The role of mitochondrial dysfunction in neurological disorders - Unraveling the connection

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Abstract

Mitochondria play a crucial role in all eukaryotic cells, as they produce adenosine triphosphate (ATP), which is a primary energy source required for various cellular processes including oxidative phosphorylation, calcium homeostasis, apoptosis, generation of reactive oxygen species. However mitochondrial dysfunction leads to impairment in energy production and neuronal functions, which are implicated in the pathogenesis of neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's disease, as well as ischemic stroke. This review explores the relation between mitochondrial dysfunction and neurological disorders with special focus on the possible molecular mechanisms involved and mitochondrial targeted therapies such as dietary supplements, ketogenic diets, antioxidants, pharmacological agents, and gene therapy.

Keywords – Mitochondria, Mitochondrial dysfunction, Neurological disorders, Oxidative phosphorylation, Targeted therapies.

1. Introduction

The Mitochondria is an intracellular organelle present in nearly all eukaryotic cells, serving as the powerhouse of the cell and it playing a major role in the production of adenosine triphosphate (ATP), the primary energy source required for various cellular processes, especially to establish appropriate electrochemical gradients and reliable synaptic transmission. Mitochondrial dysfunction has been found to be a critical factor in several neurological disorders such as Alzheimer's, Parkinson's, Huntington's disease and ischemic

stroke[1]. Mitochondrial dysfunction may leads to impairment in the electron transport chain (ETC), reducing ATP production and triggering pathological processes such as calcium accumulation, opening of the mitochondrial permeability transition pore (mPTP), cytochrome c release, apoptosis, and mitophagy. Also the defects in mitochondria leads to reactive oxygen species (ROS) overproduction, causing oxidative stress, tissue damage, and energy depletion, which further contributing to disease progression[2].This review discusses the relationship between mitochondrial dysfunction and various neurological disorders and highlights the mitochondrial targeted treatment strategies.

2. Mitochondria-physiology

Mitochondria produce cellular energy in the form of ATP by oxidative phosphorylation (OXPHOS). Apart from producing high-energy phosphates like ATP and phosphocreatine, mitochondria involved in several other cellular processes like inflammation, apoptosis, cAMP/protein kinase A (PKA) signaling, calcium homeostasis, and the generation of reactive oxygen species (ROS).

2.1. Oxidative phosphorylation

Mitochondria generate energy in the form of ATP by the process called oxidative phosphorylation (OXPHOS). In eukaryotes, catabolic processes like glycolysis and the citric acid cycle generate NADH, which donates high-energy electrons to the electron transport chain (ETC). These electrons flow through a series of (I-IV) OXPHOS complexes, within the inner mitochondrial membrane, drives the active transport of hydrogen ions (protons) from the mitochondrial matrix into the intermembrane space, creating an electrochemical gradient also called the proton-motive force, characterized by a high concentration of protons in the intermembrane space and a lower concentration in the matrix. And out four complexes, three of them are proton pumps. Protons then flow back into the matrix via ATP synthase (Complex V), driving ATP production[3].

The main enzyme in the electron transport chain (ETC) is *complex I*, also known as NADH dehydrogenase. It catalyzes the oxidation of NADH through coenzyme Q10. As two electrons pass through complex I, four protons are pumped from the mitochondrial matrix into the intermembrane space[3, 4].

Succinate dehydrogenase, also known as *Complex II*, is the respiratory chain's second independent point of electron entry. It catalyzes the oxidation of succinic acid to form fumarate and the reduction of coenzyme Q10 to ubiquinone (QH2). This reaction does not involve the transfer of electrons. Complex II does not directly contribute to the development of the proton gradient and is not a proton pump. The third entry of the protons on the electron transport chain is electron transfer flavin-coenzyme Q oxidoreductase, also known as electron transfer flavin dehydrogenase, which reduces Q10 by using electrons from electron transfer flavin in the mitochondrial matrix[4].

