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Mitochondria in crisis: The hidden engine of neurodegenration

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Abstract
The pathogenesis of major neurodegenerative disorders, including Parkinson's disease (PD), Alzheimer's disease (AD), and other age-related cognitive decline syndromes, is now known to be greatly impacted by mitochondrial malfunction. This study thoroughly investigates the complex function of mitochondria as signaling hubs and energy regulators in brain health, as well as how their dysregulation may either be the fundamental cause or a contributing factor to neurodegenerative cascades. Following the evaluation of mitochondrial bioenergetics and redox balance, the discussion shifts to the emerging field of mitochondrial epigenetics, which focuses on alterations in non-coding RNAs, mtDNA methylation, and histone modifications that impact the risk of neurodegenerative disorders.. The interplay of mitochondrial calcium homeostasis, oxidative stress, and apoptotic signals is examined, in addition to the several roles of sirtuins, particularly SIRT1 and SIRT2, in controlling neuronal fate under oxidative stress.

The idea of mitochondrial entropy in aging brains is further explored in this review, which connects energy failure to the breakdown of proteostasis and cognitive decline. It emphasizes how crucial mitochondrial dysfunction is at the "crossroads" of oxidative stress and neurodegeneration, proving that it is frequently the underlying cause rather than just a symptom. Targeted mitochondrial therapies are suggested as a potential avenue for precision neuroprotection in the future, with particular focus paid to hemisphere-specific vulnerabilities in brain diseases.

Through the integration of molecular insights with new therapeutic approaches, such as mitochondrial antioxidants, mitophagy enhancement, and nanocarrier-mediated delivery, this work promotes mitochondria-focused intervention as a game-changing method for slowing or stopping the progression of neurodegenerative diseases.

Keywords: Mitochondria dysfunction, neurodegeneration, oxidative stress, parkinson disease, alzheimer disease, half brain disorder

Introduction

In the intricate world of cellular biology, mitochondria are often praised as the powerhouses of the cell tiny engines that produce the energy necessary for survival, yet, recent scientific advancements reveal that mitochondria do far more than just fuel our cells. These dynamic organelles play critical roles in maintaining cellular health, regulating oxidative stress, balancing calcium levels, and initiating programmed cell death, nowhere are these functions more vital than in the brain, where neurons require immense and constant energy to perform complex signaling tasks., Unfortunately, this reliance also makes them particularly vulnerable to mitochondrial dysfunction, a key factor increasingly linked to the onset and progression of various neurodegenerative disorders, Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's Disease (PD), Huntington's Disease (HD) and Amyotrophic Lateral Sclerosis (ALS) have traditionally been associated with protein misfolding, genetic mutations, and environmental toxins, However, growing evidence suggests that mitochondrial damage may not merely be a side effect of these conditions it may be a central driver, As neurons degenerate, mitochondrial abnormalities become more apparent, including disrupted energy production, increased generation of reactive oxygen species (ROS), defective mitophagy (the removal of damaged mitochondria), and calcium imbalance, These dysfunctions create a cascade of harmful events that ultimately lead to cell death, inflammation, and cognitive or motor decline.

One reason mitochondria are so integral to brain health lies in their role in managing oxidative stress, While ROS are normal byproducts of mitochondrial activity, an overload can overwhelm the cell's antioxidant defenses [31]. This imbalance damages proteins, lipids, and DNA, triggering inflammation and accelerating the death of brain cells, Compounding this issue is the vulnerability of mitochondrial DNA (mtDNA), which is more susceptible to mutations than nuclear DNA due to its proximity to the source of ROS and its limited repair mechanisms, These mutations can impair the electron transport chain, reduce ATP production, and further exacerbate oxidative stress [37].

Additionally, recent research highlights the role of mitochondrial epigenetics in neurodegeneration, Modifications to mtDNA, histone proteins, and non-coding RNAs can alter gene expression without changing the underlying genetic code [44]. These changes influence mitochondrial function and are increasingly being explored as potential biomarkers and therapeutic targets.[31] For instance, abnormal DNA methylation patterns in mitochondrial genes have been observed in both Alzheimer's and Parkinson's patients [41].

The complexity of mitochondrial involvement in neurodegenerative diseases presents both a challenge and an opportunity. [51]Understanding how these organelles influence neuronal survival opens new avenues for intervention. [27]Therapies aimed at improving mitochondrial function whether through antioxidants, gene editing, or enhancing mitophagy could offer hope for slowing or even halting the progression of brain disorders, As such, the mitochondria are no longer just background players in cell biology but are emerging as central figures in the fight against neurodegeneration.

The powerhouse in peril: How mitochondria dysfunction fuels neurodegeration

Mitochondria are essential for generating the energy that keeps our cells alive and functioning, especially in the brain.[75] Often called the "powerhouse" of the cell, these organelles produce ATP, the energy currency that fuels everything from thought to movement.[70] However, when mitochondria begin to fail, the consequences for brain health can be severe. Neurodegenerative diseases such as Alzheimer's, Parkinson's, and ALS are increasingly being linked to problems within these tiny engines.

