



Melatonin: A Potent Protector of Mitochondria and Cancer

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ABSTRACT

In the mitochondrial electron transport pathway (ET-pathway) electrons are transferred from reduced substrates to oxygen which is coupled to the phosphorylation of ADP to ATP. The electron transfer pathway leads to electron leakage, mitochondria, which is the most important source of free radicals in cells. When mitochondria are damaged by oxidation, they cannot keep up with the cell's energy needs. This determines the cell to produce more free radicals. Both mechanisms, namely faulty ATP generation and elevated oxygen radicals, may promote mitochondrial-dependent apoptosis. Melatonin's high concentrations and diverse antioxidant activities provide substantial protection to organelles which are exposed to a large number of free radicals. It has been shown that melatonin reduces oxidative stress and stress-induced mitochondrial dysfunction both in vitro and in vivo. Moreover, melatonin is protective against a number of illnesses in which excessive free radical production is the primary cause of the disease. Several diseases are characterized by mitochondrial damage caused by oxidative stress. Consequently, melatonin has gained recognition as a potential therapeutic agent for treating cancer and other mitochondrial dysfunctions in cancer cells.

1. Introduction: Mitochondria generate ROS

In eukaryotic cells, mitochondria are essential organelles that provide the energy source adenosine triphosphate (ATP), which powers the majority of a cell's biological functions. During the synthesis of ATP, electron transporters transfer electrons to oxygen, where they bond to produce water [1]. Membrane-bound electron transfer pathway consists of sets of electron carriers distributed across four enzyme complexes, namely complex I, complex II, complex III, and complex IV [2]. Across the inner mitochondrial membrane, a proton gradient is formed by the process of electron transport. Complex V (ATP synthase) then uses this proton gradient to create ATP. The other components of the mitochondrial electron transfer pathway are tricarboxylic acid (TCA) cycle, mitochondrial matrix dehydrogenases, and the carriers involved in metabolite transport across the mitochondrial membrane. As a result, the mitochondria are responsible for the synthesis of a wide variety of chemicals, such as amino acids, nucleotides, and reactive oxygen species (ROS) [3]. Complex IV generates water as the last product of the respiratory chain by a four-electron reduction of molecular oxygen (O₂). The transfer of electrons from one carrier to the next in the ET pathway is not a perfect process; some electrons are lost in translation and end up interacting with nearby ground-state oxygen molecules, which results in the production of ROS [4]. Some of these are the superoxide anion radical (O₂⁻), the hydroxyl radical (·OH), the hydroperoxyl radical (HOO·), the peroxy radical (ROO·), and the alkoxy radical (RO·) [5].

The cell's natural antioxidative defense mechanism typically decomposes free radicals and neutralizes their peroxidation products. When these metabolites build up out of control, free radicals trigger chain reactions that damage proteins, lipids, and DNA. Since mitochondria play a crucial role in ROS production, they have been the major target, causing injury to the mitochondrial respiratory system and an increase in free radical creation. Increased cellular oxidative stress is a contributing factor to the development of illnesses including diabetes [6], cardiovascular disease [7], neurodegenerative disease, and cancer [8] under these conditions. However, cells have evolved defense mechanisms to fight the oxidative stress caused by ROS. Due to this, the main defense is to use different types of antioxidants, such as small antioxidant molecules like melatonin. It is well acknowledged that melatonin serves as a crucial regulator of mitochondrial integrity and function and protects cells from oxidative damage [9]. This has also been shown in several in vivo and in vitro studies [8,10].

2. The Origins of Melatonin and Its Diverse Roles

Melatonin is thought to have evolved for the first time with the task to get rid of harmful O₂ derivatives made by photosynthetic bacteria during photosynthesis [11,12]. The fact that the structure of melatonin in cyanobacteria is the same as the structure of melatonin in mammals today is an important sign that its chemical structure has not changed [13]. Therefore,

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the original property of being an antioxidant was kept and helped by evolution and other properties. Melatonin, which was first isolated and described by Lerner et al in 1958, is synthesized by the pineal gland and released into circulation [14]. Melatonin production also occurs in lymphocytes [15], the skin [16], the gastrointestinal tract [17], the thymus, various areas of the eye, and bone marrow, also it is involved in paracrine and autocrine signaling. Therefore, the pineal glands' melatonin release is connected to the circadian rhythm and synced with the light-dark cycle. In mammals, unlike other species, its production is restricted to darkness. It is a crucial physiological ingredient that signals circadian time and synchronizes several activities in the body [18].