The *Complex III*, also known as cytochrome c oxidoreductase, which oxidizes ubiquinone to ubiquinol, which allows it to pump two protons into the intermembrane gap. Cytochromes b and c1 of complex III transfer the electrons from ubiquinol to the carrier cytochrome c through them[4].

Cytochrome C Oxidase, often known as *complex IV*, is the final enzyme in the mitochondrial electron transport chain sequence. It transfers electrons to an oxygen molecule to split it into two water molecules by accepting electrons from cytochrome c. During this action, four protons are pushed into the intermembrane gap. ATP synthase or *complex V* uses the energy stored in a proton gradient to turn ADP into ATP[3, 4].

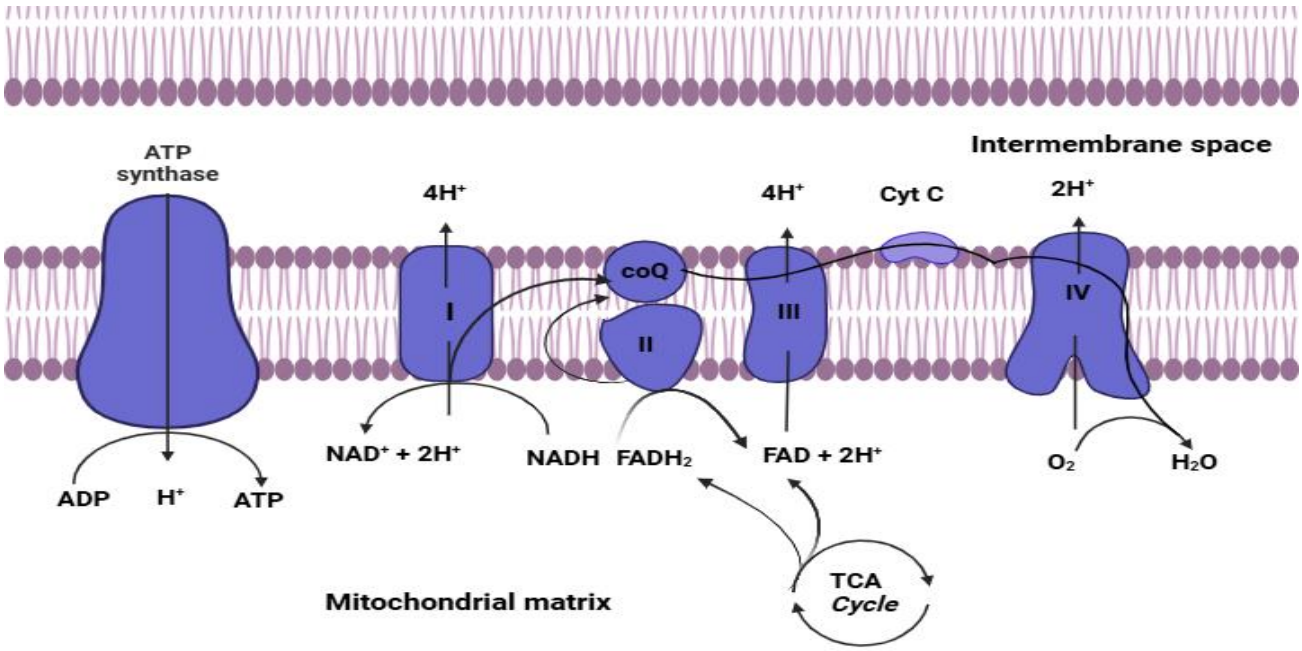

Fig-1: Electron transport chain

2.2. Mitochondria and calcium homeostasis

Mitochondria play a critical role in calcium (Ca^{2+}) homeostasis, which collaborates with other cell organelles like the endoplasmic reticulum (ER) and the extracellular matrix to store and control the dynamic balance of Ca2+ concentration in cells. Calcium (Ca2+) is one of the most prevalent second messengers in cells, engaged in a wide range of crucial cellular processes, such as learning, memory, and cognition. It also plays a role in signaling pathways, gene transcription, cell proliferation, and the regulation of neuronal activities[5].
Mitochondria constantly exchange calcium with the cytosol to monitor and adjust to the cell's energy requirements. Calcium influx into the mitochondrial matrix enhances the activity of several dehydrogenases in the tricarboxylic acid (TCA) cycle, boosting ATP production via oxidative phosphorylation (OXPHOS). Mitochondria express calcium uptake and extrusion pathways to regulate the cellular Ca^{2+}[6].

