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REVIEW

A review on melatonin action as therapeutic agent in cancer

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BACKGROUND: Melatonin is a hormone which is produced from pineal gland in human and is said to have various impacts in human body like controlling sleep wake cycle, regulating the immune and cardiovascular system and regulating the peripheral organ functioning to name a few. Researchers have reported that the melatonin levels correlates with cancer risks.
OBJECTIVE: In this review article, focus has been given to the therapeutic applications and impact of melatonin hormone in human behavior and physiologic activities. Through this article we aim in compiling the scattered information regarding melatonin and its various aspects of importance in human system.
METHODS: We made an analysis of existing hypothesis and studies published on melatonin and circadian rhythm, factors effecting Melatonin secretions in body, sleep disturbances and cancer risks and melatonin therapy in cancer patients.
RESULTS: Melatonin's role as an endogenous synchronizer, growing evidence suggests its anti-oxidative activity as well as its having a role in modulating immune responses. Fluctuating melatonin levels can be boosted by ingesting products containing melatonin. A large portion of the examinations detailed by the researchers clearly conclude that keeping up an impeccable sleep-wake cycle and having a healthy diet is extremely important to keep up the regular melatonin levels and in order to stay fit.
CONCLUSION: Melatonin is considered as a critical hormone that controls and regulates many functions in our body. Melatonin production is emphatically related to the night time duration. Its most absolute biological role is to convey information to the body about day length for a variety of physiologic functions. In addition to melatonin's role as an endogenous synchronizer, growing evidence suggests its anti-oxidative activity as well as its having a role in modulating immune responses. At present, a growing interest is focused on the validity of the anti-tumor mechanisms of melatonin.

Keywords Melatonin, circadian rhythm, breast cancer, pineal gland, melatonin therapy, peripheral organ functioning

Introduction

Melatonin (5-methoxy-N-acetyltryptamine) is the primary secretory end product of the pineal gland in animals (Claustrat et al., 2005). Pineal gland is positioned in brain. It is regulated by the suprachiasmatic nucleus or SCN in the hypothalamus which is situated right above the optic chiasm (Benarroch, 2008). The main function of the hormone is to regulate the sleep-wake cycle. Melatonin is also reported to be produced by the plants by many groups of researchers. In plants, melatonin functions as the first line of defense mechanism against different oxidative stress caused due to the over accumulation of reactive oxygen species. Reports suggest that the melatonin hormone is involved in the synchronism and the co-ordination of the circadian rhythms including rest-wake cycle, blood pressure regularisation, seasonal reproduction etc. Activation of the specific melatonin receptors result in most of the biological aftermath in animals (Nosjean et al., 2001; Dimitrov et al., 2004; Pandi-Perumal et al., 2008; Dubocovich et al., 2010). Melatonin also plays a vital role as an antioxidant with special reference to its role in the protection of the genetic material (nuclear and mitochondrial DNA).

The hormone melatonin is a perfect example of tryptophan derivative which has been widely investigated due to its versatile function as an antioxidant or free radical scavengers (Karbownik et al., 2001). As a result, it can also lead to several disorders and is one of the reasons for cancer. People suffering from cancer tend to become immunosuppressed and show the symptoms of aging faster (Jung et al., 2010). As mentioned earlier, this hormone is also responsible for the

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maintenance of biological clock in humans. In fact it is the human body which decides the level of melatonin they require. The level varies throughout the day. Melatonin production begins at dawn and increases as the day passes. Its production will be high during night time (sleeping hours). It will slowly decrease during early morning which leads to the wake up. It also has a good role in circadian rhythm regulation, which is also affected by light and temperature. Circadian rhythms control various aspects of body including regulating the body temperature, metabolism etc. It is basically controlled by genes and proteins, thereby preventing cancer. The varying levels of melatonin can lead to cancer studies involving night shift workers (Schernhammer and Hankinson, 2003). It is proved that the night shift employees have a high risk rate for cancer. In such cases, melatonin is prescribed as it is helpful for people who are working in night shifts, for patients after surgery, or for chronic headaches for a better sleep. Now melatonin is developed as a supplement and it can be used as long-term and short-term medicines as a cure for disorder and even cancer especially breast cancer (Lee, 2004). But there may be side effects like excess sleeping, weird dreams, lowering of body temperature, change in blood pressure etc.

Melatonin hormone has been reported to be used in the treatment of a number of disease conditions: Alzheimer's disease, Bipolar disorder, Endometriosis, Chronic fatigue syndrome, Infertility, Aging, Schizophrenia, Migraine etc. to name a few (Krueger et al., 1998; Pacchierotti et al., 2001; Cardinali et al., 2013).

Melatonin can be characterized as a neuro-hormone secreted by the pineal gland responsible for sleep regulation. Light suppresses melatonin synthesis and its secretion from the pineal gland (Cos et al., 2006; Maronde and Stehle, 2007; Zee et al., 2013). Melatonin is widely used as a supplement in the form of tablets in order to regularize irregular sleep patterns. Abnormal sleep patterns are related and linked to a number health problems and premature aging. Melatonin supplementation is seen as a way to get regular sleep with special reference to people engaged in shift work or experiencing jet lag.

The hormone is exploited for other benefits provided by it such as universal neuroprotective effects or as a potent antioxidant. It also serves as an anti-cancerous agent. For the past few years, melatonin is being screened and investigated for its role in combating cancer; especially breast cancer is in the limelight due to its increase in occurrence over the years. Reports suggest that melatonin do not show much effect on people with less body fat, in fact it is shown to inhibit the deposition of body fat (Reiter, 1980; Ewa et al., 2014). Melatonin supplementation likewise benefits the eye, reduce tinnitus, and enhance the state of mind. It is a well-established fact that melatonin is prescribed for sleep. There is a sector of population that have a tendency to have an asymmetrical and a non-uniform melatonin synthesis in their body. Smokers have a tendency to be less receptive to melatonin supplementation, and elderly individuals tend to produce less concentration of melatonin amid evening time. Depression has additionally been related with the reduction in the melatonin levels (Spiegel et al., 2003).

