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Melatonin and human mitochondrial diseases

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Abstract

Mitochondrial dysfunction is one of the main causative factors in a wide variety of complications such as neurodegenerative disorders, ischemia/reperfusion, aging process, and septic shock. Decrease in respiratory complex activity, increase in free radical production, increase in mitochondrial synthase activity, increase in nitric oxide production, and impair in electron transport system and/or mitochondrial permeability are considered as the main factors responsible for mitochondrial dysfunction. Melatonin, the pineal gland hormone, is selectively taken up by mitochondria and acts as a powerful antioxidant, regulating the mitochondrial bioenergetic function. Melatonin increases the permeability of membranes and is the stimulator of antioxidant enzymes including superoxide dismutase, glutathione peroxidase, glutathione reductase, and catalase. It also acts as an inhibitor of lipoxygenase. Melatonin can cause resistance to oxidation damage by fixing the microsomal membranes. Melatonin has been shown to retard aging and inhibit neurodegenerative disorders, ischemia/reperfusion, septic shock, diabetes, cancer, and other complications related to oxidative stress. The purpose of the current study, other than introducing melatonin, was to present the recent findings on clinical effects in diseases related to mitochondrial dysfunction including diabetes, cancer, gastrointestinal diseases, and diseases related to brain function.

Keywords: Antioxidant, free radical, melatonin, mitochondrial dysfunction, neurodegenerative disorders, nitric oxide, pineal gland hormone

INTRODUCTION

Enhanced generation of reactive oxygen species (ROS) is considered as one of the main contributory factors in a wide variety of diseases and age-related degeneration. Oxidative stress induced by these free radicals has been implicated in etiology of cancer,[1,2] diabetes mellitus,[3,4] cardiovascular diseases,[5,6] neurodegenerative diseases,[7,8] neuropsychological disorders,[9,10] and infectious disease.[11,12]

Mitochondria are considered as the main source of ROS/reactive nitrogen species (RNS) generators which are the predominant target of their actions, resulting in widespread damage to mitochondrial respiratory chain. This process produces further increase in free radical generation, causing a self-induced vicious cycle.[13,14] This process and some other conditions may cause mitochondrial diseases which are a group of complications caused by mitochondrial dysfunction. Mitochondrial diseases are also caused by mutations in the mitochondria affecting mitochondrial function. Mutations in mitochondria are also facilitated by high level of oxidative stress.[15]

Melatonin has been shown to play a crucial role in regulation of mitochondrial homeostasis. Melatonin, in addition to being a powerful antioxidant, decreases nitric oxide (NO) generation in mitochondria and maintains bioenergetic functions of the cell.[16,17]

The purpose of the current study was to identify melatonin production, metabolism, and clinical effects in diseases related to mitochondrial dysfunction including diabetes, cancer, and diseases related to brain function. Furthermore, the mechanisms through which melatonin can exert neuroprotection against neurodegenerative disorders related to mitochondrial dysfunctions are reviewed.

MITOCHONDRIA AND FREE RADICAL GENERATION IN MITOCHONDRIA

The main function of mitochondria is production of adenosine triphosphate (ATP) through the electron transport chain (ETC). The primary function of the ETC is conversion of redox energy to an electrochemical gradient which causes synthesis of ATP from adenosine diphosphate and production of phosphate by ATP synthase. The ultimate generation of the respiratory chain is water which is produced in a four-electron reduction of molecular oxygen (O_2). During this process, a section of O_2 is converted to ROS, including superoxide anion radical ($O_2^{\bullet-}$), reactive hydroxyl radical ($^{\bullet}OH$), and hydrogen peroxide (H_2O_2).[18]

Mitochondrial NO synthase (NOS) is responsible for production of NO radical ($^{\bullet}NO$) from L-arginine. The free radical $^{\bullet}NO$ is produced by several forms of NOS. $^{\bullet}NO$ is able to easily cross membranes and enter mitochondria regardless of its origin. $^{\bullet}NO$ can strongly interfere with the respiratory chain components such as cytochrome C-oxidase.[19]

These free radicals can damage proteins of respiratory complexes. When $^{\bullet}NO$ reaches high levels, it can start free radical-mediated chain reactions which destroy DNA molecules, proteins, and lipids.[19,20] Damage to the mitochondrial respiratory chain leads to further generation of free radicals and breakdown of proton potential, apoptosis, and cell death.[21]

Free radicals are usually generated in cells during normal activity. Among the mechanisms which control the ROS/RNS production is the enzyme superoxide dismutase function in mitochondrial membrane that removes $O_2^{\bullet-}$. The $^{\bullet}OH$ generated from H_2O_2 is scavenged by glutathione peroxidase (GPx).[22] These enzymes which are the important parts of antioxidant defense system reduce free radicals within the mitochondria.

