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Pharmacological Strategies for Modulating Mitochondrial Dysfunction in Neurodegenerative Disease

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KEYWORDS

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ABSTRACT:

Neurodegenerative diseases present a formidable challenge as they progressively compromise neuronal structures and functions. This paper explores the intricate landscape of neurodegenerative disorders, encompassing Alzheimer's, Parkinson's, Huntington's, Amyotrophic Lateral Sclerosis, and Multiple Sclerosis. Mitochondria, acknowledged as cellular powerhouses, crucially maintain neural health by influencing energy production, calcium homeostasis, ROS regulation, apoptosis, metabolism, neurotransmitter synthesis, neuroplasticity, dynamics, and neuroprotection. Mitochondrial dysfunction emerges as a common denominator linking neurodegenerative diseases, affecting vital pathways like energy production, oxidative stress, apoptosis, DNA mutations, calcium dysregulation, mitophagy, and dynamics. The paper underscores the implications of mitochondrial dysfunction in diseases such as Alzheimer's, Parkinson's, Huntington's, and ALS. This paper underscores the importance of diagnostic biomarkers and envisions future prospects, including genetic therapies, mitochondrial replacement therapy, small molecule therapeutics, metabolic regulation, and diagnostic biomarkers. Acknowledging the complexity of mitochondrial dysfunction, ongoing research holds promise for advancing understanding, diagnosis, and treatment of neurodegenerative diseases. Regular updates are crucial for staying informed in this dynamic field of mitochondrial medicine. Thus we explore different recent advances to create a descriptive illustration of how modulation of neurodegenerative diseases can be done by help of mitochondrial changes.

Introduction

Neurodegenerative diseases that is a concern now a days represent a group of conditions is identified by the gradual dysfunction and loss of structure or function of neurons in the brain. (1) These disorders, often associated with aging, manifest as a progressive decline in cognitive, motor, and/or sensory functions. Several prominent neurodegenerative diseases have been extensively studied, each with distinct pathological features and clinical manifestations. Alzheimer's disease stands as the predominant type of dementia, marked by the buildup of irregular protein clusters like beta-amyloid plaques and tau tangles. This accumulation contributes to synaptic dysfunction and the demise of neurons. Parkinson's disease on the other hand is characterized by the deterioration of neurons producing dopamine in the substantia nigra region of the brain. Prominent motor symptoms encompass tremors,

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rigidity, and bradykinesia, accompanied by non-motor symptoms, including cognitive impairment. (2) Huntington's disease is an inherited disorder marked by the gradual breakdown of nerve cells in the brain. (3) Amyotrophic Lateral Sclerosis (ALS), is a condition that is classified as a motor neuron disease involving the degeneration of both upper and lower motor neurons, causing muscle weakness and atrophy. (4) The progressive decline in voluntary muscle control gives rise to challenges in speaking, swallowing, and breathing. In the case of Multiple Sclerosis, an autoimmune disease unfolds as the immune system targets the safeguarding myelin sheath encasing nerve fibers within the central nervous system.
(5) Symptoms vary widely and may include fatigue, impaired coordination, and cognitive dysfunction.

The Role of Mitochondria in Neural Function:

Frequently known as the cellular "powerhouses" mitochondria are essential for preserving the well-being and operational efficiency of neurons. The intricate relationship between mitochondria and neural function encompasses various aspects, ranging from energy production to calcium regulation. Here is an exploration of the multifaceted role of mitochondria in neural function:

1. Energy Production:

ATP Generation: The primary role of mitochondria is to generate adenosine triphosphate (ATP) through oxidative phosphorylation (OXPHOS). (6) Neurons have high energy demands, and mitochondria ensure a constant supply of ATP to support essential cellular processes.

2. Calcium Homeostasis:

Buffering Calcium Ions: Mitochondria are involved in regulating intracellular calcium levels. They act as buffers, sequestering excess calcium ions to prevent cytosolic overload, which, if uncontrolled, can lead to neuronal excitotoxicity and cell death.

