Therapeutic applications of melatonin

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Abstract: Melatonin is a methoxyindole synthesized within the pineal gland. The hormone is secreted during the night and appears to play multiple roles within the human organism. The hormone contributes to the regulation of biological rhythms, may induce sleep, has strong antioxidant action and appears to contribute to the protection of the organism from carcinogenesis and neurodegenerative disorders.

At a therapeutic level as well as in prevention, melatonin is used for the management of sleep disorders and jet lag, for the resynchronization of circadian rhythms in situations such as blindness and shift work, for its preventive action in the development of cancer, as additive therapy in cancer and as therapy for preventing the progression of Alzheimer's disease and other neurodegenerative disorders.

Keywords: antioxidant agents, circadian rhythms, jet lag, melatonin, sleep

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Melatonin

Melatonin, N-acetyl-5-methoxytryptamine, is a methoxyindole which is synthesized within the pineal cells [Zawilska *et al.* 2009]. Steadily accumulating data show that melatonin has many beneficial effects in humans.

The pineal is involved in many functions of the organism via secretion of the hormone melatonin, which is characterized by functional pleiotropy [Reiter, 1995]. Melatonin is synthesized from tryptophan within the pineal cells, its secretion starting in the absence of light, being high during the night, the reverse happening during the day. Melatonin receptors have been detected on the cell surface [Reiter *et al*. 2010; Dubocovich *et al*. 2010]. In humans, melatonin receptors have been detected in the retina, brain, suprachiasmatic nucleus, pars tuberalis, ovaries, cerebral and peripheral arteries, kidney, pancreas, adipocytes and immune cells [Dubocovich and Markowska, 2005; Dubocovich *et al.* 2010].

Melatonin is thought to be involved in the adaptation of the organism to the light–dark cycle of the environment. There is evidence that it is involved in the regulation of biological rhythms. The hormone affects the function of both the anterior and posterior lobe of the pituitary [Kostoglou-Athanassiou *et al.* 1998b, 1998c]. Nocturnal melatonin secretion is increased in premenopausal women on contraceptive pills [Kostoglou-Athanassiou *et al.* 1998a], as well as in postmenopausal women. Administration of the hormone in humans may contribute to the management of jet lag [Herxheimer and Petrie, 2002], the disorder observed after transatlantic flights. The hormone is involved in the regulation of the immune system [Giannoulia-Karantana *et al.* 2006] and is a potent antioxidant agent [Tan *et al.* 2007]. Melatonin may contribute to the conservation of DNA integrity and may thus be involved in cancer prevention. Other research data show that the hormone is a natural oncostatic agent, being involved in protection from the development of malignant neoplasms. Melatonin may soon find clinical applications as it has been successfully used in cancer therapy and in the management of the adverse effects of anticancer therapy.

In this review a referral will be made to the relationship of melatonin with sleep disorders, the use of melatonin in the entrainment of biological rhythms and the management of jet lag, the antioxidant action of melatonin, the relationship of melatonin with cancer, the relationship of melatonin with the immune system, the relationship of melatonin with rheumatoid arthritis and the relationship of melatonin with Alzheimer's disease and other neurodegenerative disorders.

Melatonin and sleep disorders

Melatonin may be used for the management of sleep disorders, such as insomnia and the disorder arising from night or shift work [Cardinali *et al.* 2011; Fares, 2011; Hardeland *et al.* 2008; Khan *et al.* 2011; Malow *et al.* 2012; Morin *et al.* 2007; Ochoa-Sanchez *et al.* 2011; Skene and Arendt, 2006; Srinivasan *et al.* 2008, 2011a]. When endogenous melatonin secretion is decreased, such as in people of advanced age or in those who use β blockers [Fares, 2011], or the natural circadian rhythm of melatonin is affected, such as in shift workers or people who are blind [Khan *et al.* 2011], exogenous melatonin administration may improve the quality and duration of sleep. In patients with insomnia, melatonin seems to induce the onset of sleep, however its hypnotic action is mild. The advantages of melatonin in relation to other sleep-inducing agents are the absence of hangover the morning after, the absence of withdrawal symptoms and the absence of addiction [Hardeland *et al.* 2008; Srinivasan *et al.* 2008]. However, melatonin has a short half life in the circulation and mild hypnotic action. Therefore, melatonin analogs have been introduced, such as ramelteon (CAS 196597-26-9) and agomelatine (CAS 138112-76-2) [Hardeland *et al.* 2008]. Ramelteon has a high affinity for melatonin receptors MT_1 and MT_2 in the suprachiasmatic nucleus and a longer half life than melatonin, having been used successfully for the management of insomnia. Agomelatine has a high affinity for melatonin receptors MT_1 and MT_2 in the suprachiasmatic nucleus, also acting as a serotonin antagonist, and it has hypnotic and antidepressive action.

