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Melatonin and Its Indisputable Effects on the Health State

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Abstract

Melatonin is a hormone synthesized from the amino acid tryptophan produced especially at night in the pineal gland and helps induce sleep. It is reported to play a role in preventing the production of free radicals and is thus a potent antioxidant. It can also enhance the function of the immune system and appears to have an antitumor effect. Melatonin secretion, mediated by photoperiod, directly influences reproductive function and dopamine which moves into frontal lobe regulating flow of information coming in from other areas of the brain. Additional side effects may be produced from treatment with melatonin and include stomach cramps, dizziness, headache, irritability, breast enlargement in men (called gynecomastia), and decreased sperm count. For clinical trials, the direct effect of exogenous melatonin administration on patients manifested with cancer should be studied to find its oncostatic effects on some cancers and provide information on its dosage and long-term safety. Moreover, mechanisms of action should be further investigated.

Keywords: melatonin, anti-aging, anticancer antiproliferative effect, geroprotector

1. Hormone description

Melatonin is a hormone (N-acetyl-5 methoxytryptamine) produced especially at night in the pineal gland which helps in the maintenance of the body's hormone balance and regulation, in immune system integrity, and in circadian rhythm (daily metabolic balance). This gland functions as a biological clock and time keeper of the brain by secreting melatonin and many other neuropeptides at night, helps to govern the sleep-wake cycle and, in animals, seasonal rhythms

of migration, mating, and hibernation. Secretion of melatonin is stimulated by the dark and inhibited by light. Melatonin levels start to be released at sunsets, where neural signals are triggered which stimulate the pineal gland to begin releasing the hormone.

Melatonin is synthesized from the amino acid tryptophan. Tryptophan (l-tryptophan) is an essential amino acid formed from proteins during digestion by the action of proteolytic enzymes. Tryptophan is converted to serotonin, a brain chemical involved with mood during the day and the latter finally converted to the indole melatonin (**Figures 1 and 2**). Melatonin occurs naturally in some foods but in fairly small amounts. Of all the plant-based foods, oats, sweet corn and rice are the richest source in melatonin, containing between 1000 and 1800 picograms while ginger, tomatoes, bananas and barley levels amount to 500 picograms per gram. In the human population, melatonin levels are highest in children and middle-aged adults and usually about 5–25 micrograms of melatonin are secreted each night. This amount tends to decline with age, a possible link with an age-related rise in difficulty sleeping and in the production of free radicals [1]. Synthetic melatonin and melatonin derived from bovine pineal glands are available as dietary supplements over-the-counter.

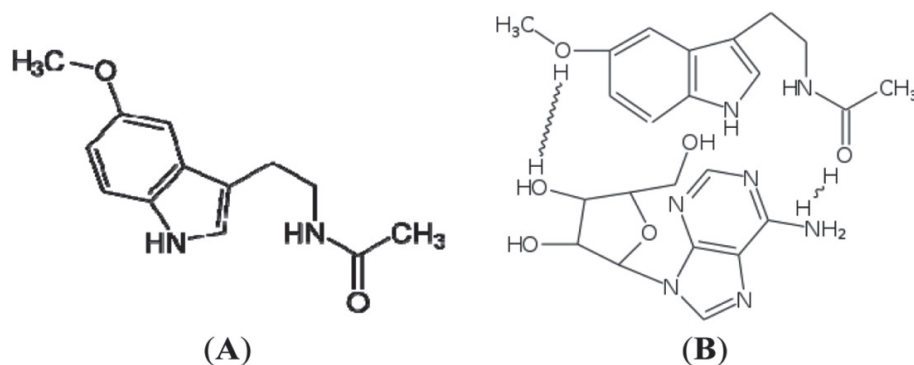


Figure 1. Chemical structure of Tryptophan (A) and Melatonin (B).