One of the biggest issues is the overproduction of reactive oxygen species (ROS), which are harmful byproducts of energy production, When ROS levels become excessive, they start to damage essential molecules like proteins, fats, and DNA. This creates a cycle of damage that worsens mitochondrial function and leads to more ROS., Neurons, which depend heavily on energy and are limited in their ability to regenerate, are particularly vulnerable.

Additionally, the natural processes that maintain healthy mitochondria like fusion, fission, and mitophagy (removal of damaged mitochondria) can become disrupted [119]. When damaged mitochondria accumulate, they not only produce less energy but also trigger cell death pathways, contributing to the loss of brain cells [129].

Calcium imbalance is another factor. Mitochondria help regulate calcium levels inside cells, but dysfunction can lead to calcium overload, which harms neurons [137, 152]. In diseases like Parkinson's, genetic mutations further interfere with mitochondrial quality control, worsening the problem,

As a result, scientists are now focusing on mitochondria as potential targets for treatment. If we can find ways to protect or restore their function, we may be able to slow down or prevent the progression of neurodegenerative diseases.

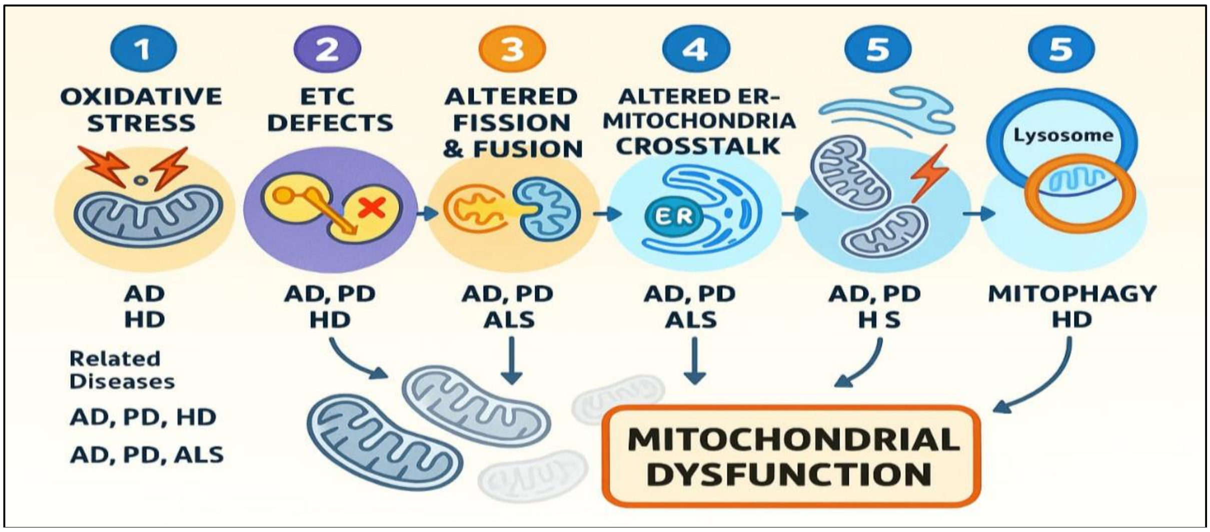

Fig 1: Show Mitochondrial dysfunction

Table 1: Show Role, Dysfunction and Potential therapeuics targets

Role	Dysfunction	Potential therapeuics targets
Energy Production (ATP)	ETC defects, reduced ATP synthesis	ETC complex stabilizers, coenzyme Q10
Reactive Oxygen Species (ROS)	Excessive ROS generation	Antioxidants (e.g, MitoQ, NAC)
Mitochondrial Dynamics	Altered fission and Fusion	DRP1 inhibitors, MFN1/2 activators
Calcium Homeostasis	Dysregulated calcium uptake/release	MCU modulators calcium channel blockers
ER-mitochondria Crosstalk	Impaired signalling, calcium and lipid exchange	Sigma-1 receptor modulators
Mitophagy	Defective mitochondrial clearance	PINK1/Parkin pathway activators
Apoptosis Regulation	Premature or excessive cell death	Bcl-2 family inhibitors/modulators
Mitochondrial Biogenesis	Reduced mitochondrial replication	PGC-1α activators, AMPK agonist

ATP-Adenosine Triphosphate, ETC-Electron Transport Chain ROS-Reactive oxidative Species MitoQ, Mitochondria Targeted ubiquinone NAC, N-acetylcysteine MFN1, Mitofusin 1 MCU, Mitochondrial Calcium Uniporter PINK-1, PTEN Induce Kinase 1 BCL-2, B-Cell Lymphoma 2 PGC-1, Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1 Alpha

Energy crisis in brain: role of mitochondria in neurodegeneration

The human brain, despite representing only about 2% of total body weight, consumes nearly 20% of the body's energy resources, This high metabolic demand is predominantly met by mitochondria, the cellular structures responsible for producing adenosine triphosphate (ATP) through oxidative phosphorylation, Within neurons, which are long-living and rarely replaced, efficient mitochondrial function is crucial for maintaining synaptic activity, electrical signaling, and overall cell survival, However, as research progresses, it is becoming increasingly clear that mitochondrial dysfunction is at the heart of many neurodegenerative diseases. The failure of these energy-producing organelles initiates a cascade of cellular disturbances that ultimately leads to the loss of neuronal integrity and function.

