Melatonin, a Prognostic Marker in Oncologic Pathology

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Abstract

Melatonin is the major secretion product of the pineal gland. The main function of melatonin is to control the sleep-wake mechanism and the circadian rhythm. Pineal secretion follows a circadian rhythm with low levels during the day and high levels at night. In people who work in night shifts, melatonin suppression following nocturnal exposure to artificial light alters the inhibition of ovarian estrogen secretion resulting in high estrogen levels, directly linked with the incidence of breast and endometrial cancer. Melatonin also plays a role in neuroendocrine regulation, in boosting immunity, in neutralizing free radicals, in reducing angiogenesis and in increasing apoptosis. Over the past years, studies on animals and humans have demonstrated that melatonin has important oncostatic effects.
Blood melatonin levels are reversely correlated with the tumor proliferation index in patients with breast, endometrial and ovarian cancer. All this evidence supports the idea that melatonin levels can be a useful biochemical marker in the prevention, the diagnosis, the treatment monitoring and the prognosis of various types of cancer.
Keywords: *melatonin, cancer, oncostatic effect, apoptosis, angiogenesis.*

Melatonin (N-acetyl-5-metoxytryptamine) is the major secretion product of the pineal gland. Melatonin can also be synthesized in the eye, skin, gastrointestinal tract, bone, liver, kidney, thyroid, ovary, placenta, as well as in the mast cells, natural killer (NK) cells, thrombocytes or eosinophils. Unlike pineal melatonin, melatonin produced by other tissues does not reach high blood concentrations, acting in particular locally as an autocrine or paracrine signal.

The melatonin half-life is 30 minutes[1]. Pineal secretion follows a circadian rhythm with low levels during the day and high levels at night. Both the circadian rhythm and the amplitude of nocturnal melatonin secretion have been studied extensively over the past few years; individual secretion variations have been noted in humans[2]. Melatonin production gradually decreases when ageing, melatonin levels being quite low in elders. Some studies demonstrated a season-induced variation of melatonin synthesis in humans (higher melatonin levels during winter)[3].

Melatonin synthesis is not specific to vertebrates; species of algae, plants, insects (Drosophila) also produce melatonin[4]. These species also exhibit circadian variations of melatonin synthesis. Melatonin concentrations in saliva, milk, amniotic fluid, urine, maintains exhibit the same circadian rhythm[5,6].

In humans, the maturation of the circadian rhythm is gradual[7]. Melatonin synthesis is present since intrauterine life; five to six months after birth the melatonin synthesis rate is already rigorously established[8].

Authors reported several disorders altering serum melatonin concentrations

as well as urinary melatonin metabolite concentrations. An important decrease of melatonin levels is found in coronary disorders, schizophrenia, cephalea, Alzheimer disease and when using antidepressants. Melatonin levels are higher in patients with nervous anorexia, nervous bulimia, Turner syndrome, amenorrhea of hypothalamic cause[9].

The main function of melatonin is to control the sleep-wake mechanism, as well as the circadian rhythm. The day/night cycle regulates melatonin synthesis through the retinohypothalamic tract. The regulation of the sleep-wake cycle (as well as other melatonin effects) is due to direct effects on specific receptors (MT1 and MT2).

Exposure to early morning light may accelerate the circadian pacemaker, as responses vary non-linearly with illumination. The dose/response relationship in late evening light has not yet been established. It is well known that humans are highly sensitive to the effects of the light to which they are exposed at the beginning of the night and that the response to light and the suppression of plasma melatonin follow a logical cause-effect pattern[10]. Small changes in usual light exposure during the night may significantly alter plasma melatonin concentration.

Recent studies on both animals and humans have shown that melatonin also has important oncostatic properties. The anti-oncogenic effect of melatonin on neoplastic cells is based on antioxidant, immunostimulating and apoptotic properties. Melatonin directly neutralizes free radicals (indirect antioxidants). The oncostatic effects of melatonin includes the direct growth of NK cells, the stimulation of cytokine production (IL2, 6, 12, IF γ)[9].