Melatonin and circadian rhythms

In people who are blind or those who work shifts the administration of melatonin may help in the synchronization of biological rhythms to the environment [Bjorvatn and Pallesen, 2009; Cardinali *et al.* 2006; Claustrat *et al.* 2001; Coogan and Thorne, 2011; Dallaspezia and Benedetti, 2011; Hickie and Rogers, 2011; Lewy *et al.* 1996; Morgenthaler *et al.* 2007; Pandi-Perumal *et al.* 2007, 2008; Pevet and Challet, 2011; Sanchez-Barcelo *et al.* 2011; Skene *et al.* 1999; Thorpy, 2011; Warman *et al.* 2011; Zisapel, 2001; Zee and Manthena, 2007]. Melatonin may prove to be useful in the management of affective disorders, such as seasonal affective disorder [Coogan and Thorne, 2011; Dallaspezia and Benedetti, 2011; Hickie and Rogers, 2011]. Melatonin acts on MT_1 and MT_2 receptors in the suprachiasmatic nucleus of the hypothalamus, the locus of the main circadian regulator. Melatonin resynchronizes the disordered circadian rhythms and induces sleep in people with delayed sleep phase syndrome and in shift workers. Ramelteon and agomelatine, melatonin receptor agonists with a longer half life and higher affinity for melatonin receptors, have great potential for the management of biological rhythm disorders.

Melatonin and jet lag

Melatonin may be used successfully for the prevention and treatment of jet lag [Herxheimer and Petrie, 2002; Jackson, 2010; Michalik and Bobinski, 2009; Sack, 2010; Paul *et al.* 2010; Rios *et al.* 2010; Sánchez-Barceló *et al.* 2010; Srinivasan *et al.* 2008; Zee *et al.* 2010; Zee and Goldstein, 2010]. Jet lag is often observed in transatlantic travelers crossing several time zones. It arises as a result of lack of synchronization of the endogenous rhythm of the organism with the light–dark cycle of the environment in the destination area. Melatonin plays a central role in the regulation of biological rhythms. The effect of oral administration of melatonin on jet lag after transatlantic flights crossing several time zones was evaluated [Herxheimer and Petrie, 2002]. Controlled studies in the Cochrane database and in the databases Medline, Embase, Psychlit and Science Citation Index were reviewed. It was found that melatonin, when taken before sleep time in the destination area, that is between 10 p.m. and 12 p.m., reduces jet lag arising after flights crossing five or more time zones. Daily melatonin doses from 0.5 to 5 mg are equally effective, people sleeping quicker and better after taking 5 mg. Doses larger than 5 mg do not seem to be more effective. The benefit seems to be greater the more time zones are crossed and smaller for western flights. The timing of melatonin administration seems to be important because if melatonin is taken early during the day it induces sleepiness, thus delaying adaptation to the local time. Other side effects are rare. It appears that patients with epilepsy and those on warfarin may have adverse effects from melatonin administration. Melatonin use is indicated in adult travelers crossing five or more time zones, especially those traveling eastwards who have previously been affected by jet lag. Travelers crossing two to four time zones may also use melatonin if they need it. In travelers crossing seven to eight time zones the administration of melatonin on arrival at the destination area is enough; however,

when more time zones are crossed melatonin should be administered for 2–3 days before the flight, its hypnotic and sedative action being appropriately managed [Srinivasan *et al.* 2008]. Recently, the field of circadian typology has been developing, that is, the field describing individual differences in the behaviour of the individual according to the time of day, which affects biological and psychological functioning, not only in healthy people but also in those with disease. Melatonin is a biological marker involved in defining the circadian typology of each individual [Adan *et al.* 2012]. The circadian typology of the individual also affects the type of adjustment to shift work and jet lag and the need for melatonin treatment. It appears that chronobiological aspects of human behaviour should be taken into account when jet lag should be managed or the need for adjustment to shift work arises. Melatonin products need systematic quality control. In conclusion, melatonin is effective in the prevention and treatment of jet lag.

