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REVIEW

Melatonin and mitochondria in aging

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Abstract The worldwide prolongation of mean life expectancy has resulted in a rapid increase of the size of the elderly population, both in numbers and as a proportion of the whole. In addition, the incidence of age-related diseases is obviously increasing as the population ages. Finding means to preserve optimal health in old age has become a primary goal of biomedical research. Aging is a multifactorial process that includes progressive cellular loss, endocrine and metabolic deficits, reduced defense mechanisms and functional losses that increase the risk of death. Mitochondria fulfill a number of essential cellular functions and play a key role in the aging process. Melatonin, which is synthesized in the pineal gland and other organs, plays a role in the biologic regulation of aging. Noctural melatonin serum levels are high during childhood and diminish substantially as people age. Melatonin preserves mitochondrial homeostasis, reduces free radical generation, e.g., by enhancing mitochondrial glutathione levels; it also safeguards proton potential and ATP synthesis by stimulating complex I and IV activities. In this article, we review the role of melatonin and mitochondria in aging.

Keywords aging, melatonin, mitochondria, respiratory, reactive oxygen species

1 Introduction

Aging can be characterized as a time dependent decline of maximal functionality that affects tissues and organs of the entire body. These changes induce progressive loss of redundant components and lead to an increased susceptibility to disease and risk of death (Figueiredo et al., 2008). The worldwide prolongation of mean life expectancy has resulted in a rapid increase of the size of the elderly population, both in numbers and as a proportion of the whole. In addition, the incidence of age-related diseases also increases as individuals age. As a consequence, there is a search for any therapeutic agent that will improve quality of life in the elderly. A role for melatonin as such a compound has been suggested (Karasek et al., 2002; Poeggeler, 2005; Karasek, 2007).

Melatonin (N-acetyl-5-methoxytryptamine) is synthesized in the pineal gland during the dark phase of the circadian cycle (Reiter, 1991). Melatonin is also produced in many organs and tissues of the body, reaching concentrations higher than that in the blood. This suggests multiple actions of melatonin (Menendez-Pelaez and Reiter, 1993; Martín et al., 2000a; Reiter and Tan, 2003). Melatonin has a number of physiological functions, including regulating circadian rhythms, clearing free radicals (Tan et al., 1993, 2003), improving immunity (Carrillo-Vico et al., 2005), and generally inhibiting the oxidation of biomolecules (Ersahin et al., 2009; Hardeland et al., 2009; Kedziora-Kornatowska et al., 2009; Samantaray et al., 2009). Melatonin decreases during the aging process (Reiter et al., 1980, 1981; Reiter, 1992). Studies show that melatonin serum levels are high during childhood and diminish substantially in elder people (Carranza-Lira and García López, 2000). There is an age-related loss in the sensitivity of melatonin in restoration of serotonin levels and its rhythmicity (Jagota and Kalyani, 2010). It is generally accepted that a melatonin deficit may be closely related to age-related diseases (Wu and Swaab, 2005). Classically, the effects of melatonin were considered to be receptor mediated; more recently, non-receptor mediated actions, including its free radical scavenging activities, have been uncovered (Reiter et al., 2002; Allegra et al., 2003). Although two groups of receptors/binding sites have been identified, i.e. membrane (Witt-Enderby et al., 2003) and nuclear (Acuna-Castroviejo et al., 1994; Becker-André et al., 1994), they may not act separately (Carlberg, 2000; Tomás-Zapico and Coto-Montes, 2005). Recent studies suggest that calreticulin may also represent a new class of high-affinity melatonin-binding sites involved in some functions of the indoleamine including genomic

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regulation (Macías et al., 2003). For example, some of the antioxidant properties of melatonin relate to its genomic effects in regulating protein expression and activities of antioxidant enzymes (Antolín et al., 1996) as well as the inducible and mitochondrial isoforms of nitric oxide synthase (NOS) (Crespo et al., 1999; Escames et al., 2003; León et al., 2005).

