Review

Melatonin and redox homeostasis

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ABSTRACT

Redox homeostasis and redox signaling are constituents of preservation of a normal physiological state. Whereas the equilibrium between oxidants and nucleophiles is conserved in redox homeostasis, oxidative stress promotes the formation of a radically altered redox state. It is known that modification of circadian clock may lead to severe alteration in redox balance. Melatonin [N-acetyl-5-methoxytryptamine, (MLT)] regulates numerous physiological functions including circadian rhythm, sleep-wake cycle, gonadal activity, redox homeostasis, neuroprotection, immune-modulation, and anticancer activity in organisms. Insufficient MLT production is closely related to development of aging process, tumorigenesis, visceral adiposity, neurodegenerative disorders, etc. Reactive oxygen species (ROS) are not intrinsically harmful or beneficial in cellular redox metabolism. Redox homeostasis is an integrative status for both of the hormetic response to ROS overproduction and subsequent redox signaling. MLT and its derivatives are traditionally classified as hormone-like substances. Their redox sensitive regulatory activity and direct interaction with intracellular ROS serve as second messenger in cell signaling. This review involves the role of redox homeostasis in the pathogenesis of age-related disorders and its relationship with MLT, therefore, targeting the circadian rhythm may propose new therapeutic approach for these disorders.

Key words: redox homeostasis, melatonin, oxidative stress, aging, neurodegenerative diseases, autophagy

1. INTRODUCTION

Cells preserve a stable cytosolic redox state to uphold both the oxidative bioenergetic reactions and the reductive anabolic progressions that underlie biological systems. This process

promotes redox signaling and avoids oxidative damage to cellular macromolecules. Redox homeostasis is a crucial and active process that confirms the equilibrium between reducing and oxidizing reactions within cells and controls a variety of biological reactions and procedures (1).

Metabolism, redox homeostasis, circadian rhythm, and nutrition are closely related to aging. Mitochondria plays an essential role in redox homeostasis, circadian rhythm and aging (2). Mitochondria as the energy producing organelles, take place in upholding cellular homeostasis. Accumulating evidence has shown that the mitochondrion is a suitable target to combat the oxidative stress (OS) (3). Mitochondria hold their individual genome with an adjusted genetic code. It is proposed that transcription of some mitochondrial genes could be responsible for the redox potential of the mitochondrial membrane. The impacts of mitochondria on neurodegenerative and neuromuscular disorders including modifications in both nuclear (nDNA) and mitochondrial (mtDNA) DNA have been demonstrated. Metabolic disorders including diabetes, cardiovascular and neurodegenerative diseases as well as obesity and aging may implicate an exceedingly multifaceted breakdown in physiological systems, with the syndrome becoming determined if the injury cannot be restored (4).

The suprachiasmatic nucleus (SCN) synchronizes the biological circadian rhythms, including sleep and wakefulness, temperature, nutrition, neuroendocrine and autonomic effects, with the 24 h cycle based on the environmental light/dark cycle (5). Melatonin [N-acetyl-5-methoxytryptamine, (MLT)] is a chief biological sleep regulator in humans. A neural signal generated from the SCN prompts the production of MLT at night in the pineal gland. Besides the pineal gland, many organs and tissues have the ability to produce MLT (6). As a potent antioxidant melatonin displays its advantageous properties against OS-based macromolecular injury, counting those in which mitochondrial action is affected (7). Accumulating evidence reveals that MLT has significant roles in many metabolic functions as an anti-oxidant, anti-inflammatory and conceivably as an epigenetic regulator. The actions of MLT are primarily mediated by G-protein coupled MT1 and MT2 receptors; however, several intracellular protein and nuclear receptors also modulate these activities (8).

MLT exhibits pleiotropic activities on mitochondria. Mitochondria are the main source of free radical production in the cells and are associated with aging progression. Mitochondria play a crucial role in apoptosis. MLT's antioxidant capability is established not only on direct radical scavenging but also with various other means (9). Furthermore, the mechanisms by which MLT and its metabolites defend against oxidants and OS involve stimulation of the expression of antioxidant enzymes, reduction of the triggering pro-oxidant enzymes, and preservation of mitochondrial homeostasis (10). The suitable pharmacokinetics of melatonin also favor its antioxidant ability. For example, MLT is rapidly absorbed after its oral administration and go through first-pass hepatic metabolism between 20 min and 2 h, then levels continue for up to 1.5 h (11).

The role of MLT in the management of the circadian rhythm has led to investigation of MLT as a therapeutic agent of many disorders, specifically neurodegenerative and cardiovascular diseases. It regulates various physiological functions, including sleep and circadian rhythm, neuro and cardiovascular activities, acting as powerful antioxidant and protecting tissues from lipid peroxidation, inflammation, reducing tumor growth, inducing apoptosis, and enhancing mitochondrial activity (12). Recently, MLT is found to participate in immunomodulatory, antiangiogenic, antiaging and antioxidant activities (13). Insufficient levels of MLT could escalate the possibility of neurodegeneration, aging, immunoregulation disorder, and senescence.

