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REVIEW ARTICLE

Melatonin in diseases of the oral cavity

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BACKGROUND: Melatonin is the principal secretory product of the pineal gland. It has immunomodulatory and antioxidant activities, stimulates the proliferation of collagen and osseous tissue and acts as a protector against cellular degeneration associated with aging and toxin exposure. Arising out of its antioxidant actions, melatonin protects against inflammatory processes and cellular damage caused by the toxic derivates of oxygen. As a result of these actions, melatonin may be useful as a co-adjuvant in the treatment of certain conditions of the oral cavity.

METHODS: An extensive review of the scientific literature was carried out using PubMed, Science Direct, ISI Web of Knowledge and the Cochrane base.

RESULTS: Melatonin, which is released into the saliva, may have important implications for oral diseases. Melatonin may have beneficial effects in certain oral pathologies including periodontal diseases, herpes viral infections and *Candida*, local inflammatory rocesses, xerostomia, oral ulcers and oral cancer.

CONCLUSIONS: 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 diseases of the oral cavity. However, more specific studies are necessary to extend the therapeutic possibilities to other oral diseases.

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Keywords: melatonin; saliva; oral medicine

Introduction

Melatonin (*N*-acetyl-5-methoxytryptamine) was isolated and characterized in 1958 (Lerner *et al,* 1958) although one of its actions, i.e., its ability to blanch the skin of amphibians, had already been shown in 1917 (McCord and Allen, 1917). Melatonin is synthesized by the pineal gland and a variety of other organs; in these latter organs melatonin has local effects (Reiter *et al,* 2001). 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 (Reiter, 1986; García-Maurino *et al,* 2000; Reiter *et al,* 2000; Carrillo-Vico *et al,* 2005; Ackermann and Stehle, 2006; Tan *et al,* 2007).Briefly, the pinealocytes take up free tryptophan from the blood and convert it to serotonin, which involves the enzymes tryptophan-5-hydroxylase and 5-hydroxytryptophan decarboxylase that successively hydroxylate and decarboxylate tryptophan respectively. At night, serotonin is converted to *N*-acetylserotonin by the action of *N*-acetyltransferase. Thereafter the enzyme hydroxyindole-O-methyl transferase acts on *N*-acetylserotonin causing its methylation and forming melatonin (Figure 1). In animals including man, melatonin reaches its maximal levels near the middle of the dark period with uniformly low levels during the day (Czesnikiewicz-Guzik *et al,* 2007). Because of the association of pineal melatonin synthesis with night time, melatonin is referred to as the chemical expression of darkness (Reiter, 1991).

The nocturnal production of melatonin in the pineal is under the control of norepinephrine released from sympathetic endings that terminate on pinealocytes. Information related to the light: dark cycle is transferred from the eye, via the retinohypothalamic tract to the suprachiasmatic nucleus (SCN); these nuclei constitute the biologic clock and synchronize circadian melatonin synthesis (Ferguson and Fort, 1973; Vakkuri, 1985). The SCN sends a neural signal to the pineal gland via pre- and postganglionic neurons with the final synapse in the superior cervical ganglia.

After the release of norepinephrine from the postganglionic sympathetic neurons in the pineal, there is the postsynaptic activation of the beta-adrenergic receptors on the pinealocytes that generates the night-time rise in the synthesis of melatonin. The rate-limiting enzyme in melatonin production is generally considered to be *N*-acetyltransferase (NAT), which *N*-acetylates serotonin

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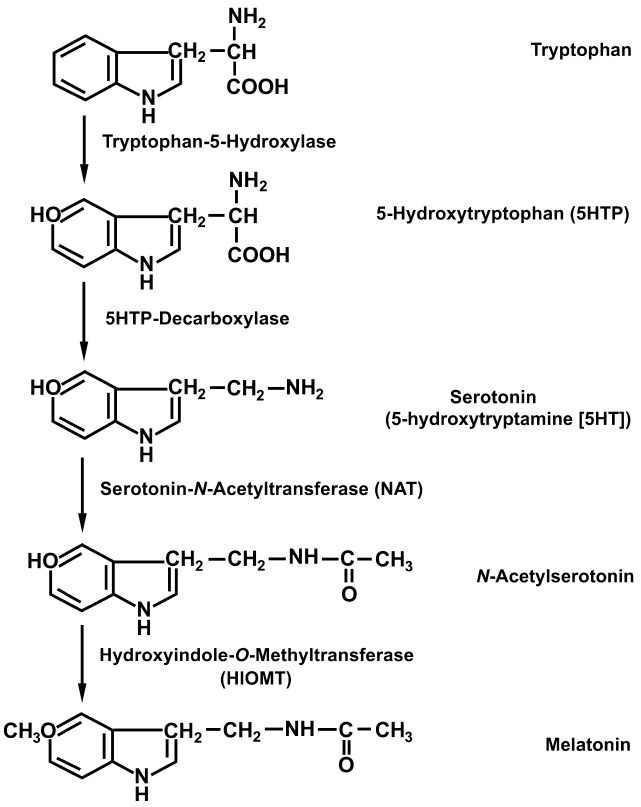

