MITOCHONDRIA: AS A PROTAGONIST IN NEUROLOGICAL DISORDERS IN BRIEF OVERVIEW

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Abstract

Neurological disorders pose a great burden in general health. It is not astounding that mitochondrial malfunction emerging as a leading factor in myriad of neurological disorders. Mitochondria are extremely active cell organelles performing various functions, most importantly providing ATP to sustain cellular processes. Mitochondrial dysfunction results in altered neuronal bioenergetics, redox equilibrium and dynamics of cell and acts as focal point of pathogenesis in many human diseases including neurological disorders. Mitochondrial dynamics regulates pathways involving oxidative stress and apoptosis. Often mitochondrial division imbalance and fusion leads to mitochondrial functional impairment. Extreme variations in mitochondrial fusion causes increased mutation rate which along with increased oxidative stress can facilitate development of various neurological disorders such as Parkinson's disease, Alzheimer's disease, Huntington's diseases and so on. Mitochondria has a key role in regulation of apoptosis. Mitochondrial dysfunction and mutations can have deleterious effects on neuronal functioning as neurons have high energy demand with restricted regenerative potential. Certain neuroprotective agents restores the functions of mitochondria and acts therapeutic regimens of neurodegenerative diseases.

Keywords
Antioxidants; Apoptosis; Mitochondrial DNA; Reactive Oxygen Species; Neuroinflammation; Neurological disorders.

1. Introduction

Neurological disorders (ND) are the second leading cause of death globally and its prevalence is further expected to increase worldwide. According to the data from 1990 to 2016 it is second leading cause of death next to cardiovascular diseases. Based on the 2015 report, prevalence of spectrum of neurological disorders in India was around 2,394 in 100,000 population. The burden of neurological disorders is expected to rise to 6.77% by 2030. It is anticipated that mortality rate will rise into 12.22% by 2030 (1). Neurons are highly dependent on mitochondria for energy currencies, high energy intermediates and ketone bodies. Mitochondria are essential cell organelles in the cytosol which is the prime source of ATP for neurons, especially in the brain. Mitochondria has its own genome, double stranded circular DNA known as mitochondria DNA (mtDNA). Disruption in the machinery of energy metabolism due to genetic variants can alter the normal homeostasis contributing to the development of neurological disorders, including neurodevelopmental syndromes, neurodegenerative diseases and neuropsychiatric disorders (2). These ND are comprised by a heterogeneous group of diseases and syndromes that encompasses different behavioural phenotypes including cognitive and different personality patterns. Specific emotional disturbances, such as autism, Asperger's syndrome, pervasive developmental disorder, attention deficit hyperactivity disorder and bipolar disorder (3).

Mitochondrial stress and morphology might render selectively vulnerable neurons more susceptible to genetic variations, environmental toxins, cellular stress and ageing thereby triggering neurodegeneration (4). Mitochondrial function and properties have important relationships to apoptosis, necrosis, or apoptosis–necrosis hybrids which emerge along a cell death continuum. Mitochondrial mutations mainly affect tissues which requires a large amount of ATP. So, mitochondrial involvement occurs when acute interruptions in O_2 supply to the brain happens. Neuronal energetic defect is seen in cerebral ischemia–reperfusion injury, trauma, toxic exposures and neurodegenerative diseases and causes cognitive/motor dysfunctions(5). Major functions of mitochondria include ATP production through ETC, intracellular Ca^{2+} homeostasis, steroid hormones synthesis and apoptosis during the period of growth (6). Mitochondria are areas of redox reactions which leads to formation of reactive oxygen species (ROS), superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2) and hydroxyl radical ($OH^{\bullet}$) and its intermediates (7).

2. Neurodegenerative Diseases

Neurodegenerative diseases include Parkinson's disease (PD), Alzheimer's disease (AD), Huntington Disease (HD) and amyotrophic lateral sclerosis (ALS). Most of these diseases revealed the abnormality of mitochondria morphology and impairment of biochemical actions. These variations are often systematic instead of brain limited. Improper functioning of mitochondria may arise from abnormality of mitochondrial DNA and mutant nuclear proteins which interacted with mitochondria either directly or indirectly. Mostly in several cases it is due to decreased respiratory activity and inhibition of specific key regulatory enzymes like pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, and cytochrome oxidase.

Superoxide dismutase-1 (SOD1), acts as a universal antioxidant enzyme, it neutralizes the superoxide radicals to hydrogen peroxide, which are further converted to molecular oxygen by other antioxidant enzymes for example glutathione peroxidase and catalase. Predominantly it is localized in cytoplasm, but in ALS affected tissues it was found that both the wild type and mutant SOD1 protein is present in the matrix, intermembrane space and outer membrane of mitochondria. In outer mitochondrial membrane the accumulation and aggregation of mutant SOD1 leads to impairment of mitochondrial protein import and disturbs the mitochondrial function. The oxidative stress was increased in ALS. In post-mortem CNS tissues of ALS, the markers of immune system activation were significantly elevated. Further, in sporadic ALS a peculiar type of mtDNA mutation, called the ≈5 kb common mtDNA or mtDNA-4977 base pair common deletion involving seven protein coding genes and five tRNA genes has an increased frequency (8,9).

