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Melatonin: Implications in dentistry: A review

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Abstract

Melatonin, known as chemical of darkness is a hormone secreted by the pineal gland. Studies have shown that it has antioxidant, antiageing, immunomodulatory, antineoplastic properties. Because of these effects, it might be used therapeutically in dentistry for the potentially malignant disorders, lesions of mechanical, bacterial, fungal or viral origin. Thus, it is important for the dental clinicians to be familiar with the possible therapeutic uses of MLT in dentistry. The aim of the present article is to review on melatonin and its applications in dentistry.

Keywords: Hormone; Melatonin; Oral Implications; Physiology

1. Introduction

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone secreted mainly by pineal gland. Since its discovery in 1917, various functions of melatonin in humans have been explored.[1] After its secretion from pineal gland into the circulation, it enters into oral cavity through saliva.[2] Studies have shown that it has inhibitory actions against periodontal diseases, inflammatory conditions and neoplastic lesions of oral cavity. Amongst them anti-inflammatory and anti-oxidant properties of melatonin against periodontal diseases is widely studied.

2. Synthesis

Pinealocytes produce melatonin through a series of well-known mechanisms .It needs polysynaptic activation of beta-adrenergic receptors, which are regulated indirectly by stimulus from suprachiasmatic nucleus (SCN). Information on light/dark environments is transmitted via the retinohypothalamic tract to the suprachiasmatic nucleus. Thereafter an electrical neural signal is transferred to the upper thoracic cord and superior cervical ganglia after which it is conveyed from the postganglionic sympathetic fibres to the pineal gland.[4] These postsynaptic terminals release norepinephrine which activates adrenergic receptors in the pinealocyte membrane. Pinealocytes take up tryptophan from the blood followed by the enzymatic reactions as shown in Figure 1, contributing to the synthesis of melatonin with the rate limiting enzyme being N-acetyltransferase (AANAT). After synthesis, melatonin is rapidly released into the capillary circulation in the pineal gland and directly into cerebrospinal fluid of third ventricle.[5]

Most of the synthesis of melatonin occurs during night. Hence it is known as chemical of darkness.[6] It occurs rhythmatically (**Circadian rhythm)** as a consequence of neural impulses from the Biological clock i.e. hypothalamus and Suprachiasmatic nucleus.

Peak serum melatonin levels in healthy individuals, seen during 12.00 a.m–2.00 a.m. and 2.00–4.00 am, with minimum secretion during the day time 12.00p.m–2.00 p.m. After the secretion, the unbound melatonin passively diffuses into the saliva and enters into oral cavity .Hence percentage of free melatonin is represented by salivary melatonin.

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2.1. Melatonin Receptors

Melanin receptors which are identified are membrane specific and nuclear receptors.[8] Initially they were named as Mel-1a, and Mel-1b, Mel-1c.[7] The Mel-1a receptor gene has been mapped to human chromosome 4q35.1.[9] The primary expression of Mel-1a receptor is in pars tuberalis of pituitary gland and suprachiasmatic nucleus. Mel-1b has been mapped to chromosome 11q21-22, expresses mainly is the retina and brain. Mel-1c is not found in mammals. Recently Mel-1a and Mel-1b are renamed as MT1 and MT2.[10]

Several techniques are used to confirm the presence of melatonin in saliva , such as automated solid phase extraction, high-performance liquid chromatography, and fluorescence detection. Melatonin levels in saliva (2–4 pg/mL) forms 25–35% of the plasma melatonin levels.

Various factors like smoking, exposure to light, consumption of alcohol, and aging process decrease the levels of salivary melatonin. [11]

2.2. Melatonin in oral health and disease

Recent studies show that, melatonin has a cell protective role rather than a hormone, because of its presence in extra-pineal synthesis in oral cavity and other organs like gastric mucosa and retina. Melatonin exhibits various physiologic functions in the body .

It passively diffuses into the oral cavity and is released into the saliva. A significant correlation between concentrations of melatonin in saliva and serum was reported with a general conclusion that melatonin concentration is a reliable index of serum melatonin levels.[12]

2.3. Melatonin in Tooth Development

Melatonin plays a role in physiologic growth and development of teeth by the regulation of odontogenic cells in tooth germs.[13]Immunohistochemical analysis revealed that melatonin 1a receptor (Me 1a R) has been expressed in secretary ameloblasts, the cells of stratum intermedium and stellate reticulum, external dental epithelial cells, odontoblasts, and dental sac cells. Seasonal variation in the secretion of melatonin was related with the changes in development of caries in hamsters.[14]

2.4. Melatonin in Inflammatory Conditions of the Oral Cavity

Melatonin in Gingival crevicular fluid (GCF) plays an important role in periodontal health. The pathogenesis of periodontitis is related to increased oxidative stress, which leads to damage of tissues and alveolar bone loss. Melatonin, with its antioxidative and free radical scavenging action may reduce this tissue damage.[15] In addition, the positive effects of melatonin and its derivatives on inflammatory mediators and bone cells may be beneficial in improving periodontal health.