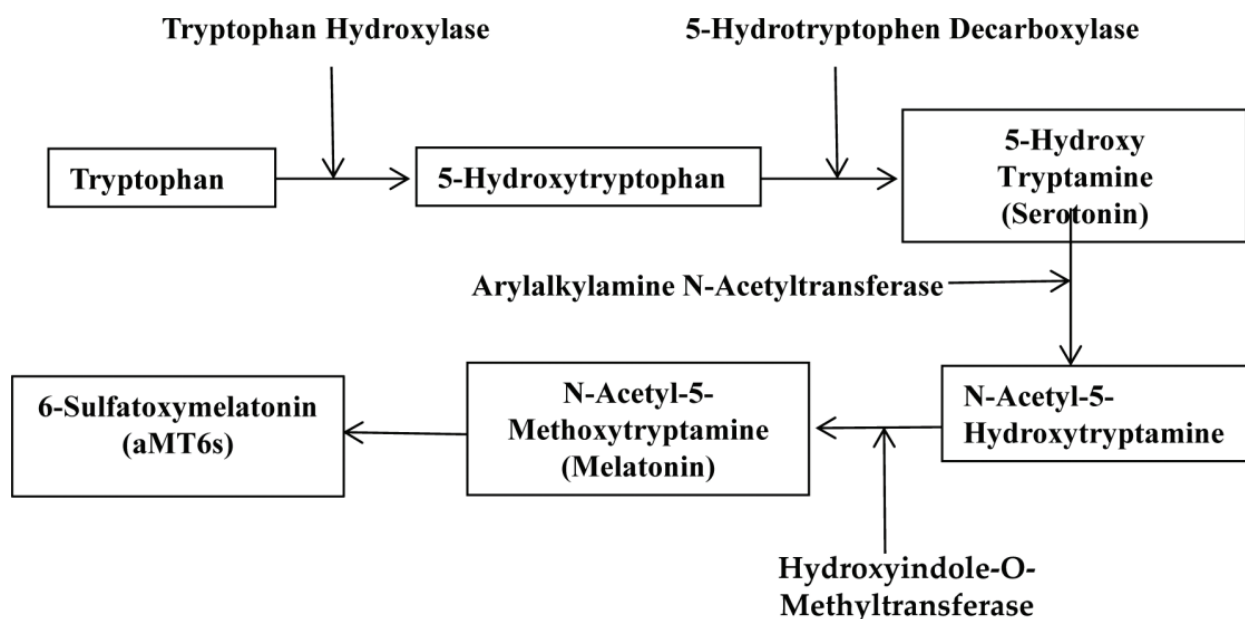


Figure 2. The biosynthesis and metabolism process of melatonin. www.impactjournals.com/oncotarget.

2. Biological functions

Melatonin, stimulated by darkness and inhibited by light, is involved in synchronizing the body's hormone secretions and in regulating their levels, setting the brain's internal biological clock and hence controlling circadian rhythms (daily biorhythms) or sleep-wake. Melatonin regulates many neuroendocrine functions and can inhibit secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the anterior pituitary gland. When the timing or intensity of melatonin peak is disrupted (as in aging, stress, jet-lag, or artificial jet-lag syndromes), the biological clock is upset and many physiological and mental functions are adversely affected including the ability to think, remember, and make sound decisions can be profoundly hampered. Melatonin also controls the timing and release of female reproductive hormones and hence helps determine when menstruation begins and ends (menopause), and the frequency and duration of menstrual cycles [1].

In addition to its hormone actions, melatonin also has strong antioxidant properties and may scavenge and eliminate cell-damaging free radicals. The latter are chemical constituents that have an unpaired electron and cause lipid peroxidation, DNA damage and protein oxidation. Besides, it inhibits nitric oxide synthetase enzyme leading to reduction in the formation of peroxynitrite in tissues of brain. Melatonin stimulates the activities of antioxidant enzymes; glutathione peroxidase, superoxide dismutase and catalase. Melatonin is twice as effective at protecting cell membranes from lipid peroxidation as vitamin E and is five times more effective than glutathione for neutralizing hydroxyl radicals. As an antioxidant, it possibly helps to control or delay the development of heart disease, cancer and other conditions and may be effective in destroying malignant cells when combined with certain anticancer drugs. Since glutathione concentrations are not very high in the brain, both melatonin and adenosine may be particularly important in protecting brain cells [1].

