Introduction

Mitochondria are essential for the life of the cell. They produce most of the adenosine triphosphate (ATP) by oxidative phosphorylation. Mitochondria have two membranes (outer and inner), an intermembrane space, and an internal matrix. The inner mitochondrial membrane contains the electron transport chain (ETC), the molecular machinery for energy production ***(Mattson et al., 2008).***

Five protein complexes form the ETC. Of these, three (I, III, and IV) pump protons through the inner membrane generating H+ gradient required for the synthesis of ATP at complex V (ATP synthetase). The mitochondrial genome codes for 13 of the ETC proteins. The cell nucleus encodes other mitochondrial proteins (more than 1, 000) which mediate processes such as the regulation of ion homeostasis, stress responses, cell survival, and signal transduction ***(Mattson et al., 2008).***

Mitochondria are dynamic organells involved in many crucial cellular processes in eukaryotic organisms and are considered gatekeepers of life and death, these organelles have major functions, production of over 90% of cellular ATP through the tricarboxylic acid cycle and oxidative

phosphorylation, regulation of intracellular calcium and control of apoptosis ***(Moriera et al., 2010).***

Mitochondrial oxidative phosphorylation are essential for neurons to meet their high energy requirements,neurons are very vulnerable to bioenergetic crisis if there is dysfunction of mitochondrial organelles.dysfunctional mitochondrial enrgy metabolism comes in ATP production and calcium buffering impairment and exacerbated generation of reactive oxygen species (ROS), including hydrogen peroxide (H2O2), hydroxyle radical (OH) and superoxide anion (O2-). ROS, in turn, cause cell membrane damage via lipid peroxidation and accelerates the high mutation rate of mitochondrial DNA (mtDNA). Additionally, accumulation of mtDNA mutations enhances oxidative damage, induces energy crisis and exacerbates ROS generation, in a vicious cycle ***(Petrozzi et al., 2007).***

Mitochondrial dysfunction arises from an inadequate number of mitochondria, inability to provide necessary substrates to mitochondria, dysfunction in their electron transport and ATP-synthesis machinery. The number and functional status of mitochondria in a cell can be changed by (1) fusion of partially dysfunctional mitochondria and mixing of their undamaged components to improve overall function, (2) the generation of entirely new mitochondria (fission), and (3) the removal and complete degradation of dysfunctional

mitochondria (mitophagy). These events are controlled by complex cellular processes that sense the deterioration of mitochondria, such as the depolarization of mitochondrial membranes or activation of certain transcription pathways ***(Lee et al., 2012)***.

Alzheimer disease (AD) is defined by progressive impairments in memory and cognition and the presence of extracellular neuritic plaques and intracellular neurofibrillary tangles. B Amyloid peptide is the major component of the plaque, and the tangles are composed of hyperphosphorylated tau proteins. The molecular events leading to the development of sporadic late-onset AD have not been defined. Advanced age is the greatest risk factor for AD, and glucose/energy metabolism is diminished in AD. It has been proposed that in sporadic AD mitochondrial dysfunction is the primary event that causes βAmyloid peptide deposition, synaptic degeneration, and formation of neurofibrillary tangles ***(Swerdlow et al., 2010).***

Parkinson disease (PD) is the second most common neurodegenerative disorder. Over the last several decades, evidence has accumulated that mitochondrial dysfunction is strongly associated with PD. A mild deficiency in mitochondrial electron transport chain NADH dehydrogenase (complex I) activity was first found in the substantia nigra of patients with PD, followed by studies identifying a similar

complex I deficit in platelets, lymphocytes, and, less consistently, in muscle tissue from patients with PD ***(Beal, 2011).***

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that targets motor neurons in the brain and spinal cord, resulting in muscle weakness, atrophy, and eventual death. Although there have been extensive research efforts investigating the pathogenesis of ALS, its etiology is still largely unknown. Mutations in the valosin-containing protein (also known as transitional endoplasmic reticulum ATPase) gene were recently reported to be the cause of 1 to 2% of familial ALS cases, and they have effects on the regulation of mitochondrial calcium ***(De Vos et al, 2012).***

Huntington's disease (HD) is a dominantly inherited progressive neurodegenerative disorder, the disease is characterized by progressive motor impairment, personality changes, psychiatric illness, and gradual intellectual decline. There is extensive evidence for bioenergetic deficits and mitochondrial dysfunction in HD, such as decreased activities of OXPHOS, complexes II and III, abnormal mitochondrial membrane depolarization ***(Mochel et al., 2012).***