Figure 1 Chemical structure and synthesis of melatonin from the aminoacid tryptophan (Cutando *et al,* 2007a)

and gives rise to *N*-acetylserotonin (Mechin and Toury, 1973). During the day, light prevents the activation of NAT resulting in the minimal production (Cutando *et al,* 2003; Taubman *et al*, 2005).

Among many actions, melatonin and its metabolites are highly effective free radical scavengers (Allegra *et al,* 2003; Cutando *et al*, 2007a, 2007b, 2007c; Tan *et al,* 2007; Peyrot and Ducrocq, 2008; Gitto *et al,* 2009) and stimulators of antioxidative enzymes. Arising out of its antioxidative actions, melatonin protects cells during severe inflammatory processes and reduces oxidative damage (Rodriguez *et al,* 2004). 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 (Reiter *et al,* 2000). Melatonin also plays an immunomodulatory role (Carrillo-Vico *et al,* 2005), by regulating the secretion of interleukin-2 (IL-2) and interferon-α (INF-α) and the consequent activation of CD4+ lymphocytes (García-Maurino *et al,* 2000). Moreover, melatonin reportedly stimulates the proliferation and synthesis of type I collagen and promotes bone formation (Cutando *et al,* 2008). 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 (Czesnikiewicz-Guzik *et al,* 2007). Given the properties of melatonin and its presence in oral cavity because of its release in saliva (Vakkuri, 1985), its effect on oral health warrants further investigation.

In this survey, we consider the potential roles of melatonin in the oral conditions including (1) caries; (2) periodontal disease; (3) herpes viral infection; (4) candidiasis; (5) inflammatory processes; (6) xerostomia; (7) oral ulcers and (8) oral cancer. An extensive search of the literature was performed using PubMed, Science Direct, Web of Knowledge and Cochrane base, to accumulate the reports discussed in this survey. The review provides a description and an explanation of the clinical implications of melatonin in oral diseases.

Melatonin and caries

In hamsters, a highly seasonal species, more caries lesions develop in the spring and summer, when the duration of nocturnal elevated melatonin is minimal and, conversely, caries occur less commonly in the autumn and winter when melatonin levels are maximal (Mechin and Toury, 1973). Moreover, it is known that tooth and osseous tissue material is strongly modified by cariogenic diets (Mechin and Toury, 1973) and given that melatonin is available in the foodstuffs, the quantity of melatonin in the consumed foodstuffs may influence caries incidence.

Melatonin and periodontal disease

Periodontal tissue is destroyed in the course of periodontitis by disproportionate immunologic responses to a triggering agent such as bacteria in biofilm (Taubman *et al,* 2005). Free radicals generated by the phagocytic cells, e.g., neutrophils and macrophages, migrate to the inflammation site, and significantly damage the gingival tissue (Cutando *et al,* 2003). Lipid peroxidation is a major factor in the induction and progression of chronic periodontitis (Roth *et al,* 1999). Increased reactive oxygen species (ROS) scavenging by melatonin and its metabolites in the inflamed area would be beneficial in reducing the degree of tissue damage. Moreover, melatonin influences fibroblast activity and bone regeneration by promoting osteoblast differentiation and bone formation (Cutando *et al,* 2006), and additionally, it stimulates the synthesis of type I collagen fibers (Nakade *et al,* 1999). Melatonin mediates these effects through receptors localized on preosteoblasts, which lead to the production of bone sialoprotein, alkaline phosphatase, osteopontin and osteocalcin in these cells, thus significantly shortening the time needed for their differentiation into mature osteoblasts from 21 to 12 days (Cutando *et al,* 2007a).