3. Melatonin as an activity enhancer of antioxidative enzymes

Two decades ago, melatonin was found to be a free radical scavenger [2]. However, abundant data ascertaining its ability to reduce oxidative stress have rapidly accumulated [3, 4]. The efficacy of melatonin in functioning in this subject is related to its direct free radical scavenging actions. Owing to its chemical formula, melatonin can interact with various forms of free radicals such as H_2O_2 , $\bullet OH$, singlet oxygen (1O_2), superoxide anion ($\bullet O_2^-$), peroxynitrite anion ($ONOO^-$) and peroxy radical ($LOO\bullet$) [4]. The main photoproduct metabolites of melatonin degradation are potent antioxidants such as *N*1-acetyl-5-methoxykynuramine (AMK) or *N*1-acetyl-*N*2-formyl-5-methoxykynuramine (AFMK) [4]. Moreover, investigations on free radicals produced as a result of UV exposure, showed that by using cell-free melatonin-containing systems exposed to UV radiation (UVB: 60%, UVA: 30%) four metabolites were identified by HPLC and LC-MS: 2-OH-melatonin, 4-OH-melatonin, 6-OH-melatonin and AFMK [5]. Since these metabolites are potent antioxidants, this may suggest that, unlike other classic antioxidants, they do not induce prooxidant reactions. In addition, melatonin acts as a potent antioxidant through enhancing activity of antioxidant enzymes [6]. It should be noted that not only enzyme activity, but also gene transcription of antioxidant enzymes such as manganese

superoxide dismutase (Mn-SOD), copper-zinc superoxide dismutase (Cu/Zn-SOD), glutathione peroxidase (GPx) and gamma-glutamyl cysteine synthetase (γ -GCS) were maintained by melatonin in brain of rat [4]. This continuing enhancement proposed a possible role of activation of melatonin receptors to modulate antioxidant enzymes regulation following stress signals [7]. Actually, there are some suggestions that melatonin-modified antioxidant enzymes expression following signal pathways of membrane, cytosolic and nuclear receptors [8].

4. The melatonergic antioxidative system (MAS) of the skin

It should be mentioned that synthesis of melatonin is not only confined to the pineal gland, but also extends to various other organs including the skin [4]. After exposure to UV, melatonin is metabolized in the skin and in turn causes production of antioxidant melatonin metabolites in human keratinocytes. This antioxidant cascade can be suggested for the skin, the same as in several described melatonin-related antioxidant cascades in chemical or other tissue homogenate systems [9]. This cascade has been defined as the melatonergic antioxidative system (MAS) of the skin (**Figure 2**) forming an important barrier organ and protecting it against UV-induced oxidative stress-mediated damaging events on the nuclear, subcellular, protein and cell morphology level [5]. Melatonin forms a defense mechanism against the multifaceted threats of environmental stress, especially UV, to which the skin is life-long exposed. Owing to its chemical structure, melatonin as well as its metabolites are strongly lipophilic, which renders them easily diffusible in every skin and cell compartment, therefore penetrating beyond the epidermis, namely to the dermis and the hair follicle [10]. When the skin is exposed to UV irradiation, the reactive hydroxyl radical is generated in the skin and reacts directly with melatonin [11]. The scavenging effect of melatonin to hydroxyl radicals causes decrease in the lipid peroxides, oxidation of protein and damage of mitochondrial DNA. Thus, the cascade of melatonergic antioxidative is significant in decreasing the free radicals emerging from radiation of UV and subsequently performs, a very hopeful strategy to keep the skin versus stressor factor of environmental condition as well as causative agent for aging of skin and promotion of tumor.

5. Anti-aging

Another functional importance of melatonin is its potency to enhance, augment or neutralize the negative effects that stress, drugs and infections have on the body's immune system. The decrease in melatonin secretion by age is so reliable that blood melatonin levels have been proposed as a measurement of biological age.

Melatonin is critical for the regulation of circadian and seasonal changes in various aspects of physiology and neuroendocrine functions [12]. The reduction in life span was detected in rats as a result of a pinealectomy [12], whereas prolongation in the life span occurs upon transfer of pineal gland grafting from young mice into thymus of old mice or into pinealectomized old mice which reveals the ability of melatonin to extend life span [12]. Analysis of available

data on the effect of melatonin on longevity supports its geroprotective effect. We believe that melatonin biosafety is important for the study of its long-term effects at different doses and in different strains and species (e.g., in rats). In adequately designed work (50 rats in each group), small doses of melatonin were supplemented at the night (2.5–3 mg/kg), slow the starting of age-associated disorders in function of estrous and elevated the animals survival. There are multiple evident on the melatonin suppressive effect on the growth of impulsive mammary carcinogenesis and that initiated in mice and rats as a results of chemicals and radiation [13–15], carcinogenesis induced in colon of rats by 1,2-dimethyl hydrazine [16], while, carcinogenesis induced in uterine cervix and vagina of mice by DMBA [16] and liver cancer induced in rats by N-nitrosodiethylamine [17]. In these cases, it was observed that melatonin exerted a positive effect in the treatment of advanced cancer patients [18]. Melatonin has a dual effect: it is potent geroprotector, suppressor of tumor growth in vivo and in vitro. There are no discrepancies between results of the carcinogenic and anticarcinogenic potential of melatonin since previous reports showed that other antioxidants, such as α -tocopherol has geroprotector and tumorigenic effects and could be powerful anticarcinogens as well. The data of melatonin supplementation to perimenopausal women are hopeful [19]. Simultaneously, there are actual results on the unfavorable impacts of melatonin [12] such as melatonin may produce infertility, damage of retina and hypothermia, it stimulates high blood pressure, diabetes, and cancer by suppressing sex drive in males. It was remark that melatonin may be harmful for people with cardiovascular risk factors and it should not be obtain by individuals who have immune-system or mental disorders, or by people administered steroids.