Immunomodulatory activities of MLT have been extensively studied (14) with the observations either pro or anti-inflammatory effects depending on conditions (15). Under the regular and immunosuppressed conditions, MLT exhibits immune-enhancing properties. It also

suppresses inflammatory reactions via non-immunological activities, such as antioxidative activity and mitochondrial functional preservation, in which melatonin promotes antioxidative process as well as decline ROS generation including NO formation (16, 17). The oxidation and inflammation have a strong connection, as the high level of OS prompts an inflammatory reaction, and ROS are the main risk factors of inflammation (18). MLT production declines with the age and the accelerated aging is associates with the MLT insufficiency (19). In fact, the relationship between MLT and aging is so strong that both extrapineal and pineal MLT are currently considered the useful biomarkers of the aging rate for organisms (20).

Redox interactions maintain the parameters of varied biological actions, involving metabolism, cell death, differentiation and development, immune responses, circadian rhythm, etc. This review on MLT and redox homeostasis summarized some of the most current developments as to how redox homeostasis is maintained, and what roles of MLT play in this process. The relationship between MLT and OS that causing aging and neurodegenerative diseases, autophagy, aging, and MLT derivatives as antioxidant in aging and neurodegenerative disorders are also discussed.

2. CELLULAR REDOX HOMEOSTASIS, REACTIVE OXYGEN SPECIES

During the evolution of the photosynthetic microorganisms about 2.4 billion years ago, reactive oxygen species (ROS) appeared as unexpected byproducts of aerobic organisms (21). The gradual accumulation of molecular oxygen into the reductive atmosphere promotes the generation of ROS (22). Enrichment of molecular oxygen to Earth's ancient atmosphere causes significant evolutionary adaptations. A wide group of electron acceptor-molecules play crucial roles in energy-yielding metabolic pathways. Enzymatic reduction of O_2 yielded a several-fold increase in energy production, enabling evolution of multi-cellular organisms. More than half a century ago, Argentinian physiologist, Rebeca Gerschman and her co-workers hypothesized that free radicals are detrimental and labile products associated with oxygen poisoning (23). Each oxygen atom has two lone pair electrons in its outer obit, whereas molecular oxygen has four lone pair electrons. Stable form of molecular oxygen is found in triplet state. Triplet dioxygen has one full σ bond plus two π half-bonds. Triplet oxygen ($^3O_2$) can be defined as a form of "ground state." The ground state refers to the situation that the outer valence obit electrons are in their lowest energy configuration. Triplet state is the most stable form of oxygen molecule and able to excite to be a reactive singlet oxygen ($^1O_2$) form by spin inversion. Singlet oxygen has one full σ and π bonds.

The electron transport chain in mitochondria ensures a safeguard tetravalent reduction of molecular oxygen to produce water. The univalent reduction of molecular oxygen due to electron leak forms ROS (24). In aging cells, impaired electron transfer chain activity causes higher rates of electron leakage. Higher ROS levels may lead to the overaction of redox signaling pathways and this overaction promotes inflammation, cancer, cell death, and the accelerated aging phenotype (25). MLT alleviates the mitochondrial electron leakage and acts as an electron rich antioxidant to scavenge $^1O_2$, $O_2^{\cdot -}$, O_2^{2-}, and OH· radicals with non-equimolar reactions (26).

The cellular redox homeostasis depends on fine-tuned balance between the formation and the removal of ROS, which regulates many physiological processes by mediating signaling pathways and facilitating the activation of redox-sensitive proteins and enzymes. However, gradual accumulation of oxidative products interferes with redox signaling events, which can damage cellular signaling pathways and subcellular integrity, and may eventually cause cellular aging and death (27). Redoxtasis depends on the sustainability of a delicate balance between electron rich and poor functional groups for a healthy physiological steady state in organisms. Electrophiles and nucleophile groups are not intrinsically harmful or protective for

cell survival. Redoxtasis is an essential feature of both the ROS-related response to challenges and subsequent feedback. While the balance between electron rich and poor species is ensured with well-tuned redoxtasis, variations in ROS formation rate induces the establishment of a new radically altered redox steady state (28). Physiological level of ROS formation may induce hormesis-related redox signaling mechanisms, whereas higher levels induce senescence or programmed cell death. The indispensable role of ROS in cell survival is closely related to the essential role of these labile molecules in cell signaling. Hormesis can be defined as ROS-induced adaptive response to the effects of a variety of low level of oxidant products that render target cells to induce resistance to higher amplitude of ROS (29). As the redox shift is rapidly changed by feedback reactions, redoxtasis is ensured by continuous signaling for production and removal of electrophiles and nucleophile groups.

MLT and its derivatives have redox modulatory effects on ROS and reactive nitrogen species (RNS) (30). MLT-induced redox regulation may be accomplished with direct ROS scavenging, enzymatic and non-enzymatic antioxidant systems (31). Exogenous non-enzymatic antioxidants are supplied nutritionally such as vitamin A, E, C xanthophylls, polyphenols, and carotenoids (32). Whilst vitamin C acts as hydrophilic antioxidant, others such as vitamin A, E, polyphenols and carotenoids active in the hydrophobic environment (33). The direct antioxidant effects of MLT depend on its own electron-rich aromatic indole ring. Indole ring makes it a potent electron donor that can significantly reduce free radicals (34). Mechanistically, MLT-dependent prooxidant activity may increase ROS production rate through its interaction with calmodulin or interaction with mitochondrial complex III under certain conditions (35). Since MLT, its metabolites and synthetic analogs exhibit conditional prooxidant properties, it can be referred as multi-faceted compounds (35, 36). Although the vast majority of studies proved the antioxidant capacity of MLT and its derivatives, some *in vitro* studies found that MLT promoted the generation of ROS at pharmacological concentrations (μM to mM range); thus, MLT may function as a conditional pro-oxidant.

