



HORMONE OF DARKNESS: ROLE OF MELATONIN IN SQUAMOUS CELL CARCINOMA

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ABSTRACT

Melatonin is a hormone that is produced by the pineal gland in the brain. Melatonin levels vary in 24 hour cycles and are controlled by our body clock. Normally its production is reduced by being in bright light. Levels increase at night. Melatonin has powerful antioxidant effects, functions in an immunomodulatory role, may protect against certain cancers, delays some age-related processes, stimulates the synthesis of type I collagen fibres and promotes bone formation. These properties have been found to be beneficial in certain oral pathologies including periodontal diseases, herpes viral infections and Candida, local inflammatory processes, xerostomia, oral ulcers and oral cancer. The objective of this review is to discuss the mechanism of action and potential role of melatonin as a preventive and curative agent for oral cancer.

KEYWORDS: Candida, local inflammatory processes, xerostomia, oral ulcers and oral cancer.

INTRODUCTION

Melatonin is N-acetyl-5-methoxytryptamine and is synthesized and secreted by the pineal gland and other organs. In the mouth, it is an antioxidant, anti-inflammatory agent, rather than a hormone. The effects of melatonin were described first in 1917,^[1] but it was not isolated and identified until 1958.^[2] Since its discovery, melatonin has been shown to have a variety of important functions in all species of the animal kingdom.^[3, 4] Pinealocytes are known to synthesize melatonin with the various biochemical cascade its take up tryptophan from the blood and convert it into serotonin through hydroxylation and decarboxylation. Especially during the daily dark period, serotonin is converted into N-acetyl-serotonin by the enzyme N-acetyltransferase. N-acetyl-serotonin is methylated to form melatonin by the enzyme hydroxyindole-O-methyltransferase. Melatonin is released throughout the night by means of postsynaptic activation of the β -adrenergic receptors.^[5,9] Because of its association with the daily dark period, melatonin has been referred to as the chemical expression of darkness.^[8] Light inhibits the activation of the pinealocytes, thereby decreasing the synthesis of melatonin.^[10,11] Among many actions, melatonin and its metabolites are highly effective free radical scavengers,^[9,11] and stimulators of antioxidative enzymes. Arising out of its antioxidative actions, melatonin protects cells during severe inflammatory processes and reduces oxidative damage.^[12] Intense inflammatory processes contribute to the development of

certain cancers, cellular damage caused by ionizing radiation, alterations in metabolism and destruction of essential molecules and cells.^[3] Melatonin also plays an immunomodulatory role^[4], by regulating the secretion of interleukin-2 (IL-2) and interferon-alpha (INF-alpha) and the consequent activation of CD4+ lymphocytes.^[13] Moreover, melatonin reportedly stimulates the proliferation and synthesis of type I collagen and promotes bone formation.^[14] Once in the blood, melatonin also is discharged into the saliva. The proportion of plasma melatonin entering the mouth via the salivary glands appears to be relatively stable and ranges from 24% to 33%. It is widely agreed that 70% of plasma melatonin is bound to albumin. As only the free melatonin in plasma enters the saliva, salivary melatonin levels reflect the proportion of free-circulating melatonin.^[6, 7]

Role of melatonin in oral squamous cell carcinoma

Melatonin exerts oncostatic activity through several biologic mechanisms including antiproliferative actions, stimulation of anticancer immunity, modulation of oncogene expression and anti-inflammatory, antioxidant and antiangiogenic effects.^[15] Melatonin inhibits human cancer cell growth in culture and preliminary clinical studies seem to confirm its anticancer property in vivo as well. In addition, melatonin may have other biologic effects, which could be useful in palliative therapy for cancer, namely, anticachectic, antiasthenic and thrombopoietic properties.^[16] Melatonin appears to a

promising anticancer agent.^[17] First, melatonin scavenges ROS, which are known second messengers in the signaling pathways leading to the cell division.^[15] Additionally, melatonin amplifies the antitumor activity of interleukin-2.^[17] Melatonin is a proven powerful cytostatic drug in vitro as well in vivo.^[18-20] Fig1.

MLT has the capability of scavenging radicals and radical-associated reactants, stimulating the expression of antioxidative enzymes and reducing the expression of pro-oxidants.^[21,22] The anticarcinogenic actions of MLT associate in part with the antioxidative and free radical scavenging activities. The anti-estrogenic properties of MLT depend on the ability to decrease the expression of estrogen receptor- α (ER α) and to inhibit the binding of the E₂-ER complex to the estrogen response element on DNA.^[23] These effects are exerted through MLT binding to the specific membrane receptor, MT1. By contrast, the inactivation of calmodulin by MLT is an additional method in which this hormone may interact with the estrogen signaling pathway.^[24] MLT shares properties with the selective ER and enzyme modulators which explain the oncostatic properties of MLT on estrogen-dependent tumors. Other mechanisms of action, including the pro-apoptotic effects of MLT on tumor cells^[25] and the inhibition of telomerase activity^[26], are only partially understood.