Mitochondrial dysfunctions include also the mitochondrial myopathies, a group of neuromuscular disorders that includes Kearns-Sayre syndrome (KSS), mitochondrial

encephalopathy lactic acidosis and strokes (MELAS) , myoclonic epilepsy with ragged red fibers (MERRF), and mitochondrial neuro-gastrointestinal encephalomyopathy (MNGIE) that have genetic origins, leber hereditary optic neuropathy (LHON), which is associated with visual failure caused by the degeneration of retinal ganglion cells, is the most common disease associated with mtDNA mutations ***(Wallace, 2010)***.

Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), is defined clinically by stroke usually before age 40, encephalopathy characterized by dementia, seizures, or both, and evidence of mitochondrial dysfunction, with RRF, lactic acidosis, or both. The strokes commonly cause hemianopia or cortical blindness. An initial small study demonstrated that intravenous (IV) administration of L-arginine quickly decreased the severity of strokelike symptoms, enhanced the dynamics of microcirculation, and reduced tissue injury from ischemia in patients with mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS) In a larger study, a decrease in clinical severity and frequency of strokelike events was demonstrated in MELAS patients treated prophylactically with oral L-arginine ***(Koga, 2005).***

Mitochondrial dysfunction has been identified in several other neurodegenerative disorders. Secondary abnormalities of

mitochondrial morphology, function and gene mutation involves a mitochondrial protein have been recorded in Friedreich's ataxia and hereditary spastic paraplegia. Mutations in the MFN2 gene are a common cause of autosomal dominant Charcot Marie Tooth type 2 disease, an early onset axonal sensorimotor neuropathy. A proportion of patients have additional abnormalities, such as optic atrophy or deafness. Mutations of OPA1gene cause autosomal dominant optic atrophy, but the phenotype can include peripheral neuropathy, deafness, ataxia, and ophthalmoplegia with multiple mtDNA deletions. The part that both mitofusin 2 and optic atrophy protein 1 play in fission-fusion might at least partly explain both the pathophysiology of neuronal–axonal dysfunction and the over lapping phenotypes of mutations affecting these proteins, although an additional role in mtDNA maintenance cannot be excluded ***(Santos et al., 2010; Cho, 2010).***

Elevation of lactic acid in blood or CSF is a common phenomenon in patients with mitochondrial respiratory chain disorder (MRCD), particularly patients with severe autosomal recessive type, the blood lactate to pyruvate ratios indirectly reflect the NADH to NAD cytoplasmic redox state. Therefore, an accurate measurement of pyruvate is also necessary. Elevated plasma alanine is an indication of the accumulation of pyruvate. Defects in pyruvate metabolism such as pyruvate dehydrogenase complex deficiency, pyruvate carboxylase

deficiency, or biotinidase deficiency will cause pyruvate elevation in blood or CSF ***(Debray, 2007).***

Mitochondrial proliferation in skeletal myofiber is suggestive of a respiratory chain disorder, which is revealed as ragged red fibers (RRF) on modified Gomori trichrome staining as red granular deposits of mitochondrial in the subsarcolemmal space, the RRFs are shown as ragged blue fibers (RBFs) on histochemical staining of succinate dehydrogenase (SDH). RRFs or RBFs can also appear in myopathic forms of mtDNA depletion syndromes. SDH histochemistry is also useful for the diagnosis of complex II deficiency. Another useful histochemical evaluation is the staining for cytochrome c oxidase (COX). Muscle fibers with normal COX activity appear brown, while negative fibers stain poorly (***Tang and miles, 2012).***

PGC1α (peroxisome proliferator activated receptor gamma coactivator-1 α) is now increasingly being recognized as an important therapeutic target for neurodegenerative disorders. PGC1α expression and/or function is impaired in all major neurodegenerative diseases; therefore, pharmacologic/ transcriptional activation of the PGC1α pathway is expected to have neuroprotective effects. Over expression of PGC1α was shown to reduce plaque in an in vitro model of AD, produce neuroprotective effects in a transgenic mouse model of ALS, and enhance the mitochondrial membrane potential and reduce

mitochondrial toxicity in vitro models of huntingtons disease HD ***(Da Cruz et al., 2012).***