6. Melatonin as a protector against UV-induced skin aging

Because of its properties as wide antioxidant and scavenger of free radical, melatonin may act as a preventative factor against damage induced by UV in the skin [5]. Clinically melatonin is worthy to protect damage of sun when it is taken before irradiation of UV [20]. These effects of melatonin as a protective agent versus damage induced by UV have in vitro studies powerful support [20, 21]. Melatonin counteracting the formation of polyamine levels so it enhances cell viability in UV-irradiated fibroblasts, and malondialdehyde accumulation while inhibited apoptosis cells [21].

Regarding to Ryoo et al. [22] study in fibroblasts exposed to UV, only 56% of the cells survived (140 mJ/cm^2), while the survival rate of cells reached to 92.50% when preincubated with 1 nM melatonin which was paralleled with marked decrease in malondialdehyde and death of cells. Other experimental comparative study using fibroblasts treated by UV declared identical correlation in viability of cells using 100 nM melatonin [21]. Additionally, melatonin is considered as a powerful anti-apoptotic compound that inhibited caspase 9 and caspase 3 by suppresses mitochondria-dependent (intrinsic) apoptosis however, it does not inhibit receptor-dependent (extrinsic) pathway of apoptosis mediated by caspase 8 “[23]. UV irradiation is considered an immediate agent acted directly on skin, the oxidative stress resulting in all known successive, destruction events in the skin can distinctly, only be antagonized by antioxidants, melatonin which is already found at the target sites and at the same time of

exposure to UV ([23]. Besides, there is clear evidence that the preventive actions of melatonin against photobiological distraction are ameliorated by the powerful antioxidative characteristic of this compound. Photodamage, is tightly connected with UV-induced generation of ROS and it was shown that melatonin is a markedly powerful free radicals scavenger compared with vitamin C or Trolox, a vitamin E analog [21].

7. Anti-cancer, immunity and reproduction

Tumor growth is showed to be inhibited by melatonin. Melatonin may be of a great value in patients with untreatable metastatic cancer, especially in ameliorating their life quality. Several experiments showed that the levels of melatonin may be connected with risk of breast cancer. Some chemotherapy drugs used to treat breast cancer may be enhanced also by melatonin. Supplementation of melatonin reduces luteinizing hormone concentrations leading to inhibition of ovulation in humans. Further, melatonin administration may aid menopausal women by eliciting and sustaining sleep. Levels of melatonin may have a role in the anorexia symptoms. It was found that melatonin was used in seasonal affective disorder (SAD), due to the disorder is considered to be produced by melatonin release at an inadequate time [1].

Melatonin immunopharmacological activity has been indicated in different models. Melatonin treatment elevates antibodies production of sheep erythrocytes and immune response to primary immunization with T-dependent antigens [24]. Melatonin is involved in complicated relationships between the endocrine and nervous systems [25]. There are membrane receptors of melatonin on helper (Th). Melatonin receptors activation results to an elevate the production of Th1 cytokines, such as γ -interferon, interleukin-1, and opioid cytokines (interleukin-4 and dinorphine) [25]. At physiological concentrations of melatonin, it induces release of interleukins-1, -6 and -12 in monocytes of human. These mediators can protect stress-stimulated immunodepression maintaining mice from virus- and bacteria caused lethal diseases [25]. It is useful noticing that γ -interferon and colony-inducing factors (CSFs) can stimulate melatonin release in the pineal gland [25].