3. Reactive Oxygen Species (ROS) Regulation:

Mitochondrial ROS Production: Although mitochondria generate reactive oxygen species (ROS) as byproducts during oxidative phosphorylation (OXPHOS), they also have antioxidant defense mechanisms to uphold a delicate equilibrium. Maintaining controlled levels of ROS is crucial for cellular signaling and fortification against pathogens. (7)

4. Apoptosis Regulation:

Intrinsic Apoptotic Pathway: Mitochondria are central to the intrinsic apoptotic pathway. They release pro-apoptotic factors, triggering programmed cell death when necessary. Dysregulation of this process can contribute to neurodegenerative disorders. (8)

5. Metabolism and Neurotransmitter Synthesis:

Metabolic Integration: Mitochondria integrate metabolic pathways, including the metabolism of glucose, fatty acids, and ketones, to provide the necessary substrates for neural energy metabolism.

Neurotransmitter Synthesis: Mitochondria contribute to the synthesis of neurotransmitters, such as acetylcholine and gamma-amino butyric acid (GABA) through specific metabolic pathways. (9)

6. Neuroplasticity:

Synaptic Plasticity: Playing a pivotal role in synaptic plasticity, a foundational mechanism essential for learning and memory, mitochondria provide the energy required for synaptic transmission. Additionally, they play a part in sustaining and reshaping synaptic structures. (10)

7. Mitochondrial Dynamics:

Fission and Fusion: Mitochondria experience dynamic processes of both splitting (fission) and merging (fusion), controlling their structure and dispersion within neurons. This dynamic behaviour is crucial for adapting to changing energy demands and maintaining mitochondrial health.

8. Neuroprotection:

Antioxidant Defense: Mitochondria possess antioxidant defence mechanisms, including enzymes like superoxide dismutase, to protect neurons from oxidative stress. (11) Maintaining mitochondrial health is essential for overall neuronal survival.

9. Neurological Disorders:

Implications in Disease: Impaired mitochondria are associated with several neurological disorders, such as

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Alzheimer's disease, Parkinson's, and Huntington's diseases. (12) Understanding and targeting mitochondrial dysfunction are areas of active research for therapeutic interventions.

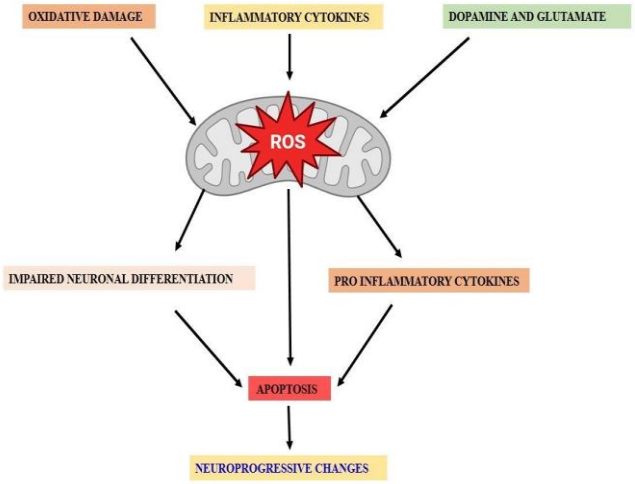

Figure 1: Mitochondrial dysfunction leading to Neurodegenerative disease by generation of Reactive Oxygen species

Mitochondrial dysfunction in neurodegenerative diseases:

Mitochondrial dysfunction has been implicated in various neurodegenerative diseases, contributing to the progression and severity of these conditions. (13) Mitochondria are essential cellular organelles responsible for energy production through oxidative phosphorylation, but they also play a crucial role in other cellular processes, including apoptosis (programmed cell death) and calcium homeostasis. (14) Here is an overview of how mitochondrial dysfunction is linked to neurodegenerative diseases:

1. Energy Depletion:

Mitochondrial dysfunction can lead to impaired ATP (adenosine triphosphate) production, the primary energy currency of cells. (15) Neurons, being highly energy-dependent cells, are particularly vulnerable to energy deficits.