MLT levels decline gradually over the lifespan and this may reduce sleep efficacy, accelerate aging process and disrupt many circadian rhythms. MLT exhibits immunomodulatory properties, and a remodeling of immune system function is an integral part of aging. Finally, because MLT is a potent free radical scavenger, its deficiency may result in reduced antioxidant protection in the aging (37).

3. MELATONIN AND OXIDATIVE STRESS

Evidence shows that neurodegenerative disorders are associated with excessive levels of OS biomarkers and reduced levels of antioxidant defense in the brain (38, 39). OS damage DNA, lipids and proteins as a result of an imbalance between oxidants and antioxidants (40, 41). Protein oxidation triggers inflammatory signal pathways to induce tissue inflammation (42) and resultant diseases including cancer, rheumatoid arthritis, cardiovascular, neurodegenerative and autoimmune diseases (43). Use of molecules with antioxidant activity such as MLT might protect against these OS-related pathologies (44-47). Moreover, under OS situations, many genes of endogenous antioxidant will be up regulated by MLT (49).

MLT shows indirect antioxidant activity by inducing antioxidant enzymes (SOD, GSH-Px, CAT and etc.) (50-52), stimulating glutathione synthesis (53), and increasing the efficiency of other antioxidants with synergistic effects (54). Therefore, understanding the antioxidant potential of MLT via different mechanisms is very valuable in order to use of this molecule to protect the organism against OS. The effects of MLT protecting against OS-associated disorders has been well documented (55, 56). Furthermore, several of its favorable activities on human health are often recognized (57, 58). Brain is exclusively vulnerable to OS. Evidence has shown the favorable effects of MLT to restrict ischemia-reperfusion damages in the central

nervous system (59, 60). MLT also able to defend other organs from OS-associated disorders including heart, kidneys, lungs, stomach, skin, and liver (61-63).

MLT and its metabolites together serve as the effective and competent defense line to defense against OS via an extensive diversity of mechanisms including electron transfer, hydrogen transfer, metal chelation, and mending pharmacological targets. Nevertheless, what appears to be exclusive to the MLT is its unique activities. MLT and its metabolites are metabolically linked, most of them exist in organisms (64). Thus, the defense of MLT against OS is obviously due to the cascade antioxidant reaction of melatonin with its metabolites. MLT and its metabolites are quite extraordinary in this respect, presenting multipurpose and unique antioxidant defense against OS.

4. MELATONIN IN NEUROINFLAMMATION: AGING AND NEURODEGENERATIVE DISEASES

Neuroinflammation is the result of the excess immune response in central nervous system that causes to death of neurons and damage of brain tissue. Microglias in brain tissue phagocytose the damaged cells and release pro-inflammatory cytokines. In this process, ROS can be formed as the byproducts. In aging and neurodegenerative diseases, dysfunction of microglias and excess of ROS formation cause more neuronal damage and increase in pro-inflammatory cytokines which lead to exaggerated neuroinflammation and neuronal tissue impairment (65). During aging and in neurodegenerative disorders, functions of brain decrease, dementia and cognitive disorders appear. OS is considered to be responsible for age-associated neurodegenerative diseases (66). During cellular respiration, oxygen is delivered to the cells and it is reduced to water through the complexes exist in the electron transport chain (ETC) in mitochondria. In the processes of aging and neurodegenerative diseases the ETC in the neuronal cells is inhibited with excessive amounts of ROS formation which damage mitochondria (67). Free radical mediated mitochondrial dysfunction and neuroinflammation are the pathologic features of aging and neurodegeneration. When ROS trigger oxidative damage in neurons, mitochondrial DNA is injured with the decreased mitochondrial membrane potential, therefore, the cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS) pathway and caspase-1 are activated. As a result, a large quantity of pro-inflammatory cytokines are released to disturb the functions of normal neurons, finally lead to neuronal cell death (68). In addition, aging and neurodegenerative diseases are also accompanied with diminished MTL production. This makes neurons be more vulnerable to further aggregate the age-related neurodegenerative diseases including Alzhimer's Disease (AD), Parkinson's disease (PD) and multiple sclerosis (MS) (69, 70). MLT was reported to be a neuroprotective molecule via its direct/indirect antioxidant activities to maintain mitochondrial homeostasis in aging and neurodegenerative disorders (35, 71, 72). In an *in vivo* study, the long-term administration of MLT in aged animals significantly decreased OS and improved mitochondrial function and ATP production (73, 74) indicating that MLT deficiency increases neurodegeneration and aging due to the elevated oxidative damage in brains in arylalkylamine N-acetyltranferase (AANAT) knocked out mice. On other hand, MLT administration blocked the cGAS pathway, caspase-1 activation and decreased pro-inflammatory cytokines secretion in these mice. In another study, MLT administration to rats which received neurotoxin and microglia activating amyloid-β significantly decreased their pro-inflammatory cytokine levels (75). These findings indicate that MLT is a potent candidate to prevent the nervous system damage against the free radical attacks and improve mitochondrial function via its antioxidant effect. Thus, melatonin can effectively ameliorate aging associated neurodegenerative diseases.