Among the many physiological processes that melatonin regulates are those related to sleep [19], immunity [20], and seasonal control of reproduction [21]. It has been demonstrated that the pharmacological dosages of melatonin decrease tumor development and have therapeutic efficacy in several forms of cancer, including breast cancer, prostate cancer, and melanoma [22]. Melatonin membrane receptors belong to the G-protein coupled receptor families (MT1, MT2) and the quinone reductase enzyme family (MT3), making them molecularly separate [23]. Activation of MT1 receptors by melatonin is typically reliant on the inhibition of cAMP, leading to an increase in cytosolic calcium, while binding to MT2 receptors inhibits cAMP and cGMP [24]. MT1 receptors are involved in reproductive and metabolic processes, while MT2 receptors play a role in the circadian rhythm and dopamine release from the retina [25]. Similarly, the binding location in the nucleus has been found and described for RZR/ROR α and RZR β orphan receptors [26]. The interaction of melatonin with these receptors contributes to some of its genomic effects. Some of the melatonin's effects do not involve its receptors at all. Melatonin interacts with cytosolic proteins, including calmodulin, which regulates the cytoskeleton and nuclear receptors, and it functions as a direct scavenger of free radicals [27].

3. Melatonin and Mitochondria: Melatonin is a Mitochondria-Targeted Antioxidant

When examining the interaction between melatonin and mitochondria, three features of melatonin that are crucial to mitochondrial homeostasis come to the forefront. The first is that mitochondria create significant quantities of ROS and that melatonin is a potent ROS-scavenging antioxidant; the second is that melatonin is highly produced in mitochondria and the apoptotic signals associated with mitochondria are extremely strong. Thirdly, the circadian rhythm significantly affects mitochondrial structure and function [28,29]. Within a decade after the discovery of indole as potent free radical destroyer and passive antioxidant, it was shown that melatonin prevents ROS damage at the mitochondrial level [30]. The seizure-inducing fatal characteristics of cyanide, a complex IV inhibitor, were reversed by the injection of melatonin in mice, as shown by Yamamoto and Yang. Melatonin also counteracts the neurotoxic effects of 6-hydroxydopamine (6-OHDA) [31], and 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) [32]-mediated malfunction of mitochondrial Complex I. In addition, research on rats revealed that it increased complex I and IV activities and repaired mitochondrial damage simultaneously [33].

Oxygen is necessary for aerobic organisms and increases the amount of ATP produced by glucose oxidation. Even though oxygen is a biradical, it is one of the primary causes of ROS production [34]. This is especially significant in mitochondria, where electrons leak each time during electron transport, resulting in oxygen reduction and the generation of one of the most critical ROS, superoxide anion [35].

Melatonin is also known as an indirect antioxidant because it can increase the activity of several antioxidant enzymes, such as superoxide dismutase and glutathione peroxidase, and decrease the activity of pro-oxidant enzymes. As a result, this plays a significant role in the antioxidant system, helping to maintain mitochondrial homeostasis, cutting down on ROS formation, and enhancing ET-pathway activity. Due to the antioxidant action of melatonin, lipids are protected, lipid peroxidation is reduced, and membrane fluidity is maintained, therefore preventing oxidative degradation [36]. The antioxidant activity of melatonin depends on the redox cascade pathway, and this scavenger cascade ensures that melatonin works very effectively in removing free radicals and as an antioxidant. It is also known that melatonin enhances the enzymatic or non-enzymatic cellular defense mechanism by modulating the intracellular redox signaling system and protecting critical proteins in the redox pathway from oxidation, such as Trx1 [37]. Melatonin's scavenger activity does not require a receptor, according to *in vitro* studies, but certain antioxidant effects may be receptor-mediated. Melatonin's protective impact as an oncostatic agent or in the neurological system may be attributed to this quality [38].