A major hallmark of mitochondrial failure in the brain is energy depletion. When oxidative phosphorylation becomes impaired, ATP levels drop, compromising essential neuronal processes such as ion channel regulation, neurotransmitter recycling, and axonal transport.[49] Neurons, which have limited energy reserves and depend heavily on continuous mitochondrial output, quickly begin to show signs of stress under these conditions. Energy deficits contribute to impaired synaptic communication and, eventually, neurodegeneration.

Another damaging consequence of mitochondrial dysfunction is the accumulation of reactive oxygen species (ROS). Although ROS are natural by-products of mitochondrial respiration, their overproduction becomes hazardous, As this oxidative stress increases, it worsens mitochondrial damage, forming a vicious cycle that accelerates neuronal decline. This mechanism is evident in Alzheimer's disease and Parkinson's disease, where oxidative markers are consistently elevated in affected brain regions,

Calcium regulation is another critical function of mitochondria, and its disruption plays a substantial role in neurodegeneration [59]. Mitochondria buffer intracellular calcium levels, preventing toxic accumulation within neurons. However, when mitochondrial function is compromised, calcium homeostasis is lost. The resulting calcium overload activates enzymes that degrade essential cellular components and may lead to mitochondrial permeability transition, which signals the initiation of cell death pathways [64]. This dysregulation is particularly evident in excitotoxicity, a process linked to stroke and amyotrophic lateral sclerosis (ALS), where overstimulation of neurons leads to fatal calcium influx [67].

Moreover, the structural dynamics of mitochondria fission and fusion are essential for maintaining mitochondrial quality and distribution throughout neurons. In healthy cells, these processes work together to remove damaged mitochondria and distribute functional ones where needed [60]. In neurodegenerative diseases, however, an imbalance occurs. Excessive fission or impaired fusion can lead to fragmented mitochondria that are less efficient and more prone to dysfunction [69]. This imbalance hinders mitochondrial mobility, particularly to synaptic terminals, where energy demand is highest. The resulting energy shortfall contributes to synaptic failure, a key early feature of cognitive decline [58].

Equally important is the process of mitophagy, the targeted degradation of damaged mitochondria [73]. This process ensures that defective mitochondria do not accumulate and impair cellular health [79]. When mitophagy is impaired, as seen in several neurodegenerative models, damaged mitochondria persist within cells, promoting further oxidative damage and triggering immune responses. Genetic mutations affecting proteins like PINK1 and Parkin, which regulate mitophagy, have been directly linked to familial forms of Parkinson's disease [77].

Compounding all these mitochondrial issues is the aging process itself. With age, mitochondrial DNA accumulates mutations, the efficiency of the electron transport chain declines, and the cell's ability to maintain mitochondrial quality control weakens. This sets the stage for age-related neurodegenerative diseases to develop and progress.

In conclusion, mitochondria serve not only as the brain's primary energy providers but also as critical regulators of calcium balance, oxidative stress, and cellular survival [79]. Their dysfunction represents a central thread in the pathophysiology of neurodegeneration [72]. Understanding the multifaceted roles of mitochondria opens up promising avenues for therapeutic intervention [86]. Targeting mitochondrial bioenergetics, enhancing mitophagy, and protecting against oxidative stress may offer hope in slowing or preventing the progression of devastating neurological conditions [83].

Mitochondrial epigenetics and their impact on neurodegenerative diseases

Mitochondrial DNA (mtDNA) methylation has emerged as a potential regulatory mechanism in the development and progression of neurodegenerative diseases. Although once considered unmethylated, mtDNA has been shown to undergo methylation at both CpG and non-CpG sites, primarily regulated by DNA methyltransferases (DNMTs), such as DNMT1, which localize to the mitochondria.

Methylation of mtDNA can alter mitochondrial gene expression, impair oxidative phosphorylation, and reduce ATP production. These alterations contribute to increased production of reactive oxygen species (ROS), promoting neuronal damage and apoptosis. In Alzheimer's disease, altered methylation of mitochondrial genes such as *ND1* and *COX1* has been reported, leading to mitochondrial dysfunction. Similarly, in Parkinson's disease, mtDNA methylation affects complex I activity, impacting dopaminergic neurons.

The mechanism involves impaired electron transport chain function due to methylation-induced gene silencing, which elevates oxidative stress and triggers neuroinflammation and cell death. Additionally, environmental toxins and aging may exacerbate methylation changes in mitochondria, further contributing to disease onset and progression.

Understanding mtDNA methylation opens new avenues for diagnostic biomarkers and epigenetic therapies in neurodegeneration, in mitochondria, the demethylation process could be involved. Teneleven translocation (TET)

enzymes convert 5mC to 5-hydroxymethylcytosine (5hmC), starting one of the DNA demethylation processes. Both Along with the presence of 5hmC in the D-Loop, TET1 and TET2 are visible in the mitochondria.
Furthermore, it was shown that 5mC and 5hmC were stable at cytosine in mtDNA without guanine base, indicating the involvement of non-CpG methylation in mtDNA. While conserved sequence blocks and HSP promoter regions contain both CpG and non-CpG methylation sites, epigenetic changes may modify mtDNA copy and transcription.

