Role of Melatonin in Cancer Treatment

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Abstract

Melatonin is a methoxyindole synthesized and secreted principally by the pineal gland at night under normal environmental conditions. The endogenous rhythm of secretion is generated by the suprachiasmatic nuclei and entrained to the light/dark cycle. The primary physiological function of melatonin, whose secretion adjusts tonight length, is to convey information concerning the daily cycle of light and darkness to body physiology. It is secreted during darkness and plays a key role in various physiological responses, including regulation of circadian rhythms, sleep homeostasis, retinal neuromodulation and vasomotor responses. Melatonin also enhances the antioxidant potential of the cell by stimulating the synthesis of antioxidant enzymes, including superoxide dismutase, glutathione peroxidase and glutathione reductase, and by augmenting glutathione levels. Melatonin plays a role in mammary cancer by down-regulating some of the pituitary and gonadal hormones that control mammary gland development and which are also responsible for the growth of hormone-dependent mammary tumors. Furthermore, melatonin could act directly on tumoral cells, as a naturally occurring antiestrogen, thereby influencing their proliferative rate.

Key words: Melatonin; Mammary cancer; pineal gland; suprachiasmatic nuclei

Introduction

Melatonin is an indolic hormone mainly secreted by the pineal gland. Secondary sources are retina, gut, skin, platelets, bone marrow and probably other structures, whose systemic contribution is insignificant. This aspect and the fact that it lightens the frog skin by contracting melanophores led to the naming of this molecule as Melatonin [10]. One of the most striking characteristics of this hormone is that it is secreted only during the night, or more exactly, in darkness. Consequently, the melatonin concentration in plasma is low during the day (in the light) and reaches a peak value of about 1 NM during the night (in darkness) [45].

Melatonin or N-acetyl-5-methoxytryptamine is the hormone secreted mainly by the pineal gland, which is under the control of the central nervous system via the suprachiasmatic nucleus (SCN) of the hypothalamus. Since the pineal gland is active only in darkness, the levels of melatonin in the pineal gland and in the blood are high at night and low during the day [2]. The biosynthesis and metabolism of melatonin has recently been extensively reviewed [22]. Tryptophan is converted to serotonin and finally converted to melatonin, which is an Indole. Melatonin is metabolized to 6-hydroxyl-mel in the liver and the main metabolite excreted is 6- sulphatoxy-mel and this excretion urinary component is helpful in assessing pineal gland function especially in children [50].

Two types of membrane receptors have been identified in mammals: melatonin receptor type1 (MT1 in rodents or MTNR1A in humans) and type 2 (MT2 in rodents or MTNR1B in humans); they belong to the family of G-protein- coupled receptors and are increased in type 2 diabetic patients [34]. Type 1 and 2 are both involved in sleep physiology. Both the MT1 and MT2 type of receptors are linked to the inhibition of adenylyl-cyclase and subsequent decrease of cyclic AMP. The two receptors are described in almost all structures of the CNS, although the highest density is found in the hypothalamic suprachiasmatic nucleus (SCN) and the pars tuberalis of the pituitary. This distribution explains the action of melatonin as a chronobiotic as well as its modulatory effects on the neuroendocrine reproductive axis [18]. Regarding the effect of melatonin in inducing synchronization of circadian rhythms, which is generally regarded as a sleep-promoting effect, melatonin administration lowers deep body temperatures not only in those with rhythm disorders but also in healthy individuals, from children to elderly people; shortens the time required to fall asleep; and improves sleep. Melatonin has an antioxidative effect [41].

The first mechanism of this effect is to function as a free-radical scavenging antioxidant that removes hydroxy radicals (HO•), peroxyl radicals and in addition extremely highly toxic peroxynitrite. Melatonin also inhibits lipid peroxidation and blocks the production of isoprostanes [52]. The second mechanism of action is to activate endogenous enzymes that scavenge free-radicals. Administration of melatonin to pregnant rats increased the activities of superoxide dismutase (SOD) or glutathione peroxidase in fetal brain tissues [32]. Melatonin has its

own antioxidative effect and also intensifies the activity of endogenous antioxidative enzymes, which together exert a powerful antioxidative effect [51]. Melatonin thus has a variety of activities. In a rat model, melatonin inhibited age-related visceral adiposity [35].

