Melatonina protege as mitocôndrias da lesão oxidativa e mantém a produção de ATP mitocondrial sem aumentar radicais livres. Efeito anti-câncer.

07/07/10

Melatonin protects the mitochondria from oxidative damage reducing oxygen consumption, membrane potential, and superoxide anion production.

López A, García JA, Escames G, Venegas C, Ortiz F, López LC, Acuña-Castroviejo D. J Pineal Res. 2009 Mar;46(2):188-98.
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Abstract

The role of melatonin in improving mitochondrial respiratory chain activity and increasing ATP production in different experimental conditions has been widely reported. To date, however, the mechanism(s) involved are largely unknown. Using high-resolution respirometry, fluorometry and spectrophotometry we studied the effects of melatonin on normal mitochondrial functions. Mitochondria were recovered from mouse liver cells and incubated in vitro with melatonin at concentrations ranging from 1 nm to 1 mm. Melatonin **decreased oxygen consumption** concomitantly with its concentration, **inhibited any increase in oxygen flux** in the presence of an excess of ADP**, reduced the membrane potential**, and consequently **inhibited the production of superoxide anion and hydrogen peroxide**. At the same time **it maintained the efficiency of oxidative phosphorylation and ATP synthesis while increasing the activity of the respiratory complexes (mainly complexes I, III, and IV).** The effects of melatonin appeared to be due to its presence within the mitochondria, since kinetic experiments clearly showed its incorporation into these organelles. Our results support the hypothesis that **melatonin, together with hormones such as triiodothyronine, participates in the physiological regulation of mitochondrial homeostasis.**
PMID: 19054298

Melatonin, mitochondria, and cellular bioenergetics.

Acuña-Castroviejo D, Martín M, Macías M, Escames G, León J, Khaldy H, Reiter RJ. J Pineal Res. 2001 Mar;30(2):65-74.
Departamento de Fisiología, Instituto de Biotecnología, Universidad de Granada, Spain.

Abstract

Aerobic cells use oxygen for the production of 90-95% of the total amount of ATP that they use. This amounts to about 40 kg ATP/day in an adult human. The synthesis of ATP via the mitochondrial respiratory chain is the result of electron transport across the electron transport chain coupled to oxidative phosphorylation. Although ideally all the oxygen should be reduced to water by a four-electron reduction reaction driven by the cytochrome oxidase, under normal conditions a small percentage of oxygen may be reduced by one, two, or three electrons only, yielding superoxide anion, hydrogen peroxide, and the hydroxyl radical, respectively. The main radical produced by mitochondria is superoxide anion and the intramitochondrial antioxidant systems should scavenge this radical to avoid oxidative damage, which leads to impaired ATP production. During aging and some neurodegenerative diseases, oxidatively damaged mitochondria are unable to maintain the energy demands of the cell leading to an increased production of free radicals. Both processes, i.e., defective ATP production and increased oxygen radicals, may induce mitochondrial-dependent apoptotic cell death. Melatonin has been reported to exert neuroprotective effects in several experimental and clinical situations involving neurotoxicity and/or excitotoxicity. Additionally, in a series of pathologies in which high production of free radicals is the primary cause of the disease, melatonin is also protective. A common feature in these diseases is the existence of mitochondrial damage due to oxidative stress. The discoveries of new actions of melatonin in mitochondria support a novel mechanism, which explains some of the protective effects of the indoleamine on cell survival.
PMID: 11270481

Melatonin and mitochondrial function.

Leon J, Acuña-Castroviejo D, Sainz RM, Mayo JC, Tan DX, Reiter RJ. Life Sci. 2004 Jul 2;75(7):765-90.

