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Role of Mitochondrial Medicine in Neuropsychiatric Disorders

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Abstract: Mitochondria are important cytoplasmic organelles that provide cellular energy, regulate intracellular calcium levels, change a cell's reduction-oxidation potential, and control cell death. A growing body of evidence suggests that mitochondria play a key role in neurodegenerative illnesses like Alzheimer's, Parkinson's, Huntington's, amyotrophic lateral sclerosis, and Friedreich ataxia. Excessive free radical generation, reduced ATP production, mitochondrial permeability transition, mitochondrial DNA lesions, altered mitochondrial dynamics, and apoptosis are all common symptoms of mitochondrial dysfunction in neurodegenerative disorders. Though this field of research is still in its inchoate stage, mitochondrial medicine as an emerging treatment method targeting mitochondrial dysfunction in neurodegenerative illnesses has proven to have significant potential. This article discusses how mitochondrial dysfunction contributes to neurodegenerative disorders. In addition, we also discussed the recent progression of manifold mitochondrial therapies including blockade of mitochondrial permeability transition, gene therapy, and therapies with antioxidants which indicates mitochondrial medicine is a promising approach for the treatment of neurodegenerative disorders in near future.

Index Terms - Neurodegenerative diseases, Mitochondrial dysfunction, Alzheimer's disease, Parkinson's disease, Huntington's disease, Mitochondrial medicine.

I. INTRODUCTION

Mitochondria are double-membrane organelles that are structurally similar to mitochondria. Its outer and inner membranes are functionally separate, separating the intermembrane space calculated from matrix[1]. The size, shape, and amount of mitochondria in a cell can vary greatly depending on the environmental stress and cellular function[2]. The inner mitochondrial membrane consists of complexes for the respiratory chain and oxidative phosphorylation[1] which are essential for cell bioenergetics and their survival. In addition, mitochondria play many important additional roles in neurons including calcium homeostasis, neurotransmission, control of membrane excitability, and plasticity[3]. Mitochondria have their own transcriptional and translational machinery for expressing genes encoded by mitochondrial DNA (mtDNA)[1]. Because of their intricate biogenesis, these organelles are particularly prone to accumulated damage throughout a cell's life. The failure of mitochondrial function is caused by long-term mitochondrial damage. As a result, there is a drop in ATP production generation, an increase in a load of reactive oxygen species (ROS), and decreased calcium buffering, resulting in neuronal death a feature of both acute and chronic neurological degeneration disorders. Recent advances in molecular, cellular, biochemical, and animal-model studies of inherited neurodegenerative diseases have revealed that mutant proteins—such as amyloid-beta (A) in Alzheimer's disease; mutant huntingtin in Huntington's disease; mutant superoxide dismutase(SOD1) in ALS; mutant parkin, mutant DJ1, and mutant -synuclein in Parkinson's disease; and frataxin in Friedreich ataxia (FRDA)—are associated with mitochondria[4]. Mitochondrial dysfunction is increasingly recognized as a prevalent cellular alteration in the progression of various hereditary neurodegenerative disorders. The importance of developing therapeutics to address mitochondria in age-related neurodegenerative disorders is highlighted by the role of mitochondrial malfunction in both inherited and late-onset neurodegenerative diseases. This article discusses the underlying pathology behind the emerging neurological diseases as well the role of mitochondrial therapies to treat them.

Synthesis, Lifespan, and Decay of Mitochondria

Mitochondria are cytoplasmic organelles that evolved from a 1.5-billion-year-old symbiotic relationship between a glycolytic proto eukaryotic cell and an oxidative bacteria[5]. Mitochondria can be found in almost every eukaryotic cell even in neurons. Neuronal mitochondria have a half-life of roughly one month. The destruction of old mitochondria and the synthesis of new mitochondria, on the other hand, are ongoing processes in the body including neurons. The function of mitochondria in neurons is maintained due to constant mitochondrial recycling[6]. However, the mechanism behind this process is not well known yet. There is evidence that mitochondrial DNA (mtDNA) divides and facilitates mitochondrial replication and incomplete synthesis of new mitochondria in cells. Also, the number of mitochondria increases through a process called mitochondrial fission which occurs in all eukaryotic cells including neurons[5,6].

A mitochondrion contains 2-10 copies of mitochondrial DNA (mtDNA)[7]. The number of copies of mtDNA and mitochondria per cell is solely determined by the cell type and energy needs. For instance, the mean number of mtDNA for unfertilized oocytes is 164,000; on the other hand, the number of mtDNA number in normal human oocytes is nearly 250,000[8]. It is observed that in the pyramidal neurons from the hippocampus and cortex, the copy number of mtDNA and the mitochondria are high because of the high energy demand in those particular neurons.

Due to enhanced free radical generation and activation of mitochondrial fission proteins under an oxidative stress state or when cells are exposed to mitochondrial toxins, mitochondria divide rapidly[5]. In a diseased state the newly produced mitochondria may be heterogeneous (both functionally active and defective). An Alzheimer's disease (AD) study backed up this claim. They discovered increased oxidative damage in Alzheimer's patients, as well as a striking and significant increase in mtDNA in pyramidal neurons' cell bodies mitochondria and cytochrome oxidase in their neuronal cytoplasm, implying that oxidative stress is a key factor in increased mitochondrial turnover and the production of defective mitochondria[9].