Antioxidants such as Vitamins C and E are able to participate in the antioxidant defense system of mitochondria, but they cannot convert $O_2^{\bullet-}$ to O_2. It is glutathione (GSH) which scavenges $O_2^{\bullet-}$, as well as participating in several redox reactions. In the mitochondria, the redox cycling is very active and prevents significant loss of GSH. This process is very important because the mitochondrial GPx and GSH reductase activities depend only on GSH uptake from the cytoplasm for keeping adequate GSH levels. Melatonin, by stimulating the activity of the enzyme γ-glutamyl-cysteine synthetase, promotes synthesis of GSH.[23] It also plays an important role in mitochondrial physiology through its effects on gene expression of GPx, GSH reductase, catalase, and dismutase, helping in maintaining the GSH/GSSG ratio and in high recycling of GSH.[17,24]

MELATONIN AND REDUCTION OF OXIDATIVE STRESS

Free radicals are atoms or molecules with unpaired electrons which make them highly toward other substances. Free radicals such as H_2O_2 and $^{\bullet}OH$ which are called ROS can cause oxidative stress and damage to cell components.[25,26,27] Increased production of ROS and other free radicals or decreased antioxidant enzymes can cause oxidative damages to organs, tissues, and various cells such as brain, heart, and vascular cells.[28,29,30] Oxidative stress is also the background of many hard curable diseases such as high blood pressure,[31,32] atherosclerosis,[32,33] and infectious diseases.[34,35,36]

ROS are mostly produced in the mitochondria as normal cell respiration. The interrelationship between mitochondria and its ROS generation suggests shared pathogenic mechanisms in ROS-related diseases and mitochondria.[37]

In this regard, mitochondria are considered as endogenous producers of ROS and the central executioners of cell death. Increased mitochondrial Ca_2 − overload is associated with generation of superoxide which induces the release of pro-apoptotic proteins implicated in pathogenesis of neurodegenerative diseases and several features of cell death.[38]

Antioxidants such as Vitamins A, C, and E have a little ability to protect the body against free radicals. In preclinical studies, plants' antioxidants have been effective in most of ROS-related diseases such as gastrointestinal complications,[39,40,41,42] cognitive problems,[43,44] cardiovascular diseases,[45,46] pain,[10,47] and other complications.[48,49,50] However, their effects have not been confirmed in most of large clinical trials.[29] Melatonin has been shown to possess high level of antioxidant activity and the ability to counteract with oxidative stress-induced diseases, even in most of clinical trials.[13,17] Melatonin is the stimulator of antioxidant enzymes including superoxide dismutase, GPx, GSH reductase, and catalase. It also acts as inhibitor of lipoxygenase. Melatonin can cause resistance to oxidation damage by fixing the microsomal membranes.[51]

Administration of melatonin in animals with ischemia can reduce malondialdehyde level and other products obtained from the membrane lipid peroxidation as injury indices.[52] Features that help melatonin to prevent lipid peroxidation include being soluble in fat, hydroxyl free radical clearing, inhibition of lipid peroxidation, and increasing the effectiveness of other antioxidants such as Vitamin E and C, clearing of peroxide radicals, and also individual highly reactive oxygen.[53] Melatonin also increases the level of GSH and GSH S-transferase and the activity of GPx.[17] Melatonin can cross blood–brain barrier and placenta easily and reach all the cellular components without difficulty. Hence, it can protect the cell walls, organs, and nuclei against the damage of free radicals.[13]

PHARMACOLOGIC AND THERAPEUTIC ASPECTS OF MELATONIN

Melatonin was first considered as a hormone responsible for control of circadian rhythms. However, it has several biological functions which are produced by activation of its receptors or due to melatonin role as a powerful antioxidant. Melatonin has a specific role in the protection of mitochondrial DNA and other biological compounds.[54]

