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Mitochondrial Dysfunction in Ageing: Involvement of Oxidative Stress and Role of Melatonin

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ABSTRACT
Over the last decade, aggregating evidence has been suggested that there is a causative link between mitochondrial dysfunction and aging in the individuals. Several studies on animal models of ageing and neurodegenerative diseases have provided compelling evidence that mitochondria are in the development and progression of diseases such as AD. Further, a role for mitochondrial dysfunction associated with ageing is supported by studies, which have revealed that amyloid-β enters mitochondria and disrupts the electron transport chain (ETC) which generates reactive oxygen species (ROS) and inhibits the cellular ATP production which in turn results into the progression of neurodegenerative diseases like AD. In addition, "free radical mitochondrial theory" associated with oxidative stress has been reported as a key common pathway for cellular dysfunction and death and a possible therapeutic target during a broad spectrum of human medical conditions including cancer, diabetes, various neurodegenerative disorders. Furthermore, recent evidence suggests that chain reaction of lipidperoxidation due to oxidative stress leads to cell injury and DNA damage. Melatonin have ability to protect against damaging oxygen reactants under various extreme oxidative stress conditions and also, various studies have revealed that melatonin has been very effective in the prevention ofamyloid-β peptide(Aβ) induced toxic effects on neuronal cells in AD patients. Here we discuss the different theories associated with the mitochondrial dysfunction which leads to the different relevant diseases that underlie the central role of mitochondria in the aging process and role of the melatonin in diseases associated with mitochondrial dysfunction.
Keywords: Aging, Mitochondrial dysfunctions, ROS production, free radical mitochondrial theory, Lipid peroxidation, Melatonin.

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INTRODUCTION

Aging is belief to be a degenerative process which is caused by accumulated damage that leads to cellular dysfunction, tissue failure, and death. Several theories related aging have been proposed[1–5], but the mitochondrial free radical theory of aging (MFRTA) has been center stage for decades[2]. As per this theory, ROS are considered to be unwanted toxic by-products of aerobic metabolism which induce oxidative damage to various cellular macromolecules because of their high chemical reactivity. The main production site of superoxide, an abundant ROS in the cell formed at the level of complexes I and III during electron transport is the respiratory chain (RC) which is located in the inner mitochondrial membrane (Figure 1). The superoxide anion is converted to hydrogen peroxide with the help of Superoxide dismutase (SOD). Even though hydrogen peroxide itself is not a free radical, in the presence of transition metals it can be converted to the highly reactive hydroxyl radical through the Fenton reaction (Figure 1). The hydroxyl radical is highly reactive and causes oxidative damage to virtually every molecule type in the cell, including lipid, proteins and nucleic acid, therefore it is considered to be the most damaging form of ROS. The MFRTA theory is basically depends upon several observations: (a) mitochondrial ROS production increases with age, (b) activity of several ROS-scavenging enzymes decreases with the age, (c) mutations of mitochondrial DNA (mtDNA) accumulate during aging, and (d) a vicious cycle occurs due to somatic mtDNA mutations impair RC function, which in turn result in a further increase in ROS production and accumulates oxidative damage to proteins, lipids, and DNA[6–8]. According to this theory, mitochondria plays a very crucial role in mediating and amplifying the oxidative stress that drives the aging process.

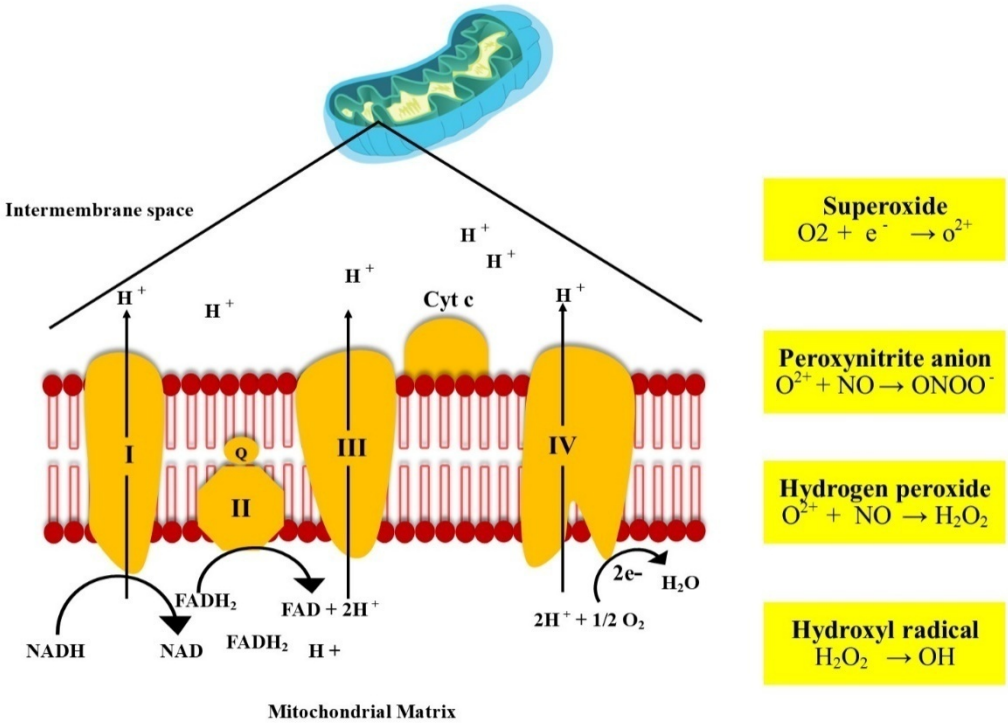

Figure 1. Schematic model of the oxidative phosphorylation system and the production of ROS. H^+- Proton, Cyt c- Cytochrome C, NADH- Nicotinamide Adenine Dinucleotide Hydrogen, NAD- Nicotinamide Adenine Dinucleotide, H_2O- Water, O_2- Oxygen, O_2^-Superoxide, $ONOO^-$- Peroxynitrite anion, H_2O_2- Hydrogen Peroxide, OH^- -Hydroxyl radical, $FADH_2$- Flavin adenine dinucleotide, ROS- Reactive Oxygen Species