The transport of mitochondria from the cell body down the axons and dendrites to meet cellular energy demands is well understood[10]. If mitochondria in the cell body are damaged or otherwise degraded, such as as a result of aging or mutant proteins, these faulty mitochondria may be transferred to synaptic terminals by normal mitochondrial trafficking, where they release low levels of ATP as a result of their breakdown[11]. Synaptic terminals are high-energy-demanding locations. As a result, enhanced mitochondrial transport to synaptic terminals may be crucial and required to deliver mitochondria. Older synaptic mitochondria may be more vulnerable to oxidative stress than cell-body mitochondria[10], and this higher damage could disrupt neurotransmission and lead to neurodegenerative diseases.

Structure and Function of Mitochondria

Mitochondria are the powerhouse of the cell involved in manifold cellular functions ranging from intracellular calcium regulation, ATP production, releasing proteins which in turn activate the caspase family of proteases, as well alters the oxidation-reduction potential of cells and free radical scavenging. Mitochondria are divided by two lipid membranes, the inner and outer mitochondrial membrane[5]. The inner mitochondrial consists of the mitochondrial respiratory chain and provides an efficient barrier to facilitate the flow of ions. The outer mitochondrial membrane is porous and allows low molecular weight substances, and creates a passage between the cytosol and the intermembrane space.

Both the nuclear and mitochondrial genomes control mitochondria. MtDNA is a 16.5 kb double-stranded circular DNA molecule that is inherited maternally[11]. MtDNA has 2 strands, a cytosine-rich light strand which is known as the inner strand, and a guanine-rich heavy strand or an outer strand. The electron transport chain (ETC) is made up of 13 polypeptide genes. The 12S and 16S rRNA genes, as well as the 22 tRNA genes, are all encoded by mtDNA which are essential for mitochondrial protein synthesis. MtDNA encodes 7 subunits out of the 46 subunits constituting complex I, 3 of 13 subunits of complex IV, 1 of 11 subunits of complex III, and 2 of 17 subunits of complex V[7]. Other than the electron transport chain (ETC), nuclear genes encode the remaining mitochondrial proteins, DNA and RNA polymerases, metabolic enzymes, and mtDNA regulatory factors, e.g. mitochondrial transcription factor A. The cytoplasm synthesizes nuclear mitochondrial proteins, which are then delivered to mitochondria. The majority of mitochondrial proteins are imported by membrane-spanning and multi-subunit translocators present in inner and outer mitochondrial membranes.

Oxidative phosphorylation (OXPHOS) produces mitochondrial ATP. OXPHOS is dependent on 5-subunit polypeptide complexes (I-V) which are located in the inner mitochondrial membrane. Flavins, nicotinamides, cytochrome, iron, and copper center are used by these polypeptide complexes for transferring electrons through a series of oxidation-reduction steps. Electrons move along the ETC complexes and establish an electrochemical gradient by fueling the extrusion of protons from the matrix over the inner mitochondrial membrane complexes through a series of oxidation-reduction processes. The dissipation of this proton gradient through complex V generates ATP. Mitochondria play an important role in the metabolism of all mammalian cells, including neurons in the brain. Age-related neurodegenerative disorders, e.g. AD may be caused by abnormalities in mitochondrial structure and function[5].

Alzheimer's Disease (AD)

Alzheimer's disease (AD) is a chronic neurological disorder, the most significant symptom is dementia. Patients with Alzheimer's disease have a variety of symptoms ranging from cognitive decline to behavioral impairment where these symptoms get worse with time. Two pathological phenomena in the brain are; the accumulation of phosphorylated tau protein tangles (NFTs) and amyloid beta-peptide (Aβ)[12]. Several hypotheses on the mechanism of AD pathology have been proposed however, the process is still unclear. Changes in the mitochondria-associated endoplasmic reticulum membranes (MAM) and the mPTP are essential factors in AD pathogenesis, according to the mitochondrial cascade hypothesis[13]. Once a specific threshold of mitochondrial malfunctions is met due to the environmental and lifestyle factors, this triggers tau phosphorylation, Aβ aggregation, synaptic loss, and degeneration[14].

Mitochondrial permeability transition is defined as an abrupt increase in the permeability of the inner mitochondrial membranes to solutes with a molecular weight of less than 1500 Da. The transition in mitochondrial permeability is triggered by the opening of the mPTP. The opening of mPTP by cyclophilin D (CypD) causes swelling of the mitochondrial matrix and a rupture on the outer mitochondrial membrane. CypD is considerably higher in Aβ-containing mitochondria within the hippocampus and temporal lobe of AD patients[15]. In addition, increase in reactive oxygen species(ROS) production, increased CypD translocation to IMM, and decreased capacity in calcium buffering all of which indicate a strong interaction of CypD with Aβ in AD patients' brains[16]. The production of mPTP is triggered by CypD's interaction with Aβ. This shows that aberrant amyloid buildup reduces the efficiency of the mitochondrial oxidative phosphorylation mechanism, resulting in lower ATP generation and higher ROS levels[15,16]. By genetically depleting CypD or utilizing a CypD inhibitor, the synthesis of the mPTP can be blocked which may, in turn, prevent the detrimental effects of AD. In mouse models, genetic depletion of CypD has been found to diminish mitochondrial swelling, oxidative stress, and apoptosis[15]. CypD deficient mice who overexpressed APP and Aβ, better regulated their mitochondrial functions including production of ATP and complex IV activity[17]. The same results were observed in AD-affected mice which confirms that depletion of CypD levels in AD patients is a potential therapeutic strategy[15].