Another potential approach to activating the PGC1α pathway and thereby improving mitochondrial function is via activation of PPARs (Peroxisome proliferator-activated receptor). The PPARs are a subfamily of nuclear receptors that are ligand-modulated transcription factors that regulate gene expression programs of metabolic pathways. PPAR agonists increase oxidative phosphorylation capacity in mouse and human cells and enhance mitochondrial biogenesis ***(Chiang et al., 2010).***

Dysfunctional mitochondria are linked to neurode-generation in many disorder processes including stroke. mitochondrial-dependent therapeutic agents that could provide neuroprotection following stroke include: (1) increasing ATP production by purinergic receptor stimulation, (2) decreasing the production of ROS by superoxide dismutase, or (3) increasing antioxidant defenses by methylene blue, and their benefits in providing neuroprotection following a stroke ***(Liu et al., 2010).***

Aim of the Work

To review updates of mitochondrial dysfunction in neurodegenerative disorders in order to understand better management of these disorders.

Molecular Biology of Mitochondrion

Mitochondrial DNA structure and function

The outer membrane of mitochondrion contains porins that allow molecules that are less than 5 KDa to freely diffuse through. However, larger proteins require the presence of a mitochondria targeted sequence that will enable binding to specific transporters (translocase of the outer membrane (TOM) and translocase of inner membrane (TIM) for entry into the organelle. The outer membrane therefore mainly serves as a permeability barrier to the cytosolic components ***(Yamamoto, 2011).***

Recently, it was presumed that the inter membrane space had no specific function and was identical to the cytosol in its contents. However, emerging studies have suggested an important role for this space in maintaining mitochondrial homeostasis, including protein sorting and lipid homeostasis ***(Yamamoto, 2011).***

The inner membrane of the mitochondria is the single most extensively studied cell membrane component due to its relative importance in oxidative phosphorylation. This membrane comprises of the highest number of proteins per phospholipid moiety in a cell. These proteins are integral to the

electron transport chain, ATP synthesis and transport. The inner membrane is also distinct from other membranes by the presence of cristae (invaginations of the membrane), which allow for compartmentalization and increases the surface area. The inner membrane is also less permeable to ions and molecules and helps in compartmentalization through separation of the mitochondrial matrix from the cytosolic environment, so acting as an electrical insulator and chemical barrier. This helps in maintenance of the electron gradient across the membrane, which enables generation of ATP ***(Davies, 2011).***

The mitochondrial matrix of mammalian cells contains the mitochondrial DNA (16.5 kilobase genome) that encodes for nearly 13 proteins, some of which are involved in oxidative phosphorylation. The remaining proteins required for the normal function of the mitochondria are encoded by the nuclear genome and imported into the mitochondria. The matrix also contains a majority of the enzymes required for the citric acid cycle, which oxidizes acetyl coenzyme A and in the process generates energy in the form of nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH2). These molecules then serve as substrates for oxidative phosphorylation by the proteins in the inner membrane to generate cellular energy in the form of ATP ***(Asin-Cayuela, 2007)***.