It is well accepted that melatonin is considered not only a hormone, but also protector for cells [26], implicated in modulation of immune system, processes of antioxidant and hematopoiesis [27]. Moreover, melatonin has a powerful oncostatic characters, through receptor-dependent and -independent mechanisms [28]. The melatonin receptors MT1 (encoded by *MTNR1A*) and MT2 (encoded by *MTNR1B*) are associated with the G-protein-coupled receptor (GPCR) group [26], and are mainly responsible for mediating melatonin downstream effects [29]. The antiproliferative effects melatonin may be due to melatonin-stimulated suppression in the uptake of linoleic acid [26]. Melatonin also demonstrated the probability to be used as adjuvant in therapies of cancer, through augmentation the effects of therapeutic drugs and decreased chemotherapies or radiation side effects [26].

Some studies recommended an inverse association between circadian melatonin level and breast cancer incidence. In addition, it was demonstrated high melatonin level up to ≤ 39.5 pg/mL in female showed high risk for breast cancer than females had high melatonin level > 39.5 pg/mL in a case-control study. Besides, in another five prospective case control,

an inverse relationship was demonstrated between risk of breast cancer and the highest levels of aMT6s in urine [30, 31]. In controversy, in case-control study declared that high aMT6s level in urine level was markedly linked with a low breast cancer risk [26]. However, it was demonstrated that, no confirmation was detected between level of melatonin and its association with risk of breast cancer in four case-control studies. Regardless of menopausal status, there is no statistically significant differences was detected in urinary aMT6s level between British women with breast cancer and healthy one in a prospective nested case-control [26]. In postmenopausal women, there was no suggestion that high melatonin levels in urine were inversely associated with risk of breast cancer [32]. In the study of Brown et al. [33], did not document an overall correlation between melatonin levels in urine and the onset risk of breast cancer [33]. Simultaneously, no markedly relation was detected between level of aMT6s and risk of breast cancer (either totally or by status of menopausal) [34].

In other types of cancer, it was found that, the men with low level of aMT6s in the urine below the median first morning connected with a four time increase in risk of in comparison with those with levels above the median. In addition, a case-control study showed that patients with high melatonin-sulfate levels or a high melatonin-sulfate/cortisol ratio were less likely to have prostate cancer or advanced stage prostate. It was found that the serum melatonin levels in women with ovarian cancer were significantly lower compared with control subjects ($p < 0.05$), demonstrating that decline in circulating melatonin level might contribute to the pathogenesis of ovarian cancer in a retrospective study [35].

It is worth mentioning that, the assessment melatonin levels are not equals, since concentrations of melatonin were determined in various sample as urine, plasma or serum. Also, the concentration of melatonin in human modifies with circadian rhythm; however, it has not been demonstrated which the best time for the sample collection could demonstrate the effects of melatonin. These variations might incorporate in the discrepancy of researches.

Research relating melatonin's effects on breast cancer is the serious, may be due to that melatonin has reported to attenuate various endocrine physiological biomarkers. Novel works showed that melatonin exhibited antiproliferative action against *in vitro* cell line of breast cancer [26], and suppressed mammary tumors development in rats [26]. Several melatonin mechanisms as anticancer were identified as it is apoptosis inducer [36], antiestrogenic effect through signaling pathway of ER α and decreased activity of aromatase enzyme [36], attenuation of receptors of melatonin [26], suppression on invasion [37] and angiogenesis [38].

Prostate cancer is the second most cancer type recorded and the fifth leading cause of cancer mortality in men [26]. It was found that melatonin at pharmacological concentrations could inhibit cell growth of both androgen-dependent and androgen-independent prostate cancer [26], through a range of mechanisms.

One of the leading causes of death among women with genital tract disorders is ovarian cancer [39]. Even though various surgical techniques and chemotherapies have been useful for treatment of ovarian carcinoma, the prognosis remains lacking [40]. In recent years, a few studies have reported the anticancer effect of melatonin on cancer of ovary.

Cervical cancer is considered the principle leading reason of female tumor worldwide, [41]. The melatonin effect on cervical cancer has been detected in insufficient works.

Visceral obesity is a risk factor of endometrial cancer, as it is associated with chronic inflammatory process [42]. Ciortea *et al.* [42] reported that the combinational treatment of melatonin and estrogen in ovariectomized rats was linked with lower body weight, less intra-retroperitoneal fat, reduction in endometrial proliferation, and less appearance of cellular atypia compared with estrogen replacement treatment. These results show that melatonin supplementation could be used in the prophylaxis of endometrial cancer in menopause women [42].

8. Oral cancer

Oral cancer is a common type of human head and neck cancers, and the majority of the cases involve oral squamous cell carcinoma [26]. In several *in vitro* studies, melatonin has shown remarkable effect on oral cancer.

