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Melatonin and breast cancer: Evidences from preclinical and human studies

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ABSTRACT

The breast cancer affects women with high mortality and morbidity worldwide. The risk is highest in the most developed world but also is markedly rising in the developing countries. It is well documented that melatonin has a significant anti-tumor activities demonstrated on various cancer types in a plethora of preclinical studies. In breast cancer, melatonin is capable to disrupt estrogen-dependent cell signaling, resulting in a reduction of estrogen-stimulated cells, moreover, it's obvious neuro-immunomodulatory effect in organism was described. Several prospective studies have demonstrated the inverse correlation between melatonin metabolites and the risk of breast cancer. This correlation was confirmed by observational studies that found lower melatonin levels in breast cancer patients. Moreover, clinical studies have showed that circadian disruption of melatonin synthesis, specifically night shift work, is linked to increased breast cancer risk. In this regard, proper light/dark exposure with more selective use of light at night along with oral supplementation of melatonin may have benefits for high-risk women.

The results of current preclinical studies, the mechanism of action, and clinical efficacy of melatonin in breast cancer are reviewed in this paper. Melatonin alone or in combined administration seems to be appropriate drug for the treatment of early stages of breast cancer with documented low toxicity over a wide range of doses. These and other issues are also discussed.

1. Introduction

Melatonin is a ubiquitous molecule widely participating in the nature, with biological activity occurring in unicellular organisms, fungi, plants, and animals. Melatonin is synthesized primarily in the pineal gland during the night (darkness) and is regulated by the environmental light/dark cycle via the suprachiasmatic nuclei. This indolamine derived from L-tryptophan, provides several biological functions in the circadian rhythm of humans. In addition to its time-keeping functions, melatonin is characterized by an apparent anti-apoptotic signaling function and it is an effective antioxidant which scavenges free radicals and up-regulates several antioxidant enzymes. Its cyto-protective properties may have serious implications in the treatment of neurodegenerative diseases. Melatonin also demonstrates

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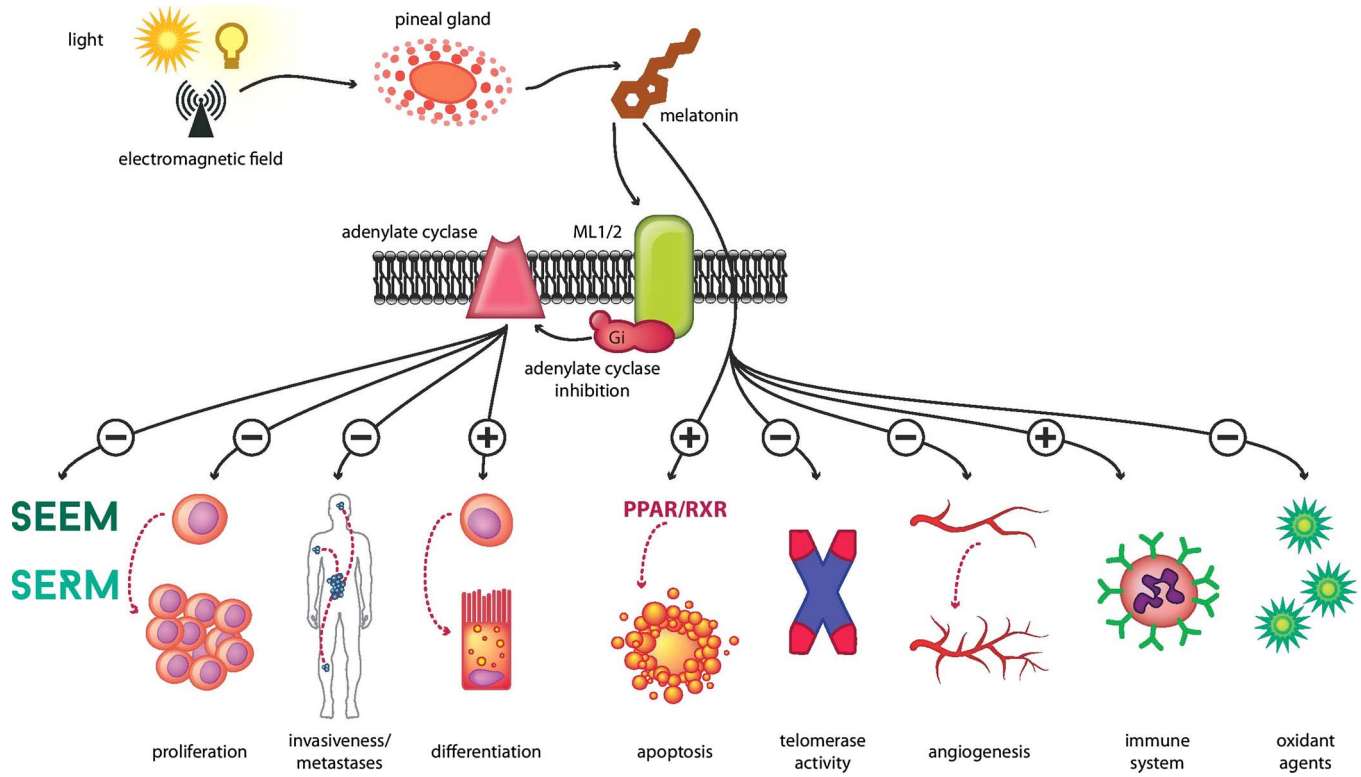

