The pineal product melatonin has remarkable antioxidant properties. It scavenges hydroxyl, carbonate and various organic radicals, peroxynitrite and other reactive nitrogen species. Melatonyl radicals formed by scavenging combine with and, thereby, detoxify superoxide anions in processes terminating the radical reaction chains. Melatonin also enhances the antioxidant potential of the cell by stimulating the synthesis of antioxidant enzymes like superoxide dismutase, glutathione peroxidase and glutathione reductase, and by augmenting glutathione levels. The decline in melatonin production in aged individuals has been suggested as one of the primary contributing factors for the development of age-associated neurodegenerative diseases, e.g., Alzheimer’s disease. Melatonin has been shown to be effective in arresting neurodegenerative phenomena seen in experimental models of Alzheimer’s disease, Parkinsonism and ischemic stroke. Melatonin preserves mitochondrial homeostasis, reduces free radical generation, e.g., by enhancing mitochondrial glutathione levels, and safeguards proton potential and ATP synthesis by stimulating complex I and IV activities. Therapeutic trials with melatonin have been effective in slowing the progression of Alzheimer’s disease but not of Parkinson’s disease. Melatonin’s efficacy in combating free radical damage in the brain suggests that it may be a valuable therapeutic agent in the treatment of cerebral edema after traumatic brain injury.

**Keywords:** Melatonin; Free radical generation; Mitochondrial homeostasis; Aging; Alzheimer’s disease; Parkinson’s disease; Ischemic stroke; Brain trauma

**List of Abbreviations**

- 6-OHDA: 6-hydroxydopamine
- AD: Alzheimer’s disease
- AFMK: N\(^1\)-acetyl-N\(^2\)-formyl-5-methoxykynuramine
- AMK: N\(^1\)-acetyl-5-methoxykynuramine
- apoE4: apolipoprotein E4
- Aβ: amyloid beta
- BBB: blood brain barrier
- Bcl-2: B cell lymphoma proto-oncogene protein
- c3OHM: cyclic 3-hydroxymelatonin
- CSF: cerebrospinal fluid
- DA: dopamine
- ETC: electron transport chain
- GPx: glutathione peroxidase
- GR: glutathione reductase
- GSH: glutathione
- GSK-3: glycogen synthase kinase 3
- HIOMT: hydroxyindole-O-methyl transferase
- IL: Interleukin
- iNOS: inducible NOS
- KA: Kainic acid
- MAO: monoamine oxidase
- MAP: microtubule-associated protein
- MDA: malondialdehyde
- MnSOD: SOD subform with manganese in the active center
- MPP\(+\): methyl 1-4 phenyl pyridinium
- MPTP: 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine
- mtNOS: mitochondrial nitric oxide synthase
- mtPTP: mitochondrial permeability transition pore
- mitochondrial permeability transition pore
INTRODUCTION

Pineal melatonin (N-acetyl-5-methoxytryptamine) is normally synthesized and secreted during the dark phase of the day in all species studied to date. A primary physiological function of pineal melatonin secretion is to convey information about daily cycles of light and darkness to body physiology. By its pattern of secretion during darkness, melatonin indicates the length of the night. This information is used for the organization of functions which respond to changes in photoperiod such as circadian and seasonal rhythms (Cardinali and Pévet, 1998; Claustrat et al., 2005).

Melatonin is synthesized from serotonin through two enzymatic steps. The first is the N-acetylation by serotonin N-acetyltransferase (SNAT) to yield N-acetylserotonin. The physiological regulation of SNAT, with its sharp increase in activity at night, has received considerable attention as a major regulatory step in melatonin synthesis. The second step in melatonin synthesis is the transfer of a methyl group from S-adenosylmethionine to the 5-hydroxy group of N-acetylserotonin to yield melatonin. This reaction is catalyzed by the enzyme hydroxyindole-O-methyltransferase (HIOMT). The day/night changes of HIOMT are less prominent (Cardinali and Pévet, 1998; Claustrat et al., 2005).