MITOCHONDRIA AND AGING

Mitochondria modulate a multitude of various metabolic and signalling pathways and also plays a key role in programmed cell death. The mitochondrial oxidative phosphorylation is the primary source of high-energy compounds in the cell. The most important function of mitochondria is to produce ATP through the process of oxidative phosphorylation, which is conducted by the four RC complexes (complexes I–IV)and the ATP synthase (complex V), all are present in the inner mitochondrial membrane. As mitochondria contain their own genetic information, a double-stranded circular molecule of 16.5 kb encoding 13 proteins, 22 transfer RNAs (tRNAs), and 2 ribosomal RNAs in mammals, therefore they are very unique among the cellular organelles. The 13 mtDNA encoded proteins are all components of the RC and oxidative phosphorylation collapses in the absence of mtDNA expression [9]. Mitochondrial function has long been accepted that it gets declined during aging concomitant with the result alteration in mitochondrial morphological, for example, abnormally rounded mitochondria in aged mammals [10]. Mitochondrial energy metabolism dysfunction leads to decreased ATP production, impaired calcium buffering and generation of ROS is increasingly recognized as playing a key role in both aging and neurodegenerative diseases. Mitochondria are likely to be the major source of ROS in eukaryotes, as it has potential for univalent transfer of electrons from the electron transport chain to oxygen. Formation of reactive oxidants, including ROS, appears to be increased in damaged mitochondria, and in cell with compromised mitochondrial function. Number of mitochondria reduces with the age in liver cells of mice [11], rats [12], and humans [13,14], concurrent with a decrease in mtDNA copy number and mitochondrial protein levels [15]. Furthermore, in comparison with juvenile animals (3-4 months), RC capacity is decreased up to 40% in rat liver mitochondria of old animals (24 months) [16]. The decrease in the RC capacity has also been reported with age in human liver, heart, and skeletal muscle[17,18] . The some of these changes may be secondary, as RC function is inducible [19]. It is reported that, the activity of specific RC complexes and certain nuclear-encoded mitochondrial proteins also declines with mammal's age [20–24]. The activity of complexes I and IV declined with age in liver, brain, heart, and kidney of mice and rats [22–24], whereas, more interestingly, the activity of complexes II, III, and V remains mostly constant [25]. The reasons for these partially contradictory differences in age-related decline in RC function are unknown, reduced expression of mtDNA as well as elevated levels of mtDNA mutations have been suggested as potential causes [24]. Moreover, it is important to note that the cell

type composition likely changes in aging organs and hence a difference in function of mitochondria in tissue homogenates from young and old individuals may be hard to interpret. Further factors, such as differences in the applied methodology [26] and difficulties in finding suitable controls to aged patient cohorts [19], leads to complicate this type of comparison. While aging is related with the decline in mitochondrial function, this observation alone does not imply causality because age-associated changes in mitochondrial function might be secondary mechanism to other mechanisms [27]. Recent genetic models suggest that mtDNA mutations induces aging phenotypes and create RC dysfunction. Furthermore, it is important to consider that mitochondrial biogenesis is controlled simultaneously at many different levels, when considering the role of mitochondrial dysfunction in aging[28–32]. As it is also reported that hormones such as thyroid and estrogens are not only plays an important role in cell growth and differentiation, but also very important regulators of mitochondrial biogenesis. Therefore, clearly shown that, physical activity and caloric restriction both can reduce oxidative damage and can improve mitochondrial function[33].

