aberrant levels of the mutant form of the protein huntingtin causes ROS generation in HD. Finally, mutations in SOD1 in FALS hinder ROS clearance and create toxic mitochondrial aggregates. Generation of ROS may in turn lead to further protein aggregation, mitochondrial dysfunction, cell damage, and cell death..

Mitochondrial Dynamics and ROS: Recent findings revealed a link between ROS and mitochondrial dynamics, highlighting a connection between cellular redox balance and mitochondrial shape regulation.[24] Without a strong antioxidant defense, high levels of ROS can cause mitochondria to fragment, swell, or shorten, while lower ROS levels encourage mitochondrial elongation. Exogenous H2O2 at different concentrations induces mitochondrial fragmentation in human umbilical vein endothelial cells (HUVECs) and affects the expression of genes involved in fusion and fission. [25] Reduced ROS levels in fibroblasts lead to MFN2-dependent mitochondrial elongation, influenced by various post-translational modifications of fission and fusion proteins and the transcriptional stimulation of factors involved in redox regulation and mitochondrial dynamics. PGC−1α, responsive to redox changes, regulates MFN2, while AMPK is pivotal in mediating the interaction between mitochondrial dynamics and ROS.[26]

7.Accumulation of mtDNA deletions in neurodegenerative disease

Several research groups have explored how large-scale deletions of mtDNA contribute to neurodegenerative diseases, revealing a significant accumulation of 4977-bp-deleted mtDNA in energy-demanding tissues of affected patients. Ro et al. examined muscle samples from 36 ALS patients and 69 age-matched controls with other neuromuscular disorders, revealing that the occurrence and average levels of the 4977-bp deleted mtDNA were significantly higher in the ALS cohort.[27] Research indicates that mitochondrial function, particularly cytochrome c oxidase (COX) activity, is reduced in the brain tissues of individuals with Alzheimer's disease (AD).[28] Patients with Alzheimer's disease who died before 75 years of age had a fourfold increase in 4977-bp-deleted mtDNA compared to those who lived longer, suggesting that the mitochondrial respiratory dysfunction caused by this deletion may influence the progression and underlying mechanisms of AD.[29] Parkinson's disease (PD) has been linked to a deficiency in the respiratory enzyme complex I, with laser microdissection revealing substantial clonal expansion of mtDNA with a 4977-bp deletion in substantia nigra neurons of PD patients. Neurons

lacking COX exhibit a significant amount of mtDNA with a 4977-bp deletion, suggesting that mitochondrial dysfunction arises from harmful mtDNA mutations, which makes high-energy-demand tissues more vulnerable to such dysfunction in neurodegenerative disease progression.[30] The content of mtDNA with a 4977-bp deletion in brain tissue samples from Alzheimer's disease patients, averaging 68 years old, was approximately 6.5 times greater than that found in normal subjects averaging 66 years old.[31]

ROS and Susceptibility to Apoptosis in Patients With Neurodegenerative Diseases :

8.1:Oxidative stress in neurodegenerative diseases : Numerous studies have shown that beyond the accumulation of ROS-induced deleted mtDNA, there are elevated levels of lipid peroxidation markers like malondialdehyde in the brain tissues of Alzheimer's and Parkinson's patients, as well as in the cerebrospinal fluid of ALS patients, along with increased protein carbonylation and nitration observed in the Lewy bodies of Parkinson's patients, as well as in the hippocampus and neocortex of Alzheimer's patients and in the motor neurons of ALS patients.[32] Recent research has found that various PD-related proteins, including α-synuclein, Parkin, DJ-1, PINK1, LRRK2, and HTR2A, can be found in mitochondria under certain conditions, and mutations in some of these proteins may heighten susceptibility to oxidative stress and apoptosis.[33]