Mitochondria play a central role in energy-generating processes within the cell through the electron transport chain (ETC), the primary function of which is ATP synthesis via oxidative phosphorylation (OXPHOS). The ETC, located in the inner mitochondrial membrane, includes a series of electron carriers grouped into four enzyme complexes: complex I (nicotinamide adenine dinucleotide (NADH) ubiquinone reductase,); complex II (succinate ubiquinone reductase); complex III (ubiquinol cytochrome C reductase); and complex IV (cytochrome C oxidase) (León et al., 2004). Mitochondria fulfill a number of essential cellular functions and play a key role in the aging process.

The recent studies showing mitochondria to be a target for melatonin opened a new perspective to understand the mechanism of action of this indoleamine (Acuña et al., 2002). Melatonin has a direct role in mitochondrial homeostasis (Martín et al., 2000a, 2000b, 2002), which may explain the protective effect of this molecule in diseases such as Alzheimer's disease, aging, and sepsis, all of which have mitochondrial dysfunction as a primary or secondary cause of the condition (Acuña-Castroviejo et al., 2001; León et al., 2005; Jou et al., 2010; Rosales-Corral et al., 2010).

2 Melatonin and aging

Aging is a multifactorial process that includes progressive cellular loss, endocrine and metabolic deficits, decreased defense mechanisms and functional losses that increase the risk of death. Although the role of melatonin during aging is not fully understood, several properties of melatonin indicate that it may be beneficial in antiaging. Serum levels of melatonin significantly decrease in aged animals compared with the young of the population, including in humans (Reiter, 1992). Moreover, the night-time serum levels and the circadian amplitude of melatonin rhythm decline with age (Pang et al., 1990; Lahiri et al., 2004) and melatonin levels drop in the pineal gland during aging (Reiter et al., 1980, 1981). Melatonin contributes to the total antioxidative capability of human serum (Benot et al., 1999). The loss of this potent anti-oxidant during aging may be, in part, the cause of the onset of age-related diseases as well as sleep disorders, cancer, and immunological disturbances commonly manifested in the elderly (Wolkove et al., 2007). This antioxidant contribution of melatonin is reduced as age advances correlating with the age-related reduction of melatonin. In humans, the total antioxidative capacity of serum correlates well with its melatonin levels (Benot et al., 1999). Thus, the reduction in melatonin with age may be a factor in the elevated oxidative damage observed in the elderly (Reiter and Tan, 2002).

Specific membrane and nuclear receptors for melatonin have been described in different tissues from many different species (Carrillo-Vico et al., 2005). Melatonin membrane receptors belong to the G-protein-coupled receptor superfamily, and two functionally active sites have been cloned and characterized, MT1 (Mel 1a) and MT2 (Mel 1b) (Dubocovich and Markowska, 2005). Furthermore, the enzyme quinone reductase type 2 (NQO2) has been identified as the cytosolic melatonin receptor, MT3 (Nosjean et al., 2000). This enzyme belongs to a group of reductases that participate in the protection against oxidative stress by preventing electron transfer reactions of quinones. On the other hand, nuclear receptors of melatonin belong to the ROR/RZR family (retinoic acid-related orphan receptor/retinoid Z receptor), a group of the steroid hormone receptor superfamily. An age-related reduction in mRNA MT1 and MT2 expression levels as well as MT1 protein expression in the spleen, liver, kidney, and heart has been reported. Melatonin concentrations decrease in the spleen, liver, and heart during aging (Sánchez-Hidalgo et al., 2009). The number and density of MT1-expressing neurons in the suprachiasmatic nucleus were reduced in aged controls compared to young controls (Wu et al., 2007).

Animal and cell culture models of several age-associated disorders have benefited from the application of melatonin. Melatonin has potential utility both in slowing normal brain aging and in treatment of neurodegenerative conditions (Pappolla et al., 2000; Bondy and Sharman, 2007; Olcese et al., 2009). Exogenous administration of this indoleamine reduces the inflammatory and oxidative processes associated with age (Matsubara et al., 2003; Rodríguez et al., 2007c). Dietary melatonin prevents an age-related decline in cortical synaptophysin levels (Bondy et al., 2010). Melatonin treatment exerts a long-term effect on the serotonin, dopamine (DA) and norepinephrine (NE) neurotransmission by enhancing monoamine synthesis in aged rats, and improves the age-dependent deficits in cognition and motor coordination (Esteban et al., 2010). One means by which melatonin may act to slow the aging process may relate to its ability to enhance membrane fluidity and maintain the associated functional pathways (García et al., 2010).