MITOCHONDRIAL DYSFUNCTIONS

Amyloid-β peptide induced ROS production: Neurodegenerative diseases

Mitochondria are the main source of ROS

Mitochondria are the cytoplasmic organelles important for life and death. Mitochondria plays a role in several cellular functions, including production of major part of cellular ATP, regulation of intracellular calcium, the release of proteins that activate the *caspase* family of proteases and free radical production and scavenging. The mitochondria contain the respiratory chain or electron transport chain (ETC) which is located in the inner mitochondrial membrane and consists of five complexes (complexes I–V), the fifth complex is directly involved in ATP synthesis. These complexes of the mitochondrial respiratory chain are basically made up of multiple subunits, and all contain proteins encoded by nuclear DNA and mtDNA, except for complex II, which is entirely encoded by nuclear DNA [34–37]. The mitochondria, also called as the powerhouses, are the chief energy-producing organelles in the most cells, which provide most energy for our normal life. Basically, energy in the form of ATP is efficiently produced via oxidative phosphorylation(OXPHOS) in the mitochondrial RC. In several reports firmly reported that mitochondria are believed to be the major intracellular source of ROS. Several years of research revealed that free radicals are produced at multiple sites in the mitochondria: Complexes I and III produces superoxide radicals via electron leaks, these radicals are dismutated by manganese superoxide dismutase, and further generating H_2O_2 and oxygen. By either glutathione peroxidase or catalase H_2O_2 is converted into H_2O [38]. Conditionally, Complex II also produces ROS [37]. Components of tricarboxylic acid, including α-ketodehydrogenase and pyruvate dehydrogenase produces superoxide radicals in the matrix. In addition to this, via monoamine oxidase mitochondrial outer membrane also produces free radicals, by catalysing the oxidative deamination of primary aromatic amines. This deamination is a quantitatively large source of H_2O_2. A little quantity of ROS may not be toxic to cells, and may have some benefit roles to cells and homoeostasis. Recent reports strongly suggest that ROS, and specifically mitochondria generated ROS, are involved in physiological signalling cascades regulating various cellular and organ functions [39,40]. However, excessive and/or sustained increase in ROS, may lead to oxidative stress, as primary factors in numerous pathologies, including aging and neurodegenerative diseases, are widely recognized [40–42]. It shown that Aβ cascade hypothesis remains the major cellular event in AD or evidence also indicates a mitochondrial cascade hypothesis, mitochondrial dysfunction which may initiate the disease [43]. This hypothesis, is supported by recent observations showing that early impairments of mitochondrial dysfunction and oxidative stress may precede Aβ overproduction and deposition [43–47].

Mitochondrial localization of Aβ

As per the above, Aβ deposit is the main hallmark of AD, and Aβ42 is the most toxic peptide and the predominant species in the parenchymal amyloid deposits in AD brain, and it is an initially deposited species [48–51]. Even though the basic view is that Aβ is deposited extracellularly, both cellular and biochemical studies carried out in different models of AD and aging have provided evidence that this peptide also can accumulate inside neurons, target mitochondria, and contribute to further disease progression [52–58]. With the use of in vivo and in vitro approaches, Hansson Peterson et al. demonstrated that Aβ is transported into rat mitochondria via the translocase of the outer membrane (TOM) and localizes within the mitochondrial cristae [59]. It has been shown that Aβ42 can promote mitochondrial mislocalization, which contributes to Aβ42-induced neuronal dysfunction in a transgenic Drosophila model. In Aβ42 fly brain, mitochondria were decreased in axons and dendrites, and gets accumulated within the somata without severe mitochondrial damage or neurodegeneration. By genetic reductions in mitochondrial transport, and modulation in cAMP levels and protein kinase A(PKA) activity, the Aβ42-induced behavioural defects were exacerbated. The perturbations in mitochondrial transport in

neurons were sufficient to disrupt PKA signalling and suggesting a mechanism whereby mitochondrial mislocalization contributes to Aβ42-induced neuronal dysfunction, which ends up demonstrate that mislocalization of mitochondria underlies the pathogenic effects of Aβ42 in vivo [60].

Aβ induces ROS production

The oxidative stress and its sequelae are likely associated to both apoptotic and necrotic mechanisms of neurotoxicity and there is an evidence suggesting that tissues from both AD patients and individuals with mild cognitive impairment have elevated levels of oxidative DNA damage [61]. Further, post-mortem tissue provides strong evidence for significant increased levels of cellular oxidative stress in vulnerable regions (cortex and hippocampus) of AD brains compared to aged controls[62,63]. Most significantly, Aβ peptides directly initiate free radical formation, cellular dysfunction, and subsequent neuronal death [64–67]. The mitochondria are thought to be the central target for oxidative stress induced damage [68]. Recent primary culture study has shown that oligomeric Aβ42 could induce reactive ROS production from cortical neurons through activation of NADPH oxidase [69]. Notably there is a defect in the antioxidant defence system, which may lead to oxidative damage in patients with AD and it has been found that erythrocyte antioxidant enzyme activities were significantly lower in patients with AD compared with controls. These results strongly suggest that alterations in these enzymes may play a role in the etiopathogenesis of AD and hence, Aβ-associated oxidative stress and related antioxidant defence system may be of fundamental importance in AD etiology and pathogenesis [70].

Mitochondrial DNA changes in AD

The Aβ cascade hypothesis remains the important pathogenic model, as suggested by familiar AD, mainly related to mutation in amyloid precursor protein(APP) and presenilin genes. Remaining more than 98% of AD patients are mostly sporadic late-onset cases, with a complex etiology because of interactions between environmental conditions and genetic features of the individuals. An energy failure, increased oxidative stress and accumulation of Aβ, observed by the somatic mutations in mtDNA. Although, no clear causative mutations in the mtDNA have been linked to AD, even some variations have functional consequences, including changes in enzymatic activity [71]. Infact, results of studies on the role of mtDNA polymorphisms or haplogroups in AD are controversial [70–72][68,69]. Recently, to investigate the possible association between mtDNA inherited sequence variations, a high-resolution analysis in 936 AD patients and 776 cognitively assessed normal controls from central and northern Italy was performed. A sub- haplogroup H5 is a risk factor for AD in particular for females and independently from the apolipoprotein E(APOE) genotype. The multivariate logistic regression shown an interaction between H5 and age [73].