8.2Apoptosis in the brains of patients with neurodegenerative diseases: In addition to mitochondrial dysfunction and oxidative stress, apoptosis has been linked to the development of neurodegenerative diseases, with Alzheimer's patients showing increased DNA fragmentation and activation of Bax and caspase-3 in their brains.[34] The absence of cyclophilin D, a crucial component of the mtPTPs, not only safeguarded neurons from cell death caused by Aβ and oxidative stress but also improved learning and memory impairments in an Alzheimer's disease mouse model.[35] Studies indicate that the activation of caspases and their cleavage of amyloid precursor protein and tau protein promote the generation of β-amyloid (Aβ) and the development of neurofibrillary tangles.[36] Research indicates that mitochondria-mediated apoptosis is crucial in the pathophysiology of Alzheimer's disease, while a rise in TUNEL-positive neurons in Parkinson’s disease patients further supports the involvement of apoptosis in this condition.[37]

OXIDATIVE DAMAGE IN NEURODEGENERATIVE DISEASES: Research has increasingly highlighted the role of oxidative damage in various neurodegenerative diseases over the past two decades, including a thorough review by Stadtman on protein oxidation in aging just over ten years ago.[38] Proteins are highly susceptible to attacks by free radicals, particularly the hydroxyl radical, which reacts with biomacromolecules at a nearly diffusion-controlled rate. The primary free radical propagation reaction is displacement, typically seen as the abstraction of hydrogen atoms, while other frequent reactions are addition, electron transfer, fragmentation, and rearrangement. In the presence of oxygen, reactions can significantly alter proteins and peptides through mechanisms like side-chain oxidation, cross-linking, and backbone cleavage, with oxidative damage indicators such as carbonyl groups in proteins having been extensively discussed in the literature.[39]

Mitochondria Dysfunction and Oxidative Stress in the Pathogenesis of Neurodegenerative Diseases

Alzheimer's disease and Parkinson's disease are the most prevalent neurodegenerative disorders linked to aging, impacting millions globally.While the exact causes of these diseases are still unclear, increasing evidence suggests a link between mitochondrial dysfunction and oxidative stress in the development and progression of neurodegenerative conditions.[40]

Alzheimer’s Disease: Alzheimer's disease is a significant neurodegenerative disorder in older adults, marked by memory loss, cognitive decline, and dementia due to the buildup of amyloid β plaques and tau protein tangles in the brain.[41]

Oxidative Stress: Aβ treatment leads to ROS buildup and mitochondrial dysfunction via BNIP3, causing death in rat primary cortical neurons, which can be reduced by antioxidant vitamins and BNIP3 knockdown.[42] In individuals with Alzheimer's disease (AD) and mild cognitive impairment (MCI), notable increases in lipid peroxidation, protein oxidation, and protein nitration products have been identified, leading to dysfunction or loss of function in essential cellular proteins.[43] Research indicates that lower levels of the antioxidant glutathione in the brains of patients with Alzheimer's disease and mild cognitive impairment are linked to Aβ-induced oxidative stress, resulting in heightened protein oxidation and disruption of the antioxidant system, which plays a role in the development of

Alzheimer's.[44] Increased production of reactive oxygen species (ROS) may lead to tau hyperphosphorylation via glycogen synthase kinase 3β activation, potentially impacting learning and memory.[45]

Alterations in Mitochondrial Dynamics: Abnormalities in mitochondrial dynamics result in excessive fragmentation and dysfunction, which decreases OXPHOS, ATP production, and mitochondrial membrane potential while increasing reactive oxygen species generation.[46] Notably, individuals with AD exhibit significantly lower levels of the fusion factors OPA1, MFN1, and MFN2, as well as the fission factors DRP1 and FIS1 in their brains.[47] The absence of production in response to Aβ protein leads to mitochondrial fission, synaptic loss, and neuronal damage through S-nitrosylation of DRP1, with abnormal interactions between Aβ, DRP1, and hyperphosphorylated tau contributing to increased mitochondrial fragmentation, neuronal and synaptic damage, and cognitive decline in Alzheimer's patients and models.[48] Aβ treatment triggers the movement of DRP1 to mitochondria and its phosphorylation at Ser616 through the activated AKT pathway, leading to mitochondrial fission, while simultaneously inhibiting autophagy via the mTOR pathway and causing excessive mitochondrial fission that ultimately results in ROS-mediated neuronal death.[49]