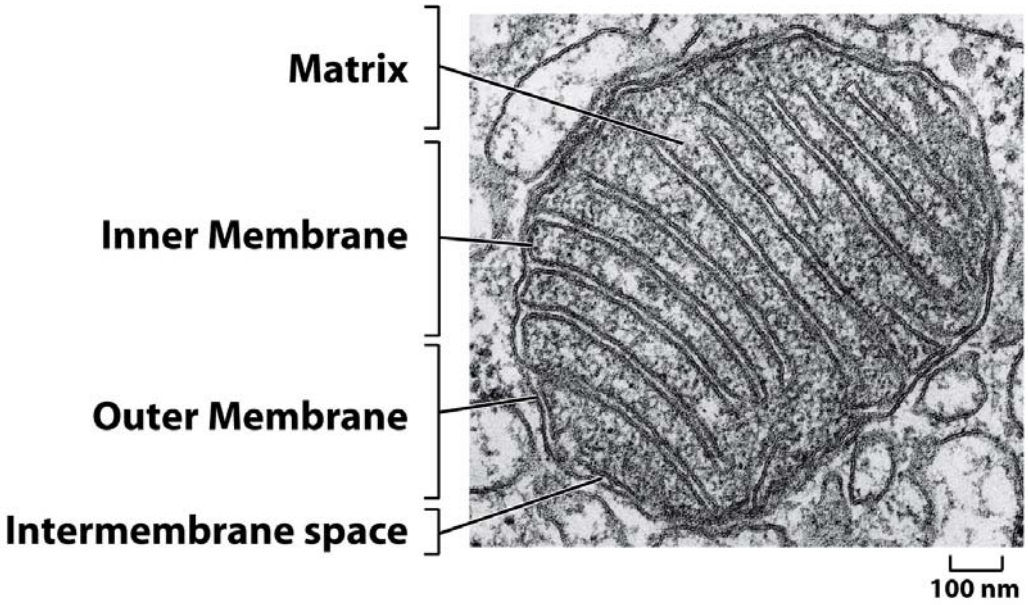

Figure (1): Molecular Biology of the Cell ***(Garland Science 2008)***

Mitochondrial Genetics

Mitochondria are unique in that they have their own DNA pool (mtDNA) distinct from that of nDNA. mtDNA is almost exclusively maternally inherited and has independent evolutionary origins from nDNA that date back to the time when mitochondria were separate organisms before forming a symbiotic relationship with eukaryotes ***(Schapira, 2006; Wallace and Fan, 2010).***

Human mtDNA is approximately 16.6 base pairs long, forming a closed, double stranded structure. Each mitochondrion contains between 2 and 10 mtDNA copies that consist of 37 genes coding for 22 transfer and 2 ribosomal DNAs and 13 proteins, the latter including the enzymes

involved in the oxidative phosphorylation (OXPHOS) pathway involved in ATP production ***(Eichner and Gigue`re, 2011)***

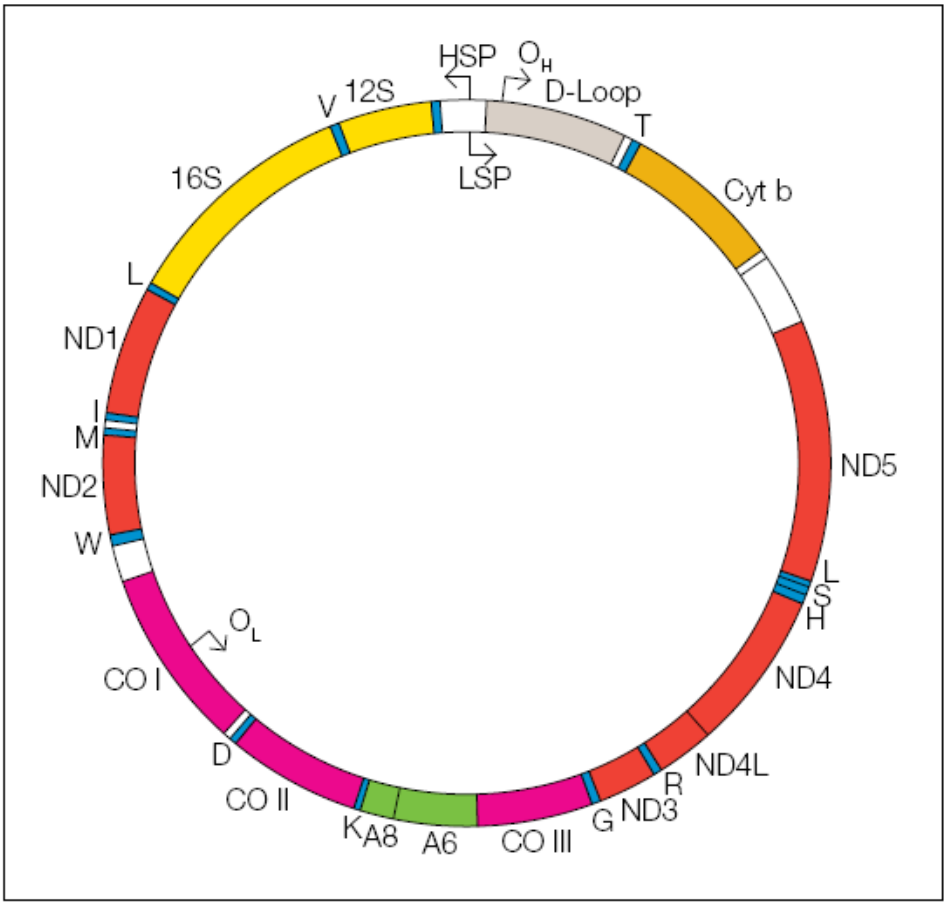

Figure (2): The human mitochondrial genome encodes for 13 polypeptides, 22 tRNA. the subunits of NADH ubiquitinone oxidoreductase (ND), cytochrome c oxidase, cytochrome b, ATP synthetase (a), 22 Trna,and two rRNAS (12s&16s) are shown. The origin of heavy & light strand replication ***(DiMauro, 2005).***

