

Melatonin protects the powerhouses of cells, the mitochondria

Mitochondria have been named the 'powerhouses of cells', because they are the main source of ATP, a carrier molecule of chemical energy for versatile use in numerous metabolic reactions. ATP is generated by the electron transport chain (ETC) at the inner mitochondrial membrane. In brief, the ETC consists of a chain of protein complexes which donate and accept electrons. However, despite their usefulness for the energy supply of the cell, mitochondria have also a dark side. In the ETC, in which electrons are passed from one complex to the other, some electrons can escape and are transferred to molecular oxygen (O_2), which is thereby converted to a free radical, the superoxide anion ($O_2^{\bullet-}$), a process called electron leakage. This free radical is *per se* rather harmless, but can be converted to highly dangerous and destructive molecules, such as the hydroxyl radical ($\bullet OH$) and peroxynitrite ($ONOO^-$). The latter compound is formed by interaction of $O_2^{\bullet-}$ with nitric oxide ($\bullet NO$), a free radical generated as a signaling molecule by NO synthases. The further metabolism of peroxynitrite leads to other free radicals, including $\bullet OH$, $\bullet NO_2$ and the carbonate radical ($CO_3^{\bullet-}$) formed from a peroxynitrite- CO_2 adduct. The secondary, highly reactive radicals endanger the functional state of a mitochondrion. A critical parameter is the availability of $\bullet NO$, which is formed in excess, e.g., under conditions of inflammation or of neuronal overexcitation. Damage to mitochondria can be fatal to cells, because this may induce apoptosis, a form of programmed cell death. If cells do not die, they may eliminate damaged mitochondria by autophagy. Thereby, neurons may be depleted of peripheral mitochondria, and the reduced presence of mitochondria in the vicinity of synapses can impair interneuronal communication. Meanwhile, numerous diseases are known in which mitochondrial dysfunction is crucial, which has given rise to the attribute of the 'powerhouse of disease'. A look at the actions of $\bullet OH$, $\bullet NO$, $\bullet NO_2$, and $CO_3^{\bullet-}$ reveals that they interact in multiple ways with the ETC, either by oxidizing and nitrating proteins of the ETC complexes, peroxidizing lipids in the inner membrane, or by binding of the nitrogen-containing compounds to iron atoms in the complexes. Thus, electron flux is partially blocked and, as a result of local bottlenecks, more electrons are leaking out from the ETC and generate more superoxide anions, thereby promoting a vicious cycle of increasing free radical generation and progressive damage. Melatonin, which has been discovered as the hormone of the pineal gland, has been shown to possess numerous protective actions. Its relationship to mitochondria is more profound than previously believed. It has been recently shown to be formed in mitochondria, which also contain melatonin receptors. Its formation in these organelles is of general relevance, especially as melatonin is not only synthesized in the pineal gland, but in numerous, perhaps almost all organs. The quantities of extrapineal melatonin exceed those in the pineal gland by orders of magnitude, but are usually poorly released to the circulation. The mitochondria protecting actions of melatonin are diverse and may be regarded as a full arsenal of defense weapons. Melatonin downregulates the activities of NO synthases in neurons, astrocytes and immune cells including the microglia of the brain, thereby reducing the levels of $\bullet NO$ and the generation of its detrimental products. It also reduces electron leakage by regulating electron flux and by preventing extended periods of opening of the mitochondrial permeability transition pore,

through which electrons can leak out. It scavenges free radicals of high reactivity, increases levels of antioxidants such as reduced glutathione (GSH) and activities of antioxidant enzymes, and it can also prevent apoptosis.

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Publication

[Melatonin and the electron transport chain.](#)

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Cell Mol Life Sci. 2017 Nov