2. Oxidative Stress:

Dysfunctional mitochondria are a significant source of reactive oxygen species (ROS), leading to oxidative stress. Increased oxidative stress can damage cellular components, including lipids, proteins, and DNA, contributing to neuronal damage and death.

3. Apoptosis:

Mitochondria play a central role in the regulation of apoptosis. When mitochondria are dysfunctional, they may release pro-apoptotic factors, triggering programmed cell death. This can lead to the loss of neurons, a common feature in neurodegenerative diseases. (16)

4. Mitochondrial DNA Mutations:

Mitochondria have their own DNA (mtDNA), and mutations in mitochondrial genes can result in impaired mitochondrial function. (17) Accumulation of mtDNA mutations has been observed in various neurodegenerative diseases. (18)

5. Calcium Dysregulation:

Mitochondria are involved in the regulation of cellular calcium levels. Dysfunctional mitochondria may lead to disrupted calcium homeostasis, which can activate various cellular pathways that contribute to neurodegeneration.

6. Mitophagy Impairment:

Mitophagy is the process by which damaged or dysfunctional mitochondria are selectively removed by autophagy. Impaired mitophagy can result in the accumulation of damaged mitochondria, exacerbating mitochondrial dysfunction in neurodegenerative diseases. (19)

7. Altered Mitochondrial Dynamics:

Mitochondria continuously undergo processes of fusion and fission, crucial for maintaining mitochondrial quality and function. Dysregulation of these processes has been implicated in neurodegenerative diseases. (20)

Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS) are among the neurodegenerative conditions linked to impaired mitochondrial function. Researchers are actively exploring strategies to target mitochondrial dysfunction as a potential therapeutic approach for these conditions. This may involve promoting mitochondrial biogenesis, enhancing mitophagy, or developing drugs that protect mitochondria from damage. (22) However,

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it's essential to note that the precise mechanisms and roles of mitochondrial dysfunction in each specific neurodegenerative disease are complex and may vary.

Biochemical Pathways affected by mitochondrial dysfunction:

Mitochondrial dysfunction can have widespread effects on various biochemical pathways within cells due to the central role mitochondria play in energy production and cellular homeostasis. Here's a more detailed look at some of the key pathways affected by mitochondrial dysfunction:

1. Citric Acid Cycle (Krebs Cycle):

The Krebs cycle or tricarboxylic acid (TCA) cycle, the citric acid cycle is a primary metabolic pathway occurring in the mitochondrial matrix of eukaryotic cells and the cytoplasm of prokaryotic cells (23). Integral to cellular respiration, the citric acid cycle is a crucial element in generating high-energy molecules like NADH and FADH2. (24) These molecules then power the electron transport chain to produce ATP (25).

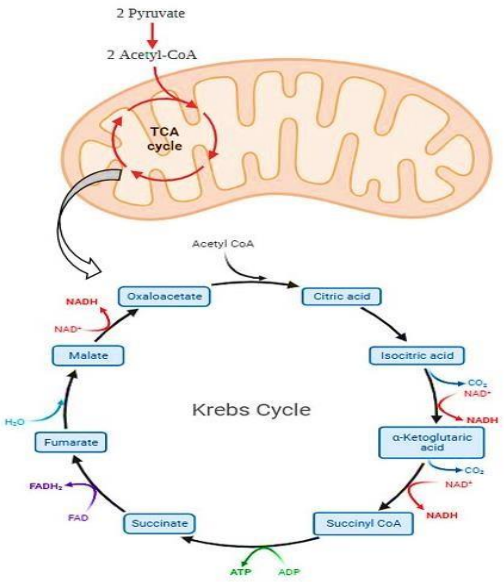

Figure 2: Dysfunction in Mitochondria affecting TCA cycle.