In addition to neurodegenerative diseases the antioxidant capacity of melatonin on OS related skin diseases has drawn a great attention of scientists. MLT and its metabolites store in

the epidermis, representing the local MLT production and metabolism. Powerful defensive activity of MLT and its metabolites against solar UV skin injury are largely facilitated via its direct radical scavenging and upregulation of the gene expression of antioxidative enzymes (76, 77). These activities of MLT and its metabolites may majorly occur at the mitochondrial level (78, 79). Evidence supports an association between declines in mitochondrial activity the aging process (80). It was observed that chronic UVR exposure is connected to photo aging and photo-cancer of skin due to the photo-induced overproduction of ROS, which attack the nuclear and mitochondrial DNA (81). MLT and its metabolites in the skin involve in photoprotection, anticancer, wound healing, inhibition of pigmentation, regulation of hair growth, anti-inflammatory action on dermatoses and regulation of skin temperature (82) as well as the regulation of skin functions (83, 84). To analyze the relationship between mitochondrial activity and melanin in melanoma cell lines, Bilska *et al*. (85) observed a certain influence of MLT, AFMK, 6(OH)MLT, 5-MLT and serotonin on mitochondrial activity. Melatonin with its metabolites considerably reduced melanin content in epidermal melanocytes (86).

MLT exhibits anti-apoptotic (87) and anti-inflammatory (88) activities which may be mediated by either MLT membrane receptors or nuclear receptors (89, 90). MLT also displays the anti-proliferative activities in cell lines of MNT-1, Sk-Mel-1, Sk-Mel-23 or Sk-Mel-28 (91, 92). Considering the good safety record of MLT and its metabolites, it is a suitable approach to use these molecules for treatments of melanoma alone or in combination with anticancer drugs to increase the efficiency of the therapy (85, 91). MLT, its metabolites and its receptors are present in skin referred as skin melatoninergic system (93). It is known that UVR reduced ATP synthesis from mitochondria (94), while MLT revised UVR-induced inhibition of ATP synthesis in skin. MLT's capacity of defending oxidative damage and UVR-induced disturbances of ATP synthesis in epidermal keratinocytes was studied by Kleszczyński *et al*. (95). They observed that MLT had powerful antioxidative properties in UVR-induced oxidative stress in epidermal keratinocytes. Furthermore, MLT upregulates the expression of the antioxidative enzymes including γ-glutamylcysteine synthetase (γ-GCS), heme oxygenase-1 (HO-1), and quinone dehydrogenase-1 (NQO1) via the Nrf2-ARE pathway.

A recent review by Reiter *et al* (96) discussed the potential mechanisms of melatonin on solid tumor inhibition, i.e., melatonin converts the tumor's cytosolic aerobic glycolysis known as "Warburg effect" to mitochondrial oxidative metabolism. Mitochondrial oxidative phosphorylation is reliant on the nighttime increased of circulating MLT production (97) and the reduced level of nighttime MLT promote the tumor development. The authors suggested (96) that this main circadian alteration in tumor cells which show aerobic glycolysis could be related to the disrupted circadian MLT rhythm. MLT directly or indirectly downregulates the expression of pyruvate dehydrogenase kinase (PDK) that plays a role on converting pyruvate to acetyl CoA in the mitochondria (98). If this is hold, it can explain the protective effects of melatonin on many disorders (99). MLT inhibits proliferation the metastatic activity and prompts apoptosis in cancer cells. The capacity of MLT to switch the cytosol glucose metabolism to the mitochondrial metabolism reduces resistance of tumor to conventional chemotherapeutics (100). MLT, as a mitochondria-targeted agent, able to suppresses PDK and motivates PDC (101) to reduce the Warburg effect. As a result, when MLT levels are low during the daytime, cancer cells, particularly the breast cancers are favorite of cytosolic aerobic glycolysis due to the less pyruvate to convert to acetyl CoA. The synthesis of MLT by mitochondria is dependable to the intact ETC (102), higher mitochondrial ATP production is usually associated to reduced ROS (103). MLT promptly stores in mitochondria after administration to promote mitochondrial progressions (104). Another interesting finding is that the insufficiency in SIRT3 in the mitochondria causes malignancy (105). MLT under normal conditions upregulates SIRT3 action (106).

Serotonin, a precursor of MLT, also exhibits a variety of biological activities in mammalians mostly via G protein coupled receptors or ligand-gated ion channels (5HTR1–7R) (107). Solominski *et al*. (108), described a serotonin-NAS system in mammalian skin to play a role in neuroendocrine structure by modifying skin homeostasis. Serotonin and NAS are endogenously produced in the epidermal, dermal and adnexal sections of mammalian skin. NAS in serum and tissue is accessible as a substrate for synthesis of MLT in organs having HIOMT. In skin, the local NAT1/2 converts the serotonin to NAS. Then, NAS defend skill cells against the UVB injury.