Mitochondria-Driven Inflammation: Numerous studies emphasize the crucial impact of neuroinflammation linked to mitochondria in the development and advancement of Alzheimer's disease (AD).[50] Research indicates that the primary proinflammatory cytokine IL−1β is found to be overexpressed in the brains of Alzheimer's disease patients.[51] Aβ oligomers and tau aggregates activate the NLRP3 inflammasome in the brain, causing caspase-1 activation, heightened IL-1β production, and neuronal degeneration, but crossing APP/PS1 mice with NLRP3–/– or caspase-1–/– mice enhances cognitive behavior, synaptic function, and Aβ clearance.[52] Pathogenic tau disrupts cognitive resilience by activating cGAS−IFN signaling via cytosolic mtDNA and interfering with the MEF2C-regulated neuronal transcriptional network, but removing cGAS or using its inhibitors can enhance MEF2C target gene expression, thereby restoring synaptic integrity, plasticity, and memory in Tau P301S transgenic mice.[53]

Parkinson’s Disease: The key pathological features include the targeted loss of dopaminergic neurons in the substantia nigra pars compacta, resulting in irregular dopamine metabolism and the formation of Lewy bodies and neurites filled with aggregated α-synuclein.[54] The exact reasons for dopaminergic neuronal cell death are still not fully understood, but progression of Parkinson's disease is attributed to factors such as protein aggregation, disruption of the ubiquitin-proteasome system, neuroinflammation, and mitochondrial dysfunction.[55] Mitochondrial dysfunction significantly contributes to the early development of Parkinson's disease, particularly through the inhibition of complex I activity, which leads to oxidative stress and disrupted Ca2+ homeostasis in dopaminergic neurons.[56]

Oxidative Stress: Environmental neurotoxins such as MPTP, 6-OHDA, and rotenone are used, notably MPTP, to create effective animal models for Parkinson's disease (PD).[57] MPTP is converted to its active form, MPP+, in glial cells, which then enters dopaminergic neurons through the dopamine transporter, where it inhibits mitochondrial complex I and increases ROS production, ultimately leading to the death of these neurons and resembling Parkinson's disease characteristics.[58]

Impaired Mitochondrial Dynamics and Function: Research indicates that genetic factors including PARKIN, PINK1, SNCA, FBXO7, DJ-1, and LRRK2 play a role in mitochondrial dysfunction in patients with Parkinson's disease.[59] The loss of PINK1 and PARKIN in PD pathology disrupts mitochondrial maintenance and speeds up the disease progression.[60] A recent study reveals that PINK1's NT-CTE module interacts with Tom20 in the TOM complex to form a supercomplex with TIM23, which is essential for removing damaged mitochondria, and mutations in this region linked to Parkinson's disease hinder mitophagy by disrupting supercomplex assembly. The A53T mutation in α-synuclein, associated with the SNCA gene, results in diminished mitochondrial respiration, membrane potential, and altered morphology, with iPSC-derived dopaminergic neurons from PD patients showing lower respiration and ATP levels while maintaining total mitochondrial mass, and displaying a rounded, donut-like shape.[61] Recent research shows that mice with a neuron-specific knockout of FBXO7 exhibit fragmented, small, round mitochondria, a decreased mitochondrial area, and are positive for tyrosine hydroxylase in dopaminergic neurons.[62]

Mitochondria-Activated Inflammatory Pathway: In patients with Parkinson's disease and various animal models, including 6-OHDA−treated mice, Tfam–/– (MitoPark) mice, and α-synuclein PFF−injected mice, there are notable increases in NLRP3, ASC, and cleaved caspase-1 proteins in the substantia nigra, which are linked to mitochondrial dysfunction, oxidative stress, and α-synuclein pathology.In hiPSC-derived microglia, oligomeric α-synuclein triggers NLRP3 inflammasome activation via TLR2, leading to mitochondrial damage characterized by mtROS overproduction, mtDNA release, and reduced mitochondrial membrane potential, while introducing hiMG with α-synuclein oligomers into the brains of humanized mice results in caspase-1 activation and subsequent neuronal cell death mediated by caspase-3.[63]

Mitochondrial Dysfunction and ROS as Therapeutic Targets for Neurodegenerative Diseases