The citric acid cycle is a central hub in cellular metabolism, connecting various metabolic pathways. Every revolution of the cycle yields three NADH molecules, one FADH2 molecule, and one GTP (or ATP) molecule, accompanied by the liberation of two CO2 molecules. The significance of these high-energy molecules, particularly NADH and FADH2, lies in their essential role in propelling the electron transport chain. This, in turn, culminates in the production of ATP through oxidative phosphorylation. Occurring in the mitochondrial matrix, the citric acid cycle is crucial for producing reducing equivalents (NADH and FADH2), which then contribute to the electron transport chain. Dysfunction in mitochondria has the potential to interfere with the effective operation of the citric acid cycle (26).

2. Beta-Oxidation of Fatty Acids:

Beta-oxidation is a catabolic process that takes place in the mitochondria of eukaryotic cells, involving the breakdown of fatty acids to generate acetyl-CoA. (27) This process is a crucial part of cellular energy metabolism, especially during periods of fasting or low glucose availability. Beta- oxidation occurs in multiple cycles, each cycle shortening the fatty acid chain and producing acetyl- CoA, which can enter the citric acid cycle for further energy production. The overall outcome of beta-oxidation is the generation of acetyl-CoA, reduced cofactors (NADH and FADH2), and depending on the length of the fatty acid, multiple rounds of acetyl-CoA. (28)

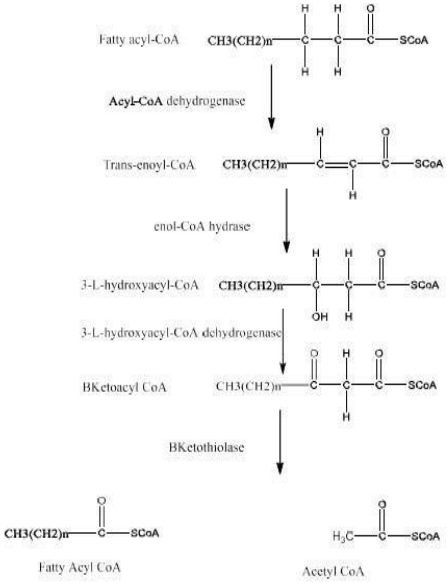

Figure 3: Beta-oxidation of fatty acids

These products feed into the citric acid cycle and the electron transport chain, contributing to the production of ATP in the process of cellular respiration. Beta-oxidation is a crucial mechanism for energy production, particularly during periods of increased energy demand

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or limited glucose availability. Mitochondria play a crucial role in the beta-oxidation of fatty acids, a process that generates acetyl-CoA for entry into the citric acid cycle. Mitochondrial dysfunction can lead to impaired fatty acid metabolism. (29)

Pharmacological Approaches To targeting Mitochondrial Dysfunction:

Since platelet function depends on mitochondrial activity, using medications that target mitochondrial malfunction in cancer therapy carries some dangers, such as an irregular bleeding propensity. Three triphenyl phosphonium (TPP)based substances, namely honokiol, lonidamine, and atovaquone, were examined for their effects on platelet function in vitro in order to solve this problem. (30) They found that TPP derivatives. had little effects on platelet aggregation and activation, suggesting that they might be used as low-risk anticancer agents. (31,32) To confirm if the results can be applied to human and animal models for clinical application in the future, more research is necessary.