How mitochondria influence histone modification in neurodegenerative diseases

By moving an acetyl group from acetyl-CoA to lysine ε-amino acids, histone acetyl transferases (Hats) relax chromatin and boost transcriptional activators' ability to bind. Histone and transcription factor acetylation levels are dynamically connected with acetyl-CoA, the sole donor of histone acetylation [122]. The energy condition of cells positively regulates the amounts of acetyl-CoA [126]. Low energy production lowers acetyl-CoA levels, which in turn lowers histone acetylation and inhibits gene expression through chromatin concentration [128]. Conversely, high energy production raises acetyl-CoA levels to encourage histone acetylation and gene expression. The cytoplasm, mitochondria, and nucleus may all make acyl-Co and various acetyl-COA pools connect to one another. Three main processes in mitochondria produce acetyl-CoA: glycolysis; fatty acid β-oxidation [123] and branched amino acid catabolism [121].
The mitochondrial membrane acts as a barrier, preventing acetyl-CoA produced inside mitochondria from directly moving into the cytoplasm [129]. However, this metabolite usually enters the tricarboxylic acid (TCA) cycle, where it contributes to the formation of free CoA and citrate.[133] Citrate can then be shuttled out of the mitochondria into the cytosol via the tricarboxylate transporter protein SLC25A1 [120]. Once in the cytoplasm or nucleus, citrate is converted back into acetyl-CoA by the enzyme ATP-citrate lyase (ACLY) [135].
In a parallel route, acetyl-CoA can be transformed into acetylcarnitine within the mitochondria [132]. This compound is transported into the cytoplasm through the carnitine/acylcarnitine translocator [149]. There, it is reconverted into acetyl-CoA by nuclear carnitine acetyltransferase.[146] These transport systems ensure that acetyl-CoA, though not able to cross the mitochondrial membrane on its own, is still made available in other parts of the cell where it plays a vital role in processes like lipid synthesis and histone modification [142].
The cellular reserves of acetyl-CoA and NAD^+, which are essential cofactors for histone acetylation and deacetylation, respectively, are disturbed by mitochondrial failure]. This metabolic imbalance disrupts transcriptional programs essential for neural resilience by impairing histone acetyltransferase (HAT) activity and sirtuin-mediated deacetylation [122]. “Tigar” is a p53-responsive regulator that redirects glucose metabolites onto the pentose phosphate pathway, modulating glycolytic flow and preserving redox equilibrium.[129] Its down regulation in neurodegeneration affects histone acetylation dynamics and acetyl-CoA availability indirectly by lowering NADPH production and compromising mitochondrial integrity, Furthermore, maintaining nucleocytosolic acetyl-CoA levels that drive epigenetic changes requires **CMS12**, a mitochondrial carrier protein involved in acetyl-CoA export [131]. A malfunctioning CMS12 limits histone acetylation, changes chromatin accessibility, and decreases nuclear acetyl-CoA availability. These mitochondrial-epigenetic intersections contribute to aberrant gene expression, synaptic dysfunction, and progressive neuronal loss [124].

Under mitochondrial dysfunction, SIRT1 and SIRT2 play opposing roles in Parkinson’s disease

As rotenone inhibited respiratory chain complex I in the PD cell model, SIRT1 coupled to H3K9 in the p53 promoter region, resulting reduced H3K9 acetylation [136] and inhibited rotenone-induced apoptosis by reducing p53 gene transcription and elevating H3K9 trimethylation [140]. Moreover, 1-methyl-4-phenylpyridinium (MPP+) inhibits respiratory chain complex I, which can boost HIF-1α expression and cause formation of ROS in SH-SY5Y cells [136]. Transcriptional activation could stem from a significant increase in H3K14 acetylation in the HIF-1α promoter area caused by inhibiting SIRT1 expression.
Prior research discovered that α-synuclein's direct binding to histones affected the extent of histone H3 acetylation in cultured cells and may have influenced to the nuclear toxicity of α-synuclein Histone deacetylation caused by α-synuclein's subsequently bound to the PGC1-α promoter diminished PGC1-α expression and degraded mitochondrial function. Consequently, raising SIRT1 in PD may operate neuroprotectively and correct mitochondrial anomalies [139]. By decreasing SIRT2, however, α-synuclein toxicity can be mitigated and mitochondrial function may be recovered [138].

Mitochondria under siege: The silent catalyst of Alzheimer, Parkinson & other Neurodegenrative diseases

Behind the scenes of cellular health, mitochondria quietly orchestrate essential functions that keep neurons alive and responsive [142]. Far more than cellular power plants, these dynamic organelles are now seen as critical players in the early stages of neurodegenerative diseases like Parkinson’s and Alzheimer’s, When mitochondrial systems falter due to genetic, environmental, or age-related factors a silent storm begins: Energy failure, oxidative stress, and cell death follow [141]. This mitochondrial vulnerability doesn’t just accompany disease; it may initiate and accelerate it. Unveiling the hidden damage within mitochondria provides a compelling foundation for understanding and ultimately intervening in these neurological disorders [143, 144].