OXPHOS units are coded by both nDNA and mtDNA, with the former contributing somewhere in excess of 1000 proteins that are essential for mitochondrial function. Of these, 705 are under the transcriptional control of estrogen related receptors, α, β, and γ, that are responsible for the integrated control of mitochondrial metabolism. Although the mtDNA sequence in most cells is identical and is consequently termed homoplasmic, the coexistence of wild-type and mutant mtDNA in the same mitochondrion and /or cell is known as heteroplasmy ***(Eichner and Gigue`re, 2011).***

The OXPHOS pathway consists of five different ETC complexes located on the inner mitochondrial membrane that together contribute to the generation of the mitochondrial electrochemical gradient, these complexes are composed of proteins that originate from both nDNA and mtDNA, Complex I consists of 45 peptide subunits, 7 originating from mtDNA with the remainder from nDNA. Complex II has four subunits, all of which are derived from nDNA, and Complex III has 11 subunits, only one of which originates from mtDNA. Complex IV has 12 subunits, 3 of which are derived from mtDNA, and complex IV has approximately 16 subunits, 2 of which are from mtDNA. The fifth ETC complex, Complex V, is ATP synthetase ***(Schon et al., 2010).***

Complex II (succinate dehydrogenase-CoQ oxidoreductase) contains only nuclear DNA-encoded subunits.

Reducing equivalents produced in the Krebs cycle and in the β-oxidation spirals are passed along a series of multimeric protein complexes (the electron transport chain) and the energy produced by the reactions of the electron transport chain is utilized to condense inorganic phosphate and adenosine diphosphate to produce adenosine triphosphate (ATP) ***(DiMauro, 2005).***

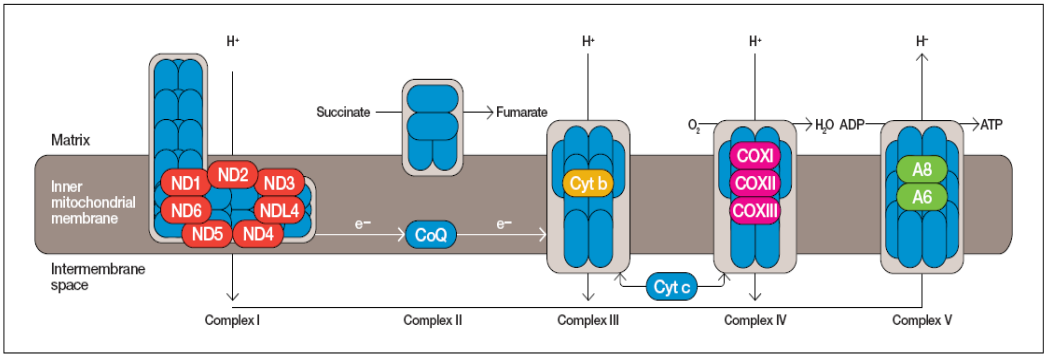

Figure (3): Schematic representation of the respiratory chain system. Subunits encoded by mtDNA are shown in red and subunits encoded by nuclear DNA are shown in blue. Electrons (e-) flow along the electron transport chain, and protons (H+) are pumped from the matrix to the intermembrane space through complexes I, III, and IV, then back into the matrix through complex V, producing ATP. Coenzyme Q (CoQ) and cytochrome c are electron carriers ***(DiMauro, 2005).***

Mitochondrial genetics is unusual in many ways. First, mitochondria and mtDNAs are unique in that they are inherited only from the mother. Thus, most pathogenic errors in mtDNA are maternally inherited, women will transmit the defect to all of their children (males and females), but only the daughters will transmit the disease to their children. A disease expressed in both sexes but with no evidence of paternal transmission is