Factors affecting melatonin biosynthesis

There are many factors that influence the melatonin discharge. The level of melatonin is incredibly depended on the light and season (Lichtenstein et al., 2000). Melatonin production amid winter (shorter days and longer nights) is relatively higher than the summers. Seasonal affective disorder also called as winter disorder is one among them (Eagles, 2004; Gregg, 2004; Zawilska et al., 2006; Kriya et al., 2007; Abbas et al., 2011). Age can likewise influence the production of melatonin. Melatonin secretion will diminish with the increase in age (Richard et al., 1964; Touitou et al., 1981; Waldhauser and Waldhauser, 1988; Attenburrow et al., 1996). It is possible that it can be delivered before or might be late. It is even influenced by the artificial light in day to day life. SIRT 1, which is an enzyme that has a role in cellular process which is acting through deacetylation mechanism. It is proved to have an effect on melatonin secretion. It is related by the deacetylation process and through salvage pathway of NAD^+. Subsequently, temperature, seasons, light, other physical conditions and so on add to the reasons for the increase in the level of melatonin. δ- Aminolevulinic acid (ALA) is a precursor component of haem. It has a role in melatonin secretions since it is sensitive to light. It is also a photodynamic therapeutic agent (Wenbo et al., 2001; Malgorzata and Russel, 2002; Üstundag and Duydu, 2007). Melatonin has an efficiency to protect ALA and their oxidative stress. Other factors are as follows:

Energy restriction

Strong impact of food on melatonin production is identified in investigations of subjects experiencing times of fasting. Energy confinement diminishes the night-time secretion of melatonin. Short-term voluntary fasting by total dismissal of food or with exceptionally restricted intake of energy (< 300 kcal per day) from 2 to 7 days diminishes melatonin concentration in the blood by about 20%. Glucose supplementation amid short-term fasting restores the diminished melatonin concentration to normal, recommending that human pinealocytes, or other secreting cells, require a specific insignificant measure of glucose delivery to function normally (Ames et al., 1990).

Milk

Concentration of melatonin shows a marked daily rhythm. This phenomenon seems by all accounts widespread among vertebrates. Since milk is the primary and an essential part of

a new-born child's eating regimen and night time lactation affirms the nutritional adequacy, melatonin content of night time milk may have advance physiologic importance. This hypothesis may profit from further study, yet it appears to be conceivable that maternal melatonin may pass through milk to the new-born child bringing about enhanced night-time rest, although this is based on a very limited number of perceptions (Jakobisiak et al., 2003) (Illnerová et al., 1993; Valtonen et al., 2003).

Alcohol

Both acute and chronic consumption of liquor at a level corresponding to 10–100 g of ethanol each day, diminish melatonin levels in the blood and in the saliva. In addition to absolute amount of ethanol, other properties of alcoholic beverages may also have an influence on the overall impact (Hardeland et al., 2005). As specified above, wine and beer contain melatonin, and consequently may have extra effect on perceptible melatonin levels in the body (Fonzi et al., 1994; Lyon et al., 1981).

Nutrients

Folate, magnesium and zinc deficiencies have been linked with lower melatonin levels in rodents. Folate and B6 vitamin help in boosting the formation of serotonin from TRP as coenzymes. Zinc and magnesium, instead, enhance the formation of melatonin from serotonin by binding to AANAT arylalky lamine-N-acetyltransferase enzyme, thus activating it and increasing the affinity of serotonin for binding to AANAT (Tan et al., 2007). In humans, the role of these vitamins and minerals is less well studied in this connection (Blask et al., 2004; Katri et al., 2012).

Vitamin C

An in vitro study assessing melatonin (1μM) and vitamin C at 0.5uM showed synergism in Protecting DNA from oxidative damage caused by chromium III ion. The marginal oxidative impacts seen with vitamin C were turned around when melatonin was co-incubated with it.

α- Lipoic acid

An *in vitro* study assessing melatonin (1μM) and α-lipoic acid (5μM) found that, in shielding DNA from chromium III ion instigated oxidative damage; the two were synergistic in their defensive mechanism.

Tryptophan and 5-HTP

Tryptophan is the amino acid which is metabolized into 5-HTP, from which serotonin and consequently melatonin can be delivered. Melatonin appears to inhibit the tryptophan 2, 3-dioxygenase (TDO) enzyme, which further inhibits tryptophan from converting into 5-HTP by upgrading its catabolism mechanism. Restraint of TDO by means of melatonin can enhance the measure of bioavailable tryptophan, independent of supplementation (Maurizi, 1990; Annemieke et al., 2013).

EGCG

Epigallocatechin Gallate (EGCG) is the principle polyphenol referred to as green tea catechins. In an *in vitro* test on DNA-induced oxidation, it was discovered that co-incubation of melatonin and EGCG, both at 1uM, marginally suppressed each other's activities, showing opposition. It should be noted that the overall protection exerted with both was still greater than either in isolation, however that there was a not as much as added substance advantage.

Melatonin, sleep disturbance and cancer risk

Melatonin, the hormone produced from pineal gland is involved in the regulation of circadian and facilitation of sleep, inhibition of cancer development and growth, and enhancement of immune system (Dun et al., 2003). It is produced during 60-90 min after falling asleep. It pushes the individual to a deep sleep. Production of melatonin is light sensitive and regulatory sensors are found in the retina. Regular basis of biological rhythm disruption by irregular or disrupted sleeping patterns and sleeping in synthetic light lower the production of melatonin and this is associated with high breast cancer risk. Night shift workers have higher chances due to their lack of sleep at night. There is a clarified relationship between the endogenous melatonin amount and growth and metabolism of cancer. Reduced level of melatonin in blood enhances tumor proliferative activity and also regulates the production of estrogen which cancer cells need to grow. So lack of sleep is considered to be a carcinogen. In other hand melatonin stimulate the production of immune cells such as T cells, natural killer cells and cytokine production and on the other hand, it is also used as an addition during chemotherapy and radiotherapy (Guerrero and Reiter, 2002). There is reciprocal interaction between sleep disturbance and immune system. Enhanced sleep disruption and sleep deprivation suppresses immune system that itself lead to the shift in the balance of cytokine production (Patel et al., 2004; Blask et al., 2009). That is predominance of type 1 cytokine including anticancer cytokines such as interleukin (IL)-2, IL-12, interferon-g (INF-g) produced by Th-1cells, and tumor necrosis factor (TNF)a to type 2 cancer stimulating cytokines such as IL-10 it is an anti-inflammatory cytokine that has cancer growth promoting-activity through its immune suppressive action (Brittney et al., 2010). Conversely, cytokines such as IL-1, IL-2 enhance sleep and their levels in the brain vary with the duration of sleep this is also a humeral mechanism of sleep

regulation. Thus it is clear that sleep disturbance have the potential to exert cancer via the circadian disruption of melatonin by the presence of bright light in the night and the reversal interruption by shifting the balance of cancer-inhibiting and stimulatory cytokines.