3 Melatonin and mitochondria

Melatonin preserves mitochondrial homeostasis, reduces free radical generation, e.g., by enhancing mitochondrial glutathione levels, and safeguarding proton potential and ATP synthesis and by stimulating complex I and IV

activities (Srinivasan et al., 2005; Acuna-Castroviejo et al., 2007; Paradies et al., 2010). A defected mitochondrial respiratory chain (RC), in addition to causing a severe ATP deficiency, often augments reactive oxygen species (ROS) generation in mitochondria which enhances pathological conditions and diseases. Melatonin and its metabolites are potent scavengers of free radicals and are considered a component of the endogenous antioxidant system (Hardeland et al., 1995; Reiter, 1998; Tan et al., 2007; Schaefer and Hardeland, 2009). One molecule of melatonin may scavenge two free radicals, both a hydroxyl radical on a superoxide anion and a hydroxyl radical (Tan et al., 1993, 2000a, 2000b). The ability of melatonin to function as a free radical scavenger relates to its ability as an electron donor. Also, melatonin is lipophilic which permits the indoleamine to cross cell membranes, reaching all intracellular compartments (Menendez-Pelaez and Reiter, 1993; Costa et al., 1997) including mitochondria, where it seems to accumulate in high concentrations (Martín et al., 2000a). In addition, melatonin interacts with lipid bilayers (Costa et al., 1997) and stabilizes mitochondrial inner membranes (García et al., 1999), an effect that may improve ETC activity (Acuña-Castroviejo et al., 2001). Semak et al. (2005) reported mitochondrial cytochrome C-mediated oxidation of melatonin, which may provide direct evidence for a novel pathway in mitochondrial melatonin metabolism. Thus, melatonin may have a new function, namely, a role as an intramitochondrial sensor of local redox status. The main physiological consequence of the OXPHOS is the production of ATP (Brown, 1992). The ability of melatonin to operate as a free radical scavenger is related to its electron donor ability (Tan et al., 2000a). Since the ETC is coupled to OXPHOS, an increase in ATP synthesis should be the last event following melatonin's action on mitochondria.

In vivo experiments showed that melatonin increases the activities of the brain and liver mitochondrial respiratory complexes I and IV after its administration to rats, whereas the activities of complexes II and III were not affected (Martín et al., 2000b). Melatonin also counteracts ruthenium red-induced inhibition of complexes I and IV in brain and liver mitochondria (Martín et al., 2000b). Furthermore, melatonin increases Aβ25-35-induced inhibition of complexes I and IV in cultured hippocampal neurons (Dong et al., 2010). In sub-mitochondrial particles obtained from rat brain and liver, melatonin increases the activities of the complexes I and IV and the production of ATP in a concentration-dependent manner (Martín et al., 2000a, 2002). Melatonin treatment had a strong protective effect on rates of mitochondrial oxygen consumption, and complex I and III activities caused by H_2O_2 (Petrosillo et al., 2006). Due to the interaction of melatonin with complexes I and IV and the subsequent promotion of electron flux through the ETC, melatonin increases ATP production under basal conditions and counteracts cyanide-induced depletion of ATP associated with complex IV inhibition (Martín et al., 2002). Melatonin, but not other endogenous antioxidants such as vitamins C and E, regulates the glutathione redox status in isolated brain and hepatic mitochondria, correcting it when it is disrupted by oxidative stress (Martín et al., 2000a). *In vivo* and *in vitro* experiments have shown that melatonin reduces the oxygen consumption of liver mitochondria (Reyes-Toso et al., 2003, 2006); melatonin may protect this organelle from excessive oxidative damage (Sewerynek et al., 1999; Karbownik et al., 2000a; Tan et al., 2000a; Yamamoto and Mohanan, 2002, 2003). Melatonin prevents mitochondria ROS-mediated depolarization of mitochondrial membrane potential and subsequent opening of the mitochondrial permeability transition pore (MPTP) and cytochrome C release (Jou et al., 2007). Melatonin also reduces glutamate-induced oxytosis in the HT22 mouse hippocampal cell line through a direct antioxidant effect specifically targeted to the mitochondria (Herrera et al., 2007).