2.2.1 Mitochondrial calcium uptake pathway

The endoplasmic reticulum (ER) is the primary site of Ca^{2+} storage in cells. Activation of the IP3 receptor (IP3 R) on the ER membrane by inositol-1,4,5-trisphosphate (IP3) results in the release of Ca^{2+} into the cytosol and is the primary mechanism of ER calcium release. Later, the cytosolic Ca^{2+} enters the mitochondria via voltage-dependent anion channel (VDAC) at the outer mitochondrial membrane (OMM) and then the mitochondrial calcium uniporter (MCU) transports it across the inner mitochondrial membrane (IMM) due to the membrane potential driving force generated by the OXPHOS[5].
Members of the mitochondrial calcium uptake family (MICU) of proteins, which are found in the inner mitochondrial space (IMS), primarily control MCU. These members include MICU1, MICU2, and MICU3. The IMS proteins MICU1 and MICU2 act as gatekeepers for Ca2+ transport and limits calcium passage through MCU, prevents mitochondrial Ca^{2+} overload. When Cytosolic Ca^{2+} concentration rises, MICU1 senses this increase and undergoes a conformational change, forms a functional heterodimer with MICU2 which facilitates the activation of MCU. This allows efficient Ca^{2+} transport into the mitochondrial matrix, driven by the electrochemical gradient across the IMM[5, 7].

2.2.2 Mitochondrial calcium extrusion pathway

There are two main pathways for Ca^{2+} extrusion: the Na^+/Ca^{2+} exchanger drives one pathway, while the $H^+–Ca^{2+}$ exchanger drives the other. The $Na^+/Ca^{2+}/Li^+$ (NCLX) and H^+/Ca^{2+} (mHCX) exchangers, two Ca^{2+} extrusion molecules found in mitochondria, export Ca^{2+} outside of the mitochondria and limit Ca^{2+} accumulation within the matrix, preserving the Ca^{2+} homeostasis within the mitochondria[8].