In Parkinson

Complex I of the electron transport chain (ETC) is inhibited, which is one of the oldest and best-studied mitochondrial abnormalities in Parkinson's disease [149]. This disturbance causes oxidative stress by decreasing ATP synthesis and abnormally raising reactive oxygen species (ROS) [154]. Increased ROS contributes to neurotoxicity and cell death by causing damage to proteins, lipids, and DNA [155].
Further evidence supporting the significance of mitochondrial malfunction has come from genetic research. Damaged mitochondria accumulate when genes like PARKIN and PINK1 (PTEN-induced kinase 1), which are both involved in mitophagy-based mitochondrial quality control, are mutated, PINK1 often builds up on the outer

membrane of depolarized mitochondria and attracts the E3 ubiquitin ligase PARKIN to mark these organelles for destruction, This pathway's failure exacerbates oxidative damage and triggers apoptotic cascades by impairing the removal of defective mitochondria [151].

Furthermore, it has been demonstrated that α-synuclein, a crucial protein linked to Parkinson's disease pathology, builds up on mitochondrial membranes, further compromising mitochondrial dynamics and function [149]. The intrinsic apoptotic pathway and cytochrome c release may be triggered by this interaction, which also impairs mitochondrial trafficking and causes membrane permeabilization [147]. Furthermore, the degradation of mitochondrial integrity and function is facilitated by mutations and deletions in mitochondrial DNA (mtDNA), which are often acquired with age [150]. Defective mitophagy, oxidative stress, and compromised bioenergetics all work together to create a feed-forward cycle that accelerates neuronal degeneration [153].

In Alzheimer Disease

The most prevalent kind of dementia, Alzheimer's disease (AD), is commonly identified by symptoms such increasing memory loss, cognitive impairment, and the accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles made of aberrant tau proteins [156]. Recent research has shown a deeper involvement of mitochondrial dysfunction in the early and ongoing development of AD, despite the fact that these characteristics are well known.

For neurons to survive and function, mitochondria are necessary. They aid in controlling calcium levels, provide the ATP required for cellular functions, and manage programmed cell death., Electron transport chain complexes I and IV exhibit a discernible decrease in activity in Alzheimer's disease, which suggests a decrease in mitochondrial energy production [155]. Increased oxidative stress, lipid and protein damage from an excess of reactive oxygen species (ROS), and a reduction in energy generation efficiency are the results of this deterioration [166].

Studies have demonstrated that Aβ peptides, particularly Aβ42, build up on the mitochondrial membrane, disrupting respiratory enzymes and depolarizing the membrane [174]. This damages mitochondrial structure and function even further by increasing ROS levels and decreasing ATP synthesis. Aβ also alters the equilibrium of mitochondrial fusion and fission, resulting in defective and fragmented mitochondria.

Another important factor is tau protein disease. The usual movement of mitochondria along axons is disrupted when tau becomes hyperphosphorylated, which stops them from reaching synaptic regions with high energy requirements [175]. Neuronal energy deficits and decreased synaptic transmission are two early problems associated with AD that are exacerbated by this misplacement,

From energy to entropy: How failing mitochondria occult brain aging

With oxidative phosphorylation, mitochondria produce more than 90% of the cellular ATP, which is crucial for sustaining neural energy demands [169]. A series of metabolic and molecular abnormalities that lead to cognitive decline and neurodegeneration are brought on by the progressive deterioration of mitochondrial activity in the aging brain. A key factor in the imperceptible aging process of the brain is this change from energy generation to systemic entropy [177]. Mitochondria create more reactive oxygen species (ROS) and less ATP as they age. Proteins, lipids, and mitochondrial DNA (mtDNA), particularly those involved in the electron transport chain (ETC), are all subject to oxidative damage from these ROS, When ETC complexes I and III are damaged, more ROS are produced, which feeds the cycle of mitochondrial dysfunction. In addition to decreasing the energy supply, this also raises cellular stress, which hinders synaptic transmission and plasticity [175].

The PINK1-Parkin pathway-regulated selective kind of autophagy known as mitophagy is one of the main reactions to damaged mitochondria [167]. This mechanism deteriorates with age, causing malfunctioning mitochondria to build up in aged neurons. The health of neurons is further jeopardized by this [169]. The dynamics of the mitochondria are also changed: fission, which is driven by DRP1, starts to outnumber fusion, which is controlled by MFN1, MFN2, and OPA1. This fragments the network of mitochondria and isolates damaged mitochondria, further impairing axonal transport and energy distribution [171].

Furthermore, aging mitochondria lose their ability to buffer intracellular calcium. For neurons to avoid excitotoxicity, a condition in which excessive glutamate and calcium overload cause cell death, mitochondrial calcium control is crucial [176]. Particularly in susceptible areas like the hippocampus, mitochondrial failure upsets this equilibrium and raises the possibility of excitotoxic harm [169].