Melatonin and antioxidant action

Melatonin is a very potent free radical recipient and a general antioxidant. As an antioxidant melatonin binds potently the toxic hydroxyl and hyperoxide radicals. The antioxidant properties of melatonin have been proved in homogenized tissues and in living organisms [Acuña Castroviejo *et al.* 2011; Aversa *et al.* 2012; Galano *et al.* 2011; Gitto *et al.* 2012; Reiter *et al.* 2011a, 2011b; Tan *et al.* 2007]. The antioxidant action of melatonin is exerted both directly and via its metabolites [Tan et al. 2007]. The property of melatonin to act as an antioxidant by itself and through its metabolites makes it extremely effective, even at a low concentration, in the protection of living organisms from oxidative stress. In agreement with melatonin's protective function, significant amounts of melatonin have been detected in tissues and organs exposed to hostile environmental attacks, such as the skin and the bowel, and in organs with high oxygen consumption, such as the brain, melatonin production being increased by agents inducing low-intensity stress, such as exercise in humans. Intense oxidative stress results in an acute decrease in circulating melatonin levels as a result of its consumption, as it is known to be a suicidal antioxidant, being consumed during its antioxidant action [Galano *et al.* 2011]. During the recent disaster in Japan, melatonin was used to prevent the damage induced by ionizing radiation [Reiter *et al.* 2011b].

Melatonin and cancer

Melatonin seems to contribute to cancer prevention and may also be used as additive therapy in cancer.

Melatonin and protection from carcinogenesis

Melatonin seems to have an oncostatic action and appears to contribute to anticancer protection [Bukowska, 2011; Hrushesky *et al.* 2009; McCarty, 2012; McCune *et al.* 2011; Mao *et al.* 2010; Mediavilla *et al.* 2010; Ravindra *et al.* 2006; Santoro *et al.* 2012; Schernhammer *et al.* 2011; Vijayalaxmi *et al.* 2002].

Many studies have shown that melatonin inhibits the growth of breast cancer cells, cervical cancer cells and ovarian cancer cells. Melatonin is a new member of a group of regulatory factors controlling cell multiplication and death and is a chronobiotic hormonal regulator of the growth of neoplasmatic cells [Blask *et al.* 2002]. In physiologic concentrations melatonin is cytostatic and inhibits cancer cell multiplication via action in the cell cycle. In pharmacologic concentrations melatonin has a cytotoxic effect on cancer cells. In physiologic and pharmacologic concentrations it acts as a differentiating factor in some cancer cells, reducing their infiltrative and metastatic potential via alteration of binding molecules and conservation of intracellular communication. In other types of cancer cells melatonin either alone or in combination with other factors induces cancer cell apoptosis. Biochemical and molecular mechanisms of the oncostatic action of melatonin include regulation of expression and activation of estrogen receptors *via* calmodulin, modulation of the cytoskeleton architecture and function, and modulation of intracellular oxidative status *via* the cell surface melatonin receptors.

Data show that melatonin inhibits carcinogenesis. Exposure to magnetic fields of 50–60 Hz increases breast cancer risk, possibly via inhibition of melatonin secretion [Liburdy *et al.* 1993]. In rats, having been exposed to the carcinogen 7,12-dimethylbenz[α]anthracene (DMBA), blindness and food restriction prevent the appearance of breast adenocarcinoma, this result being dependent on the presence of the pineal [Bartsch *et al.* 1995]. Food restriction may be related to an increase in melatonin secretion, while blindness leads to the appearance of free rhythms and a strong melatonin signal. This increase seems to be

related to an improvement in the natural defense mechanisms of the organism. In rats developing breast cancer after exposure to the carcinogen DMBA, pinealectomy increased the frequency of cancer development while afternoon melatonin administration decreased it.