Breast cancer, one of the most commonly occurring cancers among women, is one of the leading causes of death among women aged 40 to 55 years (Cohen et al., 1978; Crespo et al., 1994; Molis et al., 1994). Risk factors for breast cancer are varied and include age, genetic makeup, reproductive factors, and ionizing radiation. The role of estrogen hormone has been implicated as a main factor in the development and progression of breast cancer. In recent years, evidence from a number of studies has led to the hypothesis that the increased risk for breast cancer among women involved in night shift work is due to the light-induced inhibition of melatonin secretion. Compared with those working in other professions, women working at night as nurses, flight attendants, or night workers, show a significantly greater risk for breast cancer. In a survey carried out in India, women with advanced breast cancer were found to have lower urinary levels of melatonin when compared with controls. This has also been supported by other studies where low serum melatonin concentration and urinary 6-sulfatoxymelatonin levels have been found in women with ER-positive breast cancer. Not all studies have supported this association however, and in one investigation no significant differences were found between 127 breast cancer patients and 353 control subjects in terms of excretion of 6-sulfatoxymelatonin, a major melatonin metabolite.

The oncostatic action of melatonin is studied for different kind of tumors; especially on breast cancer. The main mechanism involved is the indirect interaction of melatonin with neuroendocrine reproductive axis which leads to a downregulation of some of the important hormones which influences the tumor growth (For e.g. gonadal estrogens). With the help of the antioxidant and anti-estrogenic property, epithelial mammary cells enhance immunity and inhibit the telomerase activity in tumor cells. The reduction in the melatonin level induces a hyperestrogenism which is the root cause of the production of breast cancer. Downregulation of p53 leads to higher invasiveness, lower intracellular communication and differentiation. Melatonin hormone has an inverse effect which upregulates p53 and increases the cell differentiation. There is an interaction between the hormones-estrogen and melatonin, which balance the proliferation and differentiation of the mammary tumor cells (Riabykh et al., 2000).

Melatonin therapy in cancer patients

Melatonin has the ability to kill many different types of tumor cells directly (Jakobisiak et al., 2003). It is a cytotoxin produced naturally and induces apoptosis. If the tumor is already established itself in the body melatonin help to reduce the growth rate of tumor cells by exhibiting a natural oncostatic activity. Melatonin reduces numerous cancer symptoms and to inhibit development of new tumor blood vessels (angiogenesis), and inhibit the spread of cancer (metastasis) and also reduction of tumor metabolism by reducing the body temperature. It is a natural hypothermia inducer. Furthermore as a inducer of antioxidants so it hinder the tumor cells from participating in free radical damage to normal cells and limit the oxidative damage to DNA, lipids, proteins.

In some patients cancer affects the body's innate cancer fighting capabilities including anti-cancer activity of naturally produced melatonin. Supplemental melatonin may be useful in those conditions (Stevens and Rea, 2001). Melatonin play a critical role in the host defense system against cancer proliferation by stimulating cytotoxic activity of macrophages. Administration of supplemental melatonin has shown to be beneficial even in the supportive care of end-stage cancer patients. It reduces loss of tissue, weight, fatigue, weakness, and depression. It further enhances immune function, thereby improving wound healing and quality of life. Furthermore, melatonin supplementation improves common symptoms found in patients undergoing chemotherapy. It counteracts anemia, lymphocytopenia and stimulates platelet production and diminishes cancer pain through its natural analgesic functions. (Imai et al., 2000).

In recent years, a huge amount of research has been devoted in exploring the cancer-protective properties of melatonin. Most of the oncostatic properties of melatonin have been justly well described (Vijayalaxmi et al., 2002). Evidences from the experimental studies strongly suggest a connection between the hormone and tumor suppression. *In vitro* studies support the reduction in the growth of malignant cells of the breast and other tumor by both pharmacological and physiologic doses of melatonin (Hill and Blask, 1988; Sze et al., 1993; Ying et al., 1993; Cos et al., 1996; Panzer et al., 1998; Cos et al., 1998, Mediavilla et al., 1999; Petranka et al., 1999; Shiu et al., 1999; Kanishi et al., 2000; Cos et al., 2002). In rodent models, pinealectomy boosts the tumor growth, whereas the exogenous melatonin administration exerts anti-initiating and oncostatic activity in different chemically induced cancers (Mocchegiani et al., 1999; Musatov et al., 1999; Anisimov et al., 1999). The most prominent mechanisms proposed to explain this mode of action of melatonin includes its anti-mitotic, antioxidant activity, and its potential modulation of cell-cycle length through control of the p53–p21 pathway (Anisimov et al., 1997; Cini et al., 1998; Tamarkin et al., 1981). Melatonin increases the expression of the p53 (tumor-suppressor gene). Cells lacking p53 have shown to be genetically unstable and consequently more prone to tumor. *In vitro* studies do support the effect of melatonin on breast cancer and other tumors (Brzezinski, 1997; Laufer et al., 1999; Anisimov et al., 2000a; Anisimov et al., 2000b). Reports show that melatonin exhibits a growth inhibitory effect on endometrial and ovarian

carcinoma cell lines, Lewis lung carcinoma, prostate tumor cells and intestinal tumors. Furthermore, several clinical trials confirm the prospective nature of melatonin, either alone or in combination with other standard therapy regimens, to generate a favorable response in the treatment of human cancers.