Osteoarthritis is mostly associated with mitochondrial dysfunction, and patients may benefit from pharmaceutical intervention aimed at regulating mitochondrial homeostasis. Given that mitochonic acid-5 (MA-5) is involved in the regulation of mitochondrial energy metabolism, protection against mitochondrial damage, and activation of mitophagy, Xin et al. have investigated the potential of MA- 5 against IL-1β-induced inflammation in vitro in chondrocytes. They discovered that via upregulating the SIRT3/Parkin-related autophagy pathway, MA-5 prevented IL-1β-induced oxidative stress and shielded chondrocytes, pointing to the possibility that MA-5 may be further developed as an anti- osteoarthritis medication. (33)

Furthermore, there is an inherent connection between mitochondrial malfunction and the onset of renal disorders, a global public health problem that can lead to severe clinical difficulties. Although kidney illnesses pose challenges in drug discovery, bioactive natural compounds and their sources have been investigated as an adjunctive therapy strategy. Small-molecule natural products, or SNPs, have been shown in several studies to enhance renal function and decelerate the progression of kidney disorders. Rahman et al. give a summary of the nephroprotective characteristics of SNPs, such as salidroside, berberine, curcumin, polydatin, resveratrol, and betulinic acid, in this review. It has been shown that SNPs are useful in the treatment of kidney damage resulting from oxidative stress and damage to mitochondrial DNA, as well as in the restoration of mitochondrial biogenesis and dynamics in response to various stimuli that cause harm. (34) Consequently, these compounds must be recognized as multi-target therapeutics and potential medications to decelerate the pathophysiology of renal problems, particularly those resulting from dysfunctional mitochondria.

Experimental Model for Studying Mitochondrial Dysfunction:

A. Studies based on Mutagenesis and Loss of Function

Transposons such as P-elements, piggyBac, and Minos have the potential to disrupt the functionality of genes by inserting into either the coding sequence or regulatory regions. Utilizing P-elements, and possibly Minos as well, offers the advantage of generating a null mutation by inadvertently excising P-elements located within or near a gene.

Insertions related to transposons is an emerging area and in the upcoming years, more than 90% genes in Drosophila might be disrupted by this method. The time taking and tough mapping work related to these genes using chemical mutagenesis has been largely avoided due to the presence of these transposons. In genomic regions devoid of transposable elements, one can employ recombination that are homologous to create deletions or alleles that mimic disease-related mutations. (35)

B. In Vivo Tissue-specific overexpression and Knockdown

The UAS-GAL4 system is a bipartite transcription activation system that makes it simple to achieve tissue-specific overexpression that is regulated in vivo. (36) One transgenic in this system is the yeast transcription factor (GAL4), which can be expressed by a tissue-specific promoter like the dopaminergic neuron-specific TH or by a universal promoter like tubulin. A target gene controlled by UAS (upstream activating sequences) that trigger transcription in reaction to GAL4 binding makes up the second transgene. Thus, transgenic flies expressing UAS-PINK1 and a variant of Gal4 controlled by the tyrosine hydroxylase promoter

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(TH-Gal4), for instance, will produce PINK1 in a manner exclusive to dopaminergic neurons. This flexible mechanism makes it possible for genes to be expressed during both maturity and development, which is highly helpful for simulating illnesses.

C. Site-Specific Transgenesis Allows Precise Controls over Genetic Background and Expression Level

Additionally, fly lines containing a source of integrase and a "landing pad" target site inserted at specified locations in the genome, as well as donor plasmids carrying target sites for a site- specific integrase, can be used to achieve site-specific gene integration. For the fly, there are several iterations of landing pads and site-specific integration technologies dispersed across the genome. The significance of this technique lies in its ability to assess the activity of a set of mutant proteins, for instance, with the assurance that all other genomic variables have been maintained constant. (37)

D. Genetics and Compound Screens in PD Pathogenesis and Suppression

Genetics and Compound Screens Provide Unbiased Methods for Identifying Genes and Pathways Important for PD Pathogenesis and Its Suppression. A crucial capability within the Drosophila toolkit is the capacity to conduct extensive screenings to identify novel mutations or instances of gene overexpression or silencing that either amplify or mitigate phenotypes linked to disease models. A number of screen strategies are available. Unbiased genetic screens aim to discover novel components that operate either within the same genetic pathway as the disease model or in parallel pathways, influencing a shared process associated with the disease state. The significance of these screens cannot be overstated as they do not rely on any pre-existing knowledge regarding the function of the disease gene. (38)

Marketed Products used in mitochondrial dysfunction:

There may have been further developments in the field of mitochondrial dysfunction and related drug research. It's essential to consult the latest scientific literature or medical professionals for the most up-to-date information. Some of the general approaches and classes of medications that were being explored for mitochondrial dysfunction are mentioned here.

