Melatonin is a neuroendocrine hormone secreted by the pineal gland to transduce the body's circadian rhythms. An internal 24 hour time keeping system (biological clock) regulated by melatonin, controls the sleep-wake cycle. Melatonin production is a highly conserved evolutionary phenomenon. The indole hormone is synthesized in the pinealocytes derived from photoreceptors. Altered patterns and/or levels of melatonin secretion have been reported to coincide with sleep disorders, jetlag, depression, stress, reproductive activities, some forms of cancer and immunological disorders. Lately, the physiological and pathological role of melatonin has become a priority area of investigation, particularly in breast cancer, melanoma, colon cancer, lung cancer and leukemia. According to the ‘melatonin hypothesis’ of cancer, the exposure to light at night (LAN) and anthropogenic electric and magnetic fields (EMFs) is related to the increased incidence of breast cancer and childhood leukemia via melatonin disruption. Melatonin’s hypothermic, antioxidant and free radical scavenging properties, attribute it to an immunomodulator and an oncostatic agent as well. Many clinical studies have envisaged the potential therapeutic role of melatonin in various pathophysiological disorders, particularly cancer. A substantial reduction in risk of death and low adverse events were reported from various randomized controlled trials of melatonin treatment in cancer patients. This review summarizes the physiological significance of melatonin and its potential role in cancer therapy. Furthermore, the article focuses on melatonin hypothesis to represent the cause-effect relationship of the three aspects: EMF, LAN and cancer.

Keywords: Electric and magnetic fields, free radical scavenger, light at night, oncostatic, pineal gland

Melatonin, a circadian and circannual time keeping natural hormone is secreted from the pineal gland situated in the center of the brain. This indoleamine (N-acetyl-5-methoxytryptamine) is now extensively used as a natural health product, to supplement certain conventional therapies and improve quality of life. The rhythm of production is endogenous, generated in the suprachiasmatic nuclei (SCN), the major central rhythm generating system of the self-sustaining clock in mammals. The maximum production of melatonin occurs at night by a signal from the eye indicating the absence of light. It was assumed that the trigger arose from rods and cones, but recent experiments indicate the presence of non-rod, non-cone receptors in the retina.[1] Its primary function in all species studied so far, is to transduce information concerning light-dark cycles, to body physiology for the organization of circadian rhythms and hence it has been correctly known as the “all natural night cap”. Melatonin is synthesized within the pineocytes (cell type derived from non-rod and non-cone photoreceptors) mostly during the dark phase. The precursor for this indole hormone is tryptophan[2] (Figure 1). The melatonin rhythm is generated by a closed-loop negative feedback of clock gene expression in the SCN. Both the enzymes i.e., the rate limiting enzyme, N-acetyl transferase (NAT) and the methylating enzyme, hydroxy indole-O-methyl transferase (HIOMT), regulate the cyclic production and metabolism of melatonin.[3]

Melatonin is metabolized in the liver by microsomal enzymes. About 50-80% of the melatonin produced is converted to the principal metabolite 6-hydroxy melatonin sulphate. There is a universal agreement that melatonin is quickly released into the bloodstream and then diffuses into other body fluids such as saliva, ovarian follicular fluid and semen. Exceptionally high concentrations are documented in the cerebro-spinal fluid and bile.[4]

Figure 1: Synthesis of melatonin

Melatonin crosses all morphophysiological barriers, e.g., the blood-brain barrier and placenta and spreads throughout the cell.[5] A considerable inter-individual variability in the secretory activity of melatonin has been reported; it is between 18-40 pg/mL at night. Its half-life is less than 30 minutes, with a
Melatonin synthesis is influenced by age, gender, seasons and in certain diseases. Its levels decrease with increase in age; however, in elderly women it is higher than in elderly men. A seasonal variation is also observed in humans; the levels are higher in winter than in summer. In several pathophysiological conditions, like coronary heart disease, orthostatic hypotension, schizophrenia, chronic pain and Alzheimer's disease, reduced concentrations of melatonin have been observed. Melatonin levels influence different stages of cancer progression particularly in breast cancer, brain tumor, colorectal cancer, hepatocarcinoma, endometrial cancer and prostate cancer. The antiproliferative property of melatonin in tumor suppression potentiates it as a novel therapeutic agent.