Mechanism of action of melatonin in cancer therapy

Some of the biological effects of melatonin are signaled through a family of guanadine triphosphate–binding proteins (G protein–coupled). Two forms of high and low affinity melatonin receptors have been identified. The high-affinity ML1 receptors are designated Mel1a and Mel1b, whereas, the low-affinity receptors are designated ML2 and ML3. The Mel1a receptors are expressed in the SCN and in the hypophyseal pars tuberalis. The Mel1b receptors are mostly expressed in the retina of the eye. The distribution of the ML2 receptors is not yet determined. The melatonin receptors are coupled to the stimulation of phosphoinositide hydrolysis. The ML3 melatonin receptor functions in rapid ligand association/dissociation kinetics. Mass spectrometry and enzymatic data later confirmed that ML3 was the quinone reductase 2 (QR2). It is a known detoxifying enzyme (Dietz et al., 2005). The induction of QR2 is associated with a decreased vulnerability to cancer initiation and progression. Both ML1 and ML2 are coupled to cAMP inhibition. The decrease in cAMP production decreases the uptake of linoleic acid (fatty acid). Linoleic acid is oxidized to 13-hydroxyoctadecadienoic acid (13-HODE) by 15-lipoxygenase (15-LOX-1). It serves as an energy source for tumor growth and its signaling molecules. Inhibition of linoleic acid uptake by melatonin is regarded as the anti-proliferative effects of the hormone. On binding with nuclear receptors, melatonin alters the transcription of several genes that plays a role in cellular proliferation [e.g., 5-lipoxygenase (5-LOX), p21, and bone sialoprotein (BSP)]. A third mechanism of the biological effects of melatonin may be its ability to modulate calcium and calmodulin activity (Blask et al., 2002).

Although early studies on the correlation and effects of melatonin and cancer can be traced back to the 1950s, this area of research received attention when Cohen et al. in 1978 put forth the theory of the possible role of the pineal gland on the etiology of breast cancer. The authors suggested that a decrease in pineal function could induce relative hyperestrogenism (Cohen et al., 1978). The early and prolonged exposure of the breast tissue to the estrogens could be involved in the etiology of breast carcinogenesis (Klaunig et al., 1998). Numerous studies have suggested a link between melatonin levels and cancer progression (Table 1). Several studies have shown reduced levels of melatonin in patients with certain types of cancers, compared with normal, healthy people of the same age. Many cancer types have shown to be responsive to melatonin in different settings. The accurate timing of melatonin administration seems to be a significant factor in its chemo-preventative properties, with the most effective protocol being a diurnal cycle similar to the physiologic rhythm of melatonin secretion. Studies have suggested that melatonin given to tumor-bearing animals in the late afternoon are more effective in suppressing tumorigenesis than when administered in the morning, suggesting that tumors exhibit their own circadian rhythm of sensitivity. Thus, it can be concluded that the night-time administration of melatonin may be more beneficial than during the day time. Among cancer patients, melatonin is often used as an alternative or complimentary approach because it is believed to be safe as no adverse side effects have been observed after oral administration of recommended doses. Further, because melatonin is a naturally occurring physiologic agent, it is also perceived to be a chemical produced by the body, thus, eliminating the fear of foreignness to the living system.

Anti-cancer effects of melatonin

Clinical studies in cancer patients show that
1. Melatonin hormone lowers the toxicity of various chemotherapeutic agents (For eg.cisplatin, etoposide, anthracyclines, and 5-fluorouracil)
2. Studies concluded a statistically significant reduction in treatment-related adverse events, such as myelosuppression, neurotoxicity, nephrotoxicity, cardiotoxicity and asthenia, resulting in a decreased mortality rate.

Melatonin and radiation therapy and as an anti-oxidative agent

Radiation requires the presence of oxygen molecules in order to produce free radicals to kill tumor cells. However, the majority of the human tumors are ineffectively oxygenated due to discontinuous blood flow in the tumor microcirculation followed by the occurrence of anemia in diseased patients. Supplemented melatonin stimulates the platelet production and helps the effective treatment of cancer and other associated diseases. Likewise it has an anti-serotonergic effect, which implies that it might obstruct the restraint of blood flow by serotonin. Hence, this leads to the increase in the tumor, oxygen levels thereby increasing the radiation-incited tumor cell death. As mentioned earlier, melatonin is lipid soluble and can cross the blood-tumor barrier. This helps in the increment of conveyance of radiation to the ineffectively oxygenated areas inside the tumor microenvironment. Melatonin is also considered as a protected and an important viable factor for tissue repair procedures, and recuperation from radiation-induced damage. It is the best co-treatment approach for malignancy patients experiencing radiation treatment (Blask et al., 1992; Ram et al., 2000; Yuan et al., 2002; Blask et al., 2005; Mills et al., 2005; Lee, 2006).

Table 1 Study conducted on cancer patients

Reference	No. of patients	Aim	Result
Sturgeon et al., 2012	48725 participants in the Women's Health Initiative Observational Study, among who 452 adjudicated incident cases of endometrial cancer. 7.5 years of follow-up.	Night-shift work is associated with increase in endometrial cancer risk	Indication of reduced risk associated with longer sleep duration, although no statistically significant association was observed.
Wu et al., 2008	33528 women 525 incident cases of breast cancer	Sleep duration hypothesized to be inversely associated with breast cancer risk	Sleep duration may influence breast cancer risk, possibly via its effect on melatonin levels
Schernhammer et al., 2008	3966 eligible postmenopausal women	Low urinary melatonin levels have been associated with an increased risk of breast cancer in premenopausal women.	Results from this prospective study provide evidence for a statistically significant inverse association between melatonin levels, as measured in overnight morning urine, and invasive breast cancer risk in postmenopausal women.
Travis et al., 2004	127 patients diagnosed with breast cancer and among 353 control subjects	Experimental data from animals suggest a protective role for the pineal hormone melatonin in the etiology of breast cancer	No evidence was found that the level of melatonin is strongly associated with the risk for breast cancer.
Bartsch et al., 1992	8 young men, 7 elderly patients with benign prostatic hyperplasia 9 patients of similar age with primary prostate cancer	Depression of serum melatonin in PC is due to a reduced pineal activity and is not caused by an enhanced metabolic degradation in the liver.	These results imply it is feasible to estimate changes in pineal function of prostate cancer patients by means of non-invasive determination using urinary melatonin and aMT6s.
Bartsch et al., 1992	17 with breast cancer 4 with untreated benign breast disease	17 with breast cancer 4 with untreated benign breast disease	The nocturnal melatonin and 6-sulfatoxymelatonin concentrations were significantly depressed in the group of patients with primary breast cancer compared with controls (P less than 0.01, P less than 0.025). The circadian amplitudes of melatonin and 6-sulfatoxymelatonin were also depressed by 81% (Pless than 0.01) and 63% (P less than 0.01).
Bartsch et al., 1989	35 with breast cancer 28 with untreated benign breast disease	Stage-dependent depression of melatonin in patients with primary breast cancer	A 50% depression of peak and amplitude occurred in the group of patients with primary breast cancer compared with age-matched controls (P less than 0.001, P less than 0.01). The peak declined with increasing tumor size: 27% at Stage T1, 53% at T2 (Pless than 0.001), and 73% at T3 (P less than 0.05). In contrast, patients with secondary breast cancer, particularly those receiving antiestrogen therapy, had a melatonin peak similar to controls.