The protective effect of melatonin on lipid peroxidation induced by oxidative stress in mitochondrial membranes has been demonstrated. In human placenta, melatonin inhibits nicotinamide adenine dinucleotide phospate (NADPH)-dependent mitochondrial lipid peroxidation (Milczarek et al., 2000). Melatonin counteracted oxidative damage to nuclear DNA and microsomal and mitochondrial membranes in liver (Karbownik et al., 2000a) and kidney (Karbownik et al., 2000b). Melatonin also protects neuronal parikarya, axons, myelin and intracellular organelles, including mitochondria, and the nucleus by inhibiting lipid peroxidation during spinal cord injury in adult rats (Kaptanoglu et al., 2000).

Melatonin has neuroprotective effects in a large number of models of neurodegeneration (Reiter et al., 2004). Melatonin crosses the blood-brain barrier, and shows a decrease in its nocturnal serum peaks with age which may be associated with the development of neurodegenerative disorders. Exogenously administrated melatonin has not been shown to be toxic. These properties make melatonin a potential therapeutic agent against neurodegenerative disorders of the aged.

4 Mitochondria and aging

Mitochondria play a central role in energy-generating processes within cells; this involves the ETC, the primary function of which is ATP synthesis via OXPHOS. Mitochondria are the major intracellular source and target sites of ROS that are continually generated as by-products of aerobic metabolism in cells of all aerobic organisms. The correlation between age and mitochondria has been widely investigated. During the aging process, mitochondrial function declines and mitochondrial DNA (mtDNA) mutation increases in tissue cells. Age-related impairment in mitochondrial respiratory function not only reduces ATP

synthesis but also enhances the production of ROS through increased electron leakage from the ETC (Lee and Wei, 1997). ROS cause oxidative damage and mutations of mtDNA and alterations in the expression of several clusters of genes in aging tissues and senescent cells (Wei et al., 2009). mtDNA mutations may well have a causative role in the aging process. The mitochondrial pool of reduced glutathione declines and DNA damage is enhanced in aging tissues (Wei et al., 2001).

Mitochondrial dysfunction has also been implicated in several common age-related neurodegenerative diseases including Alzheimer's, Parkinson's and amyotrophic lateral sclerosis and Huntington's diseases (Bowling and Beal, 1995). Primary targets of oxidative damage include mitochondrial membranes, mitochondrial proteins, and the mtDNA. mtDNA is relatively unprotected in comparison to nuclear DNA since it is located near the mitochondrial inner membrane, not surrounded by basic histones, and mitochondrial DNA repair mechanism lacks the effectiveness and sophistication of their nuclear counterpart. Thus, the level of DNA damage in aging humans is 10-fold greater in the mitochondrion than in the nucleus (Mecocci et al., 1993). In addition, the level of mitochondrial damage is 15-fold greater in people over 70 years of age than in the younger population (Mecocci et al., 1993). As judged by deletion frequencies, the mutation rate of mtDNA is increased many fold in old relative to young mice (Wang et al., 1997). A high level of mutated mtDNA has been found to lead to an impairment of mitochondrial respiration (Sobreira et al., 1996).

Mitochondria also play key parts in the regulated processes of cellular self-destruction, apoptosis, autophagy and necrosis (Kim et al., 2006; Skulachev, 2006). When functioning properly, regulatory control of these processes related to cell death is exquisitely sensitive to imbalances in cellular homeostasis as gauged by such measures as Ca^{2+} levels (Halestrap, 2006) and cellular redox status (Haddad, 2004).