1. Coenzyme Q10 (CoQ10):

Coenzyme Q10 (CoQ10), also known as ubiquinone, is a naturally occurring compound found in the cells of the body. It plays a crucial role in the process of cellular energy production, specifically in the mitochondria. (39) The mitochondria are often referred to as the "powerhouses" of the cell because they generate adenosine triphosphate (ATP), the primary source of energy for cellular activities.

The mechanism of action of CoQ10 involves its participation in the electron transport chain, a series of protein complexes embedded in the inner mitochondrial membrane. In summary, Coenzyme Q10 plays a vital role in the electron transport chain, shuttling electrons between complexes and contributing to the generation of the electrochemical gradient necessary for ATP synthesis. This process is essential for the production of cellular energy and the overall functioning of cells, especially those with high energy demands like muscle cells and organs like the heart. CoQ10's antioxidant properties also make it important for protecting cells from oxidative damage. (40) CoQ10 is a naturally occurring antioxidant that plays a crucial role in mitochondrial function. Some studies have explored its use as a supplement to potentially improve mitochondrial function.

2. Idebenone:

Idebenone is a synthetic compound that belongs to the class of coenzyme Q10 (CoQ10) analogs. It has been studied for its potential therapeutic effects, particularly in the context of neurodegenerative disorders and mitochondrial diseases. (41) It's important to note that while there is ongoing research on Idebenone , its efficacy and safety for specific medical conditions are still a subject of investigation.

Idebenone has been studied in conditions such as Friedreich's ataxia and Leber's hereditary optic neuropathy (LHON), where mitochondrial dysfunction plays a role. (42) However, more research is needed to fully understand its therapeutic potential and to establish guidelines for its use in various clinical settings. (43) As with any medication or supplement, it is crucial to

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consult with healthcare professionals before using Idebenone, especially for treating specific medical conditions. (44)

3. L-Carnitine:

L-Carnitine is a naturally occurring amino acid derivative that plays a crucial role in the production of energy within cells, particularly in the mitochondria. The primary function of L-carnitine is to transport long-chain fatty acids (45) into the mitochondria, where they can be oxidized to generate energy. This process is essential for the normal functioning of cells, especially those with high energy demands, such as muscle cells.

It's important to understand that while L-Carnitine is generally considered safe when used as directed, excessive supplementation may lead to side effects. (46) As with any supplement or medication, it's advisable to consult with a healthcare professional before starting L-Carnitine supplementation, especially if you have underlying health conditions or are taking other medications. They can provide guidance based on your specific health needs and circumstances. (47)

4. Dichloroacetate (DCA):

Dichloroacetate (DCA) is a chemical compound that has been investigated for its potential therapeutic effects, particularly in the context of cancer and certain metabolic disorders. It is a derivative of acetic acid and has been studied for its ability to modulate cellular metabolism, including the function of mitochondria. (48) It's crucial to note that while DCA has been studied in various experimental models and clinical trials, it has not received widespread approval for the treatment of cancer or metabolic disorders. (49) The safety and efficacy of DCA in specific medical conditions require further research and validation. Patients considering DCA or any experimental treatment should consult with healthcare professionals who are knowledgeable about the latest research developments and can provide guidance based on individual health circumstances. (50)