NAD+ level diminution, which affects sirtuin activity (especially SIRT1 and SIRT3), is a further hallmark of mitochondrial aging [173]. These enzymes have a role in DNA repair, stress tolerance, and mitochondrial biogenesis. Decreased NAD+ availability causes ineffective mitochondrial turnover, which reduces cells even more and speeds up the stages of aging [180].

Furthermore, neuroinflammation is facilitated by mitochondrial dysfunction. The NLRP3 inflammasome and NF-κB signaling pathways are triggered when damaged mitochondria leak ROS and mitochondrial DNA into the cytosol [177]. These inflammatory reactions are part of the low-grade, chronic inflammation that is seen in the aging brain, which is referred to as "inflammaging" [179].

When taken as a whole, these interrelated pathways show how mitochondrial failure subtly damages neuronal health [169]. Synaptic weakening, poor neurogenesis, and ultimately neuronal death are the results of accumulated injury that does not show up right away. The subtle but progressive characteristic of brain aging is caused by this entropy, which is a gradual transition from organized energy generation to disordered malfunction [167].

In conclusion, reduced ATP synthesis, elevated oxidative stress, compromised mitophagy, changed dynamics, disturbed calcium handling, NAD+ depletion, and neuroinflammation are all key signs of mitochondrial malfunction, which contributes significantly to brain aging, Since these alterations cause the brain to transition from energy-driven function to entropy-driven decline, attempts to reduce or prevent age-related cognitive problems must focus on mitochondrial health [178].

Oxidative stress & neurodegradation

Mitochondria at crossroads

A number of neurodegenerative illnesses, including Parkinson's, Alzheimer's, and amyotrophic lateral sclerosis

(ALS), are accelerated by oxidative stress.[184] It arises when the body's natural antioxidant mechanisms are unable to remove as much reactive oxygen species (ROS) as it creates[188]. This imbalance becomes especially detrimental in the brain, which has a limited antioxidant capacity and a highly active metabolism [183].

When it comes to oxidative stress, mitochondria have two sides. Through a process known as oxidative phosphorylation, they are in charge of generating ATP, which is the source of energy [187]. However, ROS are spontaneously produced by mitochondria as byproducts of this activity. ROS are controlled in a healthy environment [183]. However, mitochondria's capacity to control ROS generation is diminished when they become dysfunctional, which can happen as a result of aging, environmental conditions, or genetic abnormalities, As a result, there is an excess of ROS, which begins to harm vital cellular components including DNA, proteins, and lipids [181].

Damage to mitochondrial DNA (mtDNA) is a particularly worrisome outcome since it is more susceptible than nuclear DNA because of its close proximity to the site of ROS generation and absence of protective histones [184]. The mitochondrial energy system is further disrupted when mtDNA is degraded, which exacerbates oxidative stress and other cellular damage [194].

This process is accelerated in neurodegenerative illnesses. In addition to producing more ROS, damaged mitochondria also emit warning signals that set off inflammatory reactions and induce programmed cell death, or apoptosis [183]. Dopamine-producing neurons die as a result of severe oxidative stress in diseases like Parkinson's disease [193]. Oxidative damage speeds up cognitive impairment in Alzheimer's disease by encouraging the accumulation of tau tangles and amyloid plaques [199].

The mitochondria are at the intersection of oxidative stress and neurodegeneration due to their pivotal function in energy management and redox equilibrium. Cells are more resilient to stress if their functions are maintained, Failure of their function may signal the start of neuronal disintegration. The special location of mitochondria makes them a target and a therapeutic instrument [197].

Antioxidants that can specifically target mitochondria, substances that improve mitochondrial repair, and tactics that increase natural defense mechanisms like sirtuins and NAD^+ levels are being investigated by researchers to counteract these effects [195]. Neurodegenerative disease may be prevented or its onset may be slowed by concentrating on mitochondrial health, which may break the cycle of oxidative stress.

Oxidative stress in Parkinson

Oxidative stress is a primary cause of brain damage in Parkinson's disease, particularly in the area of the brain that regulates movement called the *substantia nigra* [196]. Specialized nerve cells known as dopaminergic neurons are especially at risk in this region [190]. Dopamine, a neurotransmitter that aids in controlling muscular activity, is produced by these neurons. These cells slowly deteriorate in Parkinson's disease (PD), resulting in stiffness, tremors, and delayed movement [198].

The fact that dopamine itself can degrade into harmful metabolites is one factor contributing to the sensitivity of these neurons [201]. ROS are generated during this breakdown. These ROS can then harm the cell's proteins, lipids, and even DNA. Cell death results from the buildup of this damage over time.

Further contributing to the issue are mitochondria, which are the microscopic organelles in cells that generate energy [194]. The function of mitochondria is frequently compromised in Parkinson's disease [198]. The production of ROS by malfunctioning mitochondria leads to a vicious cycle in which oxidative stress exacerbates mitochondrial damage, which in turn exacerbates oxidative stress [206].

Moreover, genetic variables may make a person more vulnerable [203]. The accumulation of damaged mitochondria is caused by mutations in certain genes involved in mitochondrial quality regulation, such as PINK1 and Parkin. The primary cause of the excess ROS is these damaged mitochondria.