The Huntington's disease is caused by triple repeat expansion of CAG in the Huntington (HTT) gene. Generally, the HTT gene interacts with several transcription factors, like p53**,** CREBP-binding protein, Sp1, and PGC1- α (10). Among these, PGC1- α is a transcriptional coactivator that involve in the metabolic pathways of cell and regulation of mitochondrial biogenesis. Despite this, when the mutant HTT gene binds with p53 upregulates the nuclear p53 levels and transcriptional activity, through this it induces mitochondrial membrane depolarization. It is widely considered that 8-hydroxy-2-deoxyguanosine (8-OHdG) levels indicates the oxidative stress and its severity. In AD patients these 8-OHdG levels are increased in cortical brain regions. In AD subjects' brain, the mtDNA with large deletions (including a 4977 base-pair common deletion) and point mutations are high in hippocampus, parietal gyrus and cerebellum (11).

3. Mitochondrial DNA

mtDNA contains double stranded DNA ~16.5 kb pairs. It contains 37 genes encoding 13 proteins, 22 tRNAs and 2 rRNAs i.e, 12S and 16S rRNAs. The proteins are required for production of protein subunits of OXPHOS system. It is reported earlier that mitochondrial genome has about 100-fold higher mutation rate as compared to the nuclear genome and the probable reason could be increased mitochondrial ROS causing damage to mtDNA and also less efficient DNA repair mechanisms. This leads to a heterogenous population of mtDNA residing in the same cell and this is called as heteroplasmy. It has been speculated that in postmitotic tissues, mutant mtDNA could be multiplied through clonal amplification. As mitochondria works as powerhouse of cells, mitochondrial mutation produces distinguished phenotypes in tissues requiring high energy like retina, skeletal muscles, myocardium, and brain many syndromes are associated with mitochondrial mutations such as Leigh syndrome, Pearson syndrome and progressive external ophthalmoplegia. Interestingly, in different areas of human brain which is progressing towards aging the mtDNA4977 base pair common deletion has been described (9). There is ongoing research for the use of this deletion as a predictor and prognostic marker in carcinogenesis.

4. DNA repair in mitochondria

As the mtDNA does not have protective histones they are certainly more vulnerable to ROS attack and hence oxidative stress. Several diseases occurs when DNA repair mechanisms fail and various mutations accumulates. In mitochondria the major repair mechanism is base excision repair (BER) involving precise execution of gap filling and terminal processing (12). Accumulation of mtDNA mutations causes a vicious circle involving oxidative damage, energy depletion and a shoot up in ROS production. In comparison to nuclear DNA, mtDNA endures excessive steady-state damage. DNA damage occurs due to increased levels of ROS and also because of less histone mediated nuclear protection to chromatin. Mitochondria contains active DNA base excision repair proteins, which are all encoded by nuclear DNA. Although they are present at lower levels than in nuclei, these repair proteins play a crucial role in pathogenesis of various mitochondrial diseases (5). Nuclei and mitochondria use variant proteins for base excision repair. 8-oxoguanine DNA glycosylase-1 (OGG1) is a DNA glycosylase enzyme which is encoded by OGG1 gene (13). It is involved in base excision repair. Alternative splicing variants of OGG1exist. The N- terminus contains a mitochondria targeting signal which is required for mitochondrial localization. Also, endonuclease III-like protein (NTH1) is a DNA glycosylase required for the repair of oxidised bases. When DNA glycosylase excises a base, the abasic site is excised by AP endonuclease. Full length APE has a prominent role in mitochondrial repair. DNA ligase IIIβ is located in both nucleus and mitochondria and it functions as DNA ligase in mitochondria base excision repair. Isoform 1 is targeted to mitochondria (14). DNA polymerase γ (POLG) is consideeed to be totally responsible for mtDNA base excision repair and replication. Human POLG is a nuclear-encoded gene product and is required for mitochondrial BER (5).

5. Role of mitochondria in neurological disorders

It has been speculated that a significant number of syndromes arises with marked neurological phenomena in the spectrum of mitochondrial disorders. But there exists a variability in the clinical manifestation of mitochondrial function disruption, provided that there exists a limit in the degree of mitochondrial deficiency for the clinical expression of the disease and for their phenotypic effects later on. Thus, the pathophysiology and clinical manifestation are aggravated in a chronic and continuous manner, in most of the diagnosed cases of mitochondrial dysfunctions, along with the increasing age of the subjects. Hence, it is quite acceptable that organs which have very high rate of energy demand would be more sternly affected by the mitochondrial dysfunction than others which have a comparatively low level of energy requirements. So, it is the brain, the skeletal muscles, and the heart which have a particular type of involvement in adolescence and adult population, though multi-system manifestation of mitochondrial dysfunction is also a common phenomenon, especially seen in childhood(15).
Therefore, a finer look into mitochondrial genes and molecular basis of mitochondrial biology can help in better perception of neurological
disorders (5,16). Regarding this, a differing intensity of mitochondrial dysfunction and intrinsic mitochondrial mediated cell death mechanisms might be important factors in the pronouncement of diseases which usually ranges along a sequence of apoptosis–necrosis cell death. With therapies attacking specific mitochondrial properties, pathways, or molecules, like mitochondrial permeability transition pore (mPTP), might be noteworthy for evolving newer mechanism-based pharmacotherapies for a whole spectrum of neurological disorders. An example is restless legs syndrome, a neurological sensory disorder caused mainly due to deficit in the levels of mitochondrial ferritin (5).