Current evidence showed that salivary melatonin levels may differ according to the degree of periodontal disease. A negative relation was found between salivary melatonin levels and periodontal disease severity.[16]

Consequently, decreased saliva and melatonin production with age predisposes older individuals to increased risk of oral and periodontal diseases. Dental procedures including tooth extraction may result in local inflammation and oxidative stress in the oral cavity. Upon local administration, the antioxidant action of melatonin may be useful in counteracting this oxidative stress.[17]

2.5. Role of Melatonin in Osseointegration and Regeneration

Melatonin has biologic significance in terms of osseointegration around implants. 2 weeks after implant insertion, melatonin significantly increased all parameters of osseointegration like bone to implant contact (BIC), total peri-implant bone, interthread bone, and new bone formation. Implants impregnated with topical melatonin at the time of placement showed more trabecular bone and increased trabecular density at implant site.[18] Osseo integration was found to be more effective when melatonin was added with collagenised porcine bone.[19] Melatonin at micro-molecular concentration promotes the proliferation of human mandibular cells (HOB-M) and cells of a human osteoblastic cellular line (SV-HFO).[20] This effect is dose dependent and is maximum at concentrations of 50 micrometers.[21] Due to these actions on bone, its use as a biomimetic agent during endosseous dental implant surgery is proposed.[21]

2.6. Role of Melatonin in Oral Cancerous Lesions

Melatonin plays a pivotal role in many inflammatory processes of oral cavity and thus is effective in treating pathologies like squamous cell carcinoma and epidermoid carcinoma.[22] In relation to oral cancer, it is speculated that exogenous restoration of melatonin receptor 1a inhibited the growth of oral squamous cell carcinoma cells, lacking its expression.[22] By its actions against ROS, melatonin may protect against precancerous oral diseases like leukoplakia and lichen planus. Melatonin also counteracts the negative effects of immunosuppressive drug therapy by acting on T-helper lymphocytes, lymphokines such as gamma interferon and IL-2.[23]

2.7. Role in Reducing Toxicity due to Dental Materials

Several cytotoxic and genotoxic effects of dental methacrylate monomers promote oxidative processes. Melatonin's antioxidative action may protect against these effects by reducing

oxidative DNA damage induced by methacrylates.[24] Melatonin when used as a component of dental materials exhibited biocompatibility without altering the properties of these dental materials. Alternatively, the regular use of melatonin oral rinse may reduce the side effects of methacrylate monomers.[24]

2.8. Role in modification of Salivary Components

Novel evidence proposed that melatonin induced protein synthesis in the rat parotid gland and thereby affects glandular activity. This effect is MT-1- and MT-2-receptormediated and is primarily dependent on nitric oxide generation via the activity of neuronal-type nitric oxide synthase. This enzyme probably originated from parenchymal cells of the parotid gland. This novel action of melatonin may increase its clinical implications in the treatment of xerostomia, caries, periodontitis, oral mucosal infections, salivary gland inflammation, and wound healing.[25]

2.9. Therapeutic Protocols Proposed for Melatonin

Beneficial antioxidant effects of low doses of melatonin (10mg/day) are shown in several chronic diseases such as rheumatoid arthritis primary essential hypertension in elderly patients (5mg/day) type 2 diabetes in elderly patients (5mg/day) [67], and females suffering from infertility (3 mg/day). [26]

A recent study reported beneficial effects of high doses of melatonin (20mg/kg) for inhibiting apoptosis and liver damage resulting from oxidative stress in malaria, which could be a novel approach in the treatment of this disease. A formulation containing 2.5mg melatonin and 100 mg SB-73 (a mixture of magnesium phosphate, fatty acids, and protein extracted from aspergillums oryzae) promoted regression of symptoms of herpes virus infection.[27]

2.10. Adverse effects of Melatonin

Melatonin is a potent adjunctive agent in the treatment of cancer and immune deficiency. However, poorly timed administration can produce opposite effects. Melatonin injections given in the morning can stimulate tumour growth, whereas same doses given in the mid-afternoon have no effect but in the evening have a retarding effect.[28]

Melatonin administration may unduly prolong the nocturnal melatonin rise or that is given throughout the day may exacerbate bipolar and classic depression. Some people with depression may suffer from a low-melatonin syndrome. Animal studies have shown that moderately large doses of melatonin (equivalent to 30mg in adult humans) increase light induced damage to retinal photoreceptors.[29] Melatonin caused atherosclerosis in the aorta in hypercholesterolemic rats by suppressing LDL-receptor metabolic pathways.[30] Preliminary animal studies suggest that melatonin may accelerate the development of autoimmune conditions.[31]

3. Conclusion

Traditionally, melatonin was considered as the principal secretory hormone of pineal gland. Its profound systemic effects as a cell protector stimulated the quest for other extrapineal sources and functions. Novel evidence brought to light that this chemical of darkness has oral sources and implications. Based on this evidence, this review attempts to concise the role of melatonin in oral health and disease mentioning a note on its therapeutic potential. Further studies need to focus their attention on therapeutic uses of melatonin as a coadjuvant in oral hygiene aids and as an antimicrobial in local therapy to promote it as a natural inhibitor of inflammation.

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