Melatonin is a ubiquitous natural neurotransmitter involved in numerous aspects of biological and physiological regulation of body functions. The role of endogenous melatonin in circulation rhythm disturbances and sleep disorders is well established. Melatonin has been shown to modify immunity, the stress response, reproductive physiology and also certain aspects of the aging process. The oncostatic properties of melatonin could be explained in a variety of ways based on the different known actions of the indoleamine. Thus, the antitumor actions of melatonin may be considered: (i) as indirect effects derived from its interaction with the neuroendocrine reproductive axis leading to a down-regulation of some of the hormones influencing tumor growth, especially gonadal estrogens; (ii) as a consequence of its interaction with estrogen receptors (ER) on the epithelial mammary cells in a similar way as classic antiestrogens act; (iii) dependent on its immuno-enhancing effects (iv) as a consequence of its antioxidant properties or (v) derived from its inhibitory effects on telomerase activity in tumor cells [45]. Here, we review different scientific literatures to asses its synthesis and role of melatonin interaction with other neuro-endocrine hormones in mammary cancer.

Melatonin: Synthesis, Secretion and Function

Synthesis of Melatonin

Melatonin is synthesized from tryptophan taken up from the circulation and transformed into serotonin; serotonin is converted into melatonin by a two-step process involving the sequential activities of two enzymes, serotonin-N-acetyl transferase (NAT), which is the limiting enzyme for the synthesis of melatonin, and hydroxyindole-O-methyl transferase (HIOMT) [28]. The synthesis of melatonin is initiated by the binding of norepinephrine to adrenergic b1 receptors, subsequent activation of pineal adenylate cyclase, increase in cyclic AMP (cAMP) and de novo synthesis of NAT or of its activator. The cAMP-induced gene transcription repressor (ICER), an isoform of the cAMP responsive element modulator (CREM), is activated in conjunction with NAT and represents a mechanism that limits the nocturnal production of melatonin [49]. Also, melatonin synthesis depends upon tryptophan availability because it is reduced after acute tryptophan depletion; other nutritional factors could influence melatonin synthesis, for example folate status and vitamin B6, a coenzyme in tryptophan decarboxylation which is able to stimulate melatonin production in prepubertal children but not in adults. Also, fluvoxamine, an inhibitor of serotonin uptake, increases the amplitude and duration of the plasma melatonin peak [10].

Light information received by the retina passes primarily through the retino-hypothalamic pathway and is transmitted to the suprachiasmatic nucleus (SCN), where a circadian clock exists, thus enabling synchronization of the phases of the circadian clock with the light/dark cycle (over a 24-hour cycle) of the outside world. The time information at the SCN passes through a new nerve to reach the superior cervical ganglion and is then transmitted to the pineal gland. The time information at the SCN passes through a new nerve to reach the superior cervical ganglion and is then transmitted to the pineal gland. This pathway is actually activated during the night without light stimuli, as the nervous activities of the superior cervical ganglion are inhibited by light stimulation. Noradrenaline is secreted by nerve terminals derived from the superior cervical ganglion and stimulates the pineal cells, primarily via β-receptors, thereby accelerating the synthesis of cAMP, the second messenger, to activate arylalkylamine N-acetyltransferase activity (AANAT), a rate-limiting enzyme of melatonin synthesis. During the daytime, AANAT is only weakly activated [51].

Secretion of Melatonin

Melatonin displays high lipid and water solubility, which facilitates the passage across cell membranes [33]. Melatonin levels in the pineal gland and blood show a circadian variation, being high during the nighttime and low during the daytime. In human beings, melatonin secretion is highest at the age of 1 to 3 years, starts to decrease from puberty onwards, and reduces to 1/10 of the peak value at age 70 years or older. The circadian rhythm of melatonin secretion is noted not only in blood but also in almost every type of bodily fluid, including cerebrospinal fluid, saliva, aqueous humor of the anterior chamber, follicular fluid, and breast milk. Melatonin receptors are distributed over a variety of tissues and organs, and accordingly, the time information based on melatonin concentration is transmitted to tissues throughout the entire body. The presence of melatonin receptors has so far been confirmed in the brain (including the SCN), spinal cord, pituitary gland, retina, spleen, thymus, adrenal gland, liver, kidney, heart, lungs, testes, ovaries, blood vessels, lymphocytes, and osteoblasts [24]. It is therefore assumed that in addition to the melatonin-related synchronization of the circadian clock in the SCN, synchronization with sleep phase may occur at the entire body level, bringing better rest of the body [51].

In patients suffering from breast, endometrial or colorectal cancer melatonin secretion is impaired. The increased incidence of breast and colorectal cancer observed in nurses and other night-shift workers suggests a possible correlation between the reduced melatonin secretion and their increased light exposure at night [15].

The physiological surge of melatonin at night is thus considered a ‘‘natural restraint’’ on tumor initiation, promotion and progression [39].