The human body possesses anti-carcinogenic mechanisms. NK lymphocytes play an important role in the inhibition of tumor growth, but also in the inhibition of metastasis. Many studies suggest that oxidative stress is involved in 3 stages of carcinogenesis: initiation, promotion and progression[11]. Free radicals and reactive O2 species produced by environmental carcinogens or by different metabolic changes, cause DNA lesions and gene instability. DNA lesions induced by oxidative stress represent the most important factor in the development of malignancy. It is well known that natural antioxidants counterbalance the production of free radicals and the molecular destructions caused by these in DNA. One of the natural antioxidants with a protective role is melatonin.

The oxidative-antioxidative balance influences the cell proliferation rate. Tumor cells have a low lipid peroxidation level, which can stimulate cell division and growth. During oxidative reactions, the superoxide radical is generated in the organism, which reacts with hydrogen peroxide and generates highly reactive hydroxyl radicals. Most cell components (lipids, proteins, DNA molecules) can be destroyed by hydroxyl radicals[12].

The exposure of living cells to ionizing radiation results in the generation of free radicals. Ionizing radiation, as well as ultraviolet radiation, has a carcinogenic effect particularly by the induction of reactive oxygen species. Melatonin is considered a radioprotective agent due to the filtration of free radicals and to the indirect antioxidant effect[13].

It is well known that there is a high concentration of intracellular glutathione, which plays a protective role against free radicals. Glutathione reduction is catalyzed by γ glutamylcysteine synthetase. This enzyme is inhibited by butionine sulfoximine, which reduces the intracellular deposition of glutathione. Recent studies show that melatonin exerts oncostatic effects by inhibiting glutathione pathway. Melatonin regulates glutathione production by modulating the level of γglutamylcysteine synthetase[14]. This action is essential for the reduction of the production of both hydrogen peroxide and of hydroxyl radicals, thus explaining the oncostatic effect.

Melatonin used either alone or associated with radio- and/or chemotherapy has beneficial therapeutic effects in many types of cancer (including brain tumors, breast cancer, colorectal cancer, hepatic, pulmonary or renal tumors)[15].

Angiogenesis is an essential stage in the development of the primary tumor. The literature data increasingly support the influence of melatonin on angiogenesis, which is the main biological mechanism responsible for tumor growth and development.

An important role in tumor development and vascularization belongs to the vascular endothelial growth factor (VEGF). In order to study the possible influence of melatonin on angiogenesis, its effect on endogenous VEGF was monitored in three human cell lines (PANC -1, Hela, A549). The physiological concentration of melatonin did not essentially alter the VEGF expression, while increased melatonin concentrations caused an important reduction in the expression of endogenous VEGF[16].

Endothelin 1 synthesized in blood vessels is deemed as one of the most important stimulants of angiogenesis. Endothelin 1 directly stimulates the endothelium as well as perivascular cells by releasing proangiogenic substances (i.e. the endothelial growth factor). These effects are stopped by melatonin, which suppresses the formation of endothelin 1 by inhibiting its conversion enzyme[17].

Studies have also been performed investigating the melatonin effects on human umbilical vein endothelial cells, concluding that increased melatonin concentrations obviously reduce proliferation, increase apoptosis and modulate the cell cycle duration in this cell population[18].

Studies have demonstrated the **anti-apoptotic** effect of melatonin in immune cells by both direct and indirect mechanisms. In neuronal cells, melatonin prevents amyloid-induced apoptosis both in vivo and in vitro[19]. On the other hand, melatonin favors apoptosis in breast and colon cancer cells by the increased expression of proteins P21 and P53, which are in relation with the control cell cycle[20].

The majority of the studies confirm the presence of a relationship between the pineal gland and the **immune system**. The absence of the pineal gland determines the stimulation of the proliferation of immunocompetent cells and is associated with an early involution of the thymus[21].

Melatonin has important immunostimulating effects of significant therapeutic value under conditions of stress, infections or neoplastic diseases and whenever the immune system functionality gets compromised. In the elderly, a decrease of thymopoiesis and an increase in cytokine production was noted, suggesting immunodepression in this age group[22]. Older age is associated with a decrease in serum melatonin concentrations, which in turn is also a major immunodepression factor.