It was reported that melatonin presented effect on oral cancer cell lines as an anti-metastatic action (HSC-3 and OECM-1), through modulation of expression and activity of MMP-9, which was occurred by decreasing acetylation of histone [26]. Also, melatonin could minimize SCC9 and SCC25 cell lines viabilities (both tongue carcinoma), and exhibit suppressive effect on the pro-metastatic *ROCK-1* gene expression and *HIF-1 α* pro-angiogenic genes as well as *VEGF* in SCC9 cell line [43]. Overall, inhibitory effect of melatonin was demonstrated on some oral cancer cells, and its mechanisms of action mainly involved inhibitory effect on metastasis and its related angiogenesis.

Cancer of liver is considered the common reason of death globally, and hepatocellular carcinoma (HCC) is contributed to the most common type of cancer (70–80%), occurrence in developing countries [44]. Treatment with surgery still remains the most pronounced way for HCC patients, however it is only occurs in a few cases, thus it is necessary to find efficient chemotherapeutic drug [45]. Hence, several studies pointed out to the effects of melatonin on hepatocellular carcinoma. Melatonin modulates the changes produced by N-nitrosodiethylamine-initiated cancer of liver and ameliorates biomarkers of liver enzymes (ALT, AST), levels of antioxidant, as well as the disturbance in circadian clock in mice [46, 47].

SO, melatonin exerts its anti-liver cancer effects mainly due to its anti- pro-apoptotic activity (via COX-2/PI3K/AKT pathway attenuation, modulates the ratio of Bcl-2/Bax, as well as it activates ER stress), anti-angiogenesis and anti-invasive effects.

Renal cancer is considered the third high cancer accounts for 3% with predominance of a male (3 male/1 female) [26].

Lung cancer is a principal cause of cancer-related death. For instance, lung cancer is the second most frequent type of cancer in males with approximately 17,330 new cases identified in 2016 in Brazil [26]. Non-small-cell lung cancer (NSCLC) is a main form of cancer of lung [26], and the literatures have suggested that the disturbance of rhythm of melatonin could elevate the incidence of NSCLC [26]. In different researches, melatonin due to mainly because melatonin showed to enhance the effects of it enhances radiotherapy and chemotherapeutic drugs.

Gastric cancer causes a mortality rate ranking second among malignant tumors worldwide one of the most frequent forms of cancer worldwide [26]. It was recorded that there were

951,600 new cases and 723,100 deaths from gastric cancer in 2012 worldwide [26]. Melatonin has been reported to inhibit gastric cancer through various mechanisms in numerous studies.

Pancreatic cancer is a highly fatal disease with a relatively low 5-year survival rate [48]. It responds poorly to radiotherapy and chemotherapy because the tumor cells are challenging to apoptosis [49].

Colorectal cancer is one of the major causes responsible for cancer death worldwide [26], and in several studies, melatonin recorded anticancer potency for various colorectal cancers. Overall, melatonin could be a new tempting therapeutic strategy for colorectal cancer, since it could regulate carcinogenesis, development, and progression of colorectal cancer. The underlying mechanisms involve multiple signaling pathways, including regulation of Ca MKII, ET-1, Nrf2 signaling pathways, and induction of aberrant crypt foci (ACF).

9. Effect of melatonin on gene expression

The presenting results on the melatonin genomic effect is rather few. In a study of cytogenecity, it was found that a decrease in the gene activity of ribosomes as a result of a pinealectomy in rats [12]. Menendez-Pelaez et al. [50] declared that melatonin treatment reduces mRNA level in the synthesis porphyrin, and 5- aminolevulinate synthase, in the Syrian hamsters Harderian glands. Melatonin declines mRNA levels of histone H4 and stopped age-attributed mRNA Bcl-2 reduction, in mice thymocytes [12]. Also, melatonin elevated some antioxidant enzymes mRNA (Mn-SOD, Cu,Zn-SOD) in Syrian hamsters Harderian gland [12]. Supplementation of melatonin produced significant enhancement in relative levels of mRNA for Mn-SOD, Cu,Zn-SOD and glutathione peroxidase in cerebral cortexes of rat [12]. Melatonin (1 nM) markedly modulates the mRNA of gonadotropin-releasing hormone. It was observed that melatonin regulate transforming growth factor- α gene expression level, macrophage-colony stimulating factor (M-CSF), tumor necrosis factor- α (TNF α) the stem cell factor in PEC, and interleukin-1 β , M-CSF, TNF α , interferon- γ , and the stem cell factor in splenocytes [12]. These results are appropriate with results that the SCN is the main site for the exogenous melatonin effect on the amplitude rhythm of the endogenous melatonin [51]. Medication with melatonin suppressed the development of mammary tumor and regulated *HER-2/neu* onco gene in transgenic *HER-2/neu* mice [52].