6. Mitochondrial stress and immunity

A mitochondrial biogenesis deficit in neuronal cells was found to be functionally linked with the clinical advancement of neurological disorders. The endosymbiotic theory explains that mitochondria is evolutionarily derived from alpha-proteobacteria. It was found that mtDNA possess significant structural similarity with bacterial DNA. Therefore, mtDNA fragments boost host innate immunity and other acquired factors along with inflammation by activating cytokine storm and other inflammatory markers. The etiological factors of different neurological disorders are even though different, the activation of immune system by fragmented mtDNA takes place in a common biochemical pathway (17). In this way, circulating cell free mtDNA produces significant and heterogenous inflammatory responses comprising broad spectrum antimicrobial immunity and neuro-immunological disorders which proves its gravity in neurological disease progression (18).

7. Biomarkers of mitochondrial mediated neurological disorders

Mitochondrial miRNAs in neuroinflammation

miRNAs (micro RNA) are small non coding RNA which inhibit or degrade endogenous mRNA transcript. Mitochondrial miRNAs, found within mitochondria, are commonly known as mitomiRs.. miRNAs control various functions of mitochondria like OXPHOS by miR-338 and COXIV, cell signalling is controlled through miR-696 and PGC1α, fission and mitophagy is managed via miR-30, p53/Drp1 and miR-21, PTEN respectively. Some notorious mitomiRs include miR-155, miR-181c, miR142-3p/5p and miR146a and they might have a double origin. They can be either nucleus derived cytosolic precursor form which gets processed inside mitochondria or could originate from the mitochondria directly (19,20). Disruption in miRNA function occurs most probably by oxidative stress. As the miRNA moves inside the mitochondria, the miRNA dyregulations taking place either in the nucleus or cytosol might get translated into mtDNA alterations and alters mtDNA transcription. Due to blunting of the respiratory complex like cytochrome oxidase I and III by massive increase in ROS compounded by miR-13a and miR-181c, mtDNA fragmentation occurs (17). Mitochondrial function can also be affected by the action of mitomiRs on mtDNA. In fact, in a wide assortment of genes the genetic expression is modulated by the mitochondria as a main messenger while they deliver miRNAs towards the intracellular compartments. In the cytosol mitophagy is subdued because of abnormal spreading of miRNAs. Thus, damaged mitochondria, mtDNA and miRNAs exit from the cells is disrupted (20).

miRNAs such as miR-155, miR-146a and let-7b are found to be involved in neuroinflammation. They are found circulating in extracellular fluids inside the exosomes and they behave similar to Damage-associated molecular patterns (DAMPs) for activating Toll-like receptor (TLR7) in a manner similar to Circulating cell-free mitochondrial DNA (ccf-mtDNA) (21). They are found circulating in extracellular fluids inside the exosomes. These DAMP-like miRNAs are present in mitochondria. Also, their activity is triggered by NF-kB, which is facilitated by mtDNA fragments (22). These findings shows similarities between mtDNA and miRNAs as potential biomarkers for neuroinflammatory disorders.

Circulating cell-free mitochondrial DNA

ccf-mtDNA are short sections of mitochondrial DNA which are released by cells undergoing stress or any other pathology. They are recognised by immune system and activate inflammatory reactions (23). It has been proven as a diagnostic and prognostic biomarker as it could be used to detect the degree of damage in several diseases like malignancy, trauma, various microbial infections, cardiovascular accident and myocardial infarction (24). It is stable in extracellular fluids in plasma as well as the Cerebrospinal fluid (CSF). mtDNA possess higher resistance to nuclease-dependent degradation when compared with the nuclear DNA. This shows mtDNA as a highly advantageous stable biomarker (25).

ccf- mtDNA in neurological disorders

As the mitochondrial DNA particles are liberated from the cell through the cell membrane, they manifest themselves as ccf-mtDNA in the extracellular space (26). mtDNA particles act as danger-associated molecular patterns (DAMPs) to activate host innate immunity and augment inflammatory response similar to pathogen-associated molecular patterns (PAMPs). This mechanism takes a turmoil due to binding to Toll-like receptor 9 (TLR9) and successive triggering of the stimulator of interferon genes (STING) pathway. Therefore, DAMPs accumulation activates macrophages which are residing in the cells and stimulates tissue infiltration done by the leukocytes. When such a molecular mechanism takes place between DAMPs and PAMPs it might also progress to non-differentiable clinical responses which are later accompanied by infective and non-infective damage. In this context, for the clinical diagnosis the detection of genetic profile of associated pathogen remains quite essential, and quantification of ccf-mtDNA is coming up nowadays as a novel biomarker for disease screening and prognosis at early stages (27). In the early phase of infection, when mitochondrial and cell membrane damage is less, the spread of ccf-mtDNA functions as an attempt to provoke immunity against the microbes, removes non- functional mtDNA fragments and thereby preserves mitochondrial function (28).