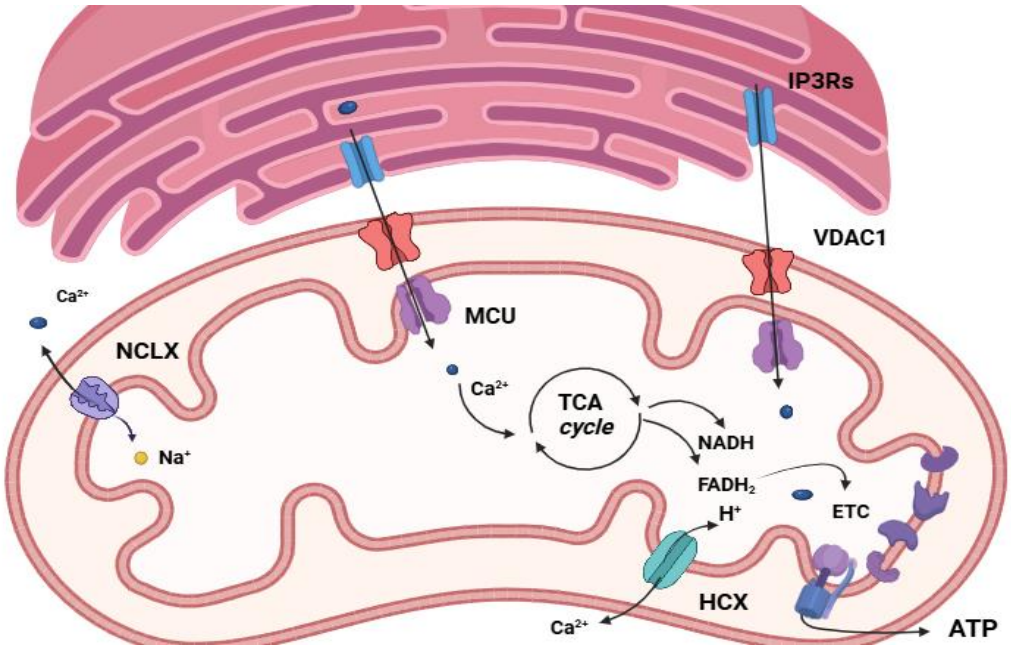

Fig-2: Mitochondrial calcium signaling

2.3. Mitochondria and generation of reactive oxygen species (ros)

Reactive oxygen species (ROS) are produced by mitochondria and are a significant source of oxidative damage in many pathologies as well as retrograde redox signaling from the organelle to the cytosol and nucleus[9]. During the oxidative phosphorylation, the mitochondrial ROS generation mainly takes place at the electron transport chain located on the inner mitochondrial membrane. It is currently believed that complexes I and III produce the majority of ROS, most likely as a result of NADH and FADH releasing electrons into the ETC. ROS includes oxygen free radicals, such as superoxide anion radical ($O2^{-}$) and hydroxyl radical (OH), and non-radical oxidants, such as hydrogen peroxide ($H2O2$) and singlet oxygen ($1O2$)[10].

In the process of normal OXPHOS, 0.4–4.0% of all oxygen consumed is converted in mitochondria to the superoxide (O2-) radical. The detoxifying enzymes manganese superoxide dismutase (MnSOD) or copper/zinc superoxide dismutase (Cu/Zn SOD) convert superoxide(O2-) to hydrogen peroxide ($H2O2$), which is subsequently converted to water by glutathione peroxidase (GPX) or peroxidredoxin III (PRX III). When these enzymes in the mitochondria, fails to convert harmful reactive oxygen species (like superoxide) into $H2O$, oxidative damage develops[11].

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) play dual roles in mitochondrial and cellular processes. It acts as an essential signaling molecule at physiological processes but causes oxidative damages when produced excessively. Superoxide (O2-) is a byproduct of mitochondrial oxidative phosphorylation and is highly reactive. It can damage the iron–sulfur (Fe−S) clusters in enzymes such as aconitase, an essential enzyme in the tricarboxylic acid (TCA) cycle. Due to this damage, the release of free iron ($Fe2+$) into the cytoplasm takes place. The released free iron ($Fe2+$), then reacts with hydrogen peroxide ($H2O2$) to produce highly reactive hydroxyl radicals (.OH) and is said to be fenton reaction. The produced hydroxyl radicals(.OH) is capable of causing severe oxidative damage to proteins, lipids, and DNA. At the same time, nitric oxide (NO) generated by mitochondrial nitric oxide synthase (mtNOS) reacts with superoxide to form peroxynitrite ($ONOO^{-}$), which is a potent Reactive Nitrogen Species that causes nitration of tyrosine residues, lipid peroxidation, and DNA damage. Combined, these free radicals form a group of active redox agents that are involved in intra and extracellular processes, such as signaling pathways, immune responses, and apoptosis regulation. Although their overproduction leads to oxidative and nitro-sative stress, contributing to mitochondrial dysfunction and disorders related to neurodegeneration[12, 13].