Interestingly, MLT can effectively treat SARS-CoV-2 infection (109). The main mechanisms are that melatonin switches glucose glycolysis to oxidative metabolism and upregulates es f hypoxia-inducible factor-1α(HIF-1α) and NF-κB pathway (110) to suppress COVID-19 septicemia (111, 112). There is a connection between the secreted phospholipase-A2 and the severity of COVID-19 illness. Reduction of sPLA2-IIA concentration might be a significant approach to prevent multiple organ failure and death due the SARS-CoV-2 infections (113). Activated sPLA2-IIA promotes inflammatory reaction and leads to tissues damage since it hydrolyzes fatty acids (114). By stopping cyclooxygenase activity, MLT reduces the severe inflammatory reaction induced by SARS-CoV-2 infection (115).

It is well documented that MLT and its metabolites or analogue compounds being able to act as free-radical scavengers and effective antioxidants. Studies also showed the significant roles of MLT and its derivatives in numerous physiological processes and therapeutic utilities including the regulation of circadian rhythm and immune functions. All evidence indicates that MLT is an valuable molecule in the prevention and/or treatment of wide spectrum of disorders (116).

5. MELATONIN, MITOPHAGY AND AGING

Mitophagy is a primary regulatory mechanism for mitochondrial redox integrity and buffers the ROS overproduction. Upon oxidative injury, mitophagy limits the accumulation of dysfunctional mitochondria and alleviates the detrimental effects of redox state failure. A wide spectrum of diseases have been implicated to associated with dysregulation of mitophagy (117). Moderate levels of ROS specifically induce mitophagy to optimize the activity of ROS signaling cascades (118). MLT-mediated mitophagy has shown the promising potency to ameliorate mitochondrial dysfunctions (119). Reduced mitophagy is closely related to decreased longevity since dysfunctional mitochondria are considered as both the source and the target of ROS (120, 121). Impairments in mitophagy may result in diabetes, neurogenerative disorders, cardiovascular pathologies, and cancer.

Mitochondria is considered as a major pool of MLT due to the reasons that melatonin is synthesized in them and it also can be imported from cytosol via the oligopeptide transporters PEPT1/2. Intramitochondrial MLT effectively scavenges ROS, via its own electron donation capacity and other defensive strategies including its metabolites; these actions of MLT facilitate the maintenance of the redox homeostasis in the mitochondria (122). Mitophagy links number of a complex redox networks which are impacted by MLT. For example, MLT reduces mitochondrial electron leak and ROS production, blocks mitochondrial permeability transition pore (MPTP) opening to preserve the mitochondrial membrane potential ($\Delta\psi$) under unfavorable bioenergetic conditions and also activates the uncoupling proteins (UCPs) to adjust the $\Delta\psi$ in normal condition. Mitoprotective effects of MLT is not only restricted to its redox modulatory ability but also related to its signaling function to upregulate expression of antioxidant enzymes, stress responsive genes and inhibition of Cyt-c release. MLT activates heterotrimeric intermembrane space-located G proteins and inhibits stress-induced cytochrome C release (123). The major pathways of MLT acts on mitophagy include:

(i) Ubiquitin-dependent PINK1 (PTEN-induced kinase 1)/Parkin-related mitophagy. Upon the occurrence of mitochondrial dysfunction, the outer mitochondrial membrane-located protein PINK1 is responsible for Parkin-mediated ubiquitination of mitochondrial proteins. Autophagy receptors like NDP52, OPTN, and p62 involve ubiquitin-mediated degradation of mitochondria. The members of autophagy core complexes such as VPS34 and ULK1 initiate the formation of autophagosomal membrane which is originated from endoplasmic reticulum. MLT can induce PINK1 expression via the MT2/Akt/NF-κB pathway, which has a protective role against neuronal injury (124). MLT pretreatment increases both the expression of PINK1 and Parkin in cardiomyocytes. MLT-induced mitophagy reduces the number of dysfunctional mitochondria, restores organelle morphology as well as mitochondrial bioenergetic and redox homeostasis (125). Disturbance of mitophagy to remove the dysfunctional mitochondria often results in cardiomyopathy. MLT enhances mitophagy, alleviates the accumulation of dysfunctional mitochondria and improves cardiac function (30). Dry eye disease is a common eye disorder in elderly population (126). It has been recently reported that MLT-loaded micelles inhibit ROS overproduction and apoptosis in human corneal epithelial cells and ameliorates hyperosmolarity-induced ocular surface damage via PINK1-mediated mitophagy. This intervention may represent an effective treatment for dry eye disease possibly through acting MLT-type 1 receptor (127). Mitochondrial dysfunction is an important underlying factor in neurogenerative diseases such as AD. It was recently reported that long-term oral MLT administration improves memory deficits with reduced amyloid accumulation, downregulation of the number of mitophagy vesicles, diminished expression of PINK1 and Parkin in transgenic mice. Various studies have reported mitochondrial dysfunction in PD animal models with gene knockout or knockdown procedures. The expression of mitochondrial-related genes, including parkin, and PINK1 were found to be inhibited in these studies. Mutations in Parkin and PINK1 genes are responsible for the development of dysfunctional mitochondrial phenotype and lead to the development of early-onset PD. Mutations in the E3 ubiquitin ligase Parkin and the protein kinase PINK1 are closely related to the development of autosomal-recessive juvenile Parkinsonism. All these mutations are considered as reasons of defective mitophagy (128). It was shown that MLT restored the expression of PINK1 and Parkin in Parkinsonian Zebrafish embryos (129).