Melatonin's potency in protecting against oxidative damage has been widely documented in various types of experiments conducted in animals, tissue culture and in cell-free systems. By measuring a variety of oxidative indices (including levels of 8-OH-dG), earlier *in vitro* and *in vitro* studies have shown that melatonin effectively protects DNA from oxidative damage induced by a variety of free radical generating agents including safrole, lipopolysaccharide, kainic acid, ferric nitrolotriacetate, carbon tetrachloride and ionizing radiation. Melatonin's efficiency as an antioxidant stems, in part, from its amphiphilic nature and as a result of its ability to scavenge among other radicals the-OH. Melatonin's scavenging efficacy of the-OH is not a ratio of mole to mole. One melatonin molecule scavenges two-OH and, furthermore, several metabolites of melatonin, such as *N*1-acetyl-*N*2-formyl-5-methoxykynuramine (AFMK), *N*-acetyl-5-methoxykynuramine (AMK) and 6-hydroxymelatonin (6-OHM) also function as free radical scavengers. Thus, the antioxidative activity of melatonin can be considered as a cascade reaction. AFMK is generated when melatonin interacts with H_2O_2. Melatonin is an antioxidant that can easily cross cell membranes and the blood-brain barrier (Hardeland et al., 2005). This antioxidant is a direct scavenger of radical oxygen and nitrogen species including $OH^{\bullet}$, $O^{\bullet}{}_2^{-}$, and $NO^{\bullet}$(Tan et al., 2007). Melatonin works with other antioxidants to improve the overall effectiveness of each antioxidant. Melatonin has been proven to be twice as active as vitamin E, believed to be the most effective lipophilic antioxidant. An important characteristic of melatonin that distinguishes it from other classic radical scavengers is that its metabolites are also scavengers in what is referred to as the cascade reaction. Also different from other classic antioxidants, such as vitamin C and vitamin E, melatonin has amphiphilic properties. When compared to synthetic, mito-

chondrial-targeted antioxidants (MitoQ and MitoE), melatonin proved to be a comparable protector against mitochondrial oxidative stress.

Conclusion

Melatonin is considered as a critical hormone that controls and regulates many functions in our body. Melatonin production is emphatically related to the night time duration. Its most absolute biological role is to convey information to the body about day length for a variety of physiologic functions. In addition to melatonin's role as an endogenous synchronizer, growing evidence suggests its anti-oxidative activity as well as its having a role in modulating immune responses. At present, a growing interest is focused on the validity of the anti-tumor mechanisms of melatonin.

Synthesis of melatonin requires tryptophan as a precursor as well as a smoothly functioning cascade of several enzyme-based reactions, first to compose serotonin and subsequently melatonin. Several vitamins and minerals act as co-factors and activators in these processes, thus a clear deficiency of needed nutrients may restrict the synthesis. Severe deficiencies, however, are rare in western countries apart from some subgroups. In addition, fluctuating melatonin levels can be boosted by ingesting products containing melatonin. The bioavailability of plant-based melatonin is evident, at least in rodents, and could explain some health benefits of vegetables, fruits, and grain products.

Eating routine and supplements balance the fluctuating melatonin levels, yet the impact is minor if contrasted with the daylight-night (light-dim cycle). Other factors related to the well-being of an individual such as one’s bodyweight, which is associated with fat metabolism, may have as much impact on melatonin levels as a particular dietary choice. Subsequently, the medical advantages of an individual’s eating regime driven melatonin production appear not to be the result of any single food or any supplements which is introduced in the eating habit. In general, the diets rich in vegetables, organic products, fruits and cereal items contain significant levels of dietary melatonin. Vitamins and minerals add to the factors responsible for the synthesis of endogenous melatonin while an individual is active. Moreover the effect of eating in the daytime on the biosynthesis of the night-time melatonin is exceptionally constrained. Indeed, even a slight variation in the levels of this hormone may prompt to a misbalance in the overall immunity of the individual concerned and thereby affects the physiologic system. Melatonin treatment is a developing and promising field of pharmaceutical which is still to be investigated. A large portion of the examinations detailed by the researchers clearly conclude that keeping up an impeccable sleep-wake cycle and having a healthy diet is extremely important to keep up the regular melatonin levels and in order to stay fit.

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References

Abbas S A, Khan U A, Helal Uddin A B M (2011). Seasonal changes effects on the serotonin and Melatonin transmission. Can J App Sci, 1 (2): 1–9

Ames B N, Gold L S (1990). Dietary carcinogens, environmental pollution, and cancer: some misconceptions. Med Oncol Tumor Pharmacother, 7(2-3): 69–85

Anisimov V N, Kvetnoy I M, Chumakova N K, Kvetnaya T V, Molotkov A O, Pogudina N A, Popovich I G, Popuchiev V V, Zabezhinski M A, Bartsch H, Bartsch C (1999). Melatonin and colon carcinogenesis. II. Intestinal melatonin-containing cells and serum melatonin level in rats with 1,2-dimethylhydrazine-induced colon tumors. Exp Toxicol Pathol, 51(1): 47–52

Anisimov V N, Popovich I G, Shtylik A V, Zabezhinski M A, Ben-Huh H, Gurevich P, Berman V, Tendler Y, Zusman I (2000a). Melatonin and colon carcinogenesis. III. Effect of melatonin on proliferative activity and apoptosis in colon mucosa and colon tumors induced by 1,2-dimethylhydrazine in rats. Exp Toxicol Pathol, 52(1): 71–76

Anisimov V N, Popovich I G, Zabezhinski M A (1997). Melatonin and colon carcinogenesis: I. Inhibitory effect of melatonin on development of intestinal tumors induced by 1,2-dimethylhydrazine in rats. Carcinogenesis, 18(8): 1549–1553

Anisimov V N, Zabezhinski M A, Popovich I G, Zaripova E A, Musatov S A, Andre V, Vigreux C, Godard T, Sichel F (2000b). Inhibitory effect of melatonin on 7, 12-dimethylbenz[a]anthracene-induced carcinogenesis of the uterine cervix and vagina in mice and mutagenesis in vitro. Cancer Lett, 156(2): 199–205

