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REVIEW ARTICLE: BREAST CANCER AND MELATONIN

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ABSTRACT
Breast cancer is one of the most frequently occurring cancers among women and one of the leading causes of death among women aged 40 to 55 years. Chemoprevention is one such strategy that involves administration of drugs to prevent, suppress, or reverse the carcinogenesis process. In breast cancer management, chemoprevention is aimed at preventing mammary cancer progression to invasive cancer. In a breast cancer prevention trial using tamoxifen, its use resulted in a 49% reduction in the incidence of estrogen receptor (ER)– positive breast cancers in high-risk women. Pineal gland and melatonin are likely to play an important role in the pathogenesis of breast cancer. Decrease in pineal function, whatever its cause, and the consequent reduction in melatonin secretion could induce a state of relative hyperestrogenism, thus leading to a prolonged exposure of breast tissue to estrogens and eventually ending in cancer induction.

KEYWORDS: Breast cancer, Estrogen, Indoleamine, Melatonin, Progesterone.

INTRODUCTION
In 1978, the seminal paper of Cohen et al.[1] first proposed that the pineal gland and melatonin are likely to play an important role in the pathogenesis of breast cancer who hypothesized that decreases in melatonin secretion could cause hyperestrogenism, which in turn promotes breast carcinogenesis. Supporting this hypothesis, an inverse relationship between melatonin and estrogen is seen in vivo[2,3] and in breast cancer where low nocturnal serum melatonin concentrations and urinary 6-sulfatoxymelatonin (urinary metabolite of melatonin) levels are found in women with ER-positive breast cancer patients.[4,5] Many factors, including hormonal environment, age, dietary and alcohol consumption, or cigarette smoking, have all been hypothesized as contributors to the development of breast cancer.[6] However, a major consequence of a modern lifestyle is the disruption of circadian rhythms, a condition that leads to several pathological conditions, including sleep disturbances and depression.[7]

Melatonin Effects on Breast Cancer: In Vitro Studies
Inhibition of Breast Cancer Cell Growth- The melatonin's attributed anticancer effects have often derived from in vitro studies carried out on estrogen-responsive human breast cancer cell lines. The first in vitro experiments on MCF-7 cells demonstrated that melatonin, even at physiological concentrations, directly suppressed cancer cell growth.[8,9] Melatonin appears to exert an inhibitory effect by causing an accumulation of cells in the G0/G1 phase of the cell cycle[10] or, otherwise, by delaying the progression of MCF-7 cells from the G1 phase to the S phase of the cell cycle[11,12], allowing the cells to achieve greater differentiation. A similar pattern was observed for other estrogen-sensitive cancer cell lines (T47D and ZR75-1).[13-15] Growth inhibition is accompanied by a significant decrease in DNA content and thymidine incorporation.[16,17] These effects seem to be related to both cancer cell characteristics and culture conditions.

Melatonin and Estrogen Receptors
Melatonin significantly inhibits cell growth only in breast cancer cells expressing estrogen receptors (ERα).[18,19] Melatonin does not inhibit the proliferation of MDA-MB-231, MDA-MB-330, or BT-20 ERα-negative human breast tumor cells lines. However, the indoleamine has been demonstrated to inhibit growth proliferation on ERα-negative breast cancer and progesterone receptornegative human breast tumor xenographs in nude rats.[20] Moreover, a significant oncostatic action has been observed in ER-negative, nonbreast tumors treated with melatonin.[21] These data suggest that some non-ER–mediated effects are likely to be elicited by the complex interplay between melatonin and living cells. Furthermore, it has been shown that the effects of the indoleamine are mainly mediated by the interaction with a specific membrane-bound melatonin