Parkinson's Disease(PD)

Parkinson's disease (PD) is the most frequent movement disorder and the second most common neurodegenerative illness in the world[18]. This currently incurable disease is characterized by gradual deterioration and death of the dopaminergic neurons. It causes a reduction in dopamine levels and expression of intracytoplasmic inclusions which consists of Lewy bodies and fibrillar α-synuclein within the surviving neurons of substantia nigra. Dopamine deficiency disrupts the circuitry of the basal ganglia, resulting in the typical triad of bradykinesia, stiffness, and resting tremor. Mitochondrial failure is thought to be a trigger in the pathophysiology of PD since mitochondria are important for energy metabolism, calcium homeostasis, and modulation of membrane excitability. PD patients have been found to have a deficit in the ETC's complex I. Complex I activity was shown to be reduced in platelets and skeletal muscle, and postmortem examinations revealed complex I insufficiency in the substantia nigra of the patients[19]. The transplanted cells displayed poorer complex I activity, lower mitochondrial membrane potential, and disturbed calcium homeostasis33 in trials where mtDNA obtained from PD patients was transfected into normal cells and mitochondrial function was assessed[20].

These studies suggest that mtDNA is involved in the neuronal degeneration seen in Parkinson's disease. Ekstrand et al.[21] used conditional deletion of the gene encoding mitochondrial transcription factor A (Tfam) in dopaminergic neurons to investigate this further. Reduced expression of mtDNA-encoded cytochrome-c subunit I mRNA was detected by in situ hybridizations, and histochemical examination demonstrated dramatically reduced cytochrome-c enzyme activity in these neurons. By 20 weeks of age, these mice had developed increasing tremors, twitching, and limb rigidity. Intraneuronal inclusions were also found, however, these inclusions were devoid of α-synuclein34.

The PINK1/Parkin pathway was recently discovered to be the most common cause of early-onset PD35. PINK1 (PTEN-induced kinase1) on the outer mitochondrial membrane is stabilized by a decrease in mitochondrial membrane potential. At this location, PINK1 phosphorylates ubiquitin, causing Parkin, an E3 ubiquitin ligase, to be recruited. Parkin is then phosphorylated by PINK1, resulting in its activation, development of the autophagosome, and lysosome-mediated mitochondrial destruction. Parkin gene mutations are linked to 50 percent of familial PD cases and are the most common cause of PD in people under the age of 20. Parkin mutations cause symmetrical parkinsonism, which progresses slowly and responds well to levodopa[22]. Autosomal recessive PD has also been linked to PINK1 mutations, notably in patients with early-onset parkinsonism before the age of 40. Patients with this mutation have a good levodopa response and progress slowly. Patients with the PINK1 mutation have substantia nigra cell loss and Lewy body development, according to autopsy results[23]. Overexpression of PINK1, on the other hand, restores normal mitochondrial morphology and protects against ROS[24].

Surprisingly, multiple clinical data show that deep brain stimulation (DBS) improves mitochondrial volume. In individuals with severe PD, DBS of the subthalamic nucleus is an effective surgical treatment that is hypothesized to minimize nigral glutamate excitotoxicity by suppressing the subthalamic nucleus. Mallach et al. recently conducted a post-mortem study of striatal dopaminergic structures and discovered that mitochondrial volume was much larger in DBS brains, with values comparable to controls. These findings are attributed to enhanced mitochondrial biogenesis, decreased mitochondrial fission, or greater fusion, according to the authors[25]. These findings, while just correlative at this time, provide more support for alternate therapeutics including mitochondrial transplantation.

Huntington's Disease (HD)

HD is a neurodegenerative disease caused by a pathological amplification of CAG repeats in the huntingtin gene, which results in polyglutamine expansion in the produced protein. The caudate and striatum are the first areas to degenerate, followed by the cerebral cortex. Progressive motor impairment and dementia are two clinical characteristics of HD. The fundamental mechanisms that lead to pathology are unknown, and the disease's pathophysiology could be complicated. Many studies have been conducted to demonstrate that mutant huntingtin causes transcriptional dysregulation and pathogenesis[26]. Huntingtin has been demonstrated to interfere with PGC-1, a transcription factor that regulates mitochondrial gene expression. This establishes a relationship between mutant huntingtin and transcriptional regulation as well as mitochondrial function. PGC-1 is a transcriptional co-activator that interacts with transcription factors that control the production of mitochondrial respiratory genes such as NRF-1 and NRF-2, both of which are important for mitochondrial function and energy homeostasis. PGC-1 expression is suppressed by mutant huntingtin, according to recent research, and PGC-1 knockout mice suffer problems in energy metabolism and spongiform degenerative alterations in the striatum[27]. Surprisingly, the striatum appears to be particularly vulnerable to mitochondrial dysfunction. Striatal mitochondria have more CypD than cortical mitochondria and are more sensitive to calcium-induced mPTP opening, which could explain the regional differences in HD degeneration timing and severity[28].