Environmental lighting, acting through the eye in adult mammals and in part directly on the pineal in lower vertebrates and birds, has profound effects on rhythms in melatonin biosynthesis. Exposure of animals to light at night rapidly depresses pineal melatonin synthesis. Based on denervation or nerve stimulation studies, a simple model of pineal regulation was envisioned, comprising two premises: (i) the neural route for environmental lighting control of melatonin secretion is the neuronal circuit “retina - retinohypothalamic tract - suprachiasmatic nuclei (SCN) - periventricular hypothalamus - intermediolateral column of the thoracic chord gray - superior cervical ganglion - internal carotid nerves - pineal gland”; (ii) norepinephrine released from sympathetic terminals at night activates postsynaptic β-adrenoceptors coupled to the adenylate cyclase-cAMP system, therefore increasing melatonin synthesis and release. However, the presence of functional α-adrenoceptors as well the characterization of central peptidergic pinealopetal pathways point out to a complexity of mechanisms regulating melatonin biosynthesis (Cardinali and Pévet, 1998; Claustrat et al., 2005).

Once formed melatonin is not stored within the pineal gland but diffuses out into capillary blood and cerebrospinal fluid (CSF) (Arendt, 2000; Tricoire et al., 2002). The delicate connective tissue capsule of the pineal gland does not prevent diffusion of melatonin into CSF. Melatonin arrives early in the third ventricle CSF as compared to the lateral ventricles. As melatonin passes through all biological membranes with ease, brain tissue may have higher melatonin levels than other tissues in the body (Reiter and Tan, 2002). Indeed CSF melatonin levels were found to be 5 to 10 times higher than simultaneous blood levels (Tricoire et al., 2002).

Melatonin is involved in the control of various physiological functions in the body like control of seasonal reproduction (Reiter, 1980), sleep regulation (Wurtman and Zhdanova, 1995; Monti et al., 1999), immune function (Guerrero and Reiter, 2002; Esquifino et al., 2004), inhibition of tumor growth (Blask et al., 2002), blood pressure regulation (Doolen et al., 1998; Scheer et al., 2004), retinal physiology (Dubocovich et al., 1999) and control of circadian rhythms (Dawson and Armstrong, 1996; Kunz, 2004), control of human mood and behavior (Srinivasan, 1997) and free radical scavenging (Reiter et al., 2004; 2005). Melatonin participates in many of the respective mechanisms by acting through G-protein coupled membrane receptors like MT1 and MT2 (Reppert et al., 1994; 1995; Dubocovich et al., 2000) and nuclear receptors like RZR/ROR (Wiesenberg et al., 1995). Within the G-protein coupled receptor family of proteins melatonin acts through a number of signal transduction mechanisms that ultimately results in specific physiological responses (Witt-Enderby et al., 2003). In addition to receptors in the proper sense, another binding site exists, which was originally considered to represent another membrane-bound receptor (MT3), but it finally turned out to be an enzyme, quinone reductase 2 (QR2) (Nosjean et al., 2000). Quinone reductases are generally believed to protect against oxidative stress resulting from electron transfer reactions of quinones (Foster et al., 2000; Long and Jaiswal, 2000), but the specific role of subform QR2 is still poorly understood. Polymorphisms in the promoter of the human QR2 gene indicate a relationship to Parkinson’s disease (Harada et al., 2001). A connection to redox metabolism is apparent in the presence of an ARE (antioxidant response element) (Long and Jaiswal, 2000). QR2 knockout mice exhibit an impairment of apoptosis induction, which results in myeloid hyperplasia in the bone marrow (Long et al., 2002). The enzyme protein

nNOS: neuronal NOS
NOS: nitric oxide synthase
QR2: quinone reductase
RNS reactive nitrogen species
ROS: reactive oxygen species
SCN: suprachiasmatic nuclei
SNAT: serotonin N-acetyltransferase
SOD: superoxide dismutase