CLINICAL STUDY

# The role of melatonin in the neurodegenerative diseases

Olakowska E, Marcol W, Kotulska K, Lewin-Kowalik J

*Department of Physiology, Medical University of Silesia, Katowice, Poland.***Vie@alpha.net.pl**

**Abstract**

**Melatonin is a product of the pineal gland. Synthesis and release of this hormone is inhibited by light. The biological activity of melatonin is associated with its receptors – ML1 and ML2. Melatonin plays a role in the biologic regulation of circadian rhythms, sleep, mood, reproduction, tumor growth and aging. It may also modulate the activity of various receptors in cancer cells. The hormone is a free radical scavenger, an antioxidant and immunomodulatory agent. Antioxidant properties of melatonin are connected with its neuroprotective activity in several degenerative disorders. The etiology of the neurodegenerative diseases which are characterized by the progressive and irreversible destruction of specific neuronal populations is complex and multifactorial. One of causes of neurodegenerative damage in the nervous system is oxidative injury, which results from an inbalance between free radical formation and antioxidative mechanisms. The efficacy of melatonin in the inhibition of the oxidative stress was estimated in various neurodegenerative disorders whose pathogenesis is associated with cytotoxic activity of free oxygen radicals, such as Alzheimer's or Parkinson's disease. Melatonin may have a clinical potential for the treatment of neurodegenerative disorders in the central as well as peripheral nervous system.** ***(Ref. 38.)***

**Key words: melatonin, oxidative stress, neuronal injury, neuroprotection, neurodegenerative diseases.**

Melatonin is a derivative of tryptophan that was isolated and identified by Lerner and his colleagues in 1958 (1). The hormone is synthetized in pineal cells- pinealocytes and its synthesis and release are regulated by a seasonal fluctuations in day length. Light exerts an inhibiting effect (2). The mammalian pineal gland is considered to be a special neuroendocrine transducer. The visual information from the retina is transmitted to the pineal gland through the suprachiasmatic nucleus and inhibits the release of norepinephrine. Norepinephrine increases the synthesis of melatonin by activation of alpha-1 and beta-1 adrenoceptors. The secretion of melatonin increases immediately after the onset of darkness and reaches its peak between 2 and 4 a.m. Concentrations of melatonin vary according to age. The peak nighttime concentrations of melatonin are the highest in children of 1–3 years old (3). Melatonin secretion is independent of the length of a sleep at night (4). After synthesis the hormone is not stored in the pineal gland, but enters the bloodstream through passive diffusion (2). The half-life of melatonin in serum is about 30 minutes. It is quickly metabolized in hepatocytes to 6-hydroxymelatonin and after conjugation with sulfuric or glucuronic acid is excreted in the urine (3). Although the pineal gland is a major site of synthesis of melatonin, it is also present in saliva, the lacrimal gland, gastrointestinal tract, bone marrow, bile and cerebrospinal fluid. Concentrations of melatonin in the bile and cereberospinal fluid are higher than in the blood (5). Two membrane receptors for melatonin have been identified: ML1 and ML2. The activation of ML1 is related to the regulation of retinal function, the circadian rhythm and reproduction (6). ML1 is expressed mainly in the suprachiasmatic nucleus, hypophysial pars tuberalis, retina and brain. This distribution of receptors suggests a key role of the hormone in chronobiology (7). Ekmekcioglu et al showed that the melatonin receptor subtype ML2 is present in human arteries and the left ventricle myocytes. They suggested that in coronary heart disease the ML2 receptor ex-

Department of Physiology, Medical University of Silesia, Katowice, and Department of Neurology, Medical University of Silesia, Katowice, Poland

**Address for correspondence:** W. Marcol, MD, Dept of Physiology, Medical University of Silesia, 18 Medyków St., 40-752 Katowice, Poland.
Phone: +48.32.2525087, Fax: +48.32.2526077

pression is altered (8). Melatonin receptors have also been localized in the small intestine. One of the physiological roles of the hormone can be the modulation of intestinal motility and the regulation and coordination of digestion and absorption (9).