Indomethacin and melatonin administration inhibits breast cancer development after the administration of DMBA [Mcikova-Kalicka *et al.* 2001]. Melatonin administration in laboratory animals, in which skin carcinogenesis had been induced by benzo-a-pyrene, reduces the number of papillomas in the initiation and progression of carcinogenesis [Kumar and Das, 2000].

Melatonin and cancer management

Melatonin may be used as an adjuvant in cancer therapy [Dopfel *et al.* 2007; Han *et al.* 2011; Hansen *et al.* 2012; Jung and Ahmad, 2006; Knower *et al.* 2012; Lissoni *et al.* 1995b, 2001; Lissoni, 2002; Seely *et al.* 2011; Shirazi *et al.* 2007; Srinivasan *et al.* 2011b; Zha *et al.* 2012].

The experimental studies led to clinical studies, in which melatonin was administered along with tamoxifen in women with metastatic breast cancer, which had progressed despite the administration of tamoxifen. It was found that the simultaneous administration of melatonin and tamoxifen may contribute to the objective regression of cancer in women with metastatic breast cancer not responding to tamoxifen alone [Lissoni *et al.* 1995b].

Studies suggested that the biological response of the host organism to the neoplasm to interleukin 2 may be modulated by the administration of immune-modulating factors, such as melatonin. The parallel administration of melatonin with interleukin 2 in patients with distant metastases in non-small cell lung carcinoma, liver carcinoma, bowel carcinoma, stomach carcinoma, pancreatic carcinoma and breast cancer contributes to cancer regression and disease stabilization [Lissoni *et al.* 1993].

Melatonin, when used in combination with interleukin 2 in cancer immunotherapy contributes to the prevention of thrombocytopenia, a frequent hematologic complication of interleukin 2 therapy [Lissoni *et al.* 1995a]. Recent studies have shown that the hemopoietic system is under neuroendocrine control [Lissoni *et al.* 2001], thrombopoeisis having been shown to be stimulated by melatonin and melatonin shown to be effective in thrombocytopenia therapy.

The number of lymphocytes is one of the most important parameters of the immune system which contribute to the prognosis of patients with progressive cancer. Interleukin 2 and interleukin 12 are the most important cytokines with antineoplastic action in the human organism. The action of these cytokines is modulated by the neuroendocrine system, especially the pineal via the diurnal variation of melatonin secretion [Srinivasan *et al.* 2011b].

The effect of melatonin was investigated in a group of 1440 patients with progressive solid cancer who received supportive therapy with or without melatonin [Lissoni *et al.* 1995b]. The frequency of cachexia, thrombocytopenia and lymphopenia was significantly lower in patients receiving melatonin than in those receiving only supportive therapy. The percentage of patients with disease stabilization and the annual survival were higher in patients receiving melatonin than in those receiving only supportive therapy. The objective response of patients to therapy was significantly greater in patients receiving melatonin and chemotherapy than those receiving only chemotherapy. Melatonin decreased the frequency of cachexia, thrombocytopenia, stomatitis, cardiotoxicity and neurotoxicity due to chemotherapy.

Radiotherapy is a frequent and effective form of cancer therapy. The sensitivity of normal tissues, which are near the neoplasm and are inevitably exposed to radiation, decreases the therapeutic benefit. As ionizing radiation has destructive effects, radiobiologists are interested in the recognition of novel, nontoxic, effective and easy to use methods for the prevention of the damage induced on healthy tissues by radiation. In many studies, melatonin has been proved to decrease the oxidative damage induced by ionizing radiation. Data show that melatonin may be used as a radioprotective agent in patients with cancer either alone for cancer inhibition or in combination with traditional radiotherapy with the aim of a better effectiveness/toxicity ratio [Shirazi *et al.* 2007].

A variety of cytokines and growth factors exert a fine-tuning action in a series of productive and differentiating functions involved in hemopoiesis. Studies have shown that neuroendocrine and

neural agents may be involved in the control of hemopoiesis. Melatonin, in particular, may salvage hemopoiesis from the toxic effect of antineoplastic drugs via opioid cytokines of T-helper cells [Maestroni, 1999a].