The immunomodulator role of melatonin is also confirmed by the size and weight decrease of the spleen induced by inhibited pineal secretion in animal (hamsters) models[23].

Associated with the stimulation of some

cytokines (IL1, 6, 12, TNFα) melatonin directly increases the immune function by the stimulation of polymorphonuclear (PMN), macrophage, NK and lymphocyte cells. Human lymph cells also synthesize melatonin. This secondary hormone source helps regulate the immune system by autocrine or paracrine mechanisms. Considerable attention has been paid to the effect of melatonin on CD4 cells. These cells secrete IFN γ and TNF α which activate and regulate the cytotoxic response of T lymphocytes[24].

Because NK cells have a destructive potential on some tumor types (leukemia, lymphoma), the regulation of NK cell activity and the melatonin-induced increase of their cytolytic function are particularly important in view of possible future therapeutic applications[25].

Melatonin is an important cancer proliferation inhibitor, while essential polyunsaturated fatty acids are promoters of carcinogenesis. Linoleic acid is rapidly incorporated in the tumor tissue, where it is oxidized to 13 hydroxyoctadecadienoic acid (13HODE - the lipoxygenase pathway), which in its turn stimulates the epidermal growth factor, therefore favoring cell proliferation. The plasma to cells passage of linoleic acid and its metabolite is inhibited by melatonin in a way that is influenced by the circadian cycle.

So far, a number of mechanisms have been identified explaining why melatonin deficiency may increase the incidence of cancer disease in some organs (i.e. breast, uterus, ovary, colon, rectum, liver, prostate, etc. - Figure 1).

Breast cancer is one of the most frequent cancers in females. Estrogens are the main factor involved in the development and progression of breast cancer. Nocturnal melatonin release suppresses ovarian estrogen production. In people working in night shifts, melatonin suppression following nocturnal exposure to artificial light decreases the inhibition of ovarian estrogen secretion, with the appearance of high estrogen levels, directly correlated with the incidence of breast and endometrial cancer[26].

The **light-melatonin-breast cancer** hypothesis is supported by:

- the low serum and urinary melatonin concentrations as well as by low urinary concentrations of 6-sulfatoxymelatonin (the major melatonin metabolite) in women with breast cancer[27];
- the inverse relationship between the incidence of breast cancer and the degree of vision impairment (women with complete vision alteration having the lowest incidence of the disease)[28];
- the high incidence of breast cancer in industrialized countries where light exposure throughout the night is significantly increased as compared to undeveloped countries[29];