5. EPI-743 (vincerinone):

EPI-743, also known as vincerinone, is a synthetic para-benzoquinone derivative that has been investigated for its potential therapeutic effects, particularly in the context of mitochondrial disorders and conditions associated with oxidative stress. (51) It is designed to act as a cofactor for the enzyme NAD(P)H:quinone oxidoreductase 1 (NQO1), which plays a role in cellular defense against oxidative stress. (52) It's important to note that while early research on EPI-743 has shown promise in preclinical and early clinical studies, the development and approval of drugs involve rigorous testing, and not all promising candidates successfully progress through clinical trials. (53)

As with any investigational drug, the safety and efficacy of EPI-743 require further validation through larger and wellcontrolled clinical trials. (54) Patients and healthcare professionals should stay updated on the latest research findings, and decisions regarding the use of EPI-743 should be made in consultation with healthcare providers who are knowledgeable about the specific condition being treated.

6. B-vitamins:

B-vitamins, including thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), cobalamin (B12), and folic acid (B9), play essential roles in mitochondrial function. Supplementation may be considered in specific cases. (55)

7. Carnitine Palmitoyltransferase (CPT) Inhibitors:

In certain mitochondrial disorders involving fatty acid oxidation defects, medications that inhibit CPT, such as etomoxir, may be considered. (56)

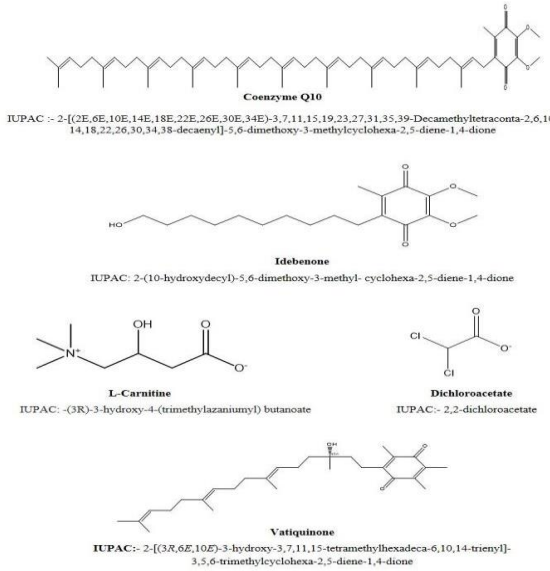

Figure 4: Structure of marketed Products used in mitochondrial dysfunction.

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Future aspects:

Some potential future aspects and areas of interest in the field of mitochondrial dysfunction based on general scientific trends and ongoing research:

1. Genetic Therapies:

Genetic therapies for mitochondrial dysfunction aim to address the underlying genetic mutations or abnormalities that contribute to impaired mitochondrial function. (57) The mitochondria have their own DNA (mitochondrial DNA or mtDNA) separate from the nuclear DNA, and mutations in either the mitochondrial or nuclear genome can lead to mitochondrial dysfunction. (58)

Advances in gene therapy and gene editing technologies may offer new possibilities for treating mitochondrial dysfunction caused by genetic mutations. Techniques such as CRISPR-Cas9 may enable the correction of faulty mitochondrial DNA or the targeted manipulation of nuclear genes involved in mitochondrial function. (59)

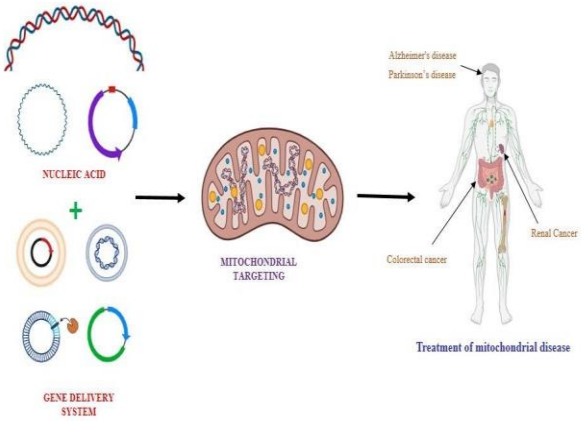

Figure 5: Mitochondrial treatment via Gene therapy

2. Mitochondrial Replacement Therapy (MRT):

MRT involves replacing defective mitochondria with healthy ones from a donor. While this technique has been primarily explored for preventing the transmission of mitochondrial diseases, ongoing research may reveal its potential for treating existing mitochondrial dysfunction. (60)