Multiple lines of evidence demonstrate that mitochondria in HD patients and genetic models of HD are aberrant. Huntingtin mutants have impaired mitochondrial morphology, energy metabolism, and oxidative damage, as well as calcium handling deficits[28,29]. In patients with HD, descriptive ultrastructural tests revealed aberrant mitochondria shape, and further research in mice and humans revealed that mutant huntingtin causes mitochondrial alterations, including fragmentation, via improper interactions with the mitochondrial fission machinery. Ultrastructural studies showed abnormal mitochondria morphology[30] and further works in humans and laboratory mice showed mutated huntingtin triggers mitochondrial changes, including fragmentation by interacting abnormally with the mitochondrial fission GTPase and dynamin-related protein-1(DRP1)[31]. DRP1 enzymatic activity is stimulated by mutant huntingtin, resulting in mitochondrial fragmentation, anterograde and retrograde mitochondrial transport abnormalities, and neuronal cell death; however, these deficiencies can be rescued by reducing DRP1 GTPase activity[31]. Mitochondrial function is also disrupted in HD patients. Mitochondrial mitochondria from huntingtin knock-in mice are more sensitive to calcium-induced alterations in respiration and mPTP opening[28]. Several studies have found that treating mitochondrial dysfunction can protect striatal neurons from mutant huntingtin-induced damage. Overexpression of PGC-1 in HD mice, for example, corrects some of the impairments caused by mutant huntingtin[32].

Ischemic Stroke

Ischemic stroke is the second largest cause of death and one of the main causes of morbidity in the world[33]. The brain is vulnerable to extended reductions in oxygen and glucose delivery caused by arterial thrombosis or embolism because of its high intrinsic metabolic activity. Ischemic stroke victims frequently endure paralysis, slurred speech, or vision loss. Because of the tight therapeutic window, only a small percentage of stroke patients receive timely medical intervention, and not all patients are suitable for thrombolysis. Additionally, certain individuals may develop reperfusion damage as a result of recanalization of blood flow, which causes leukocyte infiltration, platelet and complement activation, post-ischemic hyper-perfusion, and a breach of the blood-brain barrier.

As a result, developing novel treatment options is critical. The ischemic brain begins depolarizing mitochondrial membranes minutes after artery occlusion, resulting in ATP depletion, ROS overproduction, and PINK1 and unfolded protein response accumulation (UPR). Ischemic cascades are triggered when ATP levels are low, including membrane ion pump failure, plasma membrane depolarization, cellular potassium efflux, and inflow of sodium, calcium, chloride, and water[34]. All of these conditions cause mPTP to open, cytochrome c to be liberated, caspase 3 to be activated, and apoptotic death to occur[35]. Mitochondrial fission causes neuronal death in ischemic brain injury, but mitochondrial fusion permits damaged mitochondria to be repaired[36]. Drp1, Fis1, and Endophilin B1 proteins are necessary for mitochondrial fission, but they can also influence mitochondrial fusion regulatory processes[37].

Opa1, Mfn1, and Mfn2, on the other hand, are mitochondrial fusion proteins implicated in mitochondrial fission[38]. Changes in the expression levels of Drp1, Fis1, Opa1, and Mfn2 have been demonstrated to inhibit or promote fusion and fission in animal models of ischemic brain damage[36]. Another intriguing technique focuses on the mitophagy mechanism. Mitophagy, according to research, permits neurons to remove damaged mitochondria, stops the apoptotic cascade from activating, and so helps neurons to survive ischemia stress[39].

Mitochondria based interventional medicine

Mitochondrial medicine is quickly evolving as our understanding of mitochondrial illnesses grows. Though still a relatively new field, mitochondria-based interventional medicine benefits greatly from the growing body of knowledge about the mitochondria-related molecular mechanisms of mitochondrial illnesses. It has shown its importance by focusing its specialized modification on the origins of mitochondrial disorders, mitochondrial malfunction; this is in contrast to many existing pharmaceutical therapy techniques that simply focus on eradicating the resulting syndromes. Current mitochondrial medicine strategies can be divided into two categories:(1) preventing ongoing mitochondrial dysfunction in diseases with a known mitochondrial etiology; this is critical for the treatment of inherited mitochondrial diseases like Leber's hereditary optic neuropathy (LHON)[39]; and (2) manipulating on diseases with prevalent mitochondrial defects, such as sporadic neurodegenerative diseases[40]. Mitochondrial-based interventional medicine strategies are emerging, with the goal of treating common mitochondrial pathologies such as disrupted cellular bioenergetics, oxidative stress, mtDNA mutations, impaired mitochondrial calcium handling capacity, mitochondria-originated apoptosis, and defected mitochondrial behavior, though most of these studies are still in the early stages. Nonetheless, as additional information underlying mitochondrial disorders is discovered, interventional therapy focusing on mitochondrial alterations will become the future trend in the treatment of mitochondrial diseases.

Therapeutics target mitochondria for neurodegenerative diseases

As previously stated, mitochondrial dysfunction, which includes oxidative stress, low ATP generation, mtDNA mutation, calcium perturbation, mPTP, and mitochondrial dynamic malfunction, is common in neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease. Because damaged mitochondria exacerbate and participate in the pathogenesis of these diseases, it would seem logical to use mitochondria-targeted intervention as a therapeutic approach to treat or delay the onset of these diseases' pathophysiological process; indeed, several mitochondria-targeted treatments have been used in clinical practice or disease-related animal models. These treatments' efficacy has been tested and proved to be effective. Oxidant removal, mitochondrial gene therapy, and mPTP inhibition are some of the most common mitochondrial medicine techniques.

Redox Therapy

Oxidative stress has been extensively explored as a treatment approach for neurodegenerative illnesses, based on the premise that it is one of the most common mitochondrial pathologies involved in neurodegenerative disorders, as well as the ease with which an antioxidant strategy can be implemented.