8. Mitochondrial DNA variants and its associated neurological disorders

mtDNA possess higher mutational rate compared to nuclear DNA, associated with single nucleotide polymorphisms (~79%), deletions (~15%), copy number variations (~3%), insertions (~2%) and other genetic rearrangements (1%). Mostly these variants influence mitochondrial proteins and the rest of them is associated with tRNA and rRNA. Due to poor fidelity of DNA polymerase in mitochondria, ROS levels imbalance occurs and this drives aging process. ROS promotes oxidative stress, protein damage, mitochondrial dysfunction which can contribute to ND. In mitochondria, the OXPHOS mechanism gets interrupted when ETC genes mutation occurs. This condition diminishes ATP production and causes epilepsy and LHON (Leber's hereditary optic neuropathy) syndrome. Variations of genes of neuronal synapses grounds structural and functional alterations, this favours autism spectrum disorder (ASD), attention deficit hyperactivity disorder. In LHON the genes involved in mitochondrial replication, transcription or translation were mutated. Alzheimer's disease is the first most common ND affected due to amyloid-β aggregates. Mitochondria, an important controller of apoptosis are affected by amyloid-β aggregates. Misfolded amyloid-β protein aggregates have significant effect on components of the electron transport chain (29).

Mutations of genes like PINK1 (PTEN-induced kinase 1) and Parkin (E3 ubiquitin protein ligase) indicates loss of mitochondrial quality control, altered calcium homeostasis and reduced OXPHOS. PINK1 and Parkin acts as potential regulators of 'mitophagy' for defective mitochondria. Mutations of downstream proteins in mitophagy (NIPSNAP1 & 2) attributes to parkinsonian phenotype (30). In HD, a molecular cause of this neurodegenerative disease is trinucleotide repeats of CAG. This corresponds to polyglutamine tract of HTT protein to form misfolded aggregates. There is strong association between aging and mtDNA variations which progresses MELAS (Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes), LHON and PD (31). In MELAS and MERRF (myoclonic epilepsy and ragged-red fibres), it was reported that mutation of mitochondrial tRNA takes place which alters its structure and functions (32). Variants in mtDNA causes cognitive impairment, developmental delay, slow learning capability and behavioural abnormality. In ASD, HD, BD and Leigh Syndrome besides nuclear genes, mtDNA defects were also seen in hereditary pattern. So far various studies reported that, 105 out of 158 mtDNA mutations, 13 mitochondrial proteins coding genes had functional involvement of coding region with mtDNA variants (33).

9. Single nucleotide polymorphisms of mtDNA

Single nucleotide polymorphisms (SNPs) are the simplest DNA variations among the individuals. Out of 152 SNPs associated with various neurological disorders, 4 were related to non-coding mtDNA region and 3 were related to D-loop locus. In bipolar disorders variants are found in D-Loop region, MT-ND1, MT-ND2 and MT-CYB protein coding genes. Individuals suffering from psychiatric disorders like schizophrenia and bipolar disorders also have mtDNA mutations. Genetic variation in promoter region of NDUFV2, a mitochondrial complex 1 gene is associated with bipolar disorder. Many non-synonymous mutations were found to have affected the mitochondrial genes like MT-ND6, MT-ATP6, MT-CYB and MT-ND2 in schizophrenia. mtDNA screening was done, it was speculated that NARP (neuropathy, ataxia, retinitis pigmentosa), dementia, RTT, learning difficulty, ID present a comparatively decreased amount of mutations. NARP has been associated with 4 mutations at two sites in the ATP6 gene(34). mtDNA polymorphisms like A10398G, T3644TC, T16519C and T12027C, T195C are associated with SCZ and BD respectively. Few neurological disorders like ASD, Leigh Syndrome, MELAS and myoclonic epilepsy with ragged red fibres (MERRF) were also reported to have increased mtDNA mutations. In ASD mutations are located in MT-CO1 coding for Cytochrome C Oxidase 1 and second mutation in MT-CO2 coding for Cytochrome C Oxidase 2. These genes are involved in ATP production and reducing oxidative stress. In Leigh Syndrome point mutations were causative agent in seven out of 13 mitochondrial protein coding genes. However, maximum mutations exist in MT-ATP6, MT-ND3, MT-ND5(35). MT-TL1 was also linked with seizures, ASD and Leigh Syndrome. MERRF is a disorder affecting mainly muscles and nervous system. Usually, symptoms appear during childhood or adolescence. Mutation in MT-TK is the chief cause of MERRF with most of the mutation confining to tRNA (36). Various mtDNA mutations, alterations associated

with copy number variations, insertions and deletions interfere in the exact functional pathways of the central nervous system causing various neurological disorders. Furthermore, mtDNA deletions usually lies between the *MT-TT* and *the MT-TC* transcripts, whereas the locus between the two transcripts *MT-TP* and *MT-TN*, has no deletions. Different types of mutations were identified with protein coding genes and also with spliced RNA transcripts but surprisingly the tRNA molecules *MT-TA* and *MT-TN* were not associated with any type of mutation (37).