Mitochondrial dysfunction in AD

It has been clear that impairment occurs to all five of the mitochondrial OXPHOS complexes in the AD brain. The mitochondrial dysfunction accomplished with metabolic dyshomeostasis and reduced ATP synthesis, occurs early in AD. Besides that, mitochondrial dysfunction is proposed to link between amyloid deposition and neuronal synaptic loss. Thus, the existence of mitochondrial dysfunction is very important in AD[65–74]. The age-dependent accumulation of mutations in mtDNA and resulting rise in oxidative stress and impairment in mitochondrial respiratory chain, especially complex IV, gained attention as potential factors that could participate in the onset of sporadic AD. Indeed, the decreased activity of the cytochrome c oxidase (COX, complex IV of respiratory chain) has been reported in different brain regions of AD patients [75]. The COX activity was also reduced in AD transgenic (Tg2576) mice, as mutant APP/Aβ impair mitochondrial metabolism in AD. And a decrease in COX activity and an increase in hydrogen peroxide were found in young Tg2576 mice, leads to the appearance of Aβ plaques. And also, in vitro study using primary neuron culture and confocal microscopy demonstrates that Aβ impairs the mitochondrial movement, these findings indicate that mitochondria are the targets of Aβ, and mitochondrial dysfunction happens at early stage of the disease, suggesting that early mitochondria-targeted therapeutic interventions may be effective in delaying AD progression in treating AD patients[76]. The inhibitory potential mechanism of the Aβ42 on activity of electron transport chain enzyme complexes was investigated, in human mitochondria. Furthermore, photoinduced cross-linking of unmodified proteins revealed dimeric Aβ as the only Aβ species to provide significant temporal correlation with the observed COX inhibition. An analysis of brain and liver from an AD model mouse (Tg2576) revealed abundant Aβ immunoreactivity within the brain mitochondria fraction [55]. These data have been clearly shown that endogenous Aβ is related with brain mitochondria and that Aβ1–42, possibly in its dimeric conformation, is a potent inhibitor of COX, but only when in the presence of Cu^{2+}. Therefore, in the neurodegeneration process of AD, Cu^{2+}-dependent Aβ-mediated inhibition of COX may be an important contributor [55]. Copper may participate in the pathophysiology of AD, interestingly copper can bind to APP and Aβ, then affects their structure, and the formation of beta-sheet structure that is widely accepted as toxic secondary structure of Aβ [77]. The age-dependent decline in the

mitochondrial respiratory function, especially COX activity, may participate in the formation and accumulation of Aβ. These knockout (KO) mice showed an age-dependent COX deficiency within the cerebral mantle and hippocampus then AD-like double transgenic mice expressing mutants of APP and Photosystem 1 (PS1) during a neuron-specific COX-deficient background were generated. More surprisingly, compared with the COX-competent transgenic mice, COX10 KO mice exhibited fewer amyloid plaques in their brains. This decrease in amyloid plaques in the KO mouse was accompanied by a reduction in Aβ42 level, β-Secretase 1(BACE1) activity, and oxidative damage. Likely, production of ROS from cells with partial COX activity was not elevated [78–80]. Accordingly, these results suggest that, contrary to previous models, a defect in neuronal COX does not increase oxidative damage nor predispose for the formation of amyloidogenic APP fragments. On the other side, this study also shown that genetic modification of mitochondria can inhibit ROS overproduction, eventually reduce Aβ level, prevents the development and progress of AD, suggesting a useful target for treatment of the disease.

The free radical mitochondrial theory

Free radicals and oxidative stress

The free radicals are atoms or molecules that contain unpaired electrons in their outer orbitals, their electronic configurations render these chemical species highly reactive with membrane lipids, proteins, nucleic acids, and other cellular substrates. The examples of common, endogenously-produced reactive oxygen species (ROS) are superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), singlet oxygen, hypochlorous acid (HOCl), peroxynitrite ($ONOO^-$), and the hydroxyl radical (OH•). Transition metals, for example ferrous iron (Fe^{2+}) or cuprous copper (Cu^{1+}), plays an important role in cellular redox chemistry by reducing H_2O_2 to the highly-cytotoxic OH• radical via Fenton catalysis. Additionally, transition metals can also behave as non-enzymatic peroxidases that bio-activate benign catechol-containing compounds (like dopamine) into toxic ortho-semiquinone radicals. In mammalian tissues, evolutionarily-conserved antioxidant enzymes e.g. the superoxide dismutase, catalase, the glutathione peroxidases, and various reductases operate in concert with a host of non-enzymatic, low-molecular-weight antioxidant compounds such as *glutathione* (GSH) and thioredoxin to maintain redox homeostasis. Furthermore, by maintaining transition metals during a relatively low redox state, metal-binding proteins, like ferritin, transferrin, lactoferrin, the metallothioneins, and ceruloplasmin, contribute substantially to the antioxidant protection of tissues and body fluids. Oxidative stress has been defined as, a disturbance within the pro-oxidant/antioxidant balance in favour of the previous, resulting in possible damage [81]. It has been reported that oxidative stress as a key common pathway for cellular dysfunction and death and a possible therapeutic target during a broad spectrum of human medical conditions including cancer, diabetes, obstructive lung disease, inflammatory bowel disease, cardiac ischemia, glomerulonephritis, macular degeneration, and various neurodegenerative disorders[82].