**PHYSIOLOGICAL SIGNIFICANCE OF MELATONIN**

1. **Circadian rhythm monitor**
   The Circadian rhythmicity of the melatonin synthesis in humans is well established. Melatonin is capable of resynchronising free-running rhythms and this finding explained the theory that melatonin affects the circadian rhythm of its own synthesis, controlled by the external light. Desynchronisation between the internal circadian rhythms and the external environment occurs, following abrupt phase shifts. Clinical studies on age related amplitude modulations of circadian rhythms of melatonin secretion and core body temperature have been indicated. The involvement of melatonin in the development of diurnal rhythm is demonstrated in the blind in the Antarctic population in winter and people exposed to constant dim light. The exposure to night time occupational electromagnetic fields can also suppress the normal nocturnal rise in melatonin.

Circadian rhythmicity is significant in a wide range of physiological conditions including jetlag. The term jetlag represents the frequent traveler’s symptoms of sleep disorders, digestive troubles, headaches, lack of appetite and fatigue. Studies have shown that exogenous melatonin may significantly reduce the effect of jetlag. This is explained by the hypothesis, that melatonin resets the biological clock in the suprachiasmatic nuclei adjusting to the new time schedule.

2. **Free radical scavenger and antioxidant**
   Melatonin is a multifaceted free radical scavenger. It detoxifies a variety of free radicals and reactive oxygen intermediates including the hydroxyl radical/hydrogen peroxide, peroxy radicals, peroxyanions, singlet oxygen, nitric oxide and lipid peroxidation. The highly toxic hydroxyl radical is more efficiently neutralized by melatonin resulting in N-Acetyl-N-formyl-5-methoxy kynuramine [Figure 2].

The peroxide radical produced during the oxidation of polyunsaturated acids is scavenged by melatonin with greater efficiency than that of vitamin E and twice as efficient as strolox. Melatonin also protects lipids in membranes, proteins in cytosol, DNA in nucleus and mitochondria from free radical damage, reducing the severity of disease where free radicals are implicated.

Melatonin is reported to be a broad-spectrum antioxidant, which stimulates several antioxidative enzymes including glutathione peroxidase, glutathione reductase, glucose-6-phosphate dehydrogenase and superoxide dismutase and catalase. At the same time it inhibits a prooxidative enzyme i.e., nitric oxide synthase. The endogenous antioxidative defense system reduces molecular toxicity of oxygen and nitrogen-based reactive species. One melatonin molecule has the potential to scavenge up to four or more molecules of reactive species.

3. **Cytoprotective agent**
   The development of cytoprotective agents has reduced the side effects of certain conventional therapies improving the quality of life for cancer patients. Melatonin as a cytoprotective agent reduces the adverse toxicities of chemotherapy and radiotherapy. It has been proposed that pineal gland and its hormone melatonin have a role to play in homeostatic system controlling brain excitability. GABA-containing neurons are found to be involved in cytoprotection of melatonin. The most recently available data from biochemical and electrophysiological studies support the possibility that the anticonvulsant and depressive effects of melatonin on neuron activity may depend on its antioxidant and antioxicototoxic roles, through free radical scavenging and regulating brain glutamate receptors.

It is established that melatonin protects the skin and other cells from oxidative damage caused due to ultraviolet radiation. The incidence of abnormal cells showing genetic damage, chromosomal aberrations and sister chromatid exchanges was reduced to 60% on treatment with melatonin before exposing to ionizing radiation.

4. **Immunomodulator**
   Among melatonin’s versatile functions, immunomodulation has emerged as a major effect of the hormone. Melatonin may act in part by modifying circadian rhythmicity of neural signals conveyed to the immunocompetent organs via the autonomic nerves. The melatonin rhythm seems to be
a very important efferent pathway of the SCN to impose synchronicity to the immune system.[24] Pinealectomy is associated with precocious involution and histological disorganization of the thymus[35,36] which provides evidence of possible involvement of endogenous melatonin on humoral and cell mediated immune reactions.

