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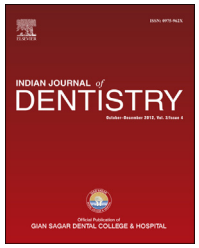

Review Article

Potential role of melatonin in prevention and treatment of oral carcinoma

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ABSTRACT

Background: Melatonin, a hormone secreted mainly by pineal gland has been found to have antioxidant and anti-inflammatory properties in the oral cavity where it reaches through saliva. 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.
Objective: 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.
Materials and method: A extensive review of databases like pubmed, medline, science direct and Cochrane reviews was conducted to find articles related to beneficial actions of melatonin in human body with focus on cancers.
Discussion: Numerous studies both in-vitro and in-vivo had shown promising results regarding role of melatonin as anti-carcinogenic agent.
Conclusion: Melatonin may play a role in protecting the oral cavity from tissue damage caused by oxidative stress. The experimental evidence suggests that melatonin may have utility in the treatment of several common cancers of the body. However, more specific studies are necessary to extend the therapeutic possibilities to oral carcinoma.

1. 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, but it was not isolated and identified until 1958. Since its discovery, melatonin has been shown to have a variety of important functions in all species of the animal kingdom.[1] Pinealocytes, the major cells of the pineal gland, are responsible for producing and secreting melatonin into the blood. The mechanisms of melatonin synthesis are well known and have been described in numerous publications (Fig. 1).[2,3]

Melatonin when released into oral cavity through saliva has been found to have protective actions against many oral conditions like periodontal diseases, herpes viral infections and *Candida*, local inflammatory processes, xerostomia, oral ulcers and oral cancer.[1] Most widely studied among them is its role in periodontal diseases, which is related to anti-

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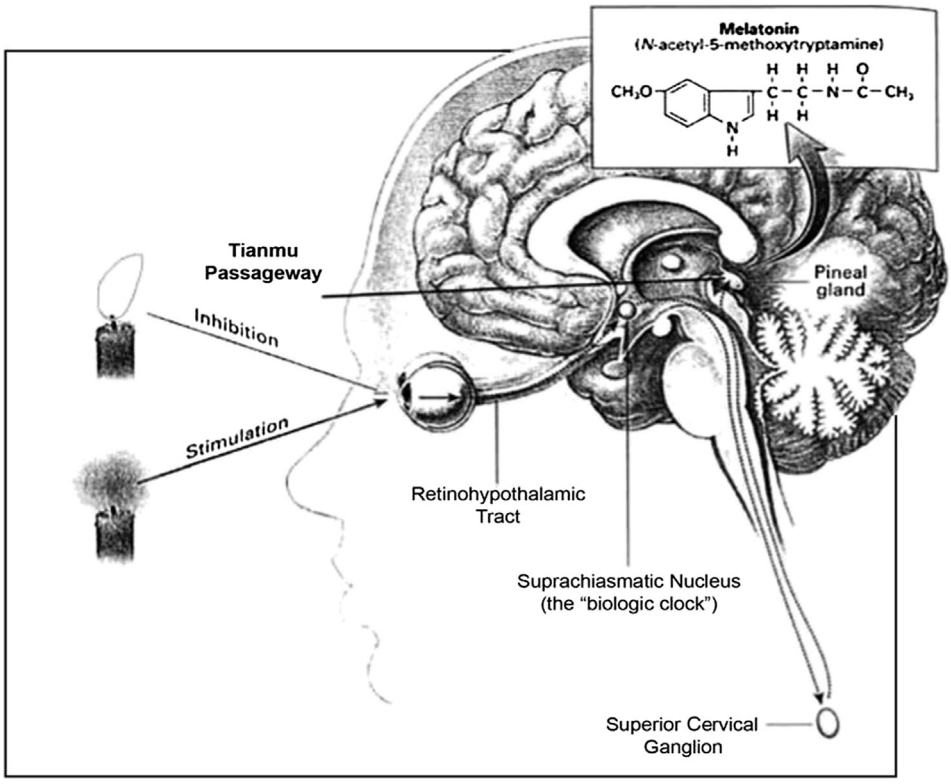

Fig. 1 – Physiology of melatonin secretion.

inflammatory and anti-oxidant properties of melatonin.[4,5] Important protective/beneficial actions of melatonin are listed in the table below.

Potential beneficial actions of melatonin in oral cavity:

1. Anti-oxidant
2. Anti-inflammatory
3. Immunoenhancement
4. Effect on angiogenesis in cancer
5. Anti-apoptotic effect on immune cells

Our focus of interest in this review is role of melatonin in prevention and control of oral squamous cell carcinoma, because oral cancer is one of the few life threatening and poor survival rate diseases, which a dentist encounters during his professional carrier. Therefore it is imperative that we find an agent, which prevents, retards or controls the occurrence of this tumor.

2. The pathogenesis of oral cancer

An obvious feature of all oral cancers is excessive proliferation of oral keratinocytes. Initially, keratinization is confined to the epithelial compartment resulting in a thickened and disorganized epithelium. Eventually, the proliferating keratinocytes break through the epithelial basement membrane. Malignant epithelial masses then expand through the underlying connective tissue and invade lymph and blood vessels resulting in distant spread. In this context, oral cancer is a lesion characterized by dysregulated division of oral keratinocytes. Knowledge of normal DNA replication and keratinocyte division is the key to understanding abnormal cell division in oral cancer. Normally, oral keratinocyte division is stimulated by growth factors (EGF-Epidermal Growth Factor) binding the receptors (EGFr-Epidermal Growth Factor Receptor) on the surface of the basal keratinocytes. This activates a cascade, which transmits the signal to the nucleus leading to DNA replication followed closely by cell division (Fig. 2).

Most of the DNA replication proteins are degraded and must be newly transcribed with each round of cell division. Many of the proteins, which transmit the growth signal from the cell membrane to the nucleus, are encoded by oncogenes. Oncogene mutation may stimulate excessive keratinocyte proliferation in oral cancer.[6] The genetic hypothesis predicts a role for hyperactive oncogenes (growth promoting genes) in oral carcinogenesis. Highly reactive free radicals react with DNA to produce monomeric damage or strand breaks etc. Tumor suppressor protein under normal circumstances detects DNA damage and halts progression through the cell cycle. Both alleles of the tumor suppressor gene must be mutated for the tumor suppressor protein to become nonfunctional, up to 80% of oral squamous cell carcinomas are sporadic, and therefore both the alleles of the p53 gene in a single oral keratinocyte are lost by somatic mutation. Tumor suppressor gene mutations correlate with the stages of carcinogenesis from normal mucosa, to squamous hyperplasia (9p), to dysplasia (3p, 17p) to carcinoma in situ (11q, 13p, 14q) to invasive carcinoma (6p, 8 and 4q).[7]

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