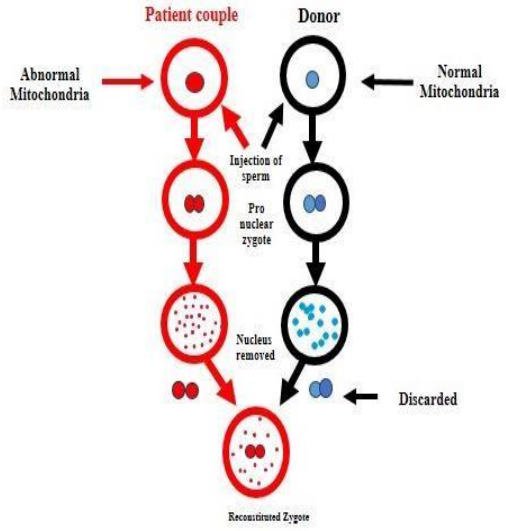

Figure 6: Mitochondrial Replacement Therapy

3. Small Molecule Therapeutics:

Continued research into small molecules that can selectively target and modulate specific mitochondrial functions may lead to the development of drugs with greater efficacy and fewer side effects for mitochondrial dysfunction. (61)

4. Metabolic Regulation:

Emerging research on the intricate connections between cellular metabolism and mitochondrial function may lead to novel therapeutic strategies. (62) Targeting metabolic pathways. (63) that influence mitochondrial health may provide new avenues for intervention.

5. Diagnostic Biomarkers:

Improved identification and characterization of mitochondrial dysfunction biomarkers could enhance early diagnosis and monitoring of the condition. This, in turn, may lead to more timely and effective interventions. (64)

It's important to note that mitochondrial dysfunction is a complex and heterogeneous field, and advancements may come from multiple areas of research. As research progresses, these potential future aspects may evolve, and new areas of focus may emerge. To stay updated on the latest developments, it's advisable to consult recent scientific literature and follow advancements in mitochondrial medicine and related disciplines. (65)

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Conclusions:

In conclusion, neurodegenerative diseases pose a formidable challenge with distinct pathological features, affecting cognitive, motor, and sensory functions. Mitochondrial disorders can manifest in various ways, affecting multiple organ systems and presenting with a wide range of symptoms**.** The management of mitochondrial dysfunction involves a multidisciplinary approach, including supportive care, symptom management, and targeted treatments. The role of mitochondria, often termed the "powerhouses of the cell," has been highlighted, elucidating their multifaceted contributions to neural function, including energy production, calcium homeostasis, ROS regulation, apoptosis, metabolism, neurotransmitter synthesis, neuroplasticity, dynamics, and neuroprotection.

Mitochondrial dysfunction emerges as a common thread connecting various neurodegenerative diseases, impacting crucial pathways. Pharmacological approaches targeting mitochondrial dysfunction have shown potential therapeutic benefits, yet comprehensive validation is essential. The exploration extends to B-vitamins, CPT inhibitors, and emerging genetic therapies, mitochondrial replacement therapy, small molecule therapeutics, and metabolic regulation, showcasing evolving research directions. Despite acknowledging the complexity of mitochondrial dysfunction, ongoing research holds promise for advancing understanding, diagnosis, and treatment of neurodegenerative diseases. Regular updates are crucial for staying informed in this dynamic field of mitochondrial medicine.

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Conflict of Interest:
Authors declare no conflict of interest.

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