There is evidence suggesting the existence of membrane specific binding sites for melatonin in immune cells.[37] Melatonin seems to bind to melatonin receptors in T helper cells or monocytes, stimulating the production of interferon gamma and interleukins 1, 2, 6 and 12, which in turn upregulate the immune response, restoring immunodeficiency / immunocompetency states.

5. Endocrine modulator
Melatonin affects the synthesis / functions of steroids like estrogens, testosterone and progesterone along with prolactin, gonadotropins and growth hormones. In particular, there seems to exist a phase relation between melatonin and synthesis of gonadotrophic hormone, [46] particularly before and during puberty, is clear. The general assumption is that very low melatonin values are found in children with precocious puberty and very high values in children with delayed puberty. The menopause is associated with a decline in melatonin secretion and increased pineal calcification.[38] The pineal melatonin has been shown in animals to be involved in the regulation of calcium and phosphorus metabolism by stimulating the parathyroid glands and by inhibiting calcitonin release and prostaglandin synthesis.

6. Oncostatic agent
Melatonin is a naturally produced cytotoxin which exhibits oncostatic activity. It has shown to alleviate numerous cancer symptoms[40] and to inhibit tumor angiogenesis,[41] tumor proliferation and metastasis.[42]

Lowered melatonin levels may exaggerate the growth of tumors since melatonin, 1. Inhibits the fatty acid growth-factor-uptake by cancer cells 2. Inhibits telomerase activity by reducing telomere length; which results in apoptosis of cancer cells. 3. Inhibits endothelin-1 synthesis, an angiogenic factor, which promotes blood vessel growth in tumors. 4. Modulates the expression of tumor suppressor gene, TP53.

The melatonin effects occur not only in vivo but also when cancer cells are treated with melatonin in vitro,[43] where about 80% growth inhibition was observed.[38]

Studies on the effect of melatonin in MCF-7 breast cancer cells have repeatedly confirmed that melatonin is oncostatic. This oncostatic activity was explained on the basis of its antiestrogenic property. This is due to the inhibition of binding of the estrogen receptor complex to its DNA responsive element. Cini et al,[44] performed a transcriptome profiling by high-density microarrays of estrogen-treated MCF-7 cells exposed to melatonin to look in for downstream gene determinants of this effect. Cyclin D1 was found to be one of the main downregulated genes by melatonin. These findings establish a molecular link between melatonin effects on the cell cycle and its antiproliferative activity.

7. Thermo regulator
Melatonin has a distinct effect on body temperature playing an important role in thermoregulation.[38] It has a stimulating effect on the brown adipose tissue[45,46] implying a subordinate role in energy metabolism. It is evident that melatonin is inversely correlated with the temperature course under both natural conditions as well when administered exogenously.

8. Therapeutic agent
Melatonin as a therapeutic agent, promotes the stabilization of the disease and induces objective tumor regression in synergy with a chemotherapeutic agent. Table 1[47,48] Table 2[63-77] Based on certain theoretical reasoning and clinical trials, it has been suggested that melatonin can boost the immune system, prevent heart disease and fight aging in general.[5,7,78-80] Systematic review of randomized controlled trials and meta analysis reported the efficacy of melatonin in solid tumor cancer patient.[80] Additionally, the presence of melatonin seemed to prolong both disease progression-free and overall 1-year survival in many randomized controlled trials. However, a meta analysis review by Buscemi et al 2006 reported no evidence of melatonin to be effective in treating secondary sleep disorders.[81]

MELATONIN HYPOTHESIS OF CANCER
Light at night (LAN), electric and magnetic fields (EMFs) and melatonin
Light of sufficient intensity, duration and spectral quality suppresses melatonin production at night; the short wavelength (around 465nm in humans) is most effective.[82,83] The epidemiological studies provided evidence about the potential risk factor of LAN in breast cancer[84,85] with its involvement in the entire circadian axis rather than just melatonin depression.