These studies show that melatonin may be used successfully in clinical oncology as supportive therapy in patients with progressive cancer and for the prevention of toxicity induced by chemotherapy and radiotherapy [Jung and Ahmad, 2006; Dopfel *et al.* 2007]. In conclusion, melatonin may contribute to the protection of organisms from carcinogenesis, being involved in cancer prevention, and may be used as an adjuvant in cancer therapy.

Melatonin and the immune system

A series of experimental studies show that there is a close connection between the pineal and the immune system [Carrillo-Vico *et al.* 2005]. In several species pinealectomy or any experimental process which inhibits the synthesis and secretion of melatonin induces a state of immunosuppression, this state being reversed by the administration of melatonin. Melatonin has an immunoenhancing effect [Carrillo-Vico *et al.* 2006]. Melatonin activates T lymphocytes, monocytes, natural killer cells and even granulocytes, activates cell-dependent cytotoxicity and induces antibody-dependent responses *in vivo*. In experimental models in animals, as well as in human studies and in experiments *in vitro*, melatonin induces the production of inflammatory cytokines and nitric oxide. The effect of glucocorticoids *in vitro* on the immune function seems to be modulated by melatonin in physiologic and pharmacologic concentrations. It has been proved that melatonin is involved in lymphocyte number control [Lissoni *et al.* 2008]. It has been found that T lymphocytes express cell membrane melatonin receptors. The activation of these receptors by melatonin induces cytokine release, such as interferon γ and interleukin 2 as well as opioid cytokines. Melatonin has been reported to increase the production of interleukin 1, interleukin 6 and interleukin 12 in human monocytes [Lissoni, 1999]. These cell mediators may be involved in the counterbalance of immunosuppression induced by stress as well as in other forms of secondary immunosuppression. Melatonin may protect mice from viral encephalitis, bacterial diseases and septic shock. Melatonin may have immunotherapeutic potential in viral and bacterial infections [Maestroni, 1999b]. Melatonin may be used for the stimulation of immune response during viral and bacterial infections and may reinforce the immune reaction during viral and bacterial infections, acting as a protective agent for the organism. However, melatonin through its proinflammatory action may have a deteriorating effect in autoimmune diseases. In multiple sclerosis the role of melatonin has not been elucidated. In mice, which are susceptible to the development of systemic lupus erythematosus, the effect of melatonin depends on the sex of the animal [Jimenez-Caliani *et al.* 2006].

Melatonin and rheumatoid arthritis

It appears that rheumatoid arthritis is more frequent and more severe in northern countries where the population is exposed to higher melatonin concentrations as a result of longer nights and longer and heavier winters as opposed to the southern Mediterranean countries [Cutolo *et al.* 2005]. Morning stiffness in rheumatoid arthritis may be related to the proinflammatory action of melatonin during the night [Cutolo *et al.* 2003, 2008]. These observations are in accordance with the immune-enhancing action of melatonin.

Nocturnal melatonin levels have been found to be higher in patients with rheumatoid arthritis than in healthy controls [Sulli *et al.* 2002]. Melatonin has been detected in high concentrations in the articular fluid in patients with rheumatoid arthritis and melatonin receptors have been detected in the macrophages of the synovial membrane. It is interesting that the production of interferon γ, interleukin 2, interleukin 6, interleukin 12 and tumor necrosis factor α has a nocturnal and an early morning peak soon after the melatonin peak and during the nadir of cortisol secretion [Petrovsky *et al.* 1998]. These observations are in accordance with the hypothesis that melatonin increases cytokine production and immune system activity.

In a double-blind controlled study investigating the effect of melatonin administration on patients with rheumatoid arthritis, melatonin was found to be a strong antioxidant *in vivo*, the red cell sedimentation rate being increased after melatonin administration and rheumatoid arthritis not improving or even deteriorating in some patients [Forrest *et al.* 2007]. These observations are in accordance with the antioxidant action of melatonin, suggesting a proinflammatory effect [Korkmaz, 2008; Korkmaz and Reiter, 2008].