In the last decade we observed a progress in understanding the role of melatonin in various processes. The hormone regulates the reproductive processes, circadian rhythms, sleeping, immunoresponsiveness and inhibition of cancer growth and aging (10). Melatonin directly influences the steroidogenesis in the ovary. It was found that abnormally high concentrations of the hormone are associated with disturbed ovarian function and anovulation. In the in vitro studies it was observed that melatonin has antigonadal and antiovulatory effects, probably by the inhibition of gonadoliberin release (3). The mechanism by which melatonin inhibits tumor growth is unknown. It may be associated with antimitotic activity of the hormone. It was shown that both physiological and pharmacologic concentrations of melatonin inhibit the proliferation of cultured epithelial breast cancer cell lines and malignant melanoma cell lines. This effect may be the result of down-regulation of gene expression and a decrease in the synthesis of different growth factors (10, 11). Melatonin can also modulate the activity of various receptors in cancer cells. Molis et al (12) showed that melatonin significantly decreased the expression of estrogen receptor and estrogen-binding activity in human breast cancer cells. Melatonin has also immunomodulatory activity. It modulates the activity of CD4 lymphocytes and increases the synthesis of opioid peptides and lymphokines, mainly interferon gamma and interleukin 2 (13). Melatonin is a potent antioxidant and free radical scavenger. The antioxidant properties of melatonin were first described by Ianas et al (14). They showed that in low concentrations (>0.1 μM/ml) this hormone has antioxidant activity, but in higher concentrations is prooxidant. This kind of melatonin activity is not associated with its receptors (15).

Exogenous melatonin used in therapy of insomnia, stress, jet lag and aging may interact with benzodiazepines, be antagonized by naloxone and flumazenil and interact with melatonin receptors in the central nervous system and in the body. It appears to be pharmacologically active and should not be considered a benign agent on overdose (16).

**Discussion**

Free oxygen radicals which are produced during the peroxidation of lipids have cytotoxic activity and play an important role in the neurodegenerative processes. The etiology of the neurodegenerative diseases which are characterized by the progressive and irreversible destruction of specific neuronal populations is complex and multifactorial. One cause of neurodegenerative damage in the nervous system is oxidative injury, which results from an inbalance between free radical formation and antioxidative mechanisms. Understanding of mechanisms underlying the pathogenesis of neurodegenerative diseases is very important (17).

The mechanism of neuronal loss from oxidative stress is still unknown. It is suggested that an increase of concentration of free radicals causes the destruction of cellular lipids, proteins and intranuclear DNA leading to necrosis or neuronal apoptosis (18). It is well known that brain neurons are particularly exposed to free oxygen radicals and the major defense mechanism for neutralizing their cytotoxic activity is a complex of antioxidant enzymes (19). Kotler et al (20) examined the influence of melatonin on gene expression for antioxidant enzymes in rat brain cortex. They showed that administration of melatonin increased levels of mRNA for glutathione peroxidase, copper-zinc superoxide dismutase and manganese superoxide dismutase in rat brain. The authors concluded that melatonin exerts an important protective role against free radical injury by stimulating gene expression for antioxidant enzymes and it may be considered as a potential therapeutic agent in some age-related neurodegenerative diseases.

The efficacy of melatonin in the inhibition of the oxidative stress was estimated in various neurodegenerative disorders in which the pathogenesis is thought to be associated with cytotoxic activity of free oxygen radicals like Alzheimer's or Parkinson's disease.

In Alzheimer's disease there are intracellular deposits of abnormal proteins which disturb the neuronal homeostasis and cause its irreversible destruction. These senile plaques contain tau filaments involved in axonal transport and neurotoxic amyloid beta-peptide (17). Sayre et al (21) observed structural changes of DNA, proteins and lipids which form the protein deposits in the result of the oxidative processes. Numerous studies showed a decrease of melatonin concentration in the cerebrospinal fluid in patients with Alzheimer's disease (22, 23). In physiological conditions melatonin is secreted directly into the cerebrospinal fluid in higher concentrations than in the blood. It is suggested that a deficiency of this hormone in the cerebrospinal fluid is critical for the development of Alzheimer's disease, because an inadequate concentration of melatonin allows production of free radicals which can damage neurons. Results from initial therapeutic trials showed a significant slowing down the progression of Alzheimer's disease after administration of melatonin (23). Papolla et al (24) demonstrated that melatonin interacted with A beta 1-40 and A beta 1-42 amyloid and inhibited formation of the protein deposits in neurons. Exposure of neurons to the amyloid beta protein is neurotoxic and harmful to neuronal homeostasis. The authors suggested that neuroprotective properties of melatonin against amyloid toxicity are the result of the antioxidant activity of the hormone. Melatonin can cross the brain-blood barrier easily, is lipophilic and has low toxicity, so it may be useful in the treatment of patients with Alzheimer's disease.