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Abstract

Melatonin is a natural occurring compound with well-known antioxidant properties. In the last decade a new effect of melatonin on mitochondrial homeostasis has been discovered and, although the exact molecular mechanism for this effect remains unknown, it may explain, at least in part, the protective properties found for the indoleamine in degenerative conditions such as aging as well as Parkinson's disease, Alzheimer's disease, epilepsy, sepsis and other injuries such as ischemia-reperfusion. A common feature in these diseases is the existence of mitochondrial damage due to oxidative stress, which may lead to a decrease in the activities of

mitochondrial complexes and ATP production, and, as a consequence, a further increase in free radical generation. A vicious cycle thus results under these conditions of oxidative stress with the final consequence being cell death by necrosis or apoptosis. Melatonin is able of directly scavenging a variety of toxic oxygen and nitrogen-based reactants, stimulates antioxidative enzymes, increases the efficiency of the electron transport chain thereby limiting electron leakage and free radical generation, and promotes ATP synthesis. Via these actions, melatonin preserves the integrity of the mitochondria and helps to maintain cell functions and survival. Copyright 2004 Elsevier Inc.
PMID: 15183071

Melatonin mitigates mitochondrial malfunction.

León J, Acuña-Castroviejo D, Escames G, Tan DX, Reiter RJ. J Pineal Res. 2005 Jan;38(1):1-9.
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Abstract

Melatonin, or N-acetyl-5-methoxytryptamine, is a compound derived from tryptophan that is found in all organisms from unicells to vertebrates. This indoleamine may act as a protective agent in disease conditions such as Parkinson's, Alzheimer's, aging, sepsis and other disorders including ischemia/reperfusion. In addition, melatonin has been proposed as a drug for the treatment of cancer. These disorders have in common a dysfunction of the apoptotic program. Thus, while defects which reduce apoptotic processes can exaggerate cancer, neurodegenerative disorders and ischemic conditions are made worse by enhanced apoptosis. The mechanism by which melatonin controls cell death is not entirely known. Recently, mitochondria, which are implicated in the intrinsic pathway of apoptosis, have been identified as a target for melatonin actions. It is known that melatonin scavenges oxygen and nitrogen-based reactants generated in mitochondria. This limits the loss of the intramitochondrial glutathione and lowers mitochondrial protein damage, improving electron transport chain (ETC) activity and reducing mtDNA damage. Melatonin also increases the activity of the complex I and complex IV of the ETC, thereby improving mitochondrial respiration and increasing ATP synthesis under normal and stressful conditions. These effects reflect the ability of melatonin to reduce the harmful reduction in the mitochondrial membrane potential that may trigger mitochondrial transition pore (MTP) opening and the apoptotic cascade. In addition, a reported direct action of melatonin in the control of currents through the MTP opens a new perspective in the understanding of the regulation of apoptotic cell death by the indoleamine.
PMID: 15617531 [

Melatonin represses oxidative stress-induced activation of the MAP kinase and mTOR signaling pathways in H4IIE hepatoma cells through inhibition of Ras.

Kimball SR, Abbas A, Jefferson LS. J Pineal Res. 2008 May;44(4):379-86.
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Abstract

Reactive oxygen species (ROS) have been implicated in the pathogenesis of a variety of diseases, and antioxidant treatment is currently being investigated as a potential therapy to attenuate the detrimental effects of ROS-mediated oxidative stress. Melatonin is a potent naturally produced antioxidant, which acts through various mechanisms to ameliorate the toxic effects of ROS. However, little is known about the mechanisms of signaling pathways through which melatonin acts to reverse the effects of ROS. In the present study, the effect of melatonin treatment on the hydrogen peroxide (H(2)O(2))-induced activation of the mitogen-activated protein kinase (MAPK) and mammalian target of rapamycin (mTOR) signaling pathways was assessed in H4IIE hepatoma cells. It was found that melatonin strongly attenuated H(2)O(2)-induced activation of the ERK1/2 and p38 MAP kinases, as well as several of their downstream targets. Melatonin also attenuated the H(2)O(2)-induced phosphorylation of Akt and the Akt substrate mTOR, as well as a downstream target of mTOR action, 4E-BP1. Upregulation of ERK1/2, p38, and Akt signaling by H(2)O(2) was accompanied by activation of Ras, an effect that was blocked by melatonin. Overall, the results suggest that melatonin acts to prevent many of the H(2)O(2)-induced alterations in the MAPK and mTOR signaling pathways through inhibition of Ras, at least in H4IIE hepatoma cells.
PMID: 18410586

Acutely administered melatonin restores hepatic mitochondrial physiology in old mice.