receptor. Furthermore, it has been shown that the effects of the indoleamine are mainly mediated by the interaction with a specific membrane-bound melatonin receptor. Several reports have demonstrated that melatonin can bind and activate the G protein–coupled membrane melatonin receptors 1 (MT1) and 2 (MT2) in a variety of tissues.[22] The oncostatic effects of melatonin on ER-positive breast cancer cells seem to be strictly dependent on the presence of the MT1, which has been found in both normal and cancerous tissues. The MT1 receptor is differentially expressed in ERα-positive and ERα-negative breast cancer cells, with the higher MT1 levels found in the former cell lines.[23] The MT1 receptor couple with different Gαi proteins in multiple cell types, while also coupling with the Gq and G11 proteins in other cell types.[22,24] Selective MT1 antagonists (as luzindole) suppress melatonin-induced anticancer effects.[25,26] On the other hand, overexpression of MT1 receptor in MCF-7 cells significantly enhances the response of these cells to the growth inhibitory actions of melatonin, both in vitro and in vivo.[27,28] Similar results have been observed when treating MCF-7 cells with valproic acid, a MT1 receptor inducer.[29] Moreover, melatonin sensitivity of different MCF-7 strains is greatly dependent on MT1 expression.[30] MT2 receptor seems not to be involved in oncostatic effects triggered by melatonin, keeping in mind that MT2 activation has little influence in mediating the antiproliferative effects of melatonin on breast tumors.[31] Recent findings demonstrated that the MT1 receptor colocalizes with the Cav-1 antibody, indicating the MT1 receptor can also reside in the caveoli, a key membrane signaling platform.[32] MT1 and MT2 receptors are G-protein–coupled receptors, which are expressed in various parts of the central nervous system and in peripheral organs (blood vessels, mammary gland, gastrointestinal tract, liver, kidney and bladder, ovary, testis, prostate, skin, and the immune system). Melatonin receptors mediate a plethora of intracellular effects depending on the cellular milieu. These effects include changes in intracellular cyclic nucleotides (cAMP and cGMP) and calcium levels, activation of certain protein kinase C subtypes, intracellular localization of steroid hormone receptors, and regulation of G protein signaling proteins.[33] MT1 expression is regulated by both melatonin and estradiol, as first documented in experiments performed on cells of the pars tuberalis.[34] The steady-state level of MT1 mRNA is significantly enhanced in MCF-7 cells cultured in estradiol-depleted medium. In cancer cells cultured in the presence of fetal bovine serum (FBS), the MT1 receptor steady-state mRNA level is suppressed by the addition of estradiol (1 nM) or significantly diminished by the addition of melatonin, confirming the ability of melatonin to down-regulate the levels of its own receptor, at least at the steady-state mRNA levels.[31,35] Estradiol-induced down-regulation of MT1 receptor could explain some contradictory results, i.e., the lack of melatonin inhibition of estradiol-induced proliferation of breast cancer cells.[36] Although removal of estradiol from the culture media up-regulates MT1 levels, several reports were unable to demonstrate an enhanced growth inhibitory response to melatonin in MCF-7 cells growing in estradiol-deficient media, as the overall growth of those cells is generally slowed in the absence of estradiol.[36] These results imply that a number of other hormones, cytokines, or growth factor-related signaling pathways modulate MT1 expression, and the hormonal milieu of the tumor at the time of melatonin administration can dramatically impact the responsiveness of the tumor to the antiproliferative action of melatonin. These actions are generally recognized as hormone-like effects. However, melatonin does not always act in this manner and several melatonin-induced effects are carried out without the intervention of a receptor. Melatonin should be rather considered as a tissue factor, behaving like a paracoid, an autocoid, an antioxidant, or a prooxidant factor depending on the physiological context.[37] The oncostatic effects triggered by melatonin are strictly context-dependent as well. Decreasing the fetal bovine serum concentration reduces the responsiveness of MCF-7 cells to melatonin, until cells are totally refractory in serum-free medium[38]; on the contrary, melatonin-induced inhibition is enhanced in both human[39] and animal cancer cells[37] cultured in charcoal-stripped serum supplemented with estradiol. Moreover, differences in MCF-7 cell strains and differences in their proliferation rate can account for the different sensitivity to the inhibitory effects induced by melatonin.[39] In addition, melatonin precursors, metabolites, or other pineal methoxyindoles do not exert any effect. The melatonin inhibitory activity is dependent on the pattern (continuous or pulsatile) of the exposure to the pineal indole in the culture media. The highest antiproliferative effects are obtained when the concentration of melatonin in culture media is changed every 12 h between 10–11 and 10–9 M, thus mimicking the physiological day/night oscillation of melatonin in the plasma of most mammals.[40] Culture conditions exert a relevant modulation on cell sensitivity to melatonin. In cells growing in anchorage-dependent monolayer culture with FBS, melatonin inhibits MCF-7 cells according to a bell-shaped curve, showing that the highest cytostatic effect is generally obtained around the physiological range (10–11 to 10–9 M), while higher or lower doses produce little or no inhibition.[10] Growth inhibition becomes evident after 48–72 hours and thereafter increases linearly up to 144 hours.[12] However, in an anchorage-independent culture system, the dose–response curve loses its characteristic form and becomes quite linear with increasing melatonin concentrations producing greater inhibition.[41] This result highlights that cellular attachment to a substratum, which is likely to modify both the cytoskeleton and cell shape, plays an important role in setting the level of sensitivity to melatonin.

CONCLUSION

Numerous studies have demonstrated the oncostatic properties of melatonin both in vivo using models of

chemically induced rat mammary tumors as well as in vitro using MCF-7 human breast cancer cells. Melatonin exerts both inhibitory as well proapoptotic effects by interacting with several molecular pathways. Generally, melatonin's cytostatic effects are mediated by interactions of the indoleamine with both ERs and melatonin receptors. However, recently some receptor- and estrogen-independent signaling pathways activated by melatonin have been discovered. In particular, increasing attention should be directed to melatonin's effects on the cytoskeleton and cell shape, as well as understanding how melatonin could inhibit both Akt activation and MAPK-related pathways. In light of its low toxicity, melatonin, either alone or in combination with chemoradiotherapy, should be considered as a potentially new anticancer treatment. There may be some difficulties in bringing a circadian rhythm-based melatonin chronotherapy to cancer clinics, but it is a challenge to use this indoleamine to derive its benefit in the practice of oncology.

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