(ii) Ubiquitin-independent receptor-mediated mitophagy. This pathway needs the recruitment of soluble autophagy receptors such as NIX, BNIP3, and FUNDC1 to the mitochondrial membrane. The receptor proteins recruit LC3, which enables the engulfment of mitochondria by autophagosomes (121).

(iii) Alternative degradation pathways. Piecemeal mitophagy and mitochondrial-derived vesicle degradation are cellular pathways that mediate localized degradation of mitochondria (130).

There are several pathologies, syndromes, and physiological processes in which autophagy is involved. Further efforts are required to clarify the possible mitophagy-related role of MLT on the last two pathways.

6. MELATONIN DERIVATIVES AS ANTIOXIDANT IN AGING AND NEURODEGENERATIVE DISEASES

It is widely accepted that ageing is the main risk factor for many neurodegenerative disorders, such as AD, PD, Huntington Disease (HD). Currently no effective drugs are available for the treatment of ageing-associated neurodegenerative diseases. In general, postmitotic cells, such as the brain, are particularly predispose to the ageing associated degeneration. Hallmarks of ageing are genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, mitochondrial dysfunction, cellular senescence, deregulated

nutrient sensing, stem cell exhaustion and altered intercellular communication associated with exposure to neurodegenerative disorders (131, 132). MLT is a molecule with capacity to target all these aging hallmarks. Importantly, its derivatives seem to share the similar capacities with melatonin. This makes possible to discover the novel molecules derived from melatonin to function as antioxidant, neuroprotector and aging retarder. There are many properties of MLT as a molecule outstanding. These include MLT's very low toxicity (133), its ability to cross blood brain barrier with ease, partially soluble in water and highly soluble in non-polar aprotic solvents such as lipids (134), its metabolites which are capable of offering protection against OS. Therefore, MLT is an outstanding motif for minor alterations to developed novel molecules possibly with broader benefits (135).

For example, a new MLT derivative (MLTBS) (Figure 1) showed the same pharmacological effects as MLT. Compared with MLT, MLTBS has a benefit of decent water solubility, minor toxicity, and better safety observed in the *in vitro* and *in vivo* conditions (136).

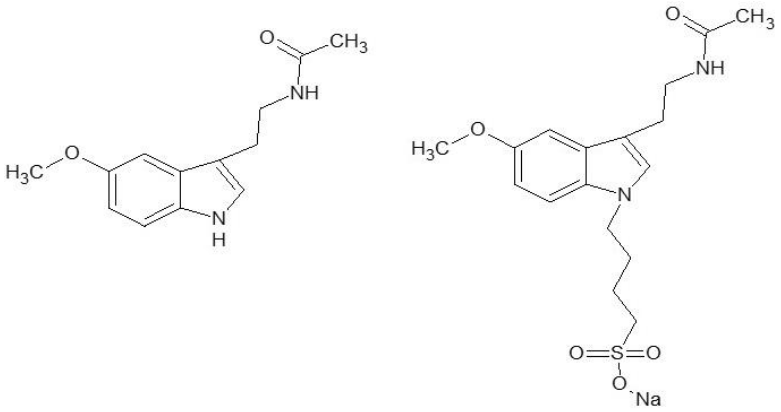

Fig. 1. Chemical formula of (a) melatonin, (b) sodium 4-(3-(2-acetamidoethyl)-5-methoxy-1*H*-indol-1-yl) butane-1-sulfonate (MLTBS).

MLT and some related natural molecules also show antioxidant properties. Among these molecules the most significant ones are MLT's metabolites N^1-acetyl-5-methoxykynuramine (AMK), N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK), cyclic 3-hydroxymelatonin (C3OHM), 5-methoxytryptamine (5MTA), and 6-hydroxymelatonin (6OHM) (Figure 2). C3OHM is a product of the MLT interaction with hydroxyl radical (96). AFMK is produced after C3OHM interacts with other free radicals. Then AMK is formed from the reaction between the radicals and AFMK (137). AFMK has inhibitory effect on lipid peroxidation and OS-induced neuronal damage (138). 6OHM is an inhibitor of quinolinic-acid induced neurotoxicity (139).

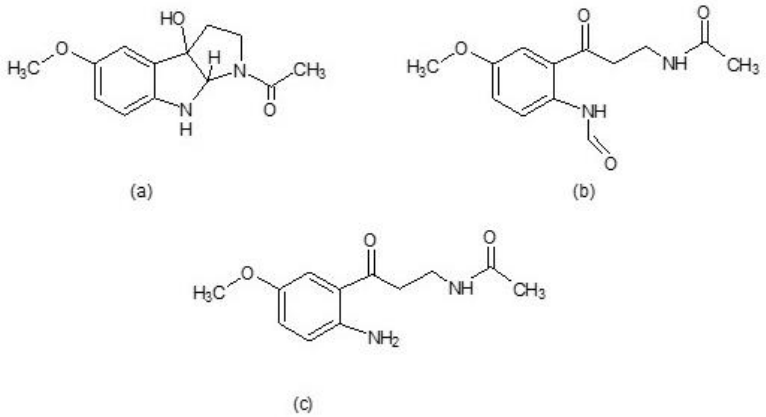

Fig. 2. Chemical formula of (a) N1 -acetyl-5-methoxykynuramine (AMK), (b) N1 -acetyl-N2 -formyl-5-methoxykynuramine (AFMK) and (c) cyclic 3-hydroxymelatonin (c3OHM).