10. Mitochondrial mediated apoptosis in Neurological disorders

"Mitophagy" is a programmed mitochondrial removal mechanism which regulates mitochondrial quality as well as quantity. Impaired mitochondria is severe threat for neuronal function because lack of ATP generation and excessive production of ROS. Increased ROS and oxidative stress causes mitochondrial membrane depolarization i.e, loss of matrix metalloproteinases (MMPs). mPTP switches on PINK1/Parkin-mediated mitophagy pathway. PINK1/Parkin pathway mainly associated with Parkinson's disease. Cell death is induced by increased free radicles, oxidative stress, deficit of neurotrophic factors and multiple other factors impairing mitochondrial function. Organelle of endomembrane system like endoplasmic reticulum (ER), chiefly balances intracellular Ca^{2+} levels along with mitochondria. The Ca^{2+} homeostasis in the ER and mitochondria are regulated by the Bcl-2 family proteins and are thus the vital components responsible for apoptosis. These changes modulate mitochondrial permeability and promotes release of proapoptotic factors such as Bax and cytochrome C to activate caspases. Finally, released caspases promotes internucleosomal cleavage of DNA in the cells (38).

11. Protagonist of mitochondrial antioxidant defense system against oxidative stress in ND

Mitochondria generates endogenous ROS as by-products of redox reactions. ROS are superoxide radical, hydroxyl radical and hydrogen peroxide which damage organellar macromolecules including mitochondrial proteins, enzymes, ETC complexes and iron–sulphur clusters. Variations in intra- and intermitochondrial redox environment leads to release of free radicals. The formation and release of ROS was processed in the form of regenerative cycle which was termed as ROS-induced ROS release (RIRR). At high levels of ROS favours oxidative stress, this terminates formation of mitochondrial permeability transition pore (mPTP) and then destruction of mitochondria. It propagates from mitochondrion to mitochondrion, of the cell itself. Increased oxidative stress also promotes lipid peroxidation which in turn releases malondialdehyde in several neurological disorders. The mitochondrial matrix contains several antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR) and thioredoxin reductase (TrxR). These enzymatic antioxidants quench the reactive oxygen species and detoxified into non-toxic products as shown in Figure-1.

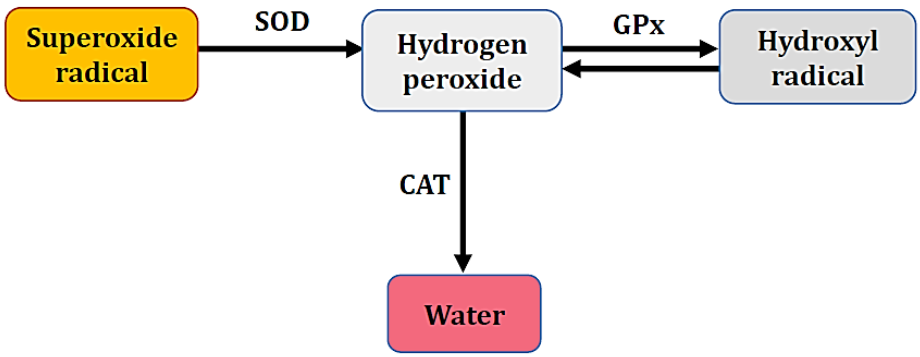

Figure 1. Detoxification of reactive oxygen species by enzymatic antioxidants.

Several metals for example copper, manganese and zinc acts as cofactors for some of these enzymes. Non-enzymatic antioxidants such as Vitamin A, C, E, glutathione, glutaredoxin, thioredoxin and peroxiredoxin (PRx) are protects mitochondria from ROS and RNS such as superoxide radical, hydroxyl radical and hydrogen peroxide by quenching mechanisms (39).

12. Protection of mitochondria by neuroprotective agents

In neurological disorders, various molecules have been investigated which enhance bioenergetics homeostasis mechanism in the mitochondria. For testing their efficiency in these disorders, creatine and CoQ_{10} are in phase III of clinical trials for AD, HD and PD (40). Methylene blue and photomodulation are used on animal models to increase the energy production and to reduce oxidative stress and neuroinflammation. Several neuroprotective agents like lipoic acid, creatine, CoQ_{10}, nicotinamide, riboflavin are also targeted for their beneficial effect on mitochondrial functions which is shown in Figure-2.