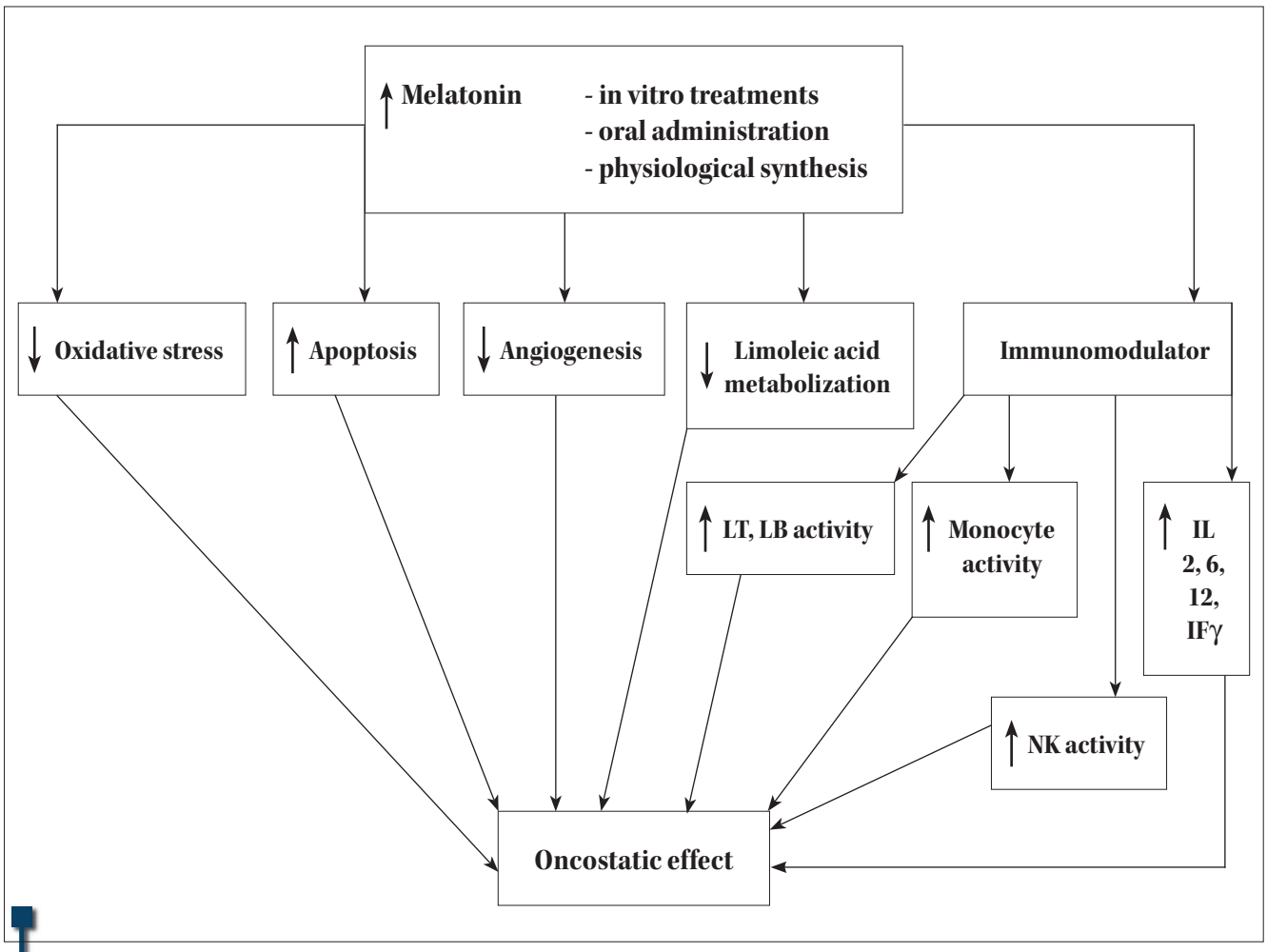

Figure 1. Oncostatic mechanisms of melatonin

- experimental studies performed in female rats transplanted with breast cancer tumor tissue showed that the rats exposed to a constant light of 300 lux had an incidence of breast cancer 7-times higher than rats with normal exposures[30];
- studies using human (breast cancer) tumor cells demonstrated that physiological melatonin levels have direct inhibitory effects on estradiol-induced cell proliferation[31];
- the intracellular cAMP concentration is modulated by melatonin and estrogen cross-reactions with specific receptors[32];
- the melatonin-induced reduction of aromatase in adipose cells plays an important role in the etiopathogenesis of estrogen-dependent cancers, due to its involvement in converting androgenic hormones to estrogen hormones[33].

The **endometrium** is a tissue prone to hormonal influences. Under the influence of estrogens, cell growth and gland proliferation are cyclically counteracted by the effects of progesterone. Although endometrial cancer (and breast cancer, too) is known to be estrogen-dependent, the effect of normal melatonin concentrations on endometrial cancer has not been quantified, yet. A dysfunctional pineal gland is considered a risk factor in the development of endometrial cancer, since melatonin has antiestrogenic properties. Melatonin secretion decreases in postmenopausal women in whom a higher incidence of endometrial cancer was found.

Diabetes, obesity and high blood pressure are known to be the main risk factors for both endometrial cancer and atherosclerosis. Atherosclerotic alterations of the capillary network that supplies the pineal gland reduce the production and release rates for melatonin, therefore favoring endometrial cancer[34]. Clinical studies have reported patients with endometrial cancer to have significantly lower serum melatonin concentrations as compared to healthy population[35].