The free radical-mitochondrial theory of ageing

Out of the various theories of ageing promulgated over the last several decades, the "free radical-mitochondrial" theory remains among the foremost successful. Within the mid-1950s, Denham Harman, was the primary to posit that "free radical reactions are involved within the ageing changes related to the environment, disease, and intrinsic ageing processes" [83]. The "free radical" theory of ageing was further defined upon recognition of the role played by mitochondria as both a leading source of ROS generation and main target of oxidative molecular damage in ageing tissues. The "free radical-mitochondrial" theory states that oxidative injury to mitochondria, triggered by intrinsic metabolic processes and environmental insults, results in a cascade of events characterized by infidelity of electron transport and a self-sustaining spiral of augmented radical generation within the inner mitochondrial membrane. Further, in turn, engenders bioenergetic failure and progressive tissue ageing [84,85]. The common clinical impression that patients with chronic systemic illness or drug abuse often appear "older than stated age" may be a reflection of this concept at the organismal level. In conversely, normal ageing tissues compromised by an increasingly unfavourable mosaic of healthy and ROS-spewing mitochondria (heteroplasmy) may become particularly susceptible to ageing-associated conditions such as atherosclerosis, neurodegeneration, and cancer [86–88]. The following observations have been considered particularly germane to the free radical-mitochondrial theory of ageing: (1) In many tissues, ROS production, oxidative substrate damage, and mitochondrial insufficiency increase as a function of advancing age. (2) With some notable exceptions, the longevity of many vertebrate and invertebrate species correlates inversely with O2 consumption and basal metabolic rate and directly with natural or artificially-bolstered antioxidant defences [89]. (3) Caloric restriction and attenuation of mitochondrial respiration diminish age-related oxidative damage and, in some cases, significantly extend longevity [89]. (4) Mitochondrial DNA is specifically vulnerable to oxidative damage, exhibiting an almost 10–100-fold greater mutation rate than nuclear DNA. Mutated mtDNA may code for abnormal cytochromes of the electron transport chain (ETC) that promote infidelity of electron transport, ROS (superoxide, hydrogen

peroxide) generation within the inner mitochondrial membrane, and a vicious cycle of further mtDNA damage. (5) Mutations linked to shortened longevity in *C. elegans* are associated with increased ROS production.

Oxidative stress, iron deposition, and mitochondrial insufficiency in human central nervous system (CNS) Disorders

An oxidative damage, iron deposition and mitochondrial insufficiency are amply documented within the normal mammalian CNS as a function of advancing age using an array of biochemical, histopathological and imaging techniques. However, there appears to be selective regional vulnerability within the ageing CNS to this pathological triad and reasonable co-localization of these changes within affected areas [90–93]. In the ageing human brain, markers of free radical injury, excessive iron accumulation, and mtDNA deletions are more robust in the basal ganglia, hippocampus and certain cerebellar nuclei than in the cerebral cortices and other brain regions [94]. The mechanisms governing the heterogeneity of these pathological features in the normal ageing CNS and in various ageing-related neurodegenerations (below) remain inadequately understood.

Products of lipid peroxidation as common markers of cancer

The oxidative stress leads to cell injury by three basic ways: (a) lipid peroxidation of membranes, (b) oxidative modification of proteins and (c) DNA damage. Lipid peroxidation primarily affects cell membranes and other lipid containing structures [95]. The β-oxidation of lipids is usually followed by a release of oxygen, which is reduced to water through the mitochondrial respiratory chain. Further, lipids can be oxidized with efficient ROS initiators, particularly hydroxyl radical and perhydroxyl radical(HO_2•), forming water and a lipid radical. This initiates the reaction of lipid peroxidation, which takes place in the cells. The lipid radical reacts directly with molecular oxygen and generates a lipid peroxyl radical and this lipid peroxyl radical is not a very stable molecule and can combine with another adjacent carboxylic fatty acid to make alipid hydroperoxide and different lipid radicals, or it can react with itself. The Lipid hydroperoxide are often also weakened into a lipid alhoxyl radical and a hydroxyl. Lipid radicals formed at the previous stage can reactwith oxygen to supply another lipid peroxyl radical, andso on, this process is named “chain reaction of lipidperoxidation” (Figure 2). The most intermediate productsof the reaction are lipid hydroperoxides (LOOHs). Recently, it was reported that the by-products of lipid peroxidation can induce carcinogenesis. The cell membranes contain a high concentration of polyunsaturated fatty acids, which are frequently subjected to peroxidation and this leads to an inhibition of growth and death of cells [96]. The oxidation of phospholipids in the inner mitochondrial membrane (IMM) can initiate the mitochondria-mediated pathway of apoptosis. The lipid peroxidation by-products firstly react to cardiolipin molecules, the IMM phospholipids, which are bound to cytochrome c [97–99]. This stimulates disturbances of cytochrome-cardiolipin interaction and dissociation of cytochrome c from the IMM [100–102]. The release of cytochrome c into the cytoplasm induces a series of biochemical reactions, results into a caspase activation and subsequent cell death. At the same point, a major regulator of mitochondrion-dependent apoptosis is B-cell lymphoma 2 (Bcl-2) family of proteins, which show both pro- and anti-apoptotic activities. The proteins belonging to the Bcl-2 family are sure to the outer mitochondrial membrane (OMM) and may modulate its permeabilization [103]. The Bax and Bak are anti-apoptotic proteins of the Bcl-2 family, which can be activated in two ways: through disturbance of their bond with antiapoptotic proteins, or interaction with activator proteins, which stimulate their conformational changes. The inactivated Bax proteins can be localized as monomers in the cytosol or closely associated with the OMM. Further, during the process of its activation, Bax forms homo-oligomers and inserts itself into the OMM as well as into Bak. This results into membrane pore formation and permeabilization, which initiates the release of cytochrome c in cytosol. An anti-apoptotic protein prevents mitochondria-mediated apoptosis through their interaction with pro-apoptotic ones [104]. The reported studies show that overexpression of Bcl-2 inhibits the release of cytochrome c from mitochondria and the subsequent apoptotic response is blocked[105]. For instance, 4-hydroxynonenal(HNE)-induced caspase activation is suppressed in Bcl-2 transfected colorectal carcinoma cells, induces an apoptosome assembly in the presence of ATP/dATP. This stimulates pro-caspase-9 directly within the apoptosome complex. Furthermore, the pro-caspase-9 is cleaved to the active caspase-9, which, in turn, activates the caspases-3, -6 and -7, leading to DNA fragmentation and cell death[105–108]. The caspase activation is blocked and the cell death is re-directed from apoptosis to necrosis, if the cellular ATP/dATP level is depleted. The apoptosome formation and release of cytochrome c can be also triggered though the extrinsic pathway of apoptosis. In addition, the accumulation of damage directly in mitochondria may also cause enhanced oxidant production and a cascade of degenerative events (Figure. 3). It should be considered that HNE might be generated directly through the oxidation of mitochondrial phospholipid cardiolipin [109]. During this case, HNE reacts with surrounding molecules near the location of its formation, thereby derived apoptosis again by promoting chain-