Okatani Y, Wakatsuki A, Reiter RJ, Miyahara Y. Int J Biochem Cell Biol. 2003 Mar;35(3):367-75.
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Abstract

Damage to mitochondria as a result of the intrinsic generation of free radicals is theoretically involved in the processes of cellular aging. Herein, we investigated whether acutely administered melatonin, due to its free radical scavenging activity, would influence mitochondrial metabolism. Mitochondrial respiratory activity and respiratory chain complex I and IV activities in liver mitochondria from a strain of senescence-accelerated-prone mice (SAMP8) and a strain of senescence-accelerated-resistant mice (SAMR1) were measured when the animals were 12 months of age. Respiratory control index (RCI), ADP/O ratio, State 3 respiration and dinitrophenol (DNP)-dependent uncoupled respiration were significantly lower in SAMP8 than in SAMR1. In contrast, State 4 respiration was significantly higher in SAMP8 than in SAMR1. Activities of complexes I and IV in SAMP8 were significantly lower than in SAMR1. Melatonin administration (10mg/kg body weight, intraperitoneally) 1h prior to sacrifice significantly increased RCI, ADP/O ratio, State 3 respiration and DNP-induced uncoupled respiration in SAMP8 while also significantly reducing State 4 respiration in SAMP8. The injection of melatonin also significantly increased complex I activity in both mouse strains and complex IV activity in the liver of SAMP8 mice. These results document an age-related decrease in hepatic mitochondrial function in SAM which can be modified by an acute pharmacological injection of melatonin; the indole stimulated mitochondrial respiratory chain activity which would likely reduce deteriorative oxidative changes in mitochondria that normally occur in advanced age.
PMID: 12531250

Hepatic mitochondrial dysfunction in senescence-accelerated mice: correction by long-term, orally administered physiological levels of melatonin.

Okatani Y, Wakatsuki A, Reiter RJ, Miyahara Y. J Pineal Res. 2002 Oct;33(3):127-33.
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Abstract

Mitochondrial oxidative damage from free radicals may be a factor underlying aging. We investigated whether long-term administration of physiological levels of melatonin, a direct free radical scavenger and indirect antioxidant, influences mitochondrial respiratory activity in liver of senescence-accelerated mice (SAM). Liver was obtained in the middle of dark period of the daily light:dark cycle from SAMP8, a strain of mice prone to accelerated senescence, and from SAMR1, a senescence-resistant strain, at 6 and 12 months of age. Respiratory control index (RCI), adenosine-5-diphosphate (ADP)/O ratio, State 3 respiration and dinitophenol (DNP)-dependent uncoupled respiration exhibited significant age-associated decreases in SAMP8. SAMP8 also showed significant age-associated reductions in respiratory chain complex I and IV activities. No age-related effects were found in these parameters in SAMR1. Daily oral melatonin administration (2 microg/mL of drinking fluid) beginning at 7 months of age significantly increased RCI, State 3 respiration, DNP-dependent uncoupled respiration, and complex I and IV activities in both mouse strains when they were 12 months old. These results reveal age-related reductions in mitochondrial function in SAM mice which are modified by melatonin; the most likely explanation for the corrective actions of melatonin relate to its antioxidative actions in mitochondria and other portions of the cell. The implication of the findings is that melatonin may be beneficial during aging as it reduces the deteriorative oxidative changes in mitochondria and other portions of the cell associated with advanced age.
PMID: 12220325

Melatonin, mitochondrial homeostasis and mitochondrial-related diseases.

Acuña CD, Escames G, Carazo A, León J, Khaldy H, Reiter RJ. Curr Top Med Chem. 2002 Feb;2(2):133-51
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Abstract

The recently described 'hydrogen hypothesis' invokes metabolic symbiosis as the driving force for a symbiotic association between an anaerobic, strictly hydrogen-dependent organism (the host) and an eubacterium (the symbiont) that is able to respire, but which generates molecular hydrogen as an end product of anaerobic metabolism. The resulting proto-eukaryotic cell would have acquired the essentials of eukaryotic energy metabolism, evolving not only aerobic respiration, but also the cost of oxygen consumption, i.e., generation of reactive oxygen species (ROS) and oxidative damage. Mitochondria contain their own genome with a modified genetic code that is highly conserved among mammals. Control of gene expression suggests that transcription of certain mitochondrial genes may be regulated in response to the redox potential of the mitochondrial membrane. Mitochondria are involved in energy production and conservation, and they have an uncoupling mechanism to produce heat instead of ATP. Also, mitochondria are involved in programmed cell death. Increasing evidence suggests the participation of mitochondria in neurodegenerative and neuromuscular diseases involving alterations in both nuclear (nDNA) and mitochondrial (mtDNA) DNA. Melatonin is now known as a powerful antioxidant and increasing experimental evidence shows its beneficial effects against oxidative stress-induced macromolecular damage and diseases, including those in which mitochondrial function is affected. This review summarizes the data and mechanisms of action of melatonin in relation to mitochondrial pathologies.
PMID: 11899097