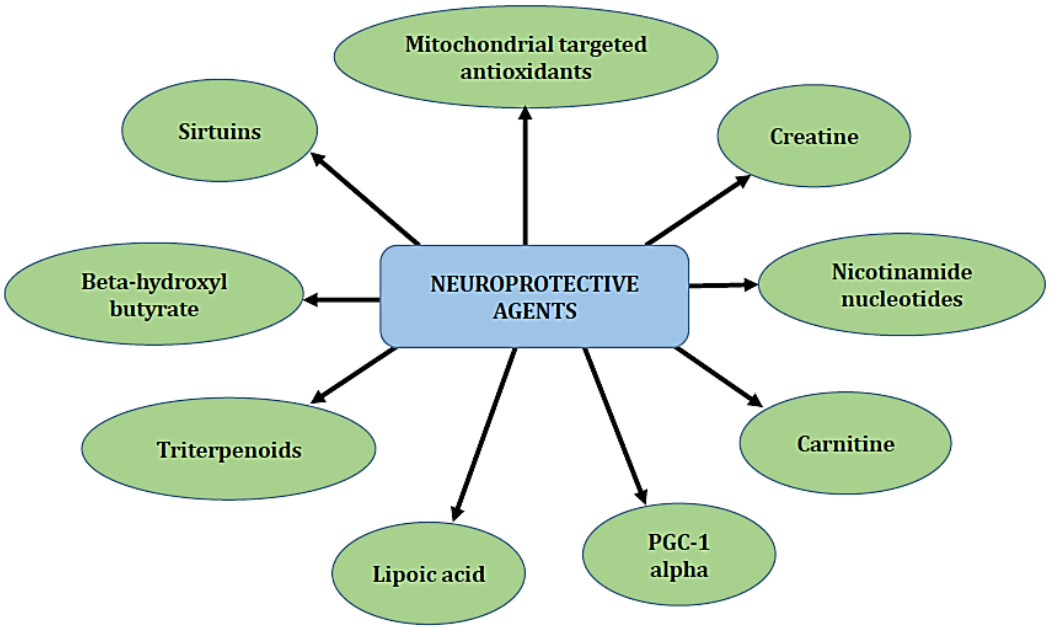

Figure 2. Restoration of mitochondrial function by several neuroprotective agents.

12.1 Creatine

Creatine is an organic compound which is found naturally in muscle cells. It is nitrogenous guanidine and it provides energy to all cells throughout the body, especially muscle and nerve cells. It is transported into the brain and skeletal muscle by a sodium-dependent creatine transporter. Mitochondrial creatine kinase catalyses the reversible reaction forming phosphocreatine and it is the main source of high energy phosphates. This system is vital for maintaining energy homeostasis in the brain. A high ATP/ADP ratio is of prime importance for ATP supply at sub-cellular level, to adjust high ATP free energy. This mechanism also minimizes the loss of adenosine nucleotides, thereby preventing cellular dysfunction. In addition, it was found that glutamate-treated neuronal/glial cells had more viability when Ras/NF-kappaB signalling was inflected with creatine (41) . This modulation augments differentiation of cultured GABA-IR neurons. Creatine also facilitates a significant level of neuroprotection against glucose, serum deprivation and 3-nitropropionic acid (3-NP) induced toxicity (42).

NMDA110 produces striatal excitotoxic lesions which could be efficiently reduced with the oral administration of 1% creatine in the diet. Malonate-induced striatal lesions could be controlled with the use of creatine along with nicotinamide. It gives refinement in cognitive and motor functions, brain atrophy decreases, brain ATP production is enhanced. Also, striatal neurons atrophy and Htt-positive aggregates formation is delayed. Glutamate and β-amyloid toxicity is prevented with the successive usage of creatine. Creatine is used in clinical trails for Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis after its beneficial effects in experimental studies in animals. Creatine monohydrate, CoQ10 and lipoic acid combination was used in a randomized, double-blind, placebo-controlled trail and it was shown to have protective effect in neurological disorders. Recommended dose of creatine is 8 g/day for 16 weeks by oral route. This dosage is is safe, endurable and has good bioavailability to the brain. Also, creatine reduces serum 8-hydroxy-2-deoxyguanosine levels which is a novel biomarker of increased oxidative stress and neuroinflammation (43).

12.2 CoQ_{10}

In order to accept electrons from complex I and II in the ETC, a biological cofactor CoQ10 (ubiquinone) plays an essential role, as an uncoupler of mitochondrial proteins. CoQ10 interacts with α-tocopherol, to directly scavenge free radicals, in mitochondrial inner membrane, hence it also serves as an anti-oxidant. CoQ10 also acts as an anti-apoptotic factor, by inhibiting Bax mediated mitochondrial apoptotic pathway, and downregulating mitochondrial permeability transition (MPT). Additionally, CoQ10 can also activate uncoupler mptpproteins (UCP) exert neuroprotective effects, associated with marked neuroprotection against the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity through reduction in mitochondrial-free radical generation (44). Further, in experimental models of stroke and epilepsy an increased expression of the mitochondrial UCP was found to have protective role against neuronal damage. CoQ10 has also been reported in protection against iron-induced apoptosis in dopaminergic neurons, as it destabilizes preformed beta-amyloid fibrils and exerts anti amyloidogenic effect. Further, inhibits the MPT pore and protects CoQ10 SHSY5Y neuronal cells from β-amyloid toxicity. Similarly, mitochondrial membrane potential can be maintained by pre-treatment of neuronal cells with CoQ10 during oxidative stress which reduces the ROS generation by mitochondria (45).