Marked melatonin effect was noticed on some oncogenesis- associated genes expression [12]. Further, myeloblastosis oncogene-like 1 (Mybl1) expression was adjusted by melatonin. On the other hand, melatonin showed a great effect on a large number of genes attributed to exchange of calcium, as cullins, Kcnn4 and Dcamk11, calmodulin, calbindin, Kcnn2 and Kcnn4. Meanwhile, cullin-1 expression in the heart of mouse is down regulated, that of cullin-5 is significantly upregulated, and cullins-2 and -3 expression are significantly not deformed. Six members of cullin family are included, and are implicated in ubiquinone-mediated protein destruction necessary for cell-cycle through the G1 and S phases. Nevertheless, cullin-1, but not other members of the cullin family, is responsible for cell proliferation and differentiation [53]. It is believe that melatonin may effect on expansion of tumor by intermediating with binding of calcium and preventing the MAPs/calmodulin and tubulin/calmodulin complexes formation to stop degradation of cytoskeletal [54]. Peutz-Jeghers syndrome, which is

associated with high risk of tumor development in multiple localizations is associated with at least one of these, Stk11 kinase with an unclear function, has anticarcinogenic effects and mutations [55]. Eventually, these data present undeviating evidence for the different effect of melatonin on the expression of different genes *in vivo*. Specific gene expression profiles are connected with the aging process in animals and humans [12]. Lund et al. [56] have detected a reduction in gene expression of heat shock protein while an elevation in the insulin-like genes expression, resulting in a decline in gene expression of insulin signaling during aging. Pletscher et al. [57], showed that down regulation of a large number of genes implicated in cell growth and maintenance following caloric restriction. Weindruch et al. [58], declared that in mice, the process of aging is describe by the high level of reactive oxygen species in both the skeletal muscle and brain, inhibition in the genes expression of biosynthetic enzyme and genes implicated in turnover of protein. Hence, caloric restriction stimulated genes are implicated in the metabolism of fatty acid, glycolysis, and gluconeogenesis. Presented results on the melatonin effects on gene expression, mainly genes of mitochondria, suggest that some of them may be accountable for the hormone capacity to block disorders resulting from aging. Further studies are need in this direction.

10. Melatonin and reproduction

Pattern of melatonin secretion, mediated by photoperiod, directly affect reproductive function which was recorded in several evidence-based researches. The daily light/dark (LD) cycle is considered the main physiological melatonin role, so, the variation in the duration of signal of melatonin occurs in attribution to the night length. The variation in melatonin signal duration is used to synchronize neuroendocrine rhythms with the annual variation in day-length in seasonal mammals. In addition, fetal and newborn animals use the maternal signal of melatonin to entrain endogenous circadian rhythms before direct photic information is presented. It was found that, very marked effect for exogenous melatonin was detected in modulating reproductive function in different organisms, depending on the animal age, melatonin supplementation time [59].

The data presented above exhibited that the antigonadal effects of melatonin in humans are apparently much less significant than in some seasonally breeding mammalian species. This is due to humans are not 'seasonally breeding'. Recently, accumulated evidences declared the efficacy of melatonin in attenuation the reproductive function in human. The suppressive effect of melatonin at the level of CNS have decreased daring growth. During development of human, such suppressive action of melatonin on GnRH function gradually reduced due to a down regulation in the functional of melatonin receptors expression. In other adult rodents, melatonin does not have noticeable action on the functioning of pituitary, whereas the association between the release of melatonin release and the functions of hypothalamic, involving the release of GnRH, are right. These actions are markedly significant in coinciding the external photoperiods and functions of reproduction through well not characterized mechanisms. The circadian rhythm regulated genes are considered seriously players in regulation of gene throughout different organism, especially for regulatory genes of cell-cycle and apoptotic genes. Melatonin may have also ameliorating effectiveness against human disorders attributed to reproductive function. Such as illumination intensity during the night

actually decreases circulating levels of melatonin and reconstruct the suprachiasmatic nuclei circadian pacemaker, leading to the elevation in risk of breast cancer, which may be due to down-regulating gonadal synthesis of steroids, by acting on receptor sites within the neuro-endocrine reproductive axis or altered estrogen receptor function [59]. Consequently, in the right circumstances, melatonin may be quite beneficial for reproductive health.