Melatonin and neurodegenerative disorders

Studies in mice show that melatonin administration may inhibit the appearance of neural cell abnormalities and the attendant memory disturbance which are observed in Alzheimer's disease. Continuous light exposure in rats induces the appearance of changes related to those observed in Alzheimer's disease while melatonin administration protects against their appearance [Ling *et al.* 2009]. In humans with Alzheimer's disease, disorders in melatonin secretion and biological rhythm disorders are observed, alterations which may be related to degeneration of the retina, suprachiasmatic nucleus, pineal axis and disturbance of the regulation of melatonin secretion from the sympathetic system. Melatonin may be used therapeutically for the resynchronization of the biological rhythms and the prevention of histological changes in Alzheimer's disease [Olcese *et al.* 2009]. Melatonin has a potential therapeutic value as a neuroprotective agent in Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease and brain trauma [Pandi-Perumal *et al.* 2012; Rothman and Mattson, 2012; Srinivasan *et al.* 2011a]. Clinical trials using melatonin are warranted before its relative merits as a neuroprotective agent are definitively established.

Mode of action of melatonin

Melatonin exerts its effects through activation of at least two high-affinity G-protein-coupled receptors, MT_1 and MT_2 [Dubocovich and Markowska, 2005; Dubocovich *et al.* 2010]. These are unique receptors as they show distinct molecular structures, pharmacological characteristics and chromosomal localization [Masana and Dubocovich, 2001]. The MT_1 and MT_2 receptors are 350 and 362 amino acids long respectively, with calculated molecular weights of 39–40 kDa. MT_1 and MT_2 melatonin receptors signal by coupling to heterotrimeric Gi proteins formed by α, β and γ subunits [Masana and Dubocovich, 2001; Dubocovich *et al.* 2003]. Activation of these receptors promotes dissociation of G proteins into α and β,γ dimers, which interact with various effector molecules involved in the transmission of cell signaling. Effector systems involved in MT_1 and MT_2 melatonin receptor signaling through G-protein coupling include adenylyl cyclase, phospholipase C, phospholipase A2, potassium channels and potentially guanylyl cyclase and calcium channels.

Tissues endowed with fully characterized functional MT_1 and MT_2 melatonin receptors include the retina, brain, suprachiasmatic nucleus, pars tuberalis, ovaries, cerebral and peripheral arteries, kidney, pancreas, adipocytes and immune cells [Dubocovich and Markowska, 2005; Dubocovich *et al.* 2010] (Figure 1).

The retina produces melatonin locally and expresses both the MT_1 and MT_2 melatonin receptors [Scher *et al.* 2002]. MT_1 melatonin receptors are expressed in rod photoreceptor cells. Both the MT_1 and MT_2 melatonin receptors are found in the suprachiasmatic nuclei, being localized primarily to neuronal elements

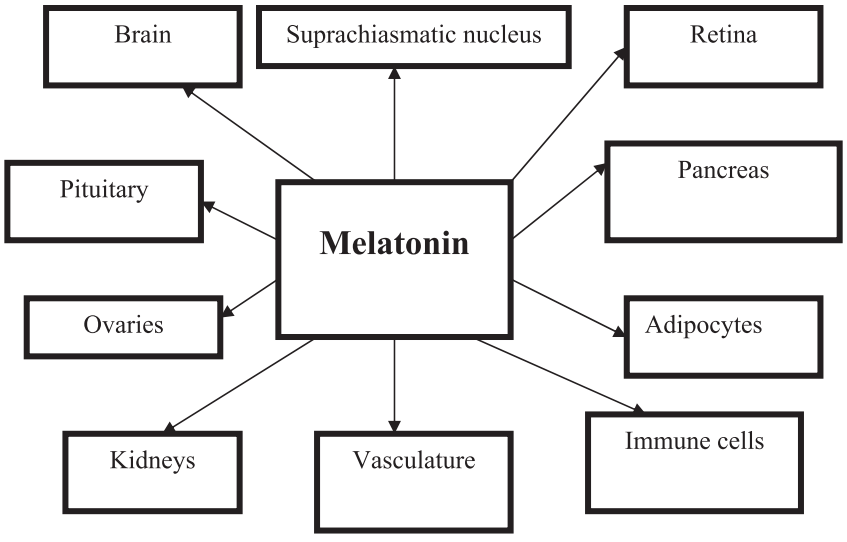

Figure 1. Target tissues of melatonin in humans.