Usage of small reducing molecules as a supplement

Vitamins C and E, glutathione, and coenzyme Q10 (CoQ10) are small reducing chemicals that play a significant part in mitochondria's natural defense strategy against oxygen free radicals. In neurodegenerative illnesses including Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis (ALS), the expression of these molecules is reduced[41,42,43,44]. Several research groups have expressed interest in augmenting these tiny reducing agents to scavenge oxidative stresses in neurodegenerative disorders.

Vitamins C and E (Vit C and Vit E) and Mito Vit E

Vitamin C, also known as L-ascorbate, is a powerful intracellular reducing chemical, while Vitamin E is a key scavenger of lipid oxidation in the brain. Multiple researchers[45,46,47] have reported that vitamin C and vitamin E are neuroprotective in vivo and in vitro against the assault of oxidative stress.

When given before or simultaneously with Aβ exposure, vitamin E protects neuroblastoma SK-N-SH cells from oxidative stress[48]. In an AD mouse model (Tg2576 animals at 11 months old), four weeks of Vit E treatment improved cognitive function and decreased Aβ deposition[49]. The administration of vitamin E to young Tg2576 mice reduced amyloidosis considerably[50]. Vitamin C injections intraperitoneally (i.p.) daily in APP/PSN1 mice from the middle (12 months) to old (24 months) age dramatically reduced spatial learning/memory deficits[51]. Mild-to-moderate stage AD patients have been shown to benefit by daily dosages of 2000 IU Vit E[52,53]. Furthermore, administration of vitamin E alone or in combination with vitamin C and vitamin E can reduce the risk of Alzheimer's disease (Boothby and Doering,2005), while the combination of vitamin E and vitamin C has been shown to reduce the

prevalence of Alzheimer's disease in the elderly[54,55,56]. In a 3-nitropropionic acid-induced HD animal model, treatment with Vit E (20 mg/kg/day) effectively preserved mitochondrial complex II function and avoided oxidative damage[57]. Furthermore, vitamin E supplementation reduced the start and progression of neuropathology in a SOD1 transgenic ALS mice model[58]. A Vit E-rich diet has been linked to a lower incidence of Parkinson's disease[59,60]. It has been suggested that combining vitamin E with vitamin C can slow the progression of PD[61]. However, there are conflicting data on the effectiveness of vitamin E and vitamin C as treatments for neurodegenerative illnesses. Zhang's recent study on the influence of vitamin E and vitamin C intake on the risk of Parkinson's disease found no reduction in the incidence of the ailment[62]. He theorized that the protective effect of high dietary Vit E levels could be attributed to other active chemicals in the food rather than Vit E. Several other studies found that giving Vit E or Vit C alone or in combination did not affect the progression or risk of AD and PD[63,64,65,66]. Furthermore, a few case-controlled studies found no benefit from vitamin therapy in ALS patients or animal models[67]. Excessive doses of vitamin E (>150 IU/day) may increase the mortality of recipients[68.]

When considering the discrepancies in vitamin treatment results, it is suggested that the restrictions of vitamin treatment may have an impact on its efficacy, causing the discrepancy. The limitations include (1) poor transport of Vitamin E and Vitamin C across the blood-brain barrier, which makes it difficult to accumulate therapeutic vitamin concentrations in neuronal mitochondria;(2) rapid oxidation of Vitamin C, which reduces its efficacy in treatment; and(3) potential side effects of high Vit E dosage. As a result, mitochondrial-focused vitamin E was created to address these issues. MitoVit E is a recently produced vitamin E derivative (made chemically from natural vitamin E) that, thanks to its triphenylphosphonium cation moiety, is particularly efficient in accumulating in mitochondria[69]. When MitoVit E was incubated with human osteosarcoma cells, the majority of MitoVit E was found inside mitochondria, indicating that it has a high cell permeability and a propensity for mitochondrial penetration, allowing it to be useful in scavenging for mitochondrial oxidants. At a dosage of 10 M, MitoVit E had no clear deleterious effect on mitochondrial membrane potential and respiratory function in vitro[70]. Oxidatively challenged (iron/ascorbate) mitochondria showed 75 percent protection in mitochondrial membrane potential when treated with 5 M MitoVit E, which was significantly superior to vitamin E at the same dose. By scavenging mitochondrial ROS, a group of researchers discovered that 1 M MitoVit E effectively reduced lipid and protein oxidation, apoptosis, and mitochondrial iron uptake in glucose oxidase-damaged bovine aortic endothelial cells[71]. The oxidative damages caused by a concentration of alcohol as high as 16 g/L were significantly attenuated by 1 nm. MitoVit E, according to a study conducted on primary cultured cerebella granule cells[72], which demonstrated suppressed cellular and mitochondrial antioxidation ability and increased lipid oxidation by alcohol. Cell viability and GSH–GPx activity were both increased in MitoVit E-treated cells. However, the efficacy of MitoVit E in the treatment of neurodegenerative illnesses is still largely unknown because of a paucity of in vivo evidence from animal models and clinical trials. Nonetheless, MitoVit E's excellent oxidant scavenging performance makes it a promising therapeutic target for neurodegenerative disease treatment.