N-acetylserotonin (NAS) is an intermediate molecule that is formed from serotonin and has neuroprotective effect in neurological disorders (140). It was found that NAS has strong antioxidant properties (141). NAS is present in some parts of the brain (142). Naturally produced MLT derivatives and some precursors such as serotonin (5HT) (143), 5-hydroxytryptophan (5HTP) and 5-methoxytryptamine (5MTA) (Figure 3) are versatile antioxidants. The serotonin system in human is very significant, particularly in neuronal conduction and neuromodulation. 5-HT shows strong antioxidant properties and reacts with a greater attraction to unsaturated lipids and able to interrupt the diffusion of free radicals (143).

There are indications associated the theory that chemical alterations to MLT's structure leads to the development of new molecules with an extensive variety of anticipated activities. Besides, these compounds might have superior therapeutic benefits than MLT.

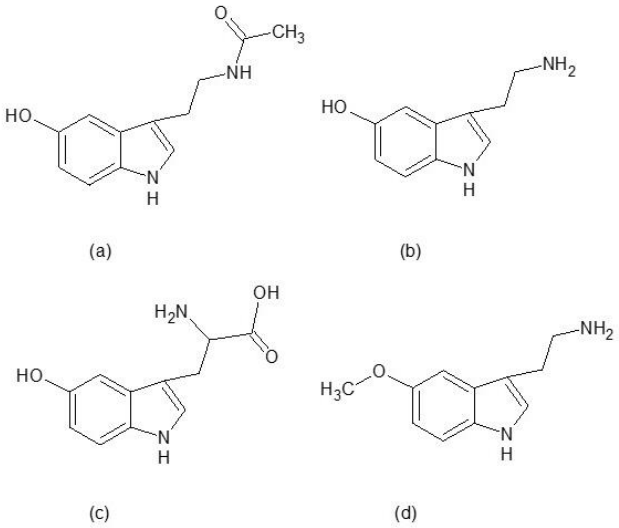

Fig. 3. Chemical formula of (a) *N*-acetylserotonin (NAS), (b) serotonin, (c) 5-hydroxytryptophan (5HTP) and (d) 5-methoxytryptamine (5MTA).

Systematic rational researches for development of the novel MLT derivatives were performed using different strategies and computer-assisted procedures. Reina *et al*. (144) was synthesized new derivatives by addition of different simple functional groups such as -OH, -NH_2, -SH and -COOH to the MLT molecule. Results revealed that 5 MLT-derivatives have been recognized as scavengers of free radicals, by electron transfer and/or H transfer.

Antioxidant defense is a multifaceted procedure that includes diverse chemical and non-chemical reactions. There are numerous features on the performance of the developed molecules. Inspired for the interesting properties of MLT, the design and synthesis of MLT-like compounds is a rapidly developing research area (145, 146). The antioxidant properties of some MLT derivatives with a sulfhydryl group have better antioxidant activity than that of MLT (147). Moreover indole-based MLT hydrazine derivatives containing 2-phenylindole (148), indole-3-propionamides (149) and N-methylindole (150) derivatives were potent free radical scavengers observed in the *in vitro* experiments. Between the hydrazide-MLT derivatives, 5-chloroindole hydrazide were established to be very effective as antioxidant (151). Alterations in modification of the 5-methoxy and 3-acylaminoethyl side chain of MLT

have shown the encouraging aspect to make novel molecules with improved antioxidant capacity compared to MLT (152). Indole-based analogues of MLT such as indole amino acid derivatives have been synthesized and analyzed for antioxidant capacity. Their activity to scavenge DPPH (2,2- difenil-1-picrylhydrazyl) was parallel to that of MLT, while their effectiveness as inhibitors of lipid peroxidation was advanced (153). Additional research of other properties of the novel MLT analogues are still desirable from both experimental and theoretical methodologies. But it is likely that further research will assist to discover new molecules concerning antioxidant protection and possibly neuroprotection.

7. CONCLUSION REMARKS

Age-associated neurodegenerative diseases are becoming a serious public health issue. OS and redox homeostasis play essential part in aging and neurodegenerative diseases. Antioxidants such as vitamin E, vitamin C, β carotene, and some flavonoids have limited success as effective prophylaxis or treatment remedy. Assumed the significance of OS in the pathogenesis of numerous diseases and aging, antioxidant should be suitable for treatment of these OS associated disorders. During aging the redox homeostasis is challenged since excessive OS with aging disturbs particularly the regulatory structures of nerve system, endocrine and immune response. MLT is universally presented molecule not only in the pineal gland but also in many organs and tissues (154). It is a potent endogenously produced antioxidant. MLT's defense against OS exhibits cascade reaction, i.e., not only melatonin but also its metabolites possess antioxidant capacity (36, 155). Circadian rhythms are essential timers establishing the routine and physiology of organisms. They are associated with cellular redox regulation. Metabolism, redox homeostasis, circadian rhythms, and nutrition directly impact aging process.