[Rivera-Bermudez *et al.* 2004]. The suprachiasmatic nucleus is the master clock controlling behavioral, metabolic and physiological rhythms, including the synthesis and release of melatonin from the pineal gland. Endogenous pineal melatonin feeds back onto the master clock and regulates neuronal activity and circadian rhythms through activation of MT_1 and MT_2 melatonin receptors. In the suprachiasmatic nucleus melatonin inhibits neuronal firing via MT_1, but it phase shifts neuronal firing rhythms through activation of MT_2 melatonin receptors [Dubocovich *et al.* 2005]. Melatonin receptors have been localized in the human brain, as MT_1 and MT_2 melatonin receptor mRNA has been amplified from human brain cerebellum, occipital cortex, parietal cortex, temporal cortex, thalamus, frontal cortex hippocampus and suprachiasmatic nucleus [Mazzucchelli *et al.* 1996].

Melatonin receptors have been found in the pars tuberalis of the anterior pituitary [Dubocovich *et al.* 2010], as well as in the ovaries [Niles *et al.* 1999]. In the pars tuberalis of the anterior pituitary gland, the nocturnal secretion of melatonin suppresses the expression of the clock gene Per 1 by inhibiting the cAMP-dependent signaling pathway through activation of the MT_1 receptor [von Gall *et al.* 2002]. At dawn when circulating melatonin levels decrease, the pars tuberalis is released from transcriptional repression, facilitating the induction of Per 1 gene expression. Furthermore, during the biological night, endogenous melatonin through activation of the MT_1 melatonin receptor inhibits prolactin release in the pars tuberalis [Dubocovich *et al.* 2010]. This appears to be a general mechanism by which the hormone melatonin regulates gene expression to link the central circadian pacemaker and peripheral tissues, resulting in modulation of circadian and seasonal rhythms.

Pancreatic islets [Peschke *et al.* 2007] and adipocytes [Brydon *et al.* 2001] express melatonin receptors. MT_1 and MT_2 melatonin receptors have been detected in peripheral and cerebral arteries [Ekmekcioglu, 2006]. MT_1 melatonin receptor localization in the arterial wall and hippocampal microvasculature of normal subjects and patients with Alzheimer's disease suggest involvement of melatonin in the regulation of cerebral blood flow [Savaskan *et al.* 2001]. In the vascular system melatonin evokes opposite responses, as it potentiates vasoconstriction through MT_1 and induces vasodilatation via MT_2 receptors [Dubocovich *et al.* 2010]. Melatonin receptors have also been detected in the human kidney [Drew *et al.* 1998]. Melatonin membrane receptors are expressed in lymphocytes and are involved at least in part in regulating immune responses [Pozo *et al.* 2004].

Membrane melatonin receptors appear to be involved in melatonin's oncostatic effect. Prostate tumor and breast cancer cells express melatonin receptors [Dillon *et al.* 2002; Gilad *et al.* 1999; Rögerlsperger *et al.* 2011]. Colon cancer cells also express melatonin receptors [Nemeth *et al.* 2011], melatonin's oncostatic action being mediated primarily through activation of MT_1 melatonin receptors.

Melatonin-mediated effects are time dependent, with the efficacy of melatonin being probably dependent on the diurnal sensitivity of MT_1 and MT_2 melatonin receptor expression. The in-depth study of melatonin receptor function will facilitate discovery and development of novel agents for the treatment of sleep, circadian, metabolic and endocrine disorders, as well as tumor cell growth.

Conclusion

Melatonin is a hormone with multiple actions. It is involved in the regulation of biological rhythms, in sleep regulation, it has potent antioxidant action and protects the organism from carcinogenesis and neurodegenerative disorders. The hormone possesses immune-enhancing activity. Therapeutically, it may be used for the management of insomnia, jet lag, the resynchronization of circadian rhythms, as an adjuvant in cancer therapy and in the inhibition of disease progression in Alzheimer's disease and other neurodegenerative disorders.

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Conflict of interest statement

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