Melatonin increases the activity of the oxidative phosphorylation enzymes and the production of ATP in rat brain and liver mitochondria.

Martín M, Macías M, León J, Escames G, Khaldy H, Acuña-Castroviejo D. Int J Biochem Cell Biol. 2002 Apr;34(4):348-57.
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Abstract

We recently showed that melatonin counteracted mitochondrial oxidative stress and increased the activity of the mitochondrial oxidative phosphorylation (OXPHOS) enzymes both in vivo and in vitro. To further clarify these effects, we studied here the activity of OXPHOS enzymes and the synthesis of ATP in rat liver and brain mitochondria in vitro. In sub-mitochondrial particles, melatonin increases the activity of the complexes I and IV dose-dependently, the effect being significant between 1 and 10nM. Blue native-PAGE followed by histochemical analysis of the OXPHOS enzymes further showed the melatonin-induced increase of complex I activity. Titration studies show that melatonin counteracts the partial inhibition of complex IV induced by 5 microM potassium cyanide. However, melatonin (up to 5mM) was unable to recover the activity of complex IV when it was completely blocked by 100 microM cyanide. These data suggest that the indoleamine could stimulate the activity of the non-inhibited part of the complex IV. Melatonin also increases the production of ATP in control mitochondria and counteracts the cyanide-induced inhibition of ATP synthesis. These results provide new hormonal mechanism regulating mitochondrial homeostasis and may explain, at least in part, the anti-aging and neuroprotective properties of melatonin.
PMID: 11854034

Disruption of mitochondrial respiration by melatonin in MCF-7 cells.

Scott AE, Cosma GN, Frank AA, Wells RL, Gardner HS Jr. Toxicol Appl Pharmacol. 2001 Mar 15;171(3):149-56.
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Abstract

Clinical and laboratory studies have provided evidence of oncostatic activity by the pineal neurohormone melatonin. However, these studies have not elucidated its mechanism of action. The following series of MCF-7 breast tumor cell studies conducted in the absence of exogenous steroid hormones provide evidence for a novel mechanism of oncostatic activity by this endogenous hormone. We observed a 40--60% loss of MCF-7 cells after 20-h treatment with 100 nM melatonin, which confirmed and extended previous reports of its oncostatic potency. Interestingly, there were no observed changes in tritiated thymidine uptake, suggesting a lack of effect on cell cycle/nascent DNA synthesis. Further evidence of a cytocidal effect came from morphologic observations of acute cell death and autophagocytosis accompanied by degenerative changes in mitochondria. Studies of mitochondrial function via standard polarography revealed a significant increase in oxygen consumption in melatonin-treated MCF-7 cells. Enzyme-substrate studies of electron transport chain (complex IV) activity in detergent permeabilized cells demonstrated a concomitant 53% increase ($p < 0.01$) in cytochrome c oxidase activity. Additional studies of succinate dehydrogenase activity (complex II) as determined by reduction of (3-4,5-dimethylthiazol-2-yl)2,5-diphenyltetrazolium bromide demonstrated a significant increase ($p < 0.05$) in melatonin-treated cells and further confirmed the accelerated ET activity. Finally, there was a 64% decrease ($p < 0.05$) in cellular ATP levels in melatonin-treated cells. The G-protein-coupled melatonin receptor antagonist luzindole abrogated the cytotoxic and mitochondrial effects. These studies suggest a receptor-modulated pathway of cytotoxicity in melatonin-treated MCF-7 tumor cells with apparent uncoupling of oxidative phosphorylation.
PMID: 11243914