reactions of the mitochondria. This process seems to be involved in cancer and atherosclerosis. Thus, it has been reported that HNE could induce mitochondria-mediated apoptosis within the pheochromocytoma (PC12) cell line and colorectal carcinoma cells [110–113].

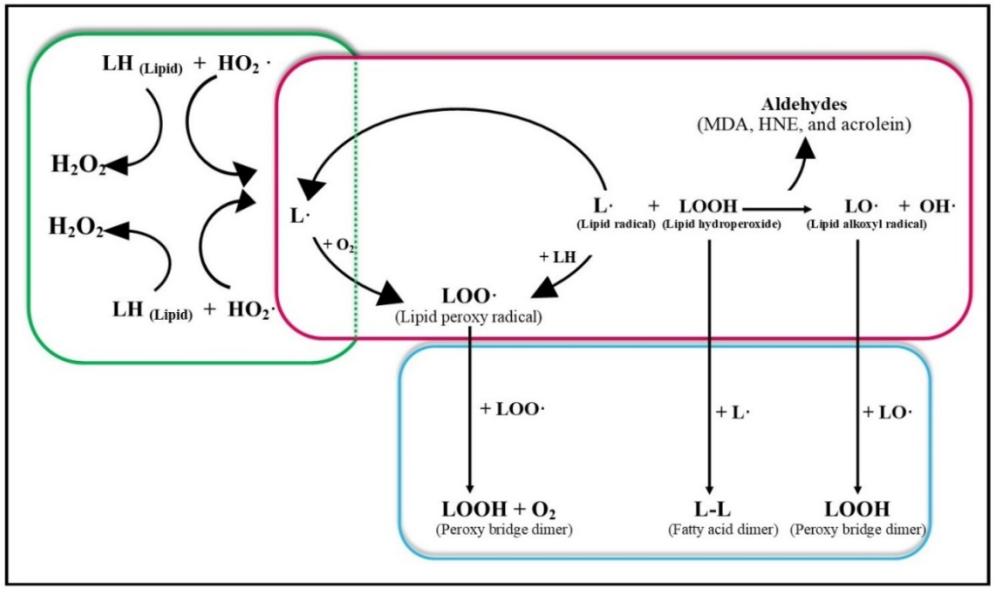

Figure 2. Scheme of lipid peroxidation chain reaction [96]. LH- Lipid, H_2O_2- Hydrogen Peroxide, OH^-- Hydroxyl Radical, O_2- Oxygen, LOOH- Lipid Hydroperoxide LO• - Lipid Alkoxyl Radical, LOO•- Lipid Peroxyl Radical, MDA- Methylenedioxyamphetamine, HNE- 4-Hydroxynonenal, L-L- Fatty Acid Dimer, L• - Lipid Radical