12.3 Mitochondrial targeted antioxidants/peptides

Mitoquinone (MitoQ) is a potential mitochondrial targeted antioxidant, increasing enzymatic antioxidant activity, including SOD and GPx, whereas it decreases the levels of malondialdehyde (MDA). MitoQ is a derivative of CoQ10, it blocks the mitochondrial ROS overproduction and lipid peroxidation. It attenuates the deficit in motor functions and loss of oligodendrocytes. In ICH, demyelination and axon swelling is reduced thereby decreasing cell death (46). Elamipretide (SS-31) is a novel mitochondrion targeted antioxidant. It was found to modulate SIRT1 levels, reduce oxidative stress, ROS and inflammation. Also, it ameliorates mitochondrial membrane potential and glutathione content (47). MitoQ augmented the Nrf2 nuclear translocation and also upregulates the expression of Nrf2 downstream proteins, such as quinone oxidoreductase-1 and heme oxygenase-1 (48).

12.4 Triterpenoids

Triterpenoids are diverse group of natural products. Structurally they are cyclic compounds having a carbon skeleton which are derived from squalene (C30 hydrocarbon) by cyclization. Usually, 5 carbon isoprene units are linked to it in various positions and they are either aldehyde, carboxylic acids or alcohols. Many of them have anti-inflammatory and anti-carcinogenic properties. To prevent the brain from neuroinflammation and oxidative stress, some triterpenoids are being used like Celastrol, lupeol, oleanolic acid, ursolic acid, betulinic acid, pomolic acid, uvaol, asiatic acid and tormentic acid (49). For preventing the progression of neurodegenerative diseases like AD, PD, HD and ALS, few experimental studies have reported that these compounds have a potential role and thus could be used as a treatment (50). Synthetic triterpenoids are also used as they have antioxidant and antinflammatory properties. CDDO-MA is a synthetic triterpenoid prepared to induce signalling cascade of Nrf2/ARE (antioxidant response element). Once Nrf2 is modulated by triterpenoid, it dissociates from Keap1. Next step is translocation to nucleus, and followed by binding to the ARE promoter sequences which causes activation of cytoprotective genes involved in reducing oxidative stress and neuroinflammation. Interestingly, triterpenoids have good anticancer efficacy. Therefore, they are utilized as chemo preventive agents for tumours like leukemia, multiple myeloma, osteosarcoma, breast and lung cancer (51).

12.5 Nicotinamide nucleotides

Nicotinamide nucleotides such as NAD+/NMN are hydrophilic amides that maintain the neuronal membrane integrity and protects neurons from apoptosis. NAD+ is synthesised from nicotinamide, with an intermediate nicotinamide mononucleotide (NMN) by the catalysis of an enzyme nicotinamide phosphoribosyl transferase (NAMPT). Even though neurons have low levels of NAMPT, the requirement of NAD+ is essential for normal functioning. NAD+ is mainly associated with energy yielding metabolic pathways and maintains normal homeostasis of neurons. NAD+ is an essential cofactor maintaining mitochondrial fitness and development of neurons from its precursors. Depletion of NAD+ leads to neuroinflammation, synaptic dysfunction and neuronal degeneration in Alzheimer's disease, Parkinson's disease and retinal degenerative diseases (52).

mtDNA are predisposed to various exogenous physical and chemical DNA damaging agents, thus increases the risk of neurodegenerative diseases. Accumulation of mutations and DNA damage hastens aging process and its associated diseases. Poly(ADP-ribose) polymerases (PARPs) are activated in response to DNA damage through reactive oxygen species. NAD+ acts as substrate for three important classes of enzymes like sirtuins, PARPs and cyclic ADP-ribose (cADPR) synthases, thereby protecting the cells from oxidative stress and apoptosis (53). NAD+ prevents neurons from ischemic brain damage and rejuvenates the remyelination process. Nicotinamide riboside improves the cognitive function and hippocampal synaptic plasticity in mice models. Nicotinamide precursors like nicotinamide mononucleotide (NMN), the immediate precursor to NAD^+ by a single step process with an enzyme NMN adenyltransferase (NMNAT) improves bioenergetics in cells and ameliorates disease phenotypes (54). In retinal degenerative diseases such as glaucoma and Leber congenital amaurosis, NAD^+ metabolism is disrupted. Hence, NAD supplementation is considered a novel therapeutic target in these conditions. Additionally, NMN reduces lactic acidosis and serum IL-6 levels which are strong predictive markers of mortality in metabolic deranged condition such as haemorrhagic shock (55). So, NMN is a key precursor for therapeutic implications to increase NAD^+ levels (56). Nicotinamide prevents MPTP induced neuronal degeneration. Wallerian degeneration, commonly occurs in chronic degenerative diseases and nicotinamide is found to be preventive in neuronal degeneration (57). Therefore NAD+ could be used for the treatment of neurodegenerative disease, ischaemic injuries and trauma.