2.4. Mitochondria and apoptosis

Mitochondria play crucial roles in initiating apoptosis in mammalian cells. Mitochondria have apoptogenic factors in the inter-membrane space (cytochrome c, AIF, DIABLO/SMAC, and procaspase-2, -3, and -9 in some cell types). On the other hand, even in the absence of

caspases, certain pro-apoptotic proteins, including the mammalian cell death protein Bax, which targets mitochondrial membranes, can cause mitochondrial damage and cell death[14]. During apoptosis cytochrome c, an apoptogenic factor, released from the mitochondria into cytoplasm induces caspase activation. cytoplasmic cytochrome c binds to Apaf-1 (apoptotic protease-activating factor-1), increasing its affinity for dATP/ATP and triggering the formation of the apoptosome. The attachment of a nucleotide to the Apaf-1/cytochrome c complex causes it to oligomerize and form the apoptosome, which is a multimeric Apaf-1 and cytochrome c complex. The formed apoptosome activates procaspase-9, which subsequently triggers executioner caspases like caspase-3, -6, and -7. The activation results in characteristic apoptotic events such as chromatin condensation, DNA fragmentation, nuclear membrane breakdown, phosphatidylserine externalization, and the formation of apoptotic bodies. Furthermore bax, a regulatory protein which is a part of Bcl-2 family causes mitochondrial damage and apoptosis independent of caspases. It is a highly regulated process which ensures efficient cell death and maintains tissue homeostasis[15].

3. Mitochondrial dysfunction and related neurological disorders:

Mitochondria are important for metabolic homeostasis in cells. The adenosine triphosphate (ATP) generated via mitochondria is required in nervous system to establish proper electrochemical gradients and sound synaptic transmission. Notably, multiple mitochondrial defects have indeed been identified in central nervous system disorders; for example, defects within oxidative phosphorylation, mitochondrial dynamics, oxidant generation, alongside cell death regulation, Ca2+ homeostasis, together with proteostasis. Membrane leakage, plus electrolyte imbalances, and also mitophagy happen to be implicated mechanisms for neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease, as well as Huntington’s disease, also ischemic stroke.

3.1. Parkinson’s disease

Parkinson’s Disease (PD) is characterized by progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc), and accumulations of Lewy bodies (LB)-containing α-synuclein protein deposits, resulting in motor symptoms (including resting tremor and rigidity) and non-motor symptoms (including depression and dementia)[16]. Mitochondrial dysfunction plays a central role in the pathogenesis of Parkinson's disease (PD) due to reduced activity of complex I ((NADH: Ubiquinone oxidoreductase) in the mitochondrial electron transport chain (ETC), especially in the substantia nigra, which was observed in the post-mortem studies of PD patients[17]. Due to Complex I deficiency, there occurs an accumulation of ROS, particularly superoxide anions. Increase in ROS levels cause oxidative damage to lipids, proteins, and DNA, which further impairing nerve cell function and survival. Dopaminergic neurons in the substantia nigra are sensitive to oxidative stress due to the metabolism of dopamine, which itself generates ROS. Mitochondrial dysfunction and oxidative stress together increases the selective loss of these neurons, which is a major characteristics of Parkinson's disease[18]. In addition, neurotoxins like MPTP (converted to MPP+), 6-hydroxydopamine (6-OHDA), and pesticides like paraquat and rotenone, which act

as complex I inhibitors, induce neuropathological changes resembling PD, highlighting their role in disease progression[19].

3.2. Alzheimer's disease

Alzheimer's disease (AD) is a chronic neurodegenerative disorder and recognized as most common cause of dementia. Symptoms, from behavioral impairment to cognitive loss, are experienced by patients with AD, and these symptoms get worse over time. Phosphorylated tau protein tangles (NFTs) and amyloid beta peptide (Aβ) aggregations, are the two degenerative brain phenomena, which indicates Alzheimer's disease (AD)[20]. Mitochondrial dysfunction has been proposed as major mechanisms in the development and progression of most neurodegenerative diseases. The circumstances such as increase in Ca^{2+} levels, increased oxidative stress, reduced ATP production, and mitochondrial depolarization converge to induce the opening of the mitochondrial permeability transition pore (PTP). When the mitochondrial PTP opens, it allows several solutes to pass across the mitochondrial membranes, which further causes mitochondrial swelling, efflux of Ca^{2+} and the release of apoptogenic proteins, including cytochrome c0 (Cyt c), from the mitochondrial intermembrane space. This process triggers the apoptotic cascade and eventually causes cell death.