Cardinali et al showed that melatonin at dose of 3 mg daily was useful for the care of patients with Alzheimer type of dementia (25). Esparza et al showed protective effects of melatonin against cellular damage caused by oxidative stress in rats treated with melatonin (10 mg/kg/day) (26).

Matsubara et al (27) showed that administration of melatonin in transgenic mice with experimentally induced Alzheimer's disease reduced the accumulation of amyloid, inhibited the synthesis of free oxygen radicals and increased survival. In another

study melatonin also reduced the deposition of amyloid fibrils in neurons. Such melatonin activity seems to be independent of its antioxidant properties (28).

Parkinson's disease is caused by a progressive destruction of dopaminergic neurons. At the cellular level a characteristic hallmark of this neurodegenerative disease is the presence of Lewy bodies consisting of various proteins, mainly alpha-synuclein (29). A significant reduction in glutathione concentration in the substantia nigra has been observed (30).

Jener and Olanow (31) found in the nigrostriatal dopaminergic neurons a presence of structural changes of lipids, proteins and nucleic acids as a result of the oxidative processes. Mayo et al (32) studied the ability of melatonin to prevent programmed neuronal death in an experimental model of Parkinson's disease. They observed that the hormone was a highly effective free radical scavenger and prevented apoptosis in neuronal cells. The authors suggested that melatonin has a high clinical potential for the treatment of Parkinson's and other neurodegenerative diseases.

Brain cells are very sensitive to ischemia. The mechanism of neuronal destruction in cerebral ischemia-reperfusion disorder is associated with an increased synthesis of free oxygen radicals. These oxygen species are directly cytotoxic to cells and may cause their destruction by inflammation or apoptosis (33). The direct effect of melatonin on human cerebral blood flow is still unknown. Van der Helm-van Mil et al demonstrated that the hormone given intravenously (10 μg) in men had no influence on cerebral blood flow (34).

Sun et al (35) observed that melatonin administered intraperitoneally in rats (10 mg/kg) before a transient occlusion of the middle cerebral artery reduced the infarct area and enhanced cell viability in the peri-ischemic brain region. Although the protective mechanisms of melatonin are complex, the authors suggested that these may be related to the modulation of DNA repair and inhibition of apoptosis. Erten et al (36) studied the neuroprotective properties of melatonin in the prevention of ischemic spinal cord injury in an animal model. Ischemia was performed experimentally by temporary (25 minutes) occlusion of the thoracic and abdominal aorta in rabbits. Melatonin was administered intraperitoneally either 10 minutes before occlusion or 10 minutes after removal of the aortic clamp. Then the lumbosacral spinal cord was removed for the determination of oxidative enzyme activity. They observed a significant decrease in catalase and glutathione peroxidase levels in the group treated with melatonin before the occlusion. The authors suggested that application of melatonin can significantly reduce the incidence of spinal cord injury following temporary aortic acclusion. Cagnoli et al (37) found that melatonin can counteract the cytotoxic action of singlet oxygen and protect cerebellar granule neurons from apoptosis induced by free oxygen radicals. Neurodegeneration in the locus coeruleus has been documented in several neurodegenerative diseases in the central nervous system. Chen et al (38) investigated iron-induced oxidative damage in the locus coeruleus in rats. After bilateral infusion of iron into the locus coeruleus they administered melatonin intraperitoneally and estimated the range of oxidative injury and apoptosis. The results indicated that melatonin not only protected neurons from oxidative stress, but also significantly prevented the apoptosis.

The incidence of neurodegenerative diseases increases with age due to diminishing antioxidant defences and the increase of mitochondrial dysfunction. These age-related effects may provide mechanisms for the high incidence of neurodegeneration in older patients (18). Due to the neuroprotective activity of melatonin, its ability to cross the brain-blood barrier easily and with relatively low toxicity, in the future the hormone may be used in the treatment of disorders associated with the progressive neuronal degeneration in the central and peripheral nervous system.

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Received October 15, 2004.
Accepted February 16, 2005.