Functions of Melatonin

The main function of melatonin is to synchronize the circadian rhythm, which means the pineal hormone melatonin actually acts as a neuroendocrine transducer of the light–dark cycle [10]. Based on its action, melatonin has been tested as a treatment for a wide range of sleep disorders, including jet lag, shift-work, primary insomnia, sleep-wake cycle disruption as well as sleep problems in both children and the elderly suffering from neuro developmental disorders [25]. The relationship between melatonin and sleep was initially investigated after registering in humans a higher level of circulating melatonin at night; furthermore, it was also noticed that the highest urinary 6-sulphatoxymelatonin excretion was actually coinciding with the highest nocturnal sleepiness. In addition it has to be mentioned that, at physiologic doses, melatonin also induces sleep onset and maintenance, decreases sleep latency, improves sleep efficiency and overall increases the total sleep time [54].

Melatonin seems also to be successful in the treatment of some aging-associated processes, such as disturbances of sleep/wake rhythm, since the endogenous production of indoleamine actually decreases with age. Melatonin is mostly known as a circadian hormone, although it also prescribed as its sedative, anxiolytic, analgesic, antihypertensive, non-inflammatory, and oncostatic effects [38, 40]. In particular, melatonin seems to produce a possible antidepressant effect probably due to the action it performs on the central circadian regulation and also to improve cognitive functions [19].

Anti oxidative effects of Melatonin

Melatonin seems to function via a number of means to reduce oxidative stress [41]. Melatonin has an antioxidative effect. The first mechanism of this effect is to function as a free-radical scavenging antioxidant that removes hydroxy radicals (HO•), peroxyl radicals, and in addition extremely highly toxic peroxynitrite. Melatonin also inhibits lipid peroxidation and blocks the production of isoprostanes [51]. It is also a potent free radical scavenger, more potent than vitamin E. Melatonin directly scavenges the highly toxic hydroxyl radical and other oxygen centered radicals. Also, melatonin displays antioxidative properties: it increases the levels of several antioxidative enzymes, including superoxide dismutase, glutathione peroxidase and glutathione reductase. On the other hand, melatonin inhibits the pro-oxidative enzyme nitric oxide synthase ([10].

Melatonin acts indirectly at the level of the mitochondria. Since mitochondria are a major source of free radicals and as a consequence, these subcellular organelles are exposed to extensive oxidative abuse [40]. That melatonin has important actions at the level of mitochondria is suggested by a number of observations: a), melatonin is an efficient scavenger of ROS/RNS which are abundantly produced in mitochondria; b) although mitochondria are incapable of GSH synthesis (they take it up from the cytosol), they do possess GPx and GRd for GSH cycling, both enzymes of which are stimulated by melatonin; c) melatonin has been shown to have antiapoptotic effects, with the apoptotic signals originating in mitochondria; d) melatonin may be in higher concentrations in mitochondria than elsewhere in the cell and higher than serum concentrations of melatonin [1].

Oncostatic Properties of Melatonin

The role of the ovarian estrogens in mammary cancer has been known since 1896 when Beatson demonstrated that ovariectomy inhibited the growth of breast tumors [6]. However, immuno-enhancing properties of melatonin have been also considered as an explanation for its antitumor actions. It is well known that estrogens modulate immune function and that high concentrations of estrogens suppress cell-mediated immune responses. Thus, the antiestrogenic action of melatonin could be linked to its immuno-enhancing effects. Finally, the inhibitory effect of melatonin on telomerase activity in MCF-7 human breast cancer cells has been considered as the basis for its antitumor action, but also in this case, the antiestrogenic effects of melatonin could be the link to its effects on telomerase, as recently it has been demonstrated that estrogens possess the ability to up-regulate telomerase activity [26].

Through downregulating the gonadal synthesis of estrogens

In seasonally breeding mammalian species, melatonin controls reproductive function through the activation of receptor sites within the hypothalamic-pituitary areas driving the gonadal activity, and melatonin down-regulation of the ovarian estrogen secretion has been observed in a variety of mammals [45]. Melatonin down-regulation of the ovarian estrogen secretion has been observed in a variety of mammals [37].

Cohen et al studied that impaired pineal secretion (hyposecretion of melatonin) results in unopposed estrogen secretion and an increased susceptibility to breast cancer, they concluded that melatonin, by suppression of estrogen secretion, or by direct inhibitory effects on breast tissue, might suppress induction of breast cancer [11]. In humans, the role of melatonin in ovarian function is still poorly understood, and most evidence of melatonin-gonadal hormone relationship came from the finding of abnormal melatonin secretion in disorders of

the reproductive system or, conversely, from alterations of melatonin secretion associated with gonadal dysfunctions [29].