Melatonin can affect mitochondrial bioenergetic parameters by regulating the oxygen flux and the mitochondrial membrane potential. *In vitro* experiments with normal mitochondria have also shown that mitochondrial function is protected against ROS-induced oxidative damage and oxygen consumption is reduced in the presence of ADP, which leads to a decrease in membrane potential and inhibition of O₂⁻ and H₂O₂ [39]. Melatonin is also known to cause a decrease in membrane potential and ATP production by increasing the gene expression of uncoupling proteins (UCPs), which play an important role in the modulation of mitochondrial membrane potential. Melatonin may counterbalance the decreased ATP generation caused by the activation of UCPs by decreasing electron leakage and increasing electron flow through the membrane bound electron carriers [40].

4. Melatonin, Mitochondria, And Cancer

Mitochondrial damage greatly contributes to the dysregulation of cellular metabolism by directing glucose breakdown from the aerobic to the anaerobic pathway. Dysregulation of mitochondrial activity, defined by Krebs cycle abnormalities, has been linked to the overproduction of ROS, which may contribute to oncogenic signaling and tumor growth by irreversibly modifying DNA and oxidizing proteins. Otto Warburg hypothesized that even if there is no change in oxygen circumstances, metabolic alterations may play a role in the switch from oxidative phosphorylation to glycolysis, resulting in cancer. This phenomenon is known as the Warburg effect or aerobic glycolysis [41].

Although it is known that the conversion of glucose to lactate via glycolysis in anaerobic conditions is inefficient when it comes to ATP generation compared to oxidative respiration, tumor cells must make the conversion of glucose to glucose-6-phosphate efficient. Based on positron emission tomography (PET) examinations conducted for this purpose, it has been shown that the glucose absorption of cancer cells is directly correlated with their aggressiveness. In addition to revealing the significance of metabolic research in cancer, these findings will boost the efficacy of targeted treatments as a consequence of a comprehensive analysis of the function of mitochondria in cancer. Research into MDA-MB231 cells undergoing metabolic reprogramming to a glycolytic phenotype has shown a strong correlation between mitochondrial and cell membrane morphology and energy consumption in cancer [42].

Many researches in recent years have proven the anti-cancer impact of melatonin on cancer cells, and its usage is expanding. According to research, increasing melatonin levels at night aid in the control of homeostatic balance. Melatonin's behavior varies depending on cell type or circumstance [43]. Melatonin has this oncostatic impact through receptor-dependent or receptor-independent mechanisms, as shown [44]. MT-1 and MT-2 receptors are G-protein coupled receptors that are involved in the downstream pathway. In this process, it is claimed that the decrease in linoleic acid intake and therefore the anti-proliferative impact of melatonin are implicated in the mechanism of action due to the suppression of cAMP [45].

Apoptosis, also known as programmed cell death, is the most essential mechanism for balancing cell growth and death. There are two key extrinsic and intrinsic pathways in apoptosis. While death receptors and caspases play a role in the extrinsic apoptotic process, Bid (tBid), which is released into the mitochondria upon Caspase activation, initiates the internal apoptotic pathway. The intrinsic apoptotic pathway is a mitochondrial-mediated pathway that is activated by factors like DNA damage, chemotherapy, and radiation therapy. This pathway involves bax-bak, a member of the pro-apoptotic bcl-2 family, and the apoptotic process starts when molecules like cytochrome c are released. Therefore, getting bax/bak to work is a very important part of treating cancer [46].

Melatonin is known to have both pro-apoptotic and anti-apoptotic properties. It prevents apoptosis from occurring in normal cells while encouraging it in cancer cells. However, this double effect remained a topic of discussion. In addition, melatonin may start apoptosis by stimulating the cytosolic cascade and triggering the release of cytochrome c or an increase in antiapoptotic proteins.