Amyloid precursor protein (APP) targets both the endoplasmic reticulum and mitochondria. In the mitochondria, APP interacts with translocases proteins located in outer and inner membrane (TOM and TIM) that assist in protein importation. APP interfere and disrupts mitochondrial protein importation, including respiratory chain subunits. These defects causes, reduction in mitochondrial function, leading to decreased ATP production, increased ROS generation, and decreased enzyme activity. Along with these defects, the protein amyloid-β (Aβ) aggravates the mitochondrial dysfunction by binding to enzyme called amyloid-binding alcohol dehydrogenase (ABAD), promoting ROS production. These mitochondrial defects contribute to Alzheimer's disease pathology [21].

3.3. Huntington's disease

Huntington's disease (HD) is a prototypical neurodegenerative disease, preferentially disrupting the neurons of the striatum and cortex. Progressive motor dysfunctions, psychiatric disturbances, behavioral impairments, and cognitive decline are the clinical symptoms of HD progression. The disease occurs due to expanded CAG repeats in exon 1 of huntingtin protein (mHtt), although the resulting pathogenic processes have not been fully elucidated. However transcriptional deregulation and mitochondrial dysfunction have been strongly implicated in the pathogenesis of HD[22]. Biochemical studies of mitochondria in striatal neurons from brain tissues of HD patients revealed reduced activity of several components of oxidative phosphorylation, including complexes II, III, and IV of the electron transport chain, although these abnormalities are not observed in pre-manifest and early-stage HD patients.

Early ultrastructural studies of cortical biopsies from patients with juvenile or adult-onset Huntington's disease (HD) revealed abnormal mitochondrial morphology and functional abnormalities[23]. A defect in succinate dehydrogenase (SDH), a component of both the Krebs cycle and complex II of the electron transport chain, was identified in the caudate and, to a lesser extent, in the cortex of postmortem HD brains. Decrease in complex II, III, and IV activities, especially in the caudate and putamen have also been observed in HD[24]. These findings suggest that impairment in mitochondrial energy metabolism and calcium handling due to mutation, leading to decreased energy levels, increased oxidative damage and secondary excitotoxic cell death, contributing to HD pathogenesis.

3.4. Ischemic stroke

An ischemic stroke occurs when the blood supply to part of the brain is blocked or reduced. Lack of blood supply deprives the brain cells of necessary glucose and oxygen and disturbs cellular homeostasis, which triggers pathophysiological processes including excitotoxicity, oxidative stress, inflammation, apoptosis and cell death. Mitochondrial dysfunction has been considered as one of the hallmarks of ischemic stroke and contributes to the pathology of ischemia and reperfusion[25].

More than 80% of strokes are ischemic and are caused by obstruction of one or more cerebral arteries. Within minutes after arterial occlusion, the ischemic brain begins depolarizing mitochondrial membranes, which leads to depletion of ATP production, overproduction of ROS and accumulation of protein PTEN induced putative kinase-1(PINK1) and unfolded protein response (UPR). The reduction of ATP triggers ischemic cascades such as membrane ion pump failure, plasma membrane depolarization and efflux of cellular potassium, influx of sodium, calcium, chloride, and water. All of these factors lead to opening of mPTP, liberation of cytochrome c, activation of caspase 3 and consequently, execution of apoptotic neuronal death[26].

4. Mitochondrial-targeted therapeutic approaches

There is no cure but recently, Mitochondria-targeted therapeutic approaches has been developed and which represent an innovative and rapidly evolving strategy in the treatment of a wide range of diseases, particularly those that are root cause in mitochondrial dysfunction. Mitochondrial treatments generally focus on enhancing mitochondrial function or addressing the consequences of dysfunction. Therapies that aim to reduce toxic metabolite accumulation, increase ATP production & storage, improve oxidative capacity and targets the underlying bioenergetic defects, helps to restore cellular energy balance & homeostasis.