The receptor activation of nuclear factor-kappa B ligand (RANKL) is an important protein in osteoclastic differentiation and proliferation (Boyle *et al,* 2003). Another protein, osteoprotegerin (OPG), interferes with its biologic potential. RANKL and OPG play critical roles in the development of periodontal disease, with periodontal bone destruction resulting from the

upregulation of RANKL with downregulation of OPG (Liu *et al,* 2003). Melatonin alters these events by modulating the molecular triad of OPG/RANK/-RANKL (Theoleyre *et al,* 2004). Also, treatment with melatonin stimulates the proliferation, differentiation and activity of osteoblasts. Recent studies have demonstrated that a melatonin derivative, i.e., 1-benzyl-2,4, 6-tribromomelatonin, has more potent activity than melatonin itself, and may have potential use in the treatment of bone diseases of the oral cavity as well as osteoporosis (Suzuki *et al,* 2008). Moreover, melatonin may act at the level of the osteoclast lacuna, because of its antioxidant properties and its ability to neutralize reactive species, where it inhibits bone resorption (Gómez-Moreno *et al,* 2007). There is some evidence that topical application of melatonin may act as a biomimetic agent in the placement of endo-osseous dental implants (Cutando *et al,* 2008).

Melatonin and herpes viral infection

To promote the regression of the symptoms of herpes virus infection, a formulation containing 2.5 mg melatonin and 100 mg SB-73 (a mixture of magnesium, phosphate, fatty acids and protein extracted from *Aspergillus oryzae*) with no reported side-effects has been developed. This formulation is based on published information indicating that melatonin has known immunomodulatory properties. One function of melatonin is to induce the production of interleukin-1 beta (IL-1β) which can be beneficial in virus infection. As the formula contains natural compounds, it may present fewer side-effects than medications currently used in clinical medicine (Nunes Oda and Pereira Rde, 2008). As it is considered a supplement, with natural ingredients, it may find utility in the treatment of herpes infections by individuals who cannot afford prescription drugs. Other studies have documented the antiviral actions of melatonin (Bonilla *et al,* 2004).

Melatonin and candidiasis

As an immunomodulator, melatonin reportedly exhibits protective effects in severe sepsis/shock induced by bacterial lipopolysaccharide in animal models. Melatonin reduced IL-6 levels and shortened time to improvement in animals with *Candida* sepsis. Levels of TNF-alpha and adhesion molecules in melatonin-treated septic rats were reduced compared with those in untreated septic rats (Yavuz *et al,* 2007). Considering these findings, melatonin may have therapeutic benefits in *Candida* sepsis and in classic antimycotic treatment because of its immune-regulatory effects. Thus, melatonin may also be useful as a topical and/or systemic treatment of oral candidiasis. Further studies are required to confirm this presumption.

Terrón *et al* (2003) evaluated the effect of melatonin on the ingestion and destruction of *Candida albicans* (live particles) by the ring dove (*Streptopelia risoria*) at different durations of incubation (30 and 60 min) with physiological (50 pg ml^{-1} diurnal and 300 pg ml^{-1} nocturnal), as well as with a pharmacological concentration (100 μM) of melatonin. The results showed that melatonin, at both times and at all concentrations studied increased both the phagocytosis index (number of *C. albicans* phagocytosed by 100 heterophils) and the candidicide power (percentage of *C. albicans* killed after been ingested by 100 heterophils). The effect was dose-dependent. With respect to the oxidative metabolism accompanying the digestion and destruction, there was a decline in superoxide anion levels after incubation with melatonin at the concentrations studied. Again, the effect was dose-dependent and most pronounced at 60 min. These results support the proposal that melatonin enhances phagocytic function and at the same time reduces oxidative stress originating during candidiasis (Terron *et al*, 2002; Terrón *et al*, 2003; Terrón *et al*, 2004).

Melatonin as anti-inflammatory in oral cavity

The antioxidant properties of melatonin may be beneficial for the treatment of the local inflammatory lesions and for accelerating the healing process, *e.g.,* after tooth extraction and other surgical procedures in the oral cavity. Favorable effects of local melatonin administration have been observed to the alveolar sockets after molar and premolar extraction in Beagle dogs (Cutando *et al,* 2007b). In the dogs in which melatonin was not used, elevated levels of products of lipid peroxidation and nitrite plus nitrate levels in plasma as well as the GSSG/GSH (oxidized glutathione/reduced glutathione ratio) in erythrocytes were measured. Dogs in which 2 mg melatonin was applied to the vacated socket immediately after extraction did not show these increases (Cutando *et al*, 2007c). Melatonin also has been shown to inhibit the inflammatory enzyme cyclooxygenase-2 (COX-2). Melatonin reportedly binds to the active sites of COX-1 and COX-2 indicating that it may act as a natural inhibitor of the function of these enzymes and thereby be and endogenous inhibitor of inflammation (de la Rocha *et al,* 2007). The anti-inflammatory and immunostimulatory actions of melatonin are well known (Carrillo-Vico *et al,* 2005).