There is an inverse seasonal relationship between melatonin and estradiol (E2) serum concentrations and significantly increased levels of E2 can be found in women exposed to light-at-night, which suppresses melatonin production [46]. Human granulose-luteal cells expresses the two forms of melatonin receptors and, in these cells, melatonin modulates the expression of LH and GnRH receptors. In vitro, melatonin reduces the LH- and FSH-induced secretion of E2 from cultured human granulose cells [7]. Furthermore, direct modulatory effects of melatonin on ovarian steroidogenesis have been demonstrated in human granulosa- luteal cells as well as the presence of functional melatonin receptors in cells of antral follicles and corpora lutea of rat ovaries [48].

Human follicular fluid has melatonin concentrations higher than serum resulting not from a local synthesis, but from an active uptake and local concentration. The melatonin concentration is higher in preovulatory follicles than in the small immature ones [31]. In short, the experimental data available up to date, with the reserves concerning those of humans, support a modulatory effect of melatonin on ovarian function, and this could be one of the explanations of the protective role of melatonin on the etiology of estrogen-dependent breast cancer.

Melatonin as selective estrogen receptor modulators (SERMs)

Melatonin, the main pineal product, may counteract the effects of estrogens at the level of the tumor. However, it was from in vitro studies, carried out basically with the estrogen-sensitive MCF-7 human breast cancer cells, that the direct antiestrogenic effects of melatonin were established. Melatonin, at concentrations similar to those found in serum of most mammals during the nocturnal period (1 nM), counteracts E2-induced MCF-7 cell proliferation and invasiveness augments the sensitivity of MCF-7 to antiestrogens such as tamoxifen and down-regulates the expression of proteins, growth factors, and proto-oncogens regulated by estrogens [30]. The mechanism involved in the antiestrogenic actions of melatonin is still being studied. Unlike the classic antiestrogens such as tamoxifen and its derivatives, melatonin neither binds to the ER nor interferes with the binding of estrogens to its receptor.

What melatonin seems to do is to decrease the expression of ERα and to inhibit the binding of the E2-ER complex to the estrogen response element (ERE) on DNA [36]. These effects have been shown to be dependent on melatonin binding to specific melatonin (MT1) membrane receptors and the overexpression of these receptors in MCF-7 cells enhances the response of these cells to the antiestrogenic effects of melatonin [12]. The MT1 receptors have also been found in human breast tissue, both normal and tumoral [16].

Thus, melatonin behaves as an antiestrogen which does not bind to the ER, but to its own membrane receptors, and via this binding to its specific receptors it is able to interact with the ER-signaling pathway. Calmodulin (CaM) has been proposed as the possible link for melatonin-E2–ER interaction as it is stated in figure 3 below. This hypothesis is based on two facts: one, that the association of CaM with the E2-ER complex facilitates its binding to an ERE, thus suggesting a role for CaM as a modulator of the transcriptional activity of the ER; the second fact is that melatonin is able to bind to Ca++/CaM and to inactivate the complex [14]. Only ERα, but not ERβ, interacts with CaM stimulating the phosphorylation of the receptor, thus facilitating the binding of estrogen as well as that of the E2-ER complex to the ERE [20].

Another possible interplay between melatonin and the ER could be the cAMP (Figure 4). The ERα may be activated by elevated intracellular concentrations of cAMP [3]. The ER alpha may be activated by elevated intracellular concentrations of cAMP. In MCF-7 cells, estrogens activate adenylate cyclase increasing intracellular cAMP by a nontranscriptional mechanism which involves steroid-induced modulation of cytoplasmic or cell membrane-bound regulatory proteins (nongenomic actions). The cAMP synergizes with the genomic actions of steroids as it enhances ER-mediated transcription [4]. Alternatively, melatonin, working through the membrane-bound Gi protein-coupled MT1 receptor, inhibits adenylate cyclase activity and decreases cAMP [21]. A melatonin-induced reduction in cAMP could be a mechanism by which the indoleamine decreases E2-induced ERα transcriptional activity. In this sense, it has been demonstrated that melatonin inhibits forskolin-induced and E2-induced elevation of cAMP in MCF-7 cells and inhibits ERα gene transcription [27]. Furthermore, in murine mammary tissue, melatonin decreases cAMP and increases cGMP in a dose- and time-dependent way [9].