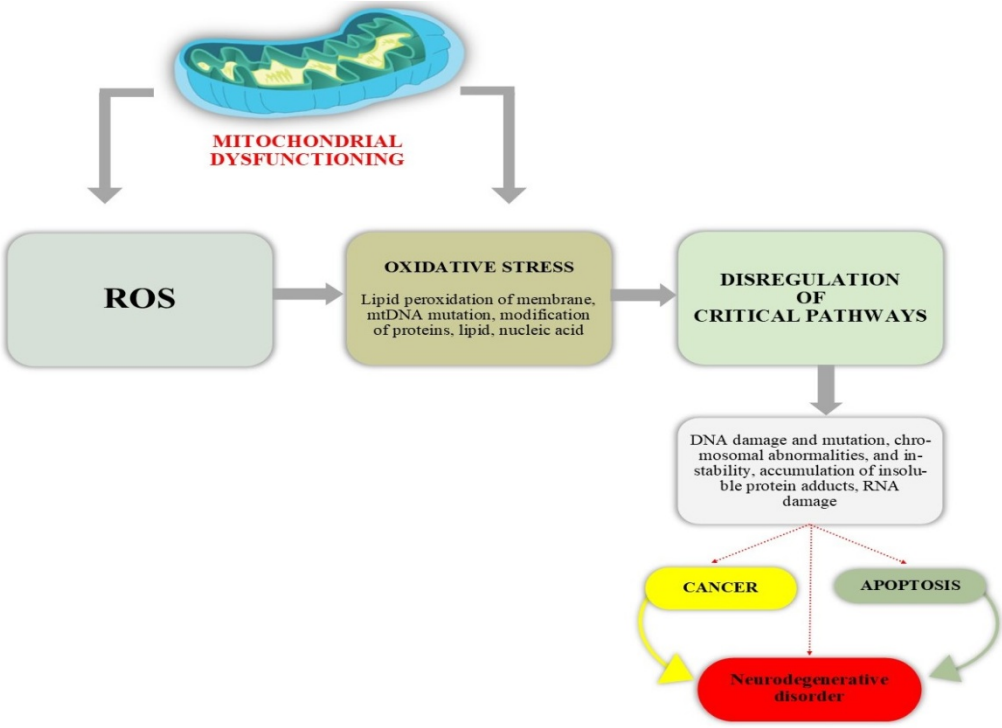

Figure 3. Schematic diagram illustrating the harmful effects of ROS on the cellular processes and subsequent results. ROS- Reactive Oxygen Species, DNA- Deoxyribose Nucleic Acid, RNA- Ribose Nucleic Acid

MELATONIN: THERAPEUTIC AGENT FOR MITOCHONDRIAL DYSFUNCTION

Melatonin is having amphiphilic nature and it can cross physiological barriers, thereby reducing oxidative damage in both the lipid and aqueous environments of cells [114]. Melatonin seems to work via a number of means to reduce oxidative stress, and both direct and indirect antioxidant properties of melatonin have

been reported[115,116]. It exhibits indirect antioxidant property by supporting superoxide dimutase (SOD), glutathione peroxidase (***GPx***), glutathione reductase (***GR***)activities [117–119]. Melatonin also stimulates glutathione production in the cells, by increasing the activity of glutamylcysteine synthase [120]. By promoting the conversion of oxidized glutathione (GSSG) back to its reduced form (GSH) [117], melatonin increases the glutathione reductase activity. Exogenous administration of melatonin given in pharmacological doses is capable of stimulating GPx activity in rat brain [121] and in several chicken tissues [122], showing that it promotes the indirect antioxidant mechanism. The studies also have been shown that melatonin may act at the genomic levels, as melatonin is present in the nuclei of neural cells and melatonin binding sites have also been found in nuclei of these cells [123–125]. Direct free radical scavenging properties of melatonin towards lipid peroxidation and DNA degradation have been shown both in vitro and in vivo [126–129]. This action of melatonin could be because of direct scavenging of free radicals and the activation of DNA repairing enzymes [130]. Melatonin can also directly act on free radicals without binding to a receptor [131]. By in vivo finding observations found that melatonin was reported to reduce the molecular damage associated with massive free radical generation [132]. Melatonin have also proven important in the ability of the melatonin to protect against damaging oxygen and nitrogen-based reactants under various extreme oxidative stress conditions [133–136]. Ebelt and his group have shown that melatonin can directly quench the free radicals like hydroxyl radicals (OH•) through electron spin resonance (ESR) studies [131,137]. In these studies, a spin trapping agent (5-diethoxyphosphoryl-5-methyl-1-pyrroline-N-oxide; DEPMPO) which is more sensitive than the one used in earlier studies, and it was found that melatonin directly quenches the emergence of the OH-DEPMPO adduct in a dose dependent manner. On other hand, Ebelt and his co-workers have found that melatonin can also prevent OH• mediated lipid peroxidation which supports the argument that melatonin can scavenge free radicals in both aqueous and lipid environments [138–140]. Under both in vitro and in vivo conditions, these observations are consistently reported with many earlier reports where in the ability of melatonin to prevent lipid oxidation were reported. Furthermore, other highly reliable methodologies have been utilized to insure the OH• scavenging activity of melatonin. Not only this, melatonin has also been shown to neutralize other reactive oxygen and nitrogen-based species in both plants and animals [141–150]. Several methods such as pulse radiolysis, salicylate trapping, reduced oxidative damage, chemiluminescence and functional theory computational tools have been used to estimate the scavenging actions of melatonin. In these studies, melatonin was found to scavenge ($NO^{\cdot}$), ($ONOO^{-}$), singlet oxygen ($1O_2$), superoxide anion radical (O_2^{-}), hydrogen peroxide (H_2O_2), and hypochlorous acid (HOCl) and these investigations were conducted by using pure chemical systems, in vitro, in vivo and in silico methodologies[115,151,160–164,152–159]. The rate of scavenging of OH• by melatonin has been found to be quite similar to that of other well-known highly efficient OH• scavengers. This is a rate constant similar to that of other highly effective scavengers such as ascorbic acid, α-tocopherol and vitamins. Along with this, the melatonin has been found to play a key role in protection of rats who exposed to ionizing radiation. Melatonin has been shown to act as peroxyl radical ($LOO^{\cdot}$) scavenger, infact during the propagation of lipid peroxidation it acts as a chain breaking antioxidant [165]. Even though melatonin was ineffective in directly neutralizing the $LOO^{\cdot}$ but it was able to retard iron-catalyzed oxidation of lipids thus acted as a preventive antioxidant of the metal ion deactivating agents [165]. Antunes suggested that melatonin can be of less importance in interrupting the lipid peroxidation under cellular environment because of its limited ability to function as a $LOO^{\cdot}$ scavenger. The previous reports indicating that melatonin is a significant antioxidant and it has been shown that the administration of melatonin highly reduce tissue damage and abnormal physiology of heart, brain and spinal cord [166–169]. Different biochemical and molecular biological studies have shown the antioxidant activity of melatonin to be beneficial for heart under anoxia/hypoxia and reoxygenation conditions [170–173]. Melatonin, a molecule with highly effective protector against radiation exposure having very low toxicity [174,175].