5 Melatonin, mitochondria and aging

The results from brain mitochondria of male and female senescent-accelerated prone (SAMP8) mice at 5 and 10 months of age indicate that there is a significant age-dependent mitochondrial dysfunction with a diminished efficiency of the ETC and reduced ATP production; this is accompanied by elevated oxidative/nitrosative stress. Melatonin administration between 1 and 10 months of age completely prevented the mitochondrial impairment, maintaining or even increasing ATP production. There were no major age-dependent differences between males and females (Carretero et al., 2009). Other recent studies using the senescence-accelerated mice (SAM) investigated the effects of chronic melatonin administration on mitochondrial oxidative stress and life span. Diaphragmatic mitochondria from female senescent prone (SAMP8) and senescent resistant (SAMR1) mice at 5 and 10 months of age were examined. The results suggest that the age-dependent mitochondrial oxidative damage in the diaphragm of SAMP8 mice was accompanied by a reduction in the electron transport chain complex activities and in ATP levels. Furthermore, melatonin administration between 1 and 10 months of age normalized the redox and the bioenergetic status of the mitochondria and increased the ATP levels (Rodríguez et al., 2007a). Melatonin also increased both the half-life and longevity of the SAMP8 animals (Rodríguez et al., 2008). Long-term melatonin treatment prevented age-dependent mitochondrial oxidative stress (Rodriguez et al., 2007b). Moreover, the age-dependent mitochondrial oxidative damage in the heart of SAMP8 mice was accompanied by a reduction in the electron transport chain complex activities and in ATP levels.

Melatonin also prevents age-related oxidative DNA damage in the brain of female senescence-accelerated (SAM-P/6) mice (Morioka et al., 1999), restores mitochondrial respiratory control index, ADP/O ratio, state 3 and dinitrophenol (DNP)-dependent uncoupled respiration (Okatani et al., 2002b). Furthermore, melatonin administration counteracts the senescence-associated reductions of complex I and IV activities in liver mitochondria from SAMP8 (Okatani et al., 2002a, 2002b). Additionally, injections of pharmacological dose of melatonin modifed mitochondrial respiratory activity and respiratory chain complex I and IV activities in liver mitochondria from SAMP8 mice (Okatani et al., 2003). The findings using synaptosomal and mitochondrial membranes isolated from the brains of SAMP8 and SAMR1 substrains show that aging caused membrane rigidity in biological membranes. Chronic treatment with melatonin prevents the age-related rigidity, especially in the mitochondrial membranes (García et al., 2010).

Petrosillo et al. (2010) investigated the effect of aging and long-term treatment with melatonin on the susceptibility to Ca^{2+}-induced membrane permeability transition (MPT) opening and cytochrome C release in rat heart mitochondria. Mitochondria from aged rats (24 months old) displayed an increased susceptibility to Ca^{2+}-induced MPT opening, associated with an elevated release of cytochrome C, when compared with young control animals (5 months old). Melatonin treatment counteracted both these processes. Various parameters related to mitochondrial bioenergetics in rat brain tissue, including complex I activity, rate of state 3 respiration, mitochondrial hydrogen peroxide production, and membrane potential, mitochondrial content of normal and oxidized cardiolipin, are significantly altered with aging; melatonin treatment was found to completely prevent these age-related alterations. In summary, there is a decline of mitochondrial bioenergetic functions in brain with aging; melatonin treatment is beneficial since it prevents deterioration of essential

mitochondrial processes (Petrosillo et al., 2008).

Dong et al. (2010) reported that melatonin increases mitochondrial membrane potential, ATP concentration and the activity of complexes I and IV in senescent hippocampal neurons. Moreover, melatonin restores the secretory function, Ca^{2+} signaling and mitochondrial potential of aged exocrine cells (Camello-Almaraz et al., 2008).

6 Conclusion

Both melatonin and mitochondria play important roles in the aging process. Melatonin levels and mitochondrial function decline with age. These results combined with the protective effect of melatonin in improving mitochondrial physiology during aging may become significant to our understanding of how this indoleamine might contribute to ameliorating physiological aging as well as age-related disorders. However, there is a need for extensive studies on the use of melatonin in antiaging in both experimental animals and humans.

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