12.6 Lipoic acid

Lipoic acid is an antioxidant available as a dietary supplement. It is present in low amount in food. Recently it has been considered as an effective aid in neurological disorders due to its modulating effect in signal transduction and gene transcription. It contains a disulphide bond and is an essential cofactor for oxidative decarboxylation of α-keto acids like pyruvate dehydrogenase (58). For the progression of neurodegenerative disorder, it has been reported that aging is the major risk factor. Factors associated with rapid ageing are oxidative stress, disruption in bioenergetic machinery causing cognitive and motor function decline. As lipoic acid functions were explored through in vivo and in vitro experimental studies it showed protection against oxidative stress, anti-apoptotic properties, and anti-inflammatory actions in neurodegenerative disorders (59). Most importantly, lipoic acid augments the epigenetic modification of the Nrf-2 required for supporting structural integrity and enabling mitochondrial activity in a proper way (60).

12.7 Carnitine

L-carnitine is an amino acid, found in the body (also available as a dietary supplement). It produces energy during beta oxidation as it transports fatty acids from the cytoplasm to mitochondria. It could be converted to other forms such as acetyl-L-carnitine (ALC) and propionyl-L-carnitine. Due to the antioxidant and neuromodulatory properties of acetyl group donated by ALC, they are considered as potential targets for treatment in neurodegenerative diseases. It also has a protective action against MPTP toxicity. Dietary supplementation of ALC is given because of its analgesic effects in neuropathies (61). Neuroprotective and anti-apoptotic action of ALC have also been investigated and could be used in future.

12.8 β-hydroxybutyrate

Ketone bodies are used as a treatment modality for various neurological disorders due to their protective effect on neurons. Ketone bodies undergo oxidation especially when glucose supply is low in brain as most of the neurons do not effectively generate high-energy phosphates from fatty acids during starvation. β-hydroxy butyrate, a ketone body, also has neuroprotective action with distinct role in MPTP toxicity (62).

12.9 PPARG (Peroxisome proliferator-activated receptor-gamma) coactivator 1 alpha

PPARG coactivator-1 alpha (PGC-1α) is a transcription coactivator that regulates cell metabolism and mitochondrial biogenesis. Along with cell metabolism PGC-1α also emerged as an important factor in the induction of many antioxidant processes by enhancing the expression of several transcription factors like nuclear respiratory factors (Nrf-1 and Nrf`-2) . It is also found to be involved in regulating the expression of mtDNA transcription via mitochondrial transcription factor A (TFAM) which is coactivated by Nrf-1. Nrf-1, together with Nrf-2, mediates the genomic coordination between nuclear and mitochondrial genomes by directly regulating the expression of several nuclear-encoded ETC proteins. Nrf-2 is also an emerging regulator of cellular resistance by controlling the basal expression of an array of antioxidant response element–dependent genes, which triggers up-regulation of antioxidants (63).

The diverse role of PGC-1α reduces oxidative stress by inducing the expression of antioxidant enzyme systems. So, overexpression of PGC-1α could completely rescue mitochondrial biogenesis and mitochondrial deficits through inhibition of 5'-adenosine monophosphate-activated protein kinase (AMPK) activity (64). The same has been confirmed in animal studies where the dopaminergic neurons in PGC-1α null mice are much more susceptible to neurological disorders which include parkinsonian-like features. Conversely, PGC-1α overexpression protects neural cells from oxidative stress-induced by the mitochondrial toxin, MPTP (65). Therefore, PGC1α is also a powerful controller of mitochondrial metabolism and rescues mitochondrial homeostasis.

12.10 Sirtuins

Sirtuins or SIRTS belong to the family of NAD-dependent histone deacetylase and play a major role in cell functioning by regulating cell metabolism and cell survival. Activation of the sirtuin helps in the extension of cell longevity and delay the onset of age-related neurodegenerative disorders (66). The same has been confirmed in the mouse model, where the activation of SIRT 1 by resveratrol increased the survival of motor neurons in ALS mice and also decreased neurodegeneration in AD mice. This mechanism works through decreasing the acetylation of SIRT1 substrates such as PGC-1α and p53 (67).

13. CONCLUSION

In conclusion, genetic and environmental risk factors are key factors in maintaining mitochondrial function, kinetics and mitophagy during the pathogenesis of neurological disorders. Attenuation of free radicals and oxidative stress could be done by enhancing expression of protective genes such as Nrf-2, enzymatic antioxidants, PPARG coactivator-1 alpha, sirtuins and also suppression of mitochondrial apoptotic mechanism by inhibiting Bax translocation and cytochrome C release from the mitochondria. Furthermore, MitoQ administration leads to activation of the Nrf2-ARE pathway. Overall, neuroprotective agents normalize the redox balance and maintains mitochondrial homeostasis. This indicates mitochondrial approaches of various components exhibit neuroprotective effects and has therapeutic potential in prevention and delaying the progress of neurological diseases. Finally, continuous progress is going on to explore the basic mechanism underlying the mitochondrial functional pathways, it is widely believed that antioxidant therapy in neurological disorders is most likely to precede breakthrough in the near future.

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