Attenburrow M E, Cowen P J, Sharpley A L (1996). Low dose melatonin improves sleep in healthy middle-aged subjects. Psychopharmacology (Berl), 126(2): 179–181

Bartsch C, Bartsch H, Fuchs U, Lippert T H, Bellmann O, Gupta D (1989). Stage-dependent depression of melatonin in patients with primary breast cancer. Correlation with prolactin, thyroid stimulating hormone, and steroid receptors. Cancer, 64(2): 426–433

Bartsch C, Bartsch H, Schmidt A, Ilg S, Bichler K H, Flüchter S H (1992). Melatonin and 6-sulfatoxymelatonin circadian rhythms in serum and urine of primary prostate cancer patients: evidence for reduced pineal activity and relevance of urinary determinations. Clin Chim Acta, 209(3): 153–167

Benarroch E E (2008). Suprachiasmatic nucleus and melatonin: reciprocal interactions and clinical correlations. Neurology, 71(8): 594–598

Blask D E (2009). Melatonin, sleep disturbance and cancer risk. Sleep Med Rev, 13(4): 257–264

Blask D E, Dauchy R T, Sauer L A (2005). Putting cancer to sleep at night: the neuroendocrine/circadian melatonin signal. Endocrine, 27 (2): 179–188

Blask D E, Dauchy R T, Sauer L A, Krause J A (2004). Melatonin uptake and growth prevention in rat hepatoma 7288CTC in response to dietary melatonin: melatonin receptor-mediated inhibition of tumour linoleic acid metabolism to the growth signaling molecule 13-hydroxyoctadecadienoic acid and the potential role of phytomelatonin. Laboratory of Chrono-Neuroendocrine Oncology, Bassett Research Institute, Cooperstown, NY, USA. Carcinogenesi, 25(6): 951–960

Blask D E, Lemus-Wilson A M, Wilson S T (1992). Breast cancer: a model system for studying the neuroendocrine role of pineal melatonin in oncology. Biochem Soc Trans, 20(2): 309–311

Blask D E, Sauer L A, Dauchy R T (2002). Melatonin as a chronobiotic/anticancer agent: cellular, biochemical, and molecular mechanisms of action and their implications for circadian-based cancer therapy. Curr Top Med Chem, 2(2): 113–132

Brzezinski A (1997). Melatonin in humans. N Engl J Med, 336(3): 186–195

Cardinali D P, Pagano E S, Scacchi Bernasconi P A, Reynoso R, Scacchi P (2013). Melatonin and mitochondrial dysfunction in the central nervous system. Horm Behav, 63(2): 322–330

Cini G, Coronnello M, Mini E, Neri B (1998). Melatonin's growth-inhibitory effect on hepatoma AH 130 in the rat. Cancer Lett, 125(1-2): 51–59

Claustrat B, Brun J, Chazot G (2005). The basic physiology and pathophysiology of melatonin. Sleep Med Rev, 9(1): 11–24

Cohen M, Lippman M, Chabner B (1978). Role of pineal gland in aetiology and treatment of breast cancer. Lancet, 2(8094): 814–816

Cos S, Fernández F, Sánchez-Barceló E J (1996). Melatonin inhibits DNA synthesis in MCF-7 human breast cancer cells in vitro. Life Sci, 58(26): 2447–2453

Cos S, Fernández R, Güézmes A, Sánchez-Barceló E J (1998). Influence of melatonin on invasive and metastatic properties of MCF-7 human breast cancer cells. Cancer Res, 58(19): 4383–4390

Cos S, González A, Martínez-Campa C, Mediavilla M D, Alonso-González C, Sánchez-Barceló E J (2006). Estrogen-signaling pathway: a link between breast cancer and melatonin oncostatic actions. Cancer Detect Prev, 30(2): 118–128

Cos S, Mediavilla M D, Fernández R, González-Lamuño D, Sánchez-Barceló E J (2002). Does melatonin induce apoptosis in MCF-7 human breast cancer cells in vitro? J Pineal Res, 32(2): 90–96

Crespo D, Fernández-Viadero C, Verduga R, Ovejero V, Cos S (1994). Interaction between melatonin and estradiol on morphological and morphometric features of MCF-7 human breast cancer cells. J Pineal Res, 16(4): 215–222

Dietz B M, Kang Y H, Liu G, Eggler A L, Yao P, Chadwick L R, Pauli G F, Farnsworth N R, Mesecar A D, van Breemen R B, Bolton J L (2005). Xanthohumol isolated from Humulus lupulus Inhibits menadione-induced DNA damage through induction of quinone reductase. Chem Res Toxicol, 18(8): 1296–1305

Dimitrov S, Lange T, Tieken S, Fehm H L, Born J (2004). Sleep associated regulation of T helper 1/T helper 2 cytokine balance in humans. Brain Behav Immun, 18(4): 341–348

Dubocovich M L, Delagrange P, Krause D N, Sugden D, Cardinali D P, Olcese J (2010). International Union of Basic and Clinical Pharmacology. LXXV. Nomenclature, classification, and pharmacology of G protein-coupled melatonin receptors. Pharmacol Rev, 62(3): 343–380

Eagles J M (2004). Seasonal affective disorder: a vestigial evolutionary advantage? Med Hypotheses, 63(5): 767–772

Fonzi S, Solinas G P, Costelli P, Parodi C, Murialdo G, Bo P, Albergati A, Montalbett i L, Savoldi F, Polleri A (1994). Melatonin and cortisol circadian secretion during ethanol withdrawal in chronic alcoholics. Chronobiologia, 21(1-2): 109–112

Gilad E, Laufer M, Matzkin H, Zisapel N (1999). Melatonin receptors in PC3 human prostate tumor cells. J Pineal Res, 26(4): 211–220

Gregg D J (2004). Seasonal affective disorder (SAD). Retrieved from http://www.talkaboutsleep.com/sleep-disorders/2004/09/circadian-jacobs-sad.htm

Guerrero J M and Reiter R J (2002). Melatonin-Immune System Relationships. Bentham Science Publishers. Current Topics in Medicinal Chemistry, 2(2): 167–179(13).