The effects of melatonin on cancer cell growth and apoptosis are the result of a number of research and processes. It has been shown that melatonin inhibits ERK and Akt when they are activated by reactive oxygen species (ROS), resulting in suppression of cyclin D1, Bcl-2, and up-regulation of bax in cancer cells. It also induces apoptosis by inhibiting the expression of the p53 negative regulator MDM2, increasing caspase-3 and caspase-9 activity [47].

Under hypoxic circumstances, it is known that cancer cells acquire resistance to TRAIL-mediated death, which is another method of action. Melatonin therapy inhibits hypoxic

conditions for bax release via modulating mitochondrial membrane potential and promoting apoptotic cell death by removing TRAIL-mediated apoptosis resistance in cancer cells [48]. In addition, it has been shown in HepG-2 cancer cells that melatonin decreases proliferation by arresting the cell cycle in the G2/M phase [49]. Melatonin has a function in early apoptosis by increasing the production of AIF via TGF-1, and in late apoptosis by reducing the bcl-2/bax ratio through caspase-7 and caspase-9 [50].

In recent years, the use of melatonin to enhance the therapeutic efficacy of anti-cancer drugs has increased. Studies have shown that the combination of melatonin and pterostilbene promotes PARP activation in colorectal cancer cells [51] and inhibits ERK phosphorylation and induces HSP-27 dephosphorylation when combined with cisplatin [52].

In addition, the millimolar concentration of melatonin lowered the S-phase population in colon cancer cells while decreasing the G2/M transition in osteosarcoma and leukemia cells without affecting cell survival. All of these findings demonstrate that the apoptotic effect varies based on the metabolic and differentiation levels of cancer cells [53, 54].

5. Conclusion

Mitochondria plays a crucial role in maintaining cellular equilibrium, including calcium balance and apoptosis, while providing essential functions such as supplying cells with chemical energy and power. The mitochondrial dysfunction caused by oxidative stress has led to the development of mitochondrial-targeted antioxidant systems. Melatonin, which is also produced by mitochondria, is one of these compounds. Diverse investigations have shown that it may reduce the harm that may arise from an increase in mitochondrial ROS production or an excessive increase in ROS. It has been demonstrated that melatonin is particularly powerful in combating oxidative stress; thus, its absorption or production by mitochondria makes it the most important participant when ROS levels rise.

Melatonin's oncostatic effects in malignancies with the Warburg effect may be explained by its capacity to regulate glucose metabolism by transferring it primarily from the cytosol to the mitochondria. However, although there are studies that hypothetically explain its ability to change this situation, it is believed to have an effect with basically the same mechanism as anti-cancer agents. The use of melatonin should be explored if the impact of melatonin is significant at the mitochondrial level, if mitochondrial dysfunctions are improved, or if the energy mechanism works better for no apparent reason.

Blockade of glycolysis metabolism is presently one of the most significant targets in anticancer investigations. Melatonin should be regarded as significant in this context due to its capacity to alter mitochondrial processes. Melatonin may also make apoptotic processes stronger because it controls the mitochondrial respiratory chain with mitochondrial apoptotic effectors and is involved in calcium release.

This degree of interdependence between mitochondria and melatonin may allow the impact to be apparent in several cell types, including tumor cells. Depending on the kind and stage of cancer, it may exhibit varied mitochondrial features,

such as improving the efficiency of chemotherapy or minimizing its negative side effects while opposing cell growth, apoptosis, or chemotherapy resistance. As a result, when evaluated together, melatonin acts as a versatile molecule in reducing ROS levels, improving mitochondrial energy mechanisms, and its effects on tumor cells, as well as its mechanism of action should be studied in depth, either alone or in combination with other agents in a variety of cancer types.

Declaration

Author Contribution: Conceive – Ş.D., C.A.; Design - Ş.D., C.A.; Supervision - Ş.D., C.A.; Experimental Performance, Data Collection and/or Processing Ş.D., C.A.; Analysis and/or Interpretation Ş.D., C.A.; Literature Review- Ş.D.; Writer- Ş.D.; Critical Reviews – Ş.D., C.A.

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