Cell culture studies demonstrated that melatonin had different antiproliferative effects on different cancer cells (differentiated by their estrogen receptor status). Melatonin had no antiproliferative action on SNG-II (without estrogen receptors), but had a significant antiproliferative effect on the Ishikawa cells (with estrogen receptors) at different cellular densities and different incubation times[36].

There are two possible mechanisms for having the estrogen block the antiproliferative effect of melatonin: estrogen may compete with melatonin for binding to a common receptor, or each ligand has its own receptor interacting with one another (by other mechanisms than those related to ligand's own receptor). But there are also additional estrogen-independent mechanisms, which may involve melatonin receptors[37]. Melatonin receptors (MT2) have been identified in the membrane of estrogen-responsive tumor cell lines and it has been shown that the antiproliferative effect of melatonin is mediated by these receptors[36,37].

A non-homogeneous response to melatonin was found in **ovarian carcinoma** cell cultures of different cell lines. Cells of the first tumor line were inhibited by 90% at a melatonin concentration of 10-8 M, whereas cells from the second tumor line showed a 30% growth inhibition[38].

Studies conducted in ovarian carcinoma patients failed to show any significant differences between melatonin secretion levels in affected individuals as compared to controls[39].

The growth of solid ovarian tumors in turkey breeder hen was promoted by long photoperiods and ceased (to the point of remission) on short photoperiods. Thus, ovarian adenocarcinoma in turkeys can be completely manipulated by photoperiod. In addition, the melatonin treatment attenuated tumor growth in the turkey hen[40].

Treeck et al. suggest that melatonin signaling is modulated by antiestrogens in ovarian cancer cells[41].

Chemo and/or radiotherapy applied to young cancer patients most often have severe effects on female fertility. Drugs capable of protecting the oocyte and its surrounding feeder cells from damage could be of great importance. Adriaens el al indicated an effect of melatonin on theca cell steroidogenesis. For prophylactic use, a dose of 10 microM should be suitable to reduce oxidative stress in cultured follicles[42].

The oncostatic effect of melatonin has also been studied in cell cultures originating in other neoplasms (prostate cancer, colon carcinoma, melanoma, neuroblastoma, pineal tumors, laryngial carcinoma, urinary bladder carcinoma etc.) and the results being encouraging.

The melatonin - **prostate cancer** correlation is supported by the variations of the prostate specific antigen (PSA) values following melatonin administration. Thus, in patients with histopathologically confirmed prostate cancer and increased PSA levels, the reduction of the values of this antigen was noted following melatonin administration[43].

Nocturnal light suppresses melatonin production and people who work in night shifts (at least 3 nights/month for 15 years) have a higher risk of developing colon cancer[44].

Human melanoma cells present receptors with high affinity for melatonin[45]. Moreover, in human melanoma cell cultures melatonin inhibited cell proliferation in direct proportionality with its concentration[46].

Melatonin proved to be a powerful cytostatic drug, both in vitro and in vivo. For human clinical use, melatonin seems to be a promising agent, albeit as a diagnostic or prognostic marker of neoplastic diseases or as an agent to be used (either alone or in combination) for standard cancer treatment.

More research is needed as regards the effects of therapeutically modulating the melatoninergic system on circadian hemodynamic and rhythm (under varying physiopathological conditions) and the possible impact on human morbidity and mortality.

Conclusions

1. There is evidence supporting the interrelation circadian rhythm - melatonin production during carcinogenesis particularly in the case of breast cancer, endometrial adenocarcinoma, and ovarian carcinoma.

2. Nocturnal melatonin synthesis is reduced in patients diagnosed with breast cancer and positive estrogen and progesterone receptors as compared to control patients. In breast cancer, a direct proportionality has been found between melatonin levels and the concentration of estrogen receptors. Thus, melatonin levels could be considered a prognostic factor in breast cancer.

3. Blood melatonin levels are inversely correlated with the tumor proliferation index in patients with endometrial, ovarian and prostate cancer.

4. All this evidence supports the idea that the melatonin level can be a useful biochemical marker in the prevention, the diagnosis, the treatment monitoring and the prognosis of different types of cancer. ■

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