By lowering electron leakage and reducing free radical generation melatonin also increases the efficiency of mitochondrial electron transport chain (ETC) [174]. Mitochondria are a serious source of free radicals and therefore the inner mitochondrial membrane is that the site of the ETC comprises a system of oxido-reductant protein complexes like (complexes I, II, III and IV). Furthermore, in aerobic cells, mitochondrial oxidative phosphorylation is responsible for the generation of about 90–95% of the total ATP. The deficiencies in the ETC can lead to the leakage of electrons which later form free radicals which results in molecular damage in mitochondria. Further, this damage can lead to a group of diseases collectively referred as mitochondria related diseases. In addition to this, the active effect of melatonin at mitochondrial level is suggested by a various number of observations like i) efficient scavenger of ROS abundantly produced in mitochondria; ii), Even mitochondria cannot synthesize GSH (it is taken from the cytosol), but they do possess GPx and GR for GSH cycling and both enzymes are stimulated by melatonin;

iii), anti-apoptotic effects of melatonin; apoptosis originating from mitochondria; iv), the concentration of melatonin is higher in mitochondria as compared to other cell organelles [176]

METABOLITES OF MELATONIN AS ANTIOXIDANTS

The metabolites of melatonin are also powerful free radical scavengers. N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK) is one among the metabolites of melatonin having antioxidant activity and is it formed by both enzymatic [176–180] and non-enzymatic [115,181–186] metabolic pathways. Further, Deformylation of AFMK in turn leads to the formation of N1-acetyl-5- methoxykynuramine (AMK). Both AFMK and AMK have been found to exhibit protective effects against oxidative stress [187]. AFMK decreases lipid peroxidation and oxidative DNA damage and prevents neuronal cell injuries caused by H2O2 and β-amyloid peptide [188]. In addition to this, AFMK has been found to protect against high energy charged particle radiation induced oxidative damage to the brain which probably has been hypothesized because of its free radical scavenging activity [189–191]. This hypothesis conducted by the assessment that AFMK can efficiently scavenge OH• radicals. As compared to AFMK, its deformylation product i.e. AMK are considered to be a really good and versatile radical scavenger with a capability of deactivating a good sort of other oxidants[186,192]. Furthermore, as per their antioxidant capability AFMK has been reported to be a less effective protector than AMK and melatonin, in fact, AMK was found to be a potent singlet oxygen scavenger. Additionally, it has been reported that the efficiency of AMK for scavenging ROS and preventing protein oxidation to be above than that of AFMK. Hence, it seems that generally, the protective role of melatonin and metabolites against oxidative stress is consistent with following increasing order AMK > melatonin > AFMK [193–198].

CONCLUSION

Due to multiple functions of the mitochondria in the cell, any disturbance in this organelle might have a considerable impact on the functioning of the cell and obviously on the entire organism. One of the main and important objectives of this review is regarding about aging of brain associated with mitochondrial dysfunction and the role of melatonin in the treatment of mitochondrial pathologies. Oxidative stress has been implicated in the pathogenesis of a number of neurodegenerative diseases and cancer. The abnormal function of mitochondria, decreased respiratory enzyme complex activities, increased electron leakage, and Ca^{2+} entry also gets increased, all of these abnormalities have been shown a key role in the pathophysiology of neurodegenerative disorders. Mitochondrial changes are not only observed at the level of ETC dysfunction or electron leakage or oxidative damage in various neurodegenerative diseases, such as AD, Parkinson's disease (PD) or Huntington's disease (HD), but also observed in a disturbed balance between mitochondrial fusion and fission, with consequences for intracellular distribution of these organelles. In neurodegenerative diseases the mitochondrial density decreases especially in the cell periphery of neurons which is associated with reduced H+ electrochemical gradient and ATP production, increases in radical formation and losses of spines at neurites. This key role of mitochondria in neurodegenerative diseases indicates that supporting the integrity and functioning of these organelles should be given a high priority, thereby reducing electron leakage and radical formation. Even though there was no convincingly effective treatment is to date available for most mitochondrial dependent diseases, an interesting and, perhaps, promising therapeutic approach might consist in the use of free radical scavengers and/or antioxidants to prevent/counteract the damage induced by ROS. In relevant to this, melatonin treatment may become a first line therapy due to its multiple actions on mitochondria. Actually, mitochondria accept melatonin in a concentration and time dependent manner and, once inside the organelle, it exerts a series of actions with the result of maintaining their bioenergetic capacity. Furthermore, melatonin increases the activity of the respiratory chain and the ATP production, reducing at the same time the O_2 consumption. Consequently, melatonin avoids an excess of ROS. Melatonin also has been reported as an effective antioxidant both in vivo and in vitro model systems. And also, various studies have revealed that melatonin has been very effective in preventing Aβ induced toxic effects on neuronal cells in AD patients. The metabolites of melatonin also having antioxidant activity.

COMPETING INTERESTS

The authors declare that they have no competing interests

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