Although the effect of EMF on melatonin release was extensively studied, the site and mechanism of action of magnetic field on the pineal gland that leads to changes in melatonin synthesis is unclear. The effect of magnetic field on melatonin synthesis can result from changes in neural input, at the level of the retina and the suprachiasmatic nuclei at the level of the biological clock or norepinephrine release.[86] Magnetic fields are perceived and interpreted by photoreceptors in eye as “light”, suppressing melatonin levels. Magnetic fields reduce the activity of the rate-limiting enzyme, N-acetyltransferase (NAT) in melatonin production and inhibit the activity of melatonin forming enzyme, hydroxy-indole-O-methyltransferase (HIOMT).[87] The free radicals generated by magnetic fields are scavenged by melatonin and due to its more rapid scavenging, there is a decline in melatonin levels. Therefore melatonin suppression maybe due to its more scavenging-utility, than the interference in its synthesis.[88] A mechanistic study showed the effect of circadian melatonin signal to tumor growth response influenced by short
EMF, melatonin and breast cancer

The relationship between EMF, melatonin and breast cancer is still a controversial issue where findings are inconclusive. Partial/complete blindness has been seen to be associated with decreased risk of breast cancer. Furthermore in female shift workers, particularly night-shift, there is suppression of melatonin, increasing the risk of breast cancer. The plausible biological explanation given from a prospective case-control study support the hypothesis of higher melanin levels association with lower risk of breast cancer. Lüscher and Mevissen reported that magnetic fields as low as 1 µT reduced nocturnal melatonin in serum of female rats. They then showed increased incidence of mammary tumors with magnetic field exposure in rats treated with the chemical carcinogen 7,12-dimethylbenz[a]anthracene (DMBA).

EMF, melatonin and childhood leukemia

Certain epidemiological studies have shown an increased risk of childhood leukemia related to the exposure to extremely low frequency magnetic fields. A meta-analysis data provided by Wartenburg et al 1998 projected a somewhat weak elevated risk of childhood leukemia in close vicinity to power lines. Another meta analysis study by Washburn et al 1994 reported no statistically significant risk of leukemia, lymphoma and nervous system tumors in children exposed to electricity transmission and distribution equipment. However, there is evidence that the initiation in acute lymphoblastic leukemia appears to take place in utero and that melatonin protects the human fetus against oxidative damage which is produced with diurnal rhythm, increases after 24 weeks of gestation and remains so until term. The biological relevance of serum melatonin levels in the development of leukemia is therefore suggestive of its antioxidative property in human hematopoietic system. Exogenous administration of melatonin indicated the protection of genetic damage in lymphocytes induced by free radical producing mutagens and carcinogens.

CONCLUSION

Current medical literature reveals that melatonin has a multi-disciplinary anti-cancer action, as it reduces toxicity after chemotherapy, radiotherapy, immunohormonal therapy and cancer surgery. Hence its efficacy and safety may eventually drive its use in clinical applications and as an adjuvant therapy for cancer.

Nonetheless, the consequences of electromagnetic exposure on human health are receiving increasing scientific concern. It renews the melatonin hypothesis where melatonin suppression explains the occurrence of clinical disorders due to magnetic field exposures. At present, the hypothesis that LAN or EMF from the use of electric power increases the risk of childhood leukemia and breast cancer remain quiet speculative. Although the indirect evidence provides a rationale, the direct evidence is inadequate to draw a conclusion. The long-term health effect of the indoor lighted environment also deserves attention particularly in terms of chronic disruption of melatonin rhythms. The melatonin hypothesis thus has far reaching implications. It could spawn trials that test whether malignancies can be slowed down by altering a person’s light environment or by using melatonin supplements. The outcome of multi-center randomized, double-blind clinical trials conducted, would be more imperative for clinicians to recommend melatonin supplementation as supportive care in conventional therapies in treatment of several pathophysiological conditions, particularly cancer.

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CANCER AND MELATONIN HYPOTHESIS