Fig. 1. Possible mechanisms of anti-tumor action of melatonin in breast cancer.
$MT_{1,2}$, melatonin receptors; Gi, G protein inhibitory; SEEM, selective estrogen enzyme modulator; SERM, selective estrogen receptor modulator; PPAR, peroxisome proliferator-activated receptors; RXR, retinoid X receptor.

immune-enhancing and anti-tumor activities. Melatonin's 'chronobiotic' properties have been used in the treatment of various circadian rhythm sleep disorders, such as jet lag or shift-work sleep disorder. Melatonin as an "internal sleep facilitator" promotes sleep, and melatonin's sleep-facilitating activities have been proved to be beneficial in the treatment of insomnia symptoms in elderly and depressive individuals. High concentrations of melatonin were found also in retina, gastrointestinal tract, bone marrow, skin and other tissues, from which it may influence other physiological functions through paracrine signaling (Sánchez-Barceló et al., 2003; Pandi-Perumal et al., 2006).

Estrogens and their receptors play a crucial role in breast cancer progression (Anisimov, 2003; Platet et al., 2004). Based on the observation that the pineal secretion, melatonin, inhibits ovarian estrogen production, pituitary gonadotrophin production, and sexual development and maturation, Cohen et al. (1978) proposed the hypothesis that a reduced function of pineal gland and thus a concomitant decrease in melatonin levels might promote the development of breast cancer in humans. This hypothesis was also supported by the presence of melatonin receptors in human ovary and whose suggest a direct influence of this hormone on the ovarian function, and possibly estrogen production, and moreover by the observation that impaired pineal secretion is believed to be an important factor triggering puberty (Cohen et al., 1978). Later, Tamarkin et al. (1982) suggested that low nocturnal melatonin concentrations may indicate the presence of estrogen receptor (ER)-positive breast cancer and could conceivably have etiologic significance. Melatonin was demonstrated to modulate the estrogen-signaling pathway in hormone-dependent breast cancer and to down-regulate estrogen production in gonads (Cos et al., 2014; Sánchez-Barceló et al., 2005). Melatonin acts as a selective estrogen receptor modulator and prevents estrogen induced effects in cells (Proietti et al., 2013). Melatonin was demonstrated as a specific inhibitor of the transcription of ER alpha in both estrogen response elements (ERE)- and AP1-containing promoters (Martínez-Campa et al., 2009) and as molecule with anti-aromatase activity in breast cells (Alvarez-García et al., 2013a, 2013b; ; Knower et al., 2012; Cos et al., 2006a).

Anti-carcinogenic, tumor-suppressive, and chemoprotective activity of melatonin has been documented in a plenty of experimental studies against a variety of cancer types such as hepatocellular, colorectal, non-small lung, renal, bladder, breast and ovarian carcinoma, neuroblastoma, melanoma, leukemia and other (Cutando et al., 2012). These effects are most pronounced in hormone-dependent cancers, particularly in mammary gland and prostate tumors. The above mentioned data suggest that melatonin is apparently involved in the processes of tumor initiation, promotion, and progression (Srinivasan et al., 2011). The oncostatic and tumor inhibitory properties of melatonin, in a variety of experimental models of breast cancer in vitro and in vivo, and its role in the risk of human breast cancer and possible therapeutical interventions are the main topics of this review.

2. Evidences from preclinical studies

A plenty of preclinical studies demonstrated significant anti-tumor effect of melatonin using basic research approaches – cancer cells and diverse animal models. *In vitro* studies using cancer cell lines represent an excellent tool for the analysis of melatonin's mechanism of anticancer action, on the other hand, animal studies *in vivo* evaluate the effect of potentially oncostatic drugs on compact organism and thus provide better extrapolation of results to human population. The mechanisms through which melatonin exerts its antitumor properties are characterized by a variety of pathways within cell signaling. Frequently described mechanisms of action include receptor-dependent and receptor-independent action of melatonin.

2.1. Cellular and molecular mechanisms of action

The role of melatonin as an anti-cancer agent has been intensively researched during the last few decades. Melatonin has been evaluated in a variety of cancer types, especially on hormone-dependent breast