Co-enzyme Q10 and MitoQ

Coenzyme Q10 (CoQ10), also known as ubiquinone, coenzyme Q, and ubidecarenone, is found mostly in the inner membrane of mitochondria. CoQ10's biological significance stems from the fact that it aids in the passage of electrons from mitochondrial complexes I and II to mitochondrial complex III[73]. In addition to its involvement in aerobic respiration, CoQ10, like Vitamin E, is a powerful lipid oxidant scavenger. CoQ10 helps to stabilize mitochondrial membrane potential, prevent cytochrome c release, inhibit mitochondrial permeability transition pore, and block Bax translocation to mitochondria when fibroblast and HEK293 cells are exposed to oxidative stress, implying multiple biochemical roles for this enzyme[74]. In afflicted regions of experimental models of PD, epilepsy, and stroke, CoQ10 has been found to protect neurons from oxidative stress and severe mitochondrial dysfunction[75,76].

CoQ10 has been extensively studied as a treatment for neurodegenerative illnesses in both experimental animal models and clinical research investigations due to its multifaceted mitochondrial protective effects. CoQ10 supplementation prevented striatal dopamine depletion and dopaminergic axonal damage in elderly mice[77]. CoQ10 and its reduced form were found to have neuroprotective effects in MPTP-induced PD animal models in a recent study[40]. In comparison to MPTP-untreated animals, dietary CoQ10 (1600 mg/kg/day for 2 months) protected striatal dopamine (DA) from MPTP toxicity by twofold. CoQ10 also prevented -synuclein aggregation in dopaminergic neurons and retained tyrosine hydroxylase (TH)-positive neurons in the substantia nigra of these mice. In an MPTP-induced monkey PD model, CoQ was found to have neuroprotective properties. Similarly, following two months of CoQ10 therapy at 1200 mg/kg/day, an AD animal model with a presenilin 1 mutation showed a decrease in A deposition and an improvement in brain mitochondrial SOD function[78].

Importantly, clinical experiments using CoQ10 to treat Parkinson's disease, Huntington's disease, and ALS have yielded promising results in terms of neuroprotection[79,77]. Treatment with coenzyme Q10 improves cognitive function considerably[80,81].

MitoQ, a lipophilic triphenyl phosphonium cation-added counterpart of Co1Q10, has a high lipid membrane permeability and readily accumulates in mitochondria[82]. When MitoQ is introduced to cultured cells in a medium, it accumulates quickly and selectively in mitochondria. At doses of MitoQ up to 10 M, cell toxicity decreased, while there was a report that MitoQ harmed N2a cells at concentrations higher than 0.3 M[83]. After detoxifying reactive oxygen species, MitoQ is a powerful antioxidant molecule that can be regenerated along the respiratory chain. Even in the presence of several apoptosis inducers, MitoQ has been proven to be efficient at preventing apoptosis.

In vivo C57BL/6 mice were used to test the safety of the MitoQ application. Mice were given 50 mM MitoQ in their drinking water for up to 28 weeks. The delivery of MitoQ to mice had no discernible negative effects on the tissues of the animals (brain, heart, and liver). Furthermore, there were a few positive effects, such as a reduction in liver fat and a reduction in blood triacyl glyceride, suggesting that long-term oral MitoQ administration is safe[84]. More clinical research is needed to determine the safety and efficacy of human administration. MitoQ is hypothesized to be a potentially beneficial therapy for neural protection from oxidative stress and related mitochondrial dysfunction, based on encouraging evidence from in vitro and in vivo animal trials, as well as the safety of long-term MitoQ administration. More research is needed to determine the efficacy of MitoQ in the treatment of neurodegenerative disorders including Alzheimer's and Parkinson's.

Small peptide antioxidants that target mitochondria

SS peptides are a new class of aromatic-cationic peptides that scavenge free radicals[85,86]. These peptides have a sequence motif that allows them to target mitochondria and bind to IMM regardless of mitochondrial membrane potential. SS02 readily passes the mouse blood-brain barrier following subcutaneous as well as intravenous injection, according to animal research. SS02 and SS31 show that they can eliminate free radicals from mitochondrial ROS produced by tert butyl hydroperoxide (tBHP) in cell cultures. Cho et al.[87] Petri et al.[85], found that SS peptides provided considerable neuronal protection in animal models of brain ischemia and ALS. These peptides are pharmaceutically useful for neurological illnesses due to their capacity to efficiently scavenge free radicals, water solubility, and high blood-brain barrier permeability[86]. Although research into the effects of SS peptides on neurological illnesses is still in its early phases, the use of SS peptides as prospective antioxidants is gaining traction.

Natural Antioxidants

Polyphenols, isoflavones, ginsenosides, and flavonoids are antioxidants isolated from medicinal plants that have been shown to protect mitochondrial function. Green tea polyphenols are thought to be powerful antioxidants that protect the body from hydroxyl radicals, nitric oxide, and lipid oxidation[88,89]. Green tea polyphenols have been shown to successfully reduce oxidative stress and apoptosis in cells[90] or neurons of afflicted brain regions of animal models when given to 6-hydroxydopamine (6-OHDA) or MPTP produced PD cell/animal models[91]. Green tea extracts increased -secretase activity, which lowered A synthesis in mice overexpressing APP/A and in APP/A overexpressed primary cultured neurons in vitro. These findings point to green extracts having the ability to protect against A-related mitochondrial dysfunction and other AD diseases[92].