Hardeland R (2005). Antioxidative protection by melatonin: multiplicity of mechanisms from radical detoxification to radical avoidance. Endocrine, 27(2): 119–130

Hill S M, Blask D E (1988). Effects of the pineal hormone melatonin on the proliferation and morphological characteristics of human breast cancer cells (MCF-7) in culture. Cancer Res, 48(21): 6121–6126

Illnerová H, Buresová M, Presl J (1993). Melatonin rhythm in human milk. J Clin Endocrinol Metab, 77(3): 838–841

Imai K, Matsuyama S, Miyake S, Suga K, Nakachi K (2000). Natural cytotoxic activity of peripheral-blood lymphocytes and cancer incidence: an 11-year follow-up study of a general population. Lancet, 356(9244): 1795–1799

Jakóbisiak M, Lasek W, Gołab J (2003). Natural mechanisms protecting against cancer. Immunol Lett, 90(2-3): 103–122

Jung-Hynes B, Huang W, Reiter R J, Ahmad N (2010). Melatonin resynchronizes dysregulated circadian rhythm circuitry in human prostate cancer cells. J Pineal Res, 49(1): 60–68

Jung-Hynes B, Reiter R J, Ahmad N (2010). Sirtuins, melatonin and circadian rhythms: building a bridge between aging and cancer. J Pineal Res, 48(1): 9–19

Kanishi Y, Kobayashi Y, Noda S, Ishizuka B, Saito K (2000). Differential growth inhibitory effect of melatonin on two endometrial cancer cell lines. J Pineal Res, 28(4): 227–233

Karbownik M, Lewinski A, Reiter R J (2001). Anticarcinogenic actions of melatonin which involve antioxidative processes: comparison with other antioxidants. Int J Biochem Cell Biol, 33 (8): 735–753

Karbownik M, Reiter R J (2002). Melatonin protects against oxidative stress caused by δ-aminolevulinic acid: implications for cancer reduction. Cancer Invest, 20(2): 276–286

Klaunig J E, Xu Y, Isenberg J S, Bachowski S, Kolaja K L, Jiang J, Stevenson D E, Walborg E FJr (1998). The role of oxidative stress in chemical carcinogenesis. Environ Health Perspect, 106(Suppl 1): 289–295

Kriya L D, Arleigh J R, Gianluca T, Wendell W K, Lawrence K D (2007). Seasonal and diurnal melatonin production in exercising sled dogs. Comparative Biochem and Physio- Part A: Molecular & Integrative Physio., (Article in Press)

Krueger J M, Fang J, Hansen M K, Zhang J, Obál FJr (1998). Humoral

regulation of sleep. News Physiol Sci, 13: 189–194

Lee C O (2006). Complementary and alternative medicines patients are talking about: melatonin. Clin J Oncol Nurs, 10(1): 105–107

Lee K, Cho M, Miaskowski C, Dodd M (2004). Impaired sleep and rhythms in persons with cancer. Sleep Med Rev, 8(3): 199–212

Lichtenstein P, Holm N V, Verkasalo P K, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A, Hemminki K (2000). Environmental and heritable factors in the causation of cancer–analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med, 343(2): 78–85

Lyon R C, McComb J A, Schreurs J, Goldstein D B (1981). A relationship between alcohol intoxication and the disordering of brain membranes by a series of short-chain alcohols. J Pharmacol Exp Ther, 218(3): 669–675

Maronde E, Stehle J H (2007). The mammalian pineal gland: known facts, unknown facets. Trends Endocrinol Metab, 18(4): 142–149

Maurizi C P (1990). The therapeutic potential for tryptophan and melatonin: possible roles in depression, sleep, Alzheimer's disease and abnormal aging. Med Hypotheses, 31(3): 233–242

Mediavilla M D, Cos S, Sánchez-Barceló E J (1999). Melatonin increases p53 and p21WAF1 expression in MCF-7 human breast cancer cells in vitro. Life Sci, 65(4): 415–420

Mills E, Wu P, Seely D, Guyatt G (2005). Melatonin in the treatment of cancer: a systematic review of randomized controlled trials and meta-analysis. J Pineal Res, 39(4): 360–366

Mocchegiani E, Perissin L, Santarelli L, Tibaldi A, Zorzet S, Rapozzi V, Giacconi R, Bulian D, Giraldi T (1999). Melatonin administration in tumor-bearing mice (intact and pinealectomized) in relation to stress, zinc, thymulin and IL-2. Int J Immunopharmacol, 21(1): 27–46

Molis T M, Spriggs L L, Hill S M (1994). Modulation of estrogen receptor mRNA expression by melatonin in MCF-7 human breast cancer cells. Mol Endocrinol, 8(12): 1681–1690

Musatov S A, Anisimov V N, André V, Vigreux C, Godard T, Sichel F (1999). Effects of melatonin on N-nitroso-N-methylurea-induced carcinogenesis in rats and mutagenesis in vitro (Ames test and COMET assay). Cancer Lett, 138(1-2): 37–44

Nosjean O, Nicolas J P, Klupsch F, Delagrange P, Canet E, Boutin J A (2001). Comparative pharmacological studies of melatonin receptors: MT1, MT2 and MT3/QR2. Tissue distribution of MT3/QR2. Biochem Pharmacol, 61(11): 1369–1379

Pacchierotti C, Iapichino S, Bossini L, Pieraccini F, Castrogiovanni P (2001). Melatonin in psychiatric disorders: a review on the melatonin involvement in psychiatry. Front Neuroendocrinol, 22(1): 18–32

Pandi-Perumal S R, Trakht I, Srinivasan V, Spence D W, Maestroni G J M, Zisapel N, Cardinali D P (2008). Physiological effects of melatonin: role of melatonin receptors and signal transduction pathways. Prog Neurobiol, 85(3): 335–353

Panzer A, Lottering M L, Bianchi P, Glencross D K, Stark J H, Seegers J C (1998). Melatonin has no effect on the growth, morphology or cell cycle of human breast cancer (MCF-7), cervical cancer (HeLa), osteosarcoma (MG-63) or lymphoblastoid (TK6) cells. Cancer Lett, 122(1-2): 17–23

Patel S R, Ayas N T, Malhotra M R, White D P, Schernhammer E S, Speizer F E, Stampfer M J, Hu F B (2004). A prospective study of sleep duration and mortality risk in women. Sleep, 27(3): 440–444

Petranka J, Baldwin W, Biermann J, Jayadev S, Barrett J C, Murphy E (1999). The oncostatic action of melatonin in an ovarian carcinoma cell line. J Pineal Res, 26(3): 129–136

Peuhkuri K, Sihvola N, Korpela R (2012). Dietary factors and fluctuating levels of melatonin. Food Nutr Res, 56(1): 17252