Melatonin is now used for insomnia, especially the insomnia associated with attention-deficit hyperactivity disorder, insomnia caused by beta-blockers, delayed sleep phase syndrome, rapid eye movement sleep behavior disorder, and the sleep difficulties in children associated with developmental disorders such as intellectual disabilities, autism, and cerebral palsy. Melatonin is also used to reduce the side effects of stopping smoking or as a sleep remedy after stopping the consumption of benzodiazepines. It might also be used for mild mental impairment, bipolar disease, depression, seasonal affective disorder, Alzheimer's disease, schizophrenia, epilepsy, dementia, stress, delirium, chronic obstructive pulmonary disease, endometriosis, fibromyalgia, tinnitus, nonalcoholic liver disease, chronic fatigue syndrome, age-related vision loss, restless leg syndrome, jaw pain, nerve pain, weakness, sarcoidosis, migraine and tension headache, benign prostatic hyperplasia, irritable bowel syndrome, osteoporosis, tardive dyskinesia, acid reflux disease, infertility, aging, menopause, metabolic syndrome, inflammatory bowel disease (IBD). Recovery after surgery, agitation due to anesthesia, inability to control urination, various cancers including breast, brain, lung, prostate, head, neck, and gastrointestinal tract cancers. Melatonin is also used to reduce some side effects of cancer chemotherapies such as weight loss, fatigue and thrombocytopenia, too.[55,56,57,58,59,60,61,62,63,64,65,66,67,68,69]

Regarding the aim of the current study, the effects of melatonin on the most important diseases related to mitochondrial dysfunction including cancer, cardiovascular disease, Alzheimer's disease, obesity, diabetes mellitus, affective disorder, gastrointestinal diseases, attention-deficit, hyperactivity disorder, and autism are discussed below. The melatonin side effects are also presented at the end.

Melatonin and cancer

The removal of the pineal gland leads to an increased tumor growth while taking melatonin reverses this effect and inhibits tumor genesis induced by carcinogen. Melatonin is likely to reduce the growth of the tumor cells through inhibiting mitosis and regulating the activity of the receptors in tumor cells. For example, this hormone inhibits the activity and expression of estrogen receptor genes in breast cancer cells.[56] Adding melatonin to tamoxifen has led to slow down the rate of progression of the disease. Consumption of high dose of melatonin (700 mg daily) caused a transient reduction in the size of some tumor populations. In addition, it is noted that added melatonin to chemotherapy and radiotherapy had the influence to reduce the injuries imposed on blood cells and made the remedy more tolerable.[56,57]

Researches results have shown that serum and urine melatonin levels in women with breast cancer are low and melatonin usage could inhibit breast tumor growth.[58] A research finding showed that interrupted sleep at 1:30 A.M. led to increase in the concentration of estradiol in the blood while exposure to light at night reduced the menstrual cycle duration. This was accompanied by increasing the risk of breast cancer. It was also reported that the prostate cancer cells treated with melatonin might significantly reduce the number of prostate cancer cells.[59]

Large intestine tumor is one of the tumors that melatonin can have effect on it. The mammalian intestine is the place of melatonin production, and an impaired circadian rhythm of melatonin secretion has been observed in patients with colorectal cancer. An inhibitory effect of melatonin on colon cancer cell was observed through reduced invasion and increased differentiation of cancer cells.[60] Other epidemiological studies have shown that melatonin in children who have exposed to low frequency magnetic field and its risk is lower and leukemia is higher than normal.[61]

Melatonin and cardiovascular disease

The finding that melatonin receptors are found in human arteries may suggest a direct role of this hormone in locally controlling the blood vessel diameter. According to the performed researches, very high concentrations of melatonin decrease the risk of atherosclerosis disease with inhibiting the oxidation of cholesterol low-density lipoprotein (LDL).[62] Circadian changes in hemodynamic parameters including heart rate, cardiac output, and blood pressure are clear. In addition, the occurrence of some acute cardiovascular events such as myocardial infarction and sudden cardiac death showed a circadian pattern as the occurrence of such cutting off blood flow is greater in the early morning.[18] Further, melatonin levels in patients with stroke, migraine, and cardiovascular disease will be reduced.[18]

Melatonin and Alzheimer's disease

Melatonin serum levels and its daily rhythm are reduced in patients affected with Alzheimer's disease. Therefore, in these patients, melatonin supplementation might reduce distractions and improve their memory. Studies have shown that inflammation causes Alzheimer's disease while taking melatonin orally reduces progression of Alzheimer's disease by decreasing pro-inflammatory cytokines.[63]