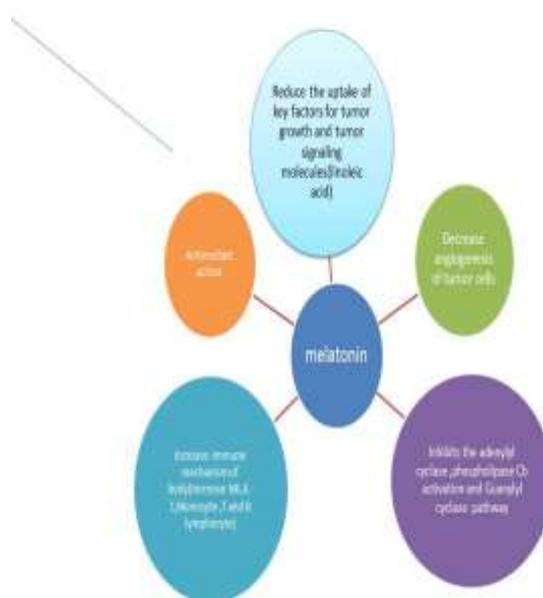
MLT exerts direct antiangiogenic effects through inhibiting vascular endothelial growth factor. Indirect effects are also exhibited by MLT through inhibiting other tumor growth factors, including epidermal growth factor, endothelin-1 and insulin-like growth factor 1, which are significant mitogens that stimulate cancer angiogenesis. In addition, MLT neutralizes reactive oxygen species. Studies on the antiangiogenic properties of MLT are of significant importance for possible future clinical applications.^[27] MLT is also synthesized by lymphoid organs, including bone marrow, the thymus and lymphocytes and is considered an immunoenhancer agent. The administration of MLT stimulates the production of natural killer cells, monocytes, leukocytes, interleukin (IL)-2, -6 and -12, interferon- γ and TNF- α through binding to specific membrane and nuclear receptors present in these cells.^[28]

Expressions of MT1 and MT2 receptors

MLT and its metabolites interact with the intracellular protein, calmodulin, RZR/ROR family nuclear-membrane receptors and MT1 and 2 receptors located in the cell membrane.^[29] The MT1 and 2 receptors were initially referred to as Mel1a and Mel1b, but were later classified as MT1 and MT2 receptors by the International Union of Basic and Clinical Pharmacology.^[30] The MT1 and 2 receptors are members of the G-protein-coupled receptor (GPCR) family and share a number of their amino acid sequences.^[31] With the use of recombinant MLT receptors, the MT1 receptor has been shown to be coupled to various G proteins that are able to mediate adenylyl cyclase inhibition and

phospholipase C β activation. The MT2 receptor is also coupled to the inhibition of adenylyl cyclase and additionally inhibits the soluble guanylyl cyclase pathway.^[32]

In patients with epidermoid carcinoma in whom the presence of the MT1 receptor has been studied through mRNA expression, MT1 has been shown to be diminished or non-existent. This is in contrast to what occurs in the normal epithelium of the oral cavity. It has been shown that in human cancers, including oral squamous cell carcinoma, DNA methylation of 5'-CpG islands (cytosine and guanine separated by phosphate) is a major cause of tumor-suppressor gene inactivity.^[33] In these tumors, there is an inverse correlation between MT1 receptor expression and DNA methylation. By contrast, the absence of immunoreactive MT1 is associated significantly with a greater tumor size and poorer survival prognosis. In a previous study, restoration of the exogenous MT1 receptor was found to inhibit the growth of epidermoid cells lacking the expression of this receptor.^[34] In this respect, it has been hypothesized that MTNR1A is a likely target for epigenetic silencing at the homozygously deleted region at 4q35, detected in these tumors.^[34] In precancerous oral diseases, including leukoplakia and lichen planus, reactive oxygen species are also involved in pathogenesis.^[34, 35] MLT may protect against these pathologies due to its antioxidant properties. However, further studies are required to assess the efficacy of MLT treatment for these cases.^[36] MLT may be useful to treat diseases of the oral cavity in patients with low concentrations of the hormone, but not where the tissues express MT1 and 2 receptors.^[37,38]



Oncostatic Properties of Melatonin

CONCLUSION

Oral cancer is among the ten most common cancers affecting human race and has one of the poorest five year survival rate among all cancers. As prevention is better than cure there is an urgent need to discover an agent which can help in preventing oral cancer.

Melatonin has important physiological functions that have not been exploited in management of oral diseases. Melatonin has the following positive aspects: it is endogenously produced, it is nontoxic, it diffuses rapidly into all cells and body fluids, it penetrates all subcellular compartments, it is generally devoid of pro-oxidant actions and it stimulates a number of antioxidant enzymes.

For high risk groups like chronic tobacco consumers, elderly etc., the administration of melatonin, in local or systemic form, might be indicated with the goal to protect their mouth against tumors. It can be used as an adjunct in management of oral cancer patients to retard the growth of tumor and enhance the immunity of patients. Further research must be carried out by dental researchers to provide better evidence of role of melatonin in management and prevention of oral squamous cell carcinoma.

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