Rb1 and Rg1 are two subgroups of ginsenosides, which are steroid-like chemicals. Ginsenosides scavenge oxidants and protect mitochondrial and neural functioning, according to studies conducted in vitro and vivo[93]. By eliminating superoxide and hydroxyl radicals, isoflavones and flavonoids are thought to provide neuroprotection[94,95]. In vitro studies have shown that isoflavones protect neurons against A-induced toxicity[96]. However, the efficiency and adverse effects of natural antioxidants for the treatment of neurodegenerative illnesses have yet to be proven due to a lack of research.

Inhibition of mitochondrial permeability transition

The development of the mitochondrial permeability transition pore (mPTP) reduces mitochondrial membrane potential, increases ROS production, causes mitochondrial calcium disturbance, and accelerates the release of proapoptotic molecules. Pathological damage in neurons undergoing the aforementioned neurodegeneration is thought to be exacerbated by mPTP-mediated severe mitochondrial dysfunction. The protective effects of mPTP blocking have been investigated in animal models of a range of neurodegenerative disorders, with current research focused on cyclophilin D (CypD) inhibition or voltage-dependent anion channel inhibition (VDAC).

When mPTP inducers, such as ROS and mitochondrial calcium overloading, are present, CypD, the intra-mitochondrial component of mPTP, stimulates its translocation from IMM to ANT. In the presence of mPTP inducers, genetic CypD deficiency reduces the mPTP threshold, which improves mitochondrial calcium buffering capacity and reduces cytochrome c release and ROS generation[97,98]. CypD depletion has been demonstrated to have therapeutic effects in neurodegenerative disorders, according to growing data. Higher mitochondrial membrane potential, reduced mitochondrial ROS production, retained mitochondrial cytochrome c oxidase activity and respiration control ratio, increased long-term potentiation, and improved spatial learning/memory were all seen in transgenic AD mice lackingCypD[98]. In an AD animal model, CypD depletion gives lifelong mitochondrial and neural protection against A toxicity in mice up to 24 months old. Another example is a study carried out on EAE mice. CypD depletion reduces the severity of symptoms and preserves axonal functions in experimental multiple sclerosis (MS) mouse model, suggesting that mPTP blockade via reducing CypD translocation is a viable treatment strategy for restoring mitochondrial function and preventing neuronal degeneration. Several CypD inhibitors have been produced, including cyclosporine A (CSA), Sanglifehrin A (SfA), and FK506, and are reported to be capable of suppressing mPTP generation and the resulting damage[99,100,101]. Neurons are considerably protected from oxidative stress-induced damage, ER stress, and apoptosis caused by H2O2, A, MPP+, and a variety of other toxins when these agents are used[102,103]. In a familial ALS (FALS) animal model (G93A), administration of CsA to the brain by intracerebroventricular CsA injections (dosage, 20 mg/week) relieved symptoms and reversed pathological abnormalities[104]. Treatment with CsA delayed the onset of hindlimb weakness and weight loss, increased the period between onset of weakness and paralysis, and increased the lifetime. CsA therapy also protected motor neurons in the cervical and lumbar spines, as well as tyrosine hydroxylase positive dopaminergic neurons in the substantia nigra. This study found no adverse effects such as systemic immunosuppression or nephrotoxicity, implying that CsA treatment at these concentrations is safe; the protective effect of CsA administration is primarily attributable to its inhibition of mPTP rather by immunological effects.

In an MS mouse model, FK506, a non-immunosuppressant derivative of FK1706, at a non-immunosuppressant dosage, dramatically reduced spinal cord injury and prevented axonal loss[105]. These mPTP inhibitors, like FK506 and CsA, have also been shown to be efficacious in HD animal models, thanks to their effects on mPTP blockage, at least in part[106].

Another potential therapy target is VDAC, which is the mPTP component of OMM. A recent study found that cholest-4-en-3-one, oxim (TRO19622) dramatically increased the lifetime of G93A SOD1 ALS mice and reduced their symptoms. The interaction of TRO19622 with VDAC, according to scientists, protects ALS mice[107]. This research backs up the role of mPTP in the etiology of ALS, as well as the possible therapeutic benefit of MPTP interference by VDAC in ALS.

Blocking mPTP development could be a promising chemotherapeutic strategy for preventing neurodegeneration and restoring mitochondrial function in neurodegenerative disorders. However, there are challenges in the creation of mPTP inhibitors. First, CypD inhibitors have a variety of biological adverse effects, including immunosuppression and calcineurin inhibition, which should both be taken into account in clinical practise[108,109]. Second, drug transport to mitochondria requires more chemical research to improve drug permeability across the blood-brain barrier and boost drug accumulation in mitochondria. CsA has the potential to be a candidate for mitochondrial medicine, according to on research on mPTP inhibitors so far. The delivery of CsA intraperitoneally to mice increased the longevity of the ALS animal model, according to a recent study. CsA accumulated in this model's brain and spinal cord[110], implying that CsA can pass the BBB in a compromised blood–brain barrier. CsA did not cause immunosuppression at the experimental dosage, according to a study[104]. However, long-term negative effects and CsA administration dosage need to be investigated further. Nonetheless, given the growing evidence of mPTP inhibition's protective role in the treatment of

neurodegenerative disorders, mPTP blockers are expected to be examined for their potential as pharmacological therapies in the treatment of neurodegenerative diseases.

Mitochondrial Gene Therapy

Given the high prevalence of pathogenic mtDNA in neurodegenerative disease, investigations focusing on mtDNA lesion amelioration, specifically genetic manipulation of mtDNA and its downstream gene, are required. Selective suppression of mutant mtDNA, recombinant mtDNA substitution, and allotropic production of mitochondrial proteins are promising discoveries in this field[111,112].