Melatonin and xerostomia

Based on new evidence, melatonin may have potential in the treatment of xerostomia. Melatonin has been shown to evoke protein/amylase secretion from the parotid gland of the anesthetized rat (Aras and Ekström, 2008). Melatonin's ability to regulate the secretory activity of the salivary glands may be exerted through a direct action on melatonin receptors on the secretory units and partially depending on NO generation at the level of neuronal NO synthase (Aras and Ekström, 2008).

Salivary melatonin levels vary according to the degree of periodontal disease. As the severity of periodontal disease increases, the salivary melatonin levels drop, indicating that melatonin may act to protect from external bacterial insults (Cutando *et al,* 2006).

Melatonin and oral ulcers

In the upper gastrointestinal tract, melatonin exhibits a wide spectrum of activities including antioxidant functions and protection of the mucosa against various irritants. Moreover, it protects the oral cavity and the gastrointestinal tract from conditions such as stomatitis, esophagitis, gastritis and peptic ulcer (Czesnikiewicz-Guzik *et al,* 2007). Reactive species have been implicated in etiopathogenesis of aphthous ulcerations (Cutando *et al,* 2006). In animal models it has been shown that exogenous melatonin prevents the formation of acute gastric lesions induced by stress and accelerates regeneration of chronic gastric ulcers resulting from the increased activities of cNOS and COX-prostaglandin E_2 system, which leads to an elevated mucosal blood flow and loss of mucosal integrity (Konturek *et al,* 2006). Melatonin, given orally, is highly effective in preventing acute esophageal lesions induced by direct perfusion of the esophagus with acid, pepsin or a bile solution (Konturek *et al,* 2007). This evidence suggests that melatonin could be considered a novel esophagoprotector, acting at least in part through the COX/prostaglandin and NOS/NO systems and via activation of sensory nerves (Konturek *et al,* 2007).

Melatonin and oral cancer

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 (Reiter, 2004). 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 the palliative therapy for cancer, namely anticachectic, antiasthenic and thrombopoietic properties (Lissoni, 2002). Melatonin appears to be a promising anticancer agent (Reiter *et al,* 2007). First, it scavenges ROS which are known second messengers in the signaling pathways leading to the cell division (Reiter, 2004). Additionally, melatonin amplifies the antitumor activity of interleukin-2 (Reiter *et al,* 2007). Melatonin is a proven powerful cytostatic drug *in vitro* as well *in vivo* (Miller *et al,* 2006; García-Santos *et al,* 2006; Herrera *et al,* 2006). The regular administration of the indolamine induces significant declines in the frequency of cachexia, asthenia, thrombocytopenia, chemotherapy-induced lymphocytopenia, stomatitis, cardiotoxicity and neurotoxicity (Lissoni, 2002). Melatonin may be successfully administered in medical oncology in the supportive care of untreatable advanced cancer patients and for the prevention of the side-effects of chemotherapy.

In relation to oral cancer, it has been speculated that exogenous restoration of melatonin receptor 1 A (MTNR1A) expression inhibited the growth of oral squamous cell carcinoma cells lacking its expression (Chaiyarit *et al,* 2005). Together with the known tumor-suppressive functions of melatonin and the presence of MTNR1A in various tumors, the MTNR1A is a likely target for epigenetic silencing at loci 4q35 and may play a pivotal role during oral carcinogenesis (Nakamura *et al,* 2008). In precancerous oral diseases such as leukoplakia (Taubman *et al*, 2005) and lichen planus, reactive species also are involved in their pathogenesis (Chaiyarit *et al,* 2005). As a result of its antioxidant activity, melatonin may protect against these pathologies although studies are urgently needed to investigate the benefits of melatonin treatment for these conditions.

Conclusions

Melatonin may have clinical applications in reducing oral diseases; limiting tissue damage that is a result of free radicals, stimulating the immune response, reducing the progressive loss of alveolar bone, promoting the regression of symptoms of herpes viral infection, impeding local inflammatory lesions, and possible treatment of xerostomia and oral cancer. Melatonin has the following positive aspects: it is endogenously produced, it is non-toxic, 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. Melatonin released into the oral cavity via the saliva may have yet-to-be-identified benefits for oral health. Individuals as the result of pathologies that are characterized by a malfunction of the salivary glands may have an elevated capacity to develop diseases of the oral cavity. The administration of melatonin, in local or systemic form, might be indicated in these patients, with the goal of protecting their mouth against inflammatory and infectious processes of a diverse nature. Clearly, the functional aspects of melatonin in the oral cavity needs additional investigating and may prove to be a fertile area for research. If melatonin has an effect in improving any aspect of oral health, the regular use of currently-available sublingual tablets may be found to be useful as a means of treatment. Tests to date have revealed that melatonin is an uncommonly safe molecule over a wide range of doses.

Author contributions

All authors have made a substantial contribution to the manuscript.

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