Melatonin as a selective estrogen enzyme modulator (SEEMs)

The high incidence of hormone-dependent breast cancer in postmenopausal women suggests an important role of extragonadal steroids on mammary carcinogenesis [42]. The local estrogen synthesis in normal and neoplastic breast tissue depends on the aromatization of androgens by the activity of enzymes of the aromatase complex. The aromatase activity in breast cancer tissue has been demonstrated to be higher than in non-malignant breast tissue or tissue distal to tumors, thus leading to the hypothesis that an increased production of estrogens within breast tumors may exert a biological effect and thereby stimulate tumor growth [47]. These are the reasons for the interest in developing drugs able to interfere with the synthesis of steroid hormones by inhibiting the

enzymes controlling the interconversion from androgenic precursors, the so-called selective estrogen enzyme modulators (SEEMs) [5].

Recently, studies demonstrated by using MCF-7 human breast cancer cells in culture, which express aromatase and the MT1 melatonin receptor that melatonin, at physiological concentrations, reduce aromatase activity in these cells both under basal conditions and when aromatase activity is stimulated by cAMP or cortisol [13] shown on figure 5 below.

In adipose tissue of tumor-bearing breasts as well as in MCF-7 human cancer cells, expression of the CYP19 gene, which encodes aromatase P450, the enzyme responsible for estrogen biosynthesis, is regulated by two proximal promoters, namely, I.3 and II [8]. These promoters respond to cAMP, which plays an important role in the positive regulation of the expression of aromatase in breast cancer cells. Consequently, any agent that modulates intracellular levels of cAMP could also influence the aromatase expression in breast cancer cells. This is the case with prostaglandin E2, which increases intracellular cAMP levels and stimulates aromatase and estrogen biosynthesis [53]. Thus, in breast cancer cells, but not in normal epithelial cells with different CYP19 promoters, estrogens may induce, through a paracrine loop, the local biosynthesis of estrogens via the increase of the cAMP and expression of aromatase. Recently it has demonstrated that by using MCF-7 cells, which express aromatase and MT1 melatonin receptors that melatonin, at physiological concentrations, reduces aromatase activity in these cells both under basal conditions and when aromatase activity is stimulated by cAMP or cortisol. Furthermore, melatonin in MCF-7 cells down-regulates aromatase expression at the transcriptional level by reverse transcriptase polymerase chain reaction [43].

Conclusion

Now-a-days pineal gland is small only structurally but functionally it is most important gland releasing a versatile functioning hormone Melatonin [17]. Despite the effect of melatonin as an antioxidant a number of reports documented under an almost unlimited number of conditions, many of which have direct clinical relevance. Thus, melatonin has been shown to reduce the toxicity of drugs and in some cases improve their efficacy, to reduce the severity and degree of tissue damage following ischemia/reperfusion in the brain and other organs, to prevent degenerative changes in the CNS in models of Alzheimer's and Parkinson's disease, to reduce free radical damage to DNA which may lead to cancer [40]. Melatonin is a neurohormone with different actions which include the down-regulation of the circulating levels of gonadal estrogens. Simultaneously, melatonin works as an antiestrogen with mechanisms of action different (and probably complementary) to those of the commercially available anti-estrogens and inhibits aromatase expression in human breast cancer cells. These properties, collectively, make melatonin an interesting anticancer drug in the prevention and treatment of estrogen-dependent tumors, as it has the advantage of acting at different levels of the estrogen-signaling pathways [44].

Abbreviations

AANAT- Arylalkylamine N- acetyltransferase; CaM- Calmodulin; cAMP- Cyclic adenosine mono- phosphate; cGMP- Cyclic guanosine mono-phosphate; CNS- Central nervous system; CREM- cAMP responsive element modulator; DNA- Deoxy ribonucleic acid, ER- Estrogen receptor; ERα- Estrogen receptor alpha; ERβ- Estrogen receptor beta; E2- estradiol, ERE- Estrogen response element; FSH- Follicular stimulating hormone; GnRH- Gonadotropin releasing hormone; HIOMT- Hydroxyindole-O-methyl transferase, ICER- cAMP-induced gene transcription repressor; LH- Luetinizing hormone; MT1- Melatonin receptor type-1; MT2- Melatonin receptor type-2; NAT- N-acetyl transferase; SCN- Suprachiasmatic nucleus; SEEMs- Selective estrogen enzyme modulators; SERMs- Selective estrogen receptors modulators; SOD- Superoxide dismutase.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Yared Godefa Debeb proceeded with the literature review and drafted the paper and Birhane Alem Berihu providing guidance, critical assessment and peer review of the writing. All authors have given their final approval of this version to be published. All authors read and approved the final manuscript.

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