Alpha-synuclein, another important protein implicated in Parkinson's disease, improperly clusters in the brains of PD patients. Lewy body clusters have the potential to worsen mitochondrial dysfunction and encourage oxidative damage.

Dysfunctional Mitochondria: The root cause or a symptom of neurodegenration

Numerous chronic illnesses and aging are mostly caused by the complex process of mitochondrial malfunction [210]. First, Oxidative Phosphorylation (OXPHOS) is impaired, wherein Electron Transport Chain (ETC) complex damage lowers ATP synthesis and results in electron leakage, which produces an excess of Reactive Oxygen Species (ROS) [212]. A self-amplifying loop of failure is created when these ROS harm proteins, lipids, and mitochondrial DNA (mtDNA), further weakening ETC function. ETC protein synthesis is compromised by mtDNA mutations, which can be inherited or acquired with age, aggravating cellular stress and respiratory inefficiency [215]. The dynamic mechanisms of mitochondrial fusion and fission become unbalanced with aging [218].

"Reduced fusion via MFN1/2 and OPA1 stops injured organelles from repairing themselves, whereas excessive fission, controlled by DRP1, causes mitochondrial fragmentation [220]. Simultaneously, the Parkin pathway malfunctions, making mitophagy the selective destruction of damaged mitochondria-less efficient and permitting the accumulation of toxic mitochondria [211]. Furthermore, the disruption of mitochondrial calcium buffering results in cell death, calcium excess, and the opening of the mitochondrial permeability transition pore (mPTP) [213]. NAD+ depletion also affects sirtuin enzymes, such as SIRT1 and SIRT3, which are essential for antioxidant defense, DNA repair, and mitochondrial biogenesis. By releasing cytochrome c, dysfunctional mitochondria can also start apoptosis by starting caspase cascades, which result in programmed cell death [219].

Additionally, when leaking into the cytosol, mitochondrial components like cardiolipin and mtDNA function as alarmins that trigger pattern recognition receptors (including TLR9 and NLRP3), causing persistent inflammation, which is a defining feature of aging known as "inflammaging", Lastly, good communication with the nucleus is essential for mitochondrial health; unfortunately, genomic instability and chronic DNA damage hinder this connection, which interferes with the production and repair of mitochondrial genes. Underpinning the progressive deterioration in cellular function that is characteristic of aging and age-related disorders, these interrelated processes work together to produce a vicious cycle of energy failure, oxidative stress, immunological activation, and cell death.

To sum up, a key, common mechanism in the etiology of CNS diseases is mitochondrial malfunction [217]. Due to the brain's need on high ATP levels, exact calcium control, and oxidative balance, neurons are particularly susceptible to compromised mitochondrial function [209]. Neuronal damage, synaptic failure, and neurodegeneration are caused by a combination of factors such as energy production disruption, excessive ROS generation, mtDNA mutations, impaired mitophagy, and changed mitochondrial dynamics [214]. Additionally, chronic neuroinflammation is fueled by the production of mitochondrial DAMPs, which accelerates the development of conditions including ALS, Parkinson's, and Alzheimer's [215]. The development and severity of CNS diseases are greatly influenced by these mitochondrial abnormalities, which worsen with age. Focusing on mitochondrial health via mitophagy enhancers, lifestyle changes, NAD+ boosters, or antioxidants affirms the mitochondria's critical position as a driver and possible therapeutic target in brain aging and illness, and shows hope for halting or preventing neurological deterioration.

Future of neuroprotection: Targeting to half brain disorder

A promising therapeutic target for ischemic stroke is the mitochondria. In recent years, it has been the subject of much research [222]. The role of healthy mitochondria is crucial part in neurological rehabilitation and neuroprotection following ischemic stroke. It is evident that one of the most popular areas of our present and future research is the study and advancement of mitochondrial transfer technology [225]. Researchers are looking into compounds that increase NAD^+ levels, improve mitophagy, or transport antioxidants straight to mitochondria in order to maintain neuronal energy balance and stop apoptosis [226]. Anti-inflammatory tactics are also becoming more popular, especially those that reduce pro-inflammatory cytokines, suppress inflammasome activation like the NLRP3 complex, or alter microglial activity [228]. These methods all contribute to chronic neuroinflammation in diseases like Parkinson's and Alzheimer's [230]. Antisense oligonucleotides (ASOs) and CRISPR-based editing are two highly targeted gene treatments that may be used to mute harmful genes or fix harmful mutations [225]. Meanwhile, viral vectors and nanocarrier systems are being used to improve the distribution of neurotrophic factors like GDNF and BDNF [224]. The potential of exosome-derived vesicles and stem cell-based strategies to promote brain healing and alter the microenvironment is also being studied. Crucially, more specialized neuroprotective treatments are becoming possible thanks to the incorporation of personalized medicine, which is directed by genetic, proteomic, and imaging biomarkers. Through the identification of new targets and the optimization of therapeutic molecules, artificial intelligence significantly improves drug research. When taken as a whole, these developments point to a future where neuroprotection is not only more efficient but also precisely tailored to the demands of each patient, possibly changing how neurodegenerative diseases progress [229].