4.1. Dietary supplements

Mitochondrial dysfunction manifests several symptoms. hence there is a need for personalized treatment approaches. Several nutritional supplements have shown promising effects in restoring functions of mitochondria, alleviating symptoms, and reducing

physiological stress. Commonly used supplements such as CoenzymeQ10 (CoQ10) and Ubiquinol, that increases ATP production and act as antioxidants. Fatty acid metabolism is increased by Carnitine. Riboflavin (Vitamin B2) and Alpha-Lipoic Acid (ALA) improves mitochondrial bioenergetics and fights against oxidative stress. Creatine serves as an energy buffer, while N-Acetylcysteine (NAC) and Magnesium support antioxidant defense and muscle function. Polyphenols, like resveratrol, promote mitochondrial biogenesis, and ketone supplements provide alternative energy sources for the brain and other tissues. These supplements, improves energy metabolism and alleviate symptoms when paired with lifestyle interventions[27, 28].

4.2. Ketogenic diet

The ketogenic diet (KD) is a high-fat diet. KD replaces carbohydrate with fat and burns it for energy. Ketogenic diet stimulates mitochondrial β-oxidation and promotes the production of ketone bodies, which serve as an alternative energy source for the brain, heart, and skeletal muscles. The produced Ketone bodies further metabolized into acetyl-CoA, which fuels Krebs cycle and avoids complex I of the OXPHOS respiratory chain boosting up ATP production. Additionally, increased ketone levels may upregulate OXPHOS gene expression, mimicking starvation-induced cellular stress, which activates factors like SIRT1, AMPK, and PGC-1α to boost mitochondrial biogenesis. KD has been linked to upregulate biogenesis-related genes and uncoupling proteins and additionally preclinical studies have shown that the Ketogenic diet (KD) reduced heteroplasmic mtDNA deletion in a cybrid model, increased mitochondrial glutathione levels in rats, and slowed mitochondrial myopathy progression in the Deletor mouse. Anecdotal human reports suggest transient benefits, particularly in epilepsy patients with mitochondrial disease, but rigorous randomized, double-blinded clinical trials are still needed to confirm these findings[29, 30].

4.3. Anti-oxidants

Oxidative stress and damage due to oxidative stress play an indispensable role in several neurodegenerative disorders. Antioxidant therapies are the most promising treatment approach. Over the past decade, in vivo and in vitro studies in animals and humans have demonstrated the potential of antioxidants in mitigating oxidative stress. The well known and most commonly used antioxidants like vitamin E and vitamin C, coenzyme Q, α-lipoic acid, and N-acetylcysteine (NAC), helps reducing excessive reactive oxygen species (ROS) generation. Furthermore, Ubiquinone-based MitoQ and vitamin E-derived MitoVit E are mitochondria-targeted antioxidants that gained attention for their effectiveness in mitochondrial dysfunction related disorders. MitoQ, a lipophilic compound combining triphenylphosphonium (TPP) cation with coenzyme Q10, accumulates extensively in mitochondria, reducing ROS and protecting brain tissue against age-related mitochondrial damage. These advancements highlight the therapeutic potential of targeted antioxidants for mitochondrial-related pathologies[31].

4.4 pharmacological interventions

4.4.1 Bezafibrate

Bezafibrate, a peroxisome proliferator activated receptors (PPARα) agonist. Recent Studies shows that bezafibrate is the major regulator of mitochondrial biogenesis. Though its effectiveness varies across different disease models, it could be a beneficial therapeutic agent for mitochondrial disorders. In Cox10 KO mice, bezafibrate demonstrated clear benefits, improving cytochrome c oxidase (COX) activity and promoting mitochondrial biogenesis. It showed promising results in Cox10 KO mice but failed to produce similar results in Surf1 KO and Deletor mice, denoting that its efficacy may depends on any particular genetic or pathological conditions. Preclinical findings suggest variability in its effects, the combination of safety in humans and early signs of efficacy, highlights the bezafibrate's potential for treating specific mitochondrial disorders. These findings warrant further clinical trials to better understand its therapeutic scope and identify patient subgroups most likely to benefit[31, 32].