Qi W, Reiter R J, Tan D X, Manchester L C, Calvo J R (2001). Melatonin prevents δ-aminolevulinic acid-induced oxidative DNA damage in the presence of Fe2 +. Mol Cell Biochem, 218(1-2): 87–92

Ram P T, Yuan L, Dai J, Kiefer T, Klotz D M, Spriggs L L, Hill S M (2000). Differential responsiveness of MCF-7 human breast cancer cell line stocks to the pineal hormone, melatonin. J Pineal Res, 28(4): 210–218

Reiter R J (1980). The pineal and its hormones in the control of reproduction in mammals. Endocr Rev, 1(2): 109–131

Riabykh T P, Nikolaeva T G, Bodrova N B (2000). [Effects of biorhythm regulator melatonin on DNA synthesis in short-term cultures of human malignant tumors]. Vestn Ross Akad Med Nauk, (8): 30–33

Schernhammer E S, Berrino F, Krogh V, Secreto G, Micheli A, Venturelli E, Sieri S, Sempos C T, Cavalleri A, Schünemann H J, Strano S, Muti P (2008). Urinary 6-sulfatoxymelatonin levels and risk of breast cancer in postmenopausal women. J Natl Cancer Inst, 100(12): 898–905

Schernhammer E S, Hankinson S E (2003). Light at night: a novel risk factor for cancer in shift workers. Clin Occup Environ Med, 3(2): 263–278

Shiu S Y, Li L, Xu J N, Pang C S, Wong J T, Pang S F (1999). Melatonin-induced inhibition of proliferation and G1/S cell cycle transition delay of human choriocarcinoma JAr cells: possible involvement of MT2 (MEL1B) receptor. J Pineal Res, 27(3): 183–192

Spiegel D, Giese-Davis J (2003). Depression and cancer: mechanisms and disease progression. Biol Psychiatry, 54(3): 269–282

Stevens R G, Rea M.0S (2001). Light in the built-in environment: potential role of circadian disruption in endocrine disruption and breast cancer. CCC, 12: 279–87.

Sturgeon S R, Luisi N, Balasubramanian R, Reeves K W (2012). Sleep duration and endometrial cancer risk. Cancer Causes Control, 23(4): 547–553

Sze S F, Ng T B, Liu W K (1993). Antiproliferative effect of pineal indoles on cultured tumor cell lines. J Pineal Res, 14(1): 27–33

Tamarkin L, Cohen M, Roselle D, Reichert C, Lippman M, Chabner B (1981). Melatonin inhibition and pinealectomy enhancement of 7,12-dimethylbenz(a)anthracene-induced mammary tumors in the rat. Cancer Res, 41(11 Pt 1): 4432–4436

Tan D X, Manchester L C, Hardeland R, Lopez-Burillo S, Mayo J C, Sainz R M, Reiter R J (2003). Melatonin: a hormone, a tissue factor, an autocoid, a paracoid, and an antioxidant vitamin. J Pineal Res, 34 (1): 75–78

Tan D X, Manchester L C, Terron M P, Flores L J, Reiter R J (2007). One molecule, many derivatives: a never-ending interaction of melatonin with reactive oxygen and nitrogen species? J Pineal Res, 42(1): 28–42

Touitou Y, Fèvre M, Lagoguey M, Carayon A, Bogdan A, Reinberg A, Beck H, Cesselin F, Touitou C (1981). Age- and mental health-related circadian rhythms of plasma levels of melatonin, prolactin, luteinizing hormone and follicle-stimulating hormone in man. J Endocrinol, 91(3): 467–475

Travis R C, Allen D S, Fentiman I S, Key T J (2004). Melatonin and breast cancer: a prospective study. J Natl Cancer Inst, 96(6): 475–482

Üstundag A, Duydu Y (2007). The influence of melatonin and N-acetylcysteine in δ-aminolevulinic acid and lead induced genotoxicity in lymphocytes in vitro. Biol Trace Elem Res, 117(1-3): 53–64

Valtonen M, Kangas A P, Voutilainen M, Eriksson L (2003). Diurnal rhythm of melatonin in young calves and intake of melatonin in milk. Anim Sci, 77(1): 149–154

van der Goot A T, Nollen E A (2013). Tryptophan metabolism: entering the field of aging and age-related pathologies. Trends Mol Med, 19 (6): 336–344

Vijayalaxmi , Thomas C R J, Reiter R J, Herman T S(2002). Melatonin: from basic research to cancer treatment clinics. J Clin Oncol, 20: 2575–2601.

Waldhauser F, Waldhauser M (1988). Melatonin and ageing. A Miles, D.R.S Philbrick, C Thompson (Eds.), Melatonin—Clinical Perspectives, Oxford University Press, Oxford. pp. 174–189

Walecka-Kapica E, Klupińska G, Chojnacki J, Tomaszewska-Warda K, Błońska A, Chojnacki C (2014). The effect of melatonin supplementation on the quality of sleep and weight status in postmenopausal women. Przegl Menopauz, 13(6): 334–338

Wu A H, Wang R, Koh W P, Stanczyk F Z, Lee H P, Yu M C (2008). Sleep duration, melatonin and breast cancer among Chinese women in Singapore. Carcinogenesis, 29(6): 1244–1248

Wurtman R J, Axelrod J, Barchas J D (1964). Age and Enzyme Activity in the Human Pineal. J Clin Endocrinol Metab, 24(3): 299–301

Ying S W, Niles L P, Crocker C (1993). Human malignant melanoma cells express high-affinity receptors for melatonin: antiproliferative effects of melatonin and 6-chloromelatonin. Eur J Pharmacol, 246(2): 89–96

Yuan L, Collins A R, Dai J, Dubocovich M L, Hill S M (2002). MT(1) melatonin receptor overexpression enhances the growth suppressive effect of melatonin in human breast cancer cells. Mol Cell Endocrinol, 192(1-2): 147–156

Zawilska J B, Lorenc A, Berezińska M, Vivien-Roels B, Pévet P, Skene D J (2006). Diurnal and circadian rhythms in melatonin synthesis in the turkey pineal gland and retina. Gen Comp Endocrinol, 145(2): 162–168

Zee P C, Attarian H, Videnovic A (2013). Circadian rhythm abnormalities. Continuum (Minneap Minn), 19(1 Sleep Disorders): 132–147