Half Brain Disorder

A medical illness where one cerebral hemisphere is either deformed, injured, or rendered nonfunctional is sometimes referred to as a "half brain disorder" [233]. While uncommon, these conditions can have significant neurological and developmental effects, particularly if they manifest early in life [235]. Hemimegalencephaly, in which one hemisphere is abnormally enlarged and disordered as a result of developmental abnormalities, and Rasmussen's encephalitis, a progressive inflammatory illness that causes degeneration of one side of the brain, are two of the most well-known disorders in this group [236]. Brain function can also be significantly asymmetrical as a result of other disorders including big unilateral strokes or cerebral hemiatrophy (as demonstrated in Dyke-Davidoff-Masson syndrome) [240]. Seizures, one-sided movement impairments, cognitive decline, and developmental delays are possible symptoms for those affected. Even though these conditions are severe, the growing brain, particularly in youngsters, may show extraordinary flexibility, which occasionally enables the unaffected hemisphere to make up for lost functions.[243] Knowing these disorders offers valuable information on the structure and resiliency of the brain as well as the possibility of surgical and rehabilitative treatments for treating severe neurological dysfunction [249].

Modern, focused techniques that maintain function in the remaining healthy hemisphere while reducing damage in the afflicted one are the key to the future of neuroprotection in the treatment of unilateral or "half brain" illnesses [244]. Prolonged inflammation, excitotoxicity, and oxidative stress are common in conditions including hemimegalencephaly, Rasmussen's encephalitis, and cerebral hemiatrophy, which cause gradual loss of neurons [239]. Early modification of these processes is probably going to be the main target of future neuroprotective strategies [237]. Key study topics include NMDA receptor antagonists that target glutamate excitotoxicity, mitochondrial antioxidants that reduce reactive oxygen species (ROS), and microglial modulation and inflammasome inhibition (e.g, NLRP3 blockers) that control neuroinflammation [233]. Activating sirtuins (SIRT1, SIRT3) and increasing mitochondrial activity with NAD^+ precursors may also aid in maintaining cellular energy and fending off apoptotic cues, Gene and cell-based treatments are also promising since they may be able to improve plasticity in the unaffected hemisphere and replace or shield susceptible neurons [238]. Personalized strategies that make use of biomarkers and neuroimaging can help direct monitoring and early intervention. The intact hemisphere can adapt and support compensatory function in children, which gives hope for functional recovery in these complex disorders. In the end, pharmacological neuroprotection combined with rehabilitation and neuromodulation may greatly improve outcomes by utilizing neuroplasticity.

Conclusion

Mitochondria as centrmitochondria as central players in the origin and progression of neurodegenerative diseases. Once regarded primarily as cellular powerhouses, mitochondria are now recognized as intricate regulators of energy production, redox balance, calcium signaling, apoptosis, and even epigenetic modifications-all of which are profoundly disrupted in conditions such as Alzheimer's, Parkinson's, Huntington’s disease, and ALS. Mitochondrial dysfunction manifests through impaired oxidative phosphorylation, Excess Reactive Oxygen Species (ROS), mtDNA mutations, disrupted mitochondrial dynamics, defective mitophagy, and calcium dysregulation. These alterations converge to trigger neuronal energy failure, inflammation, and ultimately, synaptic degeneration and cell death.

The article also highlights how aging exacerbates these mitochondrial impairments, promoting chronic inflammation ("inflammaging") and increasing vulnerability to neurodegenerative processes. Notably, mitochondrial dysfunction is not just a consequence but a likely initiator of disease pathology, as seen in early-stage bioenergetic deficits and oxidative damage preceding clinical symptoms.

Looking forward, the future of neuroprotection lies in precision strategies that restore mitochondrial health. These include NAD^+ boosters, sirtuin activators, mitochondrial-targeted antioxidants, and mitophagy enhancers. Gene therapies, stem cell-derived exosomes, and personalized medicine guided by biomarkers and imaging are also emerging as innovative tools. In cases of unilateral brain disorders such as hemimegalencephaly or Rasmussen's encephalitis, protecting the intact hemisphere while minimizing further damage is vital. Here, targeted modulation of excitotoxicity, ROS, and inflammation may preserve function and support neural compensation.

Altogether, this review makes clear that preserving mitochondrial integrity is fundamental to halting or slowing neurodegeneration. Therapeutically targeting mitochondrial pathways offers a promising, mechanistic avenue to combat CNS diseases and improve neurological outcomes. As mitochondrial science evolves, it holds the potential to redefine the paradigm of neurodegenerative disease prevention and treatment.al players in the origin and progression of neurodegenerative diseases. Once regarded primarily as cellular powerhouses, mitochondria are now recognized as intricate regulators of energy production, redox balance, calcium signalling, apoptosis, and even epigenetic modifications all of which are profoundly disrupted in conditions such as Alzheimer's, Parkinson's, Huntington's disease, and ALS. Mitochondrial dysfunction manifests through impaired oxidative phosphorylation, excess reactive oxygen species (ROS), mtDNA mutations, disrupted mitochondrial dynamics, defective mitophagy, and calcium dysregulation. These alterations converge to trigger neuronal energy failure, inflammation, and ultimately, synaptic degeneration and cell death.

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