4.4.2 Resveratrol

Resveratrol, a polyphenolic compound that activates the sirtuin SIRT1(silent mating type information regulation 2, S. cerevisiae, homolog 1), which is a promising targets for enhancing mitochondrial biogenesis that regulate key mitochondrial factors such as PGC-1α and TFAM[31]. Resveratrol-induced mitochondrial biogenesis helps restore impaired mitochondrial functions such as disrupted ATP production, cellular synthetic and secretory functions, redox balance, and nuclear gene expression via altered retrograde signaling by correcting mitochondrial impairments. Additionally, mitochondrial proliferation resulting from biogenesis reduces the electron flow per mitochondrion, thereby decreasing mitochondrial reactive oxygen species (ROS) production[33].

4.4.3 AICAR

The 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR) is an AMPK activator. The AMP Kinase enzyme serves as an energy sensor in cells which is activated by a high AMP/ATP ratio that signals when there is an energy deficiency in cell. AMPK promotes catabolic processes like increasing glucose uptake and fatty acid oxidation while inhibiting anabolic processes like glycogen synthesis and lipogenesis, after its activation. Apart from controlling energy homeostasis, AMPK also up regulates mitochondrial biogenesis through PGC-1α signaling pathway[34].

The AMPK activator (AICAR) has several benefits in human complex I-deficient fibroblasts, like increasing mitochondrial biogenesis and ATP production and reducing reactive oxygen species (ROS). AICAR has shown promising effects in mouse models of cytochrome c

oxidase (COX) deficiency which is a common mitochondrial disease. It further underscoring AMPK's potential as a target for modifying mitochondrial bioenergetics[35].

4.5 gene therapy

Gene therapy is an innovative technology. It is used to treat many disorders that are caused by mutation or defects in the mitochondrial genome (mtDNA) or nuclear genes which affect mitochondrial function. Hence it could be a promising solution to mitochondrial dysfunction related disorders. Mitochondrial genome editing, using tools like ZFNs, TALENs and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-based systems are recent
strategies.
Another approach called allotopic expression, involves genetic manipulation of nuclear DNA to produce mitochondrial proteins that are subsequently imported into the organelle. Additionally, mitochondrial replacement therapy (MRT) is a reproductive technique that prevents the transmission of defective mtDNA and replaces it with healthy donor. Though gene therapy has several beneficial effects, it also has challenges related to delivery systems, long-term safety, and ethical considerations, which requires further research and development to unlock the full potential of gene therapy for mitochondrial diseases[36-38].

5. Summary

Mitochondria performs several crucial functions such as ATP generation, Metabolic regulation, Apoptosis, ROS generation and Ca2+ homeostasis to drive cellular functions and biological processes. Impairment in such prime functions is recognized as mitochondrial dysfunction and it is implicated in the progression and development of several neurological disorders such as Alzheimer's disease, Parkinson's disease, ischemic stroke and Huntington's disease. The impact of mitochondrial dysfunction on neurological disorders demonstrates the instantaneous need for mitochondria targeted-therapeutic approaches. Available therapeutic approaches like dietary supplements, ketogenic diet, anti-oxidants, pharmacological interventions and gene therapy which are aimed at enhancing mitochondrial function, reducing oxidative stress, and restoring calcium balance hold promise for the treatment of these debilitating disorders. By developing targeted therapy and mitigating the effects of mitochondrial dysfunction, we may pave the way for innovative therapies, improve outcomes for patients and enhance the quality of life.

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