The findings of a research have shown that exposure to bright light in the elderly can improve sleep and behavioral disorders, depression, and the memory condition. In addition, it would shorten the time to fall asleep and increase sleep duration for a period of 27 min. It also reduces the time of waking. Both factors (light and melatonin) help improve the quality of sleep and night vision disturbances.[64]

Melatonin and obesity

Melatonin can affect body size, obesity, and energy intake; however, these effects sometimes are different based on the species. The direct effect of melatonin is possibly on brown fat while its indirect effect found to be through sympathetic system. However, this effect is less discernible in the species whose activity and life do not depend on light. Melatonin increases sensitivity to insulin. This increased insulin sensitivity and decreased plasma triglyceride may be due to the effect of weight loss caused by melatonin.[65]

As mentioned earlier, plasma melatonin is decreased with increasing age; however, the level of leptin and visceral fat and nonfasting insulin increases. In a study, daily melatonin supplementation for 10 weeks resulted in decrease in leptin, nonfasting insulin, and visceral fat, which based on the conducted studies, the mentioned reduction was in response to melatonin supplements independent on changes in the regulation of testicular, thyroid, adrenal, and somatotropin.[66]

Melatonin and diabetes mellitus

Administration of melatonin to middle-aged rats reduced visceral fat, plasma insulin, insulin-like growth factor, and leptin levels. In addition, administration of melatonin to women after menopause has been shown to decrease insulin sensitivity and glucose tolerance. Melatonin increases carbohydrate utilization in liver and decreases hepatic lipolysis. Long-term treatment with melatonin led to increase insulin doses, triglycerides, leptin, cholesterol and high-density lipoprotein (HDL), esterified cholesterol, free cholesterol, and total cholesterol. High doses of melatonin inhibited the oxidation of LDL cholesterol.[51]

Melatonin and affective disorder

During pregnancy and after childbirth, some degrees of depression with unknown etiology are common. In pregnant women with severe depression, the plasma melatonin level during night, especially at early morning hours, was found to be lower than that of healthy people. In severe depression, the sensitivity to estradiol or progesterone effects on melatonin receptors will decrease. Therefore, increased sexual hormones during pregnancy and melatonin secretion in healthy pregnant women will increase; however, in patients with severe depression, it does not work.[67] A study showed that decreased tryptophan followed by diminished serotonin will decrease melatonin secretion.[6] Decreased melatonin is also associated with different affective disorders. Low-melatonin syndrome or melatonin deficiency depression has been reported in a subgroup of depressed patients.[68] Administration of melatonin to unresponsive depressed patients to conventional drugs was also effective on their depression and their sleep quality.[69]

Melatonin and gastrointestinal diseases

It has been reported that melatonin supplements can reduce the risk of stomach ulcers. In the case of more severe ulcers, the melatonin concentrations in samples were lower than that of control group.[68]

Administration of melatonin is effective in reduction of damage to the oral cavity tissues through converting free radicals to inactive forms. Furthermore, pharmacological dosages of melatonin with increased expression of endogenous antioxidant enzymes such as GPx, superoxide dismutase, and catalase can be effective in the treatment of inflammatory lesions after the oral cavity surgery including dental extraction. Researchers have shown that the application of exogenous melatonin in an animal model prevented the stress-induced gastric damage and accelerated stomach ulcer healing by increasing blood flow and mucus retention. They also reported the effect of melatonin in prevention of esophageal damages caused by acid, pepsin, and bile solutions.[12]

Melatonin and attention-deficit hyperactivity disorder

Attention-deficit disorder occurs in two forms, with or without hyperactivity. People with attention-deficit disorders have been found with specific behaviors such as lack of attention to the audience, frequent mistakes in homework and career, distraction and forgetting distinguishing them from others.[70]

In a study done in 2006 to determine the association between attention-deficit disorder and sleep disorders, it was observed that in 25% of children with attention-deficit, hyperactivity disorder suffers from sleep disorders. The use of melatonin in such children improved their sleep and resulted in eliminating the symptoms.[71]

Melatonin and autism

The serum melatonin level in autistic children (a neurological disorder that is characterized by abnormalities in social behavior and communication) is lower than healthy children. In a survey conducted in this field reported that plasma melatonin concentration found to be low in healthy parents of patients with autism suggesting a genetic origin. These patients suffer from irregular sleep-wake circadian cycle which can be improved by melatonin supplementation.[72]