11. Dopamine and psychosis

Disorder in the system of dopamine has also been noticeably associated with psychosis and schizophrenia. Dopamine proceeds in the frontal lobe and regulating the information coming in from other parts of the brain. Normalization in the dopamine flow may produce interrupted or discontinuous cogitation as in schizophrenia. Schizophrenia is described by both 'positive' (additional experience and behavior) and 'negative symptoms' (lack in experience or behavior). Symptoms of positive response are classifying under the psychosis term and identically involve disorders of illusions, deliriums, and intellect. Symptoms of negative response may involve unsuitable emotional manifestation, lack of speech and stimulus. Some drugs, as cocaine, prevent dopamine return into the brain, coherently, dopamine buildup in the synapse, producing drug-initiated psychosis or schizophrenia [1].

12. Contraindications, interactions, precautions and side effects

Melatonin can produce sleepiness if given during the day. Additional, side effects that have been documented upon melatonin supplementation including cramps of stomach, vertigo, a continuous pain in the head, touchiness, moodiness, reduced sexual desire, enlargement of breast in the men and reduction in the count of sperm.

So, melatonin should not take during operating machine or drive. Further, melatonin could interrupt with human fertility and also melatonin should be not used for pregnant or nursing women. Utilization of melatonin by person who already have an augmentation level of melatonin as children, teenagers, pregnant and lactating women can result in melatonin overdose. MAOI drugs inhibit melatonin breakdown from the body, so people should not take melatonin with these drugs to prevent melatonin overdose.

Melatonin causes drug-drug interaction with antidepressants, such as Prozac (inhibitor of serotonin) or Nardil (inhibitor of monoamine oxidase). Melatonin Interaction with these kinds of drugs can produce heart attack, confusion, sweating, shaking, and fever, lack of coordination, elevated blood pressure, diarrhea, and convulsions [1].

13. Discussion and conclusion

Melatonin is considered as a potent geroprotector, anticarcinogen, and inhibitor of tumor growth *in vivo* and *in vitro*, and in some models it may induce tumors and promote tumor growth. An important mechanism of melatonin is its impact on hemopoiesis involves the

stimulation of melatonin on opioid receptors of bone marrow. Hence, we confirm further experimental studies and clinical trials which are necessary to estimate both the effectiveness and the safety for humans. Some antioxidants, including natural ones (e.g., α -tocopherol), have both geroprotector and tumorigenic potential and could be potent anticarcinogens as well. The results of administration of melatonin to perimenopausal women are promising. There are no contradictions between data on the carcinogenic and anticarcinogenic potential of melatonin but there are real data on the adverse effects of melatonin. Melatonin might own some ameliorating actions on human disorders that are contributed to the reproductive function. Such as lighting intensity during the night decreased the levels of circulating melatonin resulting in high risk of breast cancer [60]. Therefore, in the optimum condition, melatonin may have significant beneficial reproductive effects.

Epidemiological studies concerning the association between body circadian melatonin levels and cancer incidence led to controversial results, which were either significant association or no association at all. The effects of melatonin on cancers have been investigated, with a focus on hormone-dependent cancers. Different experimental works have suggested the ameliorative effect of melatonin in numerous types of metastatic tumors, including breast, ovarian, prostate, oral, gastric, and colorectal cancers. The mechanisms contributed with this improvement role of melatonin include various pathways of molecular origin, which are implicated with the activity of antioxidant enzymes, attenuation of MT1 and MT2 melatonin receptors, apoptosis regulation, metabolism of tumor, angiogenesis inhibition, invasion and metastasis, and initiation of epigenetic alteration. In different clinical trials, melatonin exhibited the capability to augment the treatment effect of chemotherapeutic drugs, and might help in enhancing the cancer patient's life quality. Collectively, melatonin is considered a promising hormone for cancers prevention and treatment. So, it could be concluded that extensive future work may be occur which involves the effect of melatonin on autophagy and mitophagy, other mechanisms of molecular origin implicated in its anticancer effect. Melatonin improves also chemotherapeutic drugs, which should be further determined on a large scale of drugs. The oncostatic effects of melatonin on some type of cancers, dosage and safety of long-term supplementation of melatonin must be also further elucidated.

Conflict of interest

The authors declared no conflict of interest.

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