MLT as antioxidant has the capacity preserves the redox homeostasis. Its mechanisms are multiple. Melatonin can directly scavenge free radicals and indirectly upregulation of expression and activities of antioxidant enzymes and downregulation of the prooxidant enzymes (156). Nevertheless, the molecular mechanism underlying the precise act of MLT is not entirely understood. Aging is related with a substantial decrease in endogenous MLT synthesis, an increase of OS and other metabolic alterations (157). MLT is an effective defender of mitochondria due to its lipophilic properties that protects the mitochondrial inner membrane against OS (136). It also conserves mitochondrial activities by prompting mitofusin-2 activity, the main controller of mitochondrial cellular metabolism (158). MLT preserves calcium homeostasis in cardiomyocytes by preventing OS-linked disorder of sarco/endoplasmic reticulum calcium ATPase (SERCA) and sodium-calcium exchanger (NCX) proteins (159). Long-term of MLT treatment benefits glucose homeostasis and reduces insulin resistance in animal studies. Antioxidant activity of MLT is adequate to improve insulin resistance via destruction of Jun kinases/stress-activated protein kinases (JNK) stimulation and phosphoenolpyruvate carboxykinase (PEPCK) expression due to decreased OS, producing better glucose homeostasis and reestablished hepatic insulin signaling (160). MLT signaling is a key regulator of glucose homeostasis and energy metabolism (161). Obesity as a syndrome of disturbed lipid homeostasis is also the target of melatonin. MLT exhibits favorable properties in refining lipid metabolism and circadian rhythm homeostasis (162). MLT regulates iron homeostasis via prompting hepcidin expression in hepatocytes (163). It also has defensive roles on the activity of the exocrine pancreas, Ca2+ signaling and the mitochondrial integrity (164). Since MLT is synthesized in mitochondria, a close connection is expected between MLT and mitochondria (Figure 4) including scavenging mitochondrial originated ROS, promoting uncoupling proteins (UCP) activity, reducing the mitochondrial permeability transition pore (mtPTP) opening, preventing mitochondrial dysfunction from oxidative damage by preserving

cardiolipin integrity, improving calcium handling, inhibiting mtDNA release and activation of cytosolic DNA-mediated inflammatory response in neurons (165-171). All these were illustrated in the Figure 4. The research on MLT activity in cellular homeostasis has produced inspiring information, which have led to investigators to share their knowledge concerning the beneficial effects of MLT in human health. Generally, MLT plays a vital role in the regulation of metabolism and redox homeostasis. Nevertheless, there remains necessity for additional convincing clinical research to clarify certain actions which MLT and its metabolites as well as the related receptors are responsible to the regulation of diverse metabolic procedures in organisms. Given that there are numerous activities of MLT, upcoming clinical studies employing MLT should be encouraged to use in the management of many diseases associated with OS.

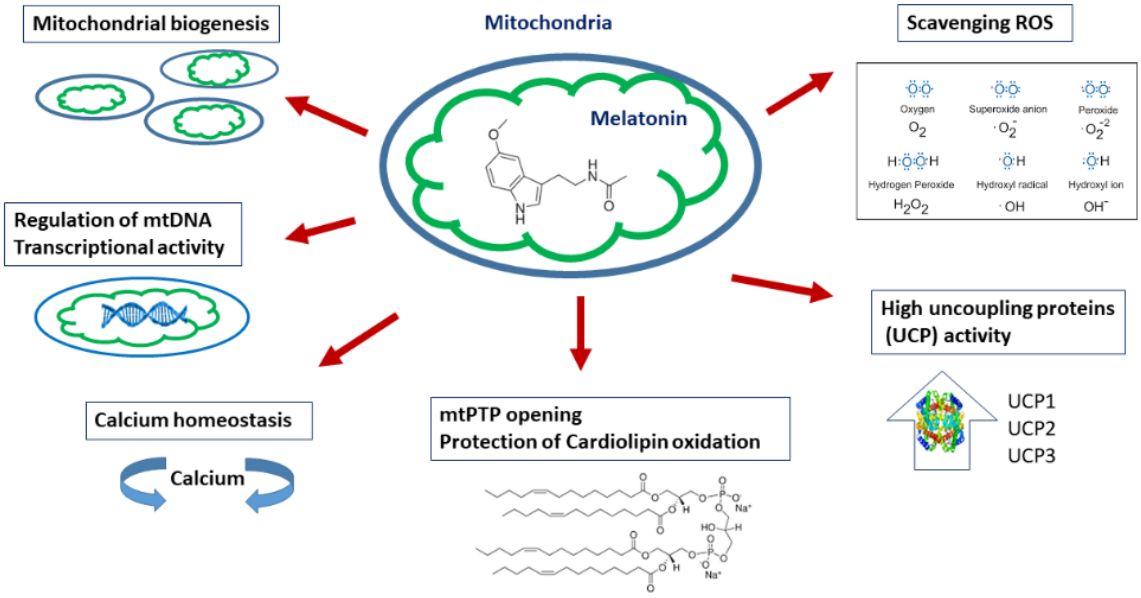

Fig. 4. Summary of the potential effects of melatonin on mitochondria.

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AUTHORSHIP

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CONFLICT OF INTERESTS

Authors declare no conflict of interest

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