Currently, there are no effective treatments for Alzheimer's or Parkinson's disease; available symptomatic treatments have limited effects and can only slow disease progression. There is a clear demand for innovative treatment targets for both Alzheimer's and Parkinson's diseases, with research indicating that addressing mitochondrial dysfunction and oxidative stress and enhancing mitochondrial dynamic balance could be effective strategies for developing new therapies.[62]

CONCLUSION

Neurodegenerative diseases pose a serious threat to the aging population, with rising case numbers worldwide, significantly impacting patients, families, and society, while the underlying mechanisms of these conditions remain largely unclear. Proposed biological mechanisms for the development and progression of these diseases include mitochondrial dysfunction and oxidative stress, with reactive oxygen species in brain tissues arising from mitochondrial issues, dopamine metabolism, and inflammation in neurons.We suggest that multiple neurodegenerative diseases may have a shared mechanism underlying neurodegeneration and cell death, supported by our research and other studies. Ab and PrP exhibit strong binding to specific metal ions, which significantly contribute to aggregation and toxicity, with Ab and PrP both reducing the oxidation state of Cu(II) and Ab also reducing Fe(III). A-synuclein likely exhibits a similar property, as the peptide-metal ion complex converts oxygen into hydrogen peroxide, which can permeate membranes and cause oxidative damage to vulnerable neuronal cells, especially in aging brains, while fe(II) and cu(I) can further convert hydrogen peroxide into the highly reactive hydroxyl radical, leading to severe oxidative harm. Mitochondrial dysfunction and apoptosis are crucial in the development and progression of mitochondrial and degenerative diseases, prompting us to propose a hypothetical model illustrating their role in these conditions. Mitochondrial DNA mutations lead to reduced mitochondrial respiration and oxidative phosphorylation, resulting in decreased ATP production and heightened ROS generation, creating a detrimental cycle. ROS-responsive nanoparticles can effectively adjust their molecular cargo release to counteract oxidative stress over time, aiding neuronal recovery and disease treatment, while researchers must consider varying ROS levels related to inflammation severity and carefully choose dosages and drug molecules to manage inflammation without inducing antioxidant stress, especially for specific neurological disorders like Alzheimer’s and stroke. Rising biological oxidations and the energy crisis cause cellular dysfunction that ultimately escalates to cell death. This working model, while mainly focused on MPTP neurotoxicity, likely reflects a comparable process driving neurodegeneration in Parkinson's disease. Activation of microglia and NADPH-oxidase may elevate superoxide production after MPTP administration, while nearby neurons with nNOS generate nitric oxide, which is later supplemented by activated glial cells containing iNOS during gliosis. Research indicates that apoptosis is crucial in various neurodegenerative diseases, where intricate biochemical and genetic processes influence cell death and repair, involving multiple molecules like Bcl2 proteins, calcium, ROS, and caspases. The regulation of apoptotic signal cascades may influence the clinical variability of various disorders, and a deeper understanding of caspase-related cell dysfunctions and their genetic interactions could pave the way for innovative therapeutic approaches. Mitochondrial antioxidants hold promise for treating neurodegenerative diseases, but additional research is necessary to clarify how these diseases elevate mtROS and lead to cell death, which could uncover new therapeutic targets to address harmful ROS while preserving essential physiological signaling. As more effective mitochondrial antioxidants emerge, it's crucial to note that while they may

prevent ROS-dependent apoptosis, they might not address underlying mitochondrial issues and could inadvertently trigger alternative cell death mechanisms; additionally, care must be taken to avoid disrupting beneficial signaling pathways linked to mtROS. We have investigated the impact of ROS-induced oxidative stress, abnormal mitochondrial dynamics, mitochondrial apoptosis, and impaired mitochondrial function on the development of Alzheimer's and Parkinson's diseases, while also highlighting various mitochondria-focused compounds—such as fusion enhancers, fission inhibitors, and specific antioxidants—that show promise as new therapeutic options for these conditions, ultimately contributing to enhanced mitochondrial function. Mitochondrial dysfunction and associated reactive oxygen species (ROS) are linked to inflammation, which plays a role in various disorders, particularly Alzheimer's and Parkinson's disease, suggesting that targeting these pathways could yield effective treatments for neurodegenerative and other inflammatory diseases.

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