Melatonin safety and interactions

Melatonin is an inexpensive and safe medication. Except a couple of studies which reported transient or mild adverse effects in a small number of subjects, other studies did not report any adverse effect for it. The side effects reported for melatonin include dizziness, confusion, daytime sleepiness, headache, irritability, mild anxiety abdominal discomfort, and short-lasting feelings of depression.[55,73] Drug interactions of melatonin with other medications have been reported for anticoagulants, immunosuppressants, antidiabetes, and birth control pills.[74]

Melatonin is one of the normal components of breast milk and is synthesized from tryptophan. Although the maternal use of melatonin during breastfeeding seems to be safe, there are no enough data to make its usage sure. The safety usage of melatonin during pregnancy is the same.[74]

DISCUSSION

Mitochondrial dysfunction is one of the main causative complications of a lot of diseases, especially the neurodegenerative diseases.[29] The main cause of these diseases is free radical-induced oxidative stress.[75,76]

Fee radical theory of aging and degenerative diseases attributes the damage to cellular components through ROS imbalance as a major determinant of life span and disease. Among the possible affecting organs, the brain and cell membranes possess high proportion of easily peroxidizable fatty acids; hence, they are the main targets for oxidative stress. Phospholipids including phosphatidylinositol, phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, and sphingomyelin make the most abundant content of cellular membrane. Therefore, extensive and persistent oxidative damage in the brain and cell membranes may easily cause the death of these cells.[77]

Antioxidant therapy is a way for slowing the oxidative damage that is responsible for functional decline or death of the cells or organs. Endogenous antioxidant defense system reduces free radicals within the mitochondria. However, in extensive oxidative stresses, the endogenous antioxidants should be restored. Various antioxidants have been extensively examined against oxidative-induced damage.[31,76] Antioxidants such as Vitamins C and E are able to participate in the antioxidant defense system of mitochondrial; however, in most cases, they are not effective. For example, they cannot convert $O_2^{\bullet-}$ to O_2, and for this process, GSH is needed. The mitochondrial GPx and GSH reductase activities depend only on GSH uptake from the cytoplasm to keep adequate GSH levels. Melatonin by stimulating the activity of the enzyme γ-glutamyl-cysteine synthetase promotes synthesis of GSH.[23] It also plays an important role in mitochondrial physiology through its effects on gene expression of GPx, GSH reductase, catalase, and dismutase, helping in maintaining the GSH/GSSG ratio and in high recycling of GSH.[17,24]

More importantly, melatonin is selectively taken up by mitochondria and acts as a powerful antioxidant. Furthermore, melatonin increases the permeability of membranes and acts as inhibitor of lipoxygenase. Melatonin also acts as stimulator of antioxidant enzymes including superoxide dismutase, GPx, GSH reductase, and catalase. Melatonin has been effective against a wide variety of pathological conditions.[1] It is also effective on the activity of fibroblasts and stimulates the synthesis of Type I collagen fibers[12] as well as puberty timing. Activation of melatonin receptors prevents from many fatal diseases by increasing the release of some immune system inhibitor cytokines due to stress.[12] Melatonin can cause to resistance against oxidative damages by stimulating the antioxidant enzymes and microsomal membranes stabilization.[16] Melatonin is considered to have protective effects against the damage caused by ultraviolet radiation.[19]

Based on the performed examinations, melatonin reduces the risk of atherosclerosis.[24] In patients with Alzheimer's disease, the use of melatonin supplements could reduce the distraction and improve memory in such patients.[25] It was revealed that melatonin could influence the body size, obesity, and energy intake as well.[28] According to the previous studies, received melatonin led to decrease enhanced insulin doses, triglycerides, and leptin, while increased HDL cholesterol, esterified cholesterol, free cholesterol, and total cholesterol, and inhibited the oxidation of LDL cholesterol.[16] The use of melatonin could improve sleep and remove attention-deficit hyperactivity disorder symptoms, as well as irregular circadian sleep-wake circle in patients with autism.[11] More importantly, melatonin is relatively an inexpensive and safe medication, and although it is not sure, it seems to be safe to use during pregnancy and lactation.[74]

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Conflicts of interest

There are no conflicts of interest.

AUTHORS' CONTRIBUTIONS

- MRK contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.
- RShC contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.
- HSh contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.
- AS contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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