Antisense inhibition of mutant mtDNA and restriction endonuclease selection for mtDNA elimination are two well-studied techniques for selective suppression of mutant mtDNA. COX-PstI, COX8-ApaLI, and ScaI have all been investigated and found to improve mitochondrial function. Antisense inhibition works by genetically blocking mutant mtDNA replication and thereby reducing the production of faulty proteins. As antisense molecules, DNA, RNA, or chemical equivalents have been explored to bind their complementary DNA or RNA target. DNA-like peptide nucleic acids (PNA), which are useful for treating heteroplasmic diseases, are the most investigated type of antisense compounds so far. Short hairpin RNA (shRNA) and tiny interfering RNA (siRNA) have also been discovered to be promising techniques for modulating mitochondrial genome abnormalities at the mRNA level. Another method for mitochondrial gene therapy is to replace faulty mtDNA with recombinant mtDNA utilizing gene-carrying vectors. Not only heteroplasmy but also homoplasmy, will profit from the replacement of faulty mtDNA with a good recombinant-mtDNA genome. Although recombinant mtDNA's therapeutic efficacy has been investigated in a few studies, the lack of human mtDNA constructs, inadequate mitochondrial import of big constructs, and competition for recombinant mtDNA with functional resident DNA severely limit its use as a therapeutic strategy.

Recent studies on the use of the allotropic expression of mitochondrial proteins show that this strategy has a bright future. The allotropic expression of NDI1, a rotenone-insensitive NADH-Q-oxidoreductase, is an example. A team discovered that introducing NDI1 into mitochondria restores NADH dehydrogenase activity and, as a result, protects neurons in the substantia nigra of a Parkinson's disease rat model from severe degeneration[113]. Another example is that allotropic expression of ND1 reduces mitochondrial dysfunction in a cell model of LHON (Leber's hereditary optic neuropathy), whereas allotropic expression of ND4 protects LHON animal models against visual impairment[114,115]. Recent research using allotropic expression of mitochondrial proteins encoded by the nucleic genome provides a fresh way to improve mitochondrial function. Hayashi discovered that overexpressing mitochondrial transcriptional factor A in old mice improves memory deficits such as working memory and hippocampus long-term potentiation (LTP), while also reducing mitochondrial ROS generation and mtDNA degradation[116]. However, research in this sector is still in its early stages, and many of the applications are merely theoretical concepts.

Mitochondrial Medicine Delivery

Permeability of the blood–brain barrier is still a major roadblock in the development of mitochondrial pharmacotherapeutics for neurodegenerative disorders. Similarly, directly directing medicines to mitochondria to achieve efficacious accumulation remains a stumbling obstacle to effective therapy. The creation of large structures and their delivery to neurons is still a challenge. For mitochondria-targeted treatment, new approaches for manipulating mitochondrial medicines are required[117,118,119]. The modification of medications to boost their cellular and mitochondrial permeability is a viable option. Lipophilic cations are useful in facilitating molecular transport over lipid bilayers' hydrophobic barrier[120]. MitoQ and MitoVit E[119] are two applications that have been carefully examined and proven to be successful.

Another option is to use mitochondrial import machinery to allow large molecules to enter mitochondria. A practical technology[121] is the attachment of a mitochondrial signaling peptide to molecules, which is complementary to lipophilic cations, especially for molecules that are too big or overly polar to be attached by lipophilic cations. However, there has yet to be a successful insertion of recombinant-mtDNA directly into mitochondria. It's incredibly difficult to transfer a large construct including human mtDNA into neuronal mitochondria, but oligonucleotides attached to a mitochondrial signaling peptide could be a viable option. To present, little progress has been made in the study of mitochondrial gene therapy carriers, which is preventing mitochondrial gene therapy from being used clinically.

Conclusion

Mitochondria are key neuronal organelles that produce ATP, which is necessary for neuronal life. The creation of vast neuron information exchange networks in the brain is dependent on functional mitochondrial distribution and energy provision in neuronal strategic places. Mitochondrial malfunction causes severe synaptic dysfunction and finally neuronal death due to increased ROS production, mitochondrial permeability transition, collapsing mitochondrial membrane potential, decreased mitochondrial ATP synthesis, and the release of proapoptotic proteins. Recent research has identified mitochondrial dysfunction as a hallmark pathological change in neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, ALS, and Huntington's disease; as a result, researchers have hypothesized that mitochondrial stress plays a significant role in the pathophysiological process of neurodegeneration. Mitochondrial-targeted interventional medicine, as a result, appears to be a promising therapeutic option for neurodegenerative disorders.

Although most of the therapy techniques detailed in this article are still in the early stages of development, they have proved to offer a lot of therapeutic potentials. Antioxidant therapy has paved the way for mitochondrial-targeted medicine, with numerous treatments presently completing clinical trials on patients with neurodegenerative illnesses, and several showing considerable benefit in clinical practice. Despite the mitochondria-targeted therapies stated above, modulations on mitochondrial dynamics and apoptotic factors retain promise as prospective efficacious therapeutic techniques, based on current experimental observations, even though most of the relevant studies are still ideas. Nonetheless, given the common occurrence and similarity of mitochondrial pathology in early-onset inherited and late-onset sporadic neurodegenerative diseases, mitochondrial medicine, which focuses on the essential pathology in neurodegeneration, is expected to be a promising future therapeutic strategy for neurodegenerative diseases.

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