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Review Article

Melatonin in the oral cavity: physiological and pathological implications

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Background and Objectives: The purpose of this article was to summarize what is known about the function of melatonin in the oral cavity.

Material and Methods: Databases were searched for the relevant published literature to 30 November, 2013. The following search items were used in various combinations: melatonin, gingiva, periodontium, inflammation, herpes, alveolar bone, periodontal ligament, dental implants, xerostomia, methacrylate, chlorhexidine, cancer. The literature uncovered is summarized herein.

Results: Salivary melatonin levels exhibit a circadian rhythm with highest values at night. Melatonin has both receptor-mediated and receptor-independent actions in cells of the oral cavity. Melatonin is released into the saliva by the acinar cells of the major salivary glands and via the gingival fluid. Functions of melatonin in the oral cavity are likely to relate primarily to its anti-inflammatory and antioxidant activities. These actions may suppress inflammation of the gingiva and periodontium, reduce alveolar bone loss, abrogate herpes lesions, enhance osteointegration of dental implants, limit oral cancer, and suppress disorders that have a free radical component. Sublingual melatonin tablets or oral melatonin sprays and topical melatonin-containing gel, if used on a regular basis, may improve overall oral health and reduce mucosal lesions.

Conclusion: Collectively, the results indicate that endogenously-produced and exogenously-applied melatonin are beneficial to the oral cavity.

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Melatonin (*N*-acetyl-5-methoxytryptamine) was discovered in extracts of the bovine pineal gland and synthesis in this organ was determined in 1958. Subsequently, however, high melatonin production has been observed in numerous other tissues (1).

Melatonin has multiple, diverse physiological functions. Some of these actions are mediated by specific receptors in the membranes of most, if not all, cells (2). Melatonin also has receptor-independent free radical scavenging actions (3). Finally, melatonin has indirect protective functions against reactive oxygen (ROS) and reactive nitrogen species via its ability to stimulate antioxidative enzymes (4,5). The combination of the direct and indirect antioxidative actions of melatonin assists this molecule in potently resisting oxidative damage throughout the body, including in the oral cavity.

Melatonin is not in equilibrium within organisms. Quite the contrary, melatonin's concentrations vary widely among different bodily fluids. In saliva, melatonin levels are lower than those in simultaneously collected blood samples. Within cells, melatonin also is not equally distributed in the organelles and these levels are commonly higher than in simultaneously collected blood samples, for example, in hepatocytes melatonin

concentrations in cell membranes > mitochondria > nucleus > cytosol (6). It is assumed that similar concentration differences exist in organelles of other cells.

Melatonin in the oral cavity

The melatonin rhythm observed in the serum of vertebrates (7,8) is also expressed in the saliva (9,10). Consequently, the cycle of melatonin in saliva is a reliable surrogate of that in the blood. Indeed, disturbances of the salivary melatonin rhythm have frequently been used to judge perturbations of the blood melatonin cycle, pineal melatonin synthesis and alterations in the biological clock (11).

The levels of melatonin in the saliva are roughly one-fourth to one-third those in the general circulation (ranging from 1 to 5 pg/mL in the day and up to 50 pg/mL at night) (9). Melatonin in the saliva is believed to be from the unbound melatonin component in the systemic circulation that passively enters the mucous/serous cells of the major salivary glands (parotid, submaxillary and sublingual glands). It is discharged from the individual acinar cells of the salivary glands due to the contraction of the myoepithelial elements of the acini. Given that the quantity of melatonin that enters the oral cavity is proportional to salivary flow, xerostomia is likely associated with low levels of melatonin in the oral cavity. Whether the lingual, buccal or palatine mucous/serous secreting glands contribute to the melatonin concentration in the oral cavity is unknown.

The salivary glands may themselves synthesize melatonin. Recently, Shimozuma *et al*. (12) immunohistochemically identified the expression of the enzymes that mediate the serotonin-to-melatonin transformation in the major salivary glands of the rat and in the human submandibular gland. Thus, both arylalkylamine *N*-acetyltransferase and hydroxyindole-*O*-methyltransferase (currently known as acetylserotonin methyltransferase) were shown to be expressed in the striated ducts and epithelial cells of these glands. These enzymes convert serotonin to melatonin (8).

Tablets, capsules and liquid products containing melatonin are widely available and are used, usually on a daily basis, as a sleep aid, antidepressant, circadian rhythm regulator, antioxidant or for other reasons (3,13,14). In particular, when an oral liquid product or the sublingual tablet is used, concentrations of melatonin in the oral cavity increase substantially, at least in the short term. Given the marked antioxidant (15,16) and anti-inflammatory (17,18) activities of the indole, use of these melatonin preparations may significantly improve oral health.

Other factors that affect the amount of measurable melatonin in the saliva are the type of food eaten before the saliva sample is collected. Fruits, grains, vegetables and nuts, e.g. tart cherries (19), rice (20), tomato (21), walnuts (22), cucumber (23) and others, as well as liquids that are commonly used, e.g. coffee (24), tea (25), beer (26) and wine (27), also contain melatonin. This may become more relevant considering that edible foods are being genetically engineered to produce increased amounts of melatonin. Plants have been genetically engineered to produce elevated amounts of melatonin to increase the nutritional value of the edible product (28) and to provide antioxidant protection for the plant itself (20).

Melatonin also has been added to dental hygiene products and a patent has been issued for melatonin-containing toothpaste and mouthwash (US2006/0127326-A1). If these latter products become available and are used before sleep at night, they could maintain higher levels of melatonin in the oral cavity at a time salivary secretion is at a minimum. Finally, a recently patented gel, which contains slowly released melatonin that can be applied in the oral cavity, is effective in reducing mucosal lesions resulting from a variety of causes (G. Escames, D. Acuna-Castroviejo unpublished).

The presence of melatonin in the gingival crevicular fluid of humans was reported by Srinath and colleagues (29). The measured levels in this fluid from individuals with a healthy mouth (absence of gingivitis) was 1.54 pg melatonin/mL compared to 2.17 pg/mL in salivary fluid. These values are low as would be expected for oral cavity fluid collected with the patients in the light (9). However, the results would have been more meaningful had the crevicular fluid been collected also during the night and the day/night melatonin levels been compared.

Cutando *et al*. (30) examined the association between daytime salivary melatonin levels and the severity of the inflammatory status in periodontal disease, evaluated using the community periodontal index. They reported an inverse correlation between plasma and salivary melatonin levels and the severity of periodontitis. While this inverse correlation does not prove a definitive association, individuals with greater salivary flow had higher concentrations of melatonin in this fluid. The negative correlation between salivary melatonin concentrations and the community periodontal index may have been related to the more rapid utilization of melatonin as an antioxidant; this could have been examined by measuring metabolites that are formed when melatonin detoxifies radicals. Alternatively, the more severe periodontitis, theoretically at least, could have been a result of reduced secretion of melatonin into the saliva. Under any circumstances, a reduction in melatonin while potentially aggravating periodontitis is not the cause of this condition.

Related to this is the finding of a positive association between xerostomia and poorer periodontal status. Dry mouth would, therefore, mean little melatonin entering the oral cavity because of reduced salivary flow. In the elderly, it is common that saliva flow is reduced by 25–33% (9). Likewise, Sjögren's disease, a condition common in females compared to its occurrence in males, would also be expected to have little melatonin in the oral cavity and poorer oral health.

Additional studies as to whether oral pathologies influence melatonin levels in oral cavity fluids reflects on growing interest in the role of this

indoleamine in the maintenance of optimally functioning mucosal and submucosal tissues in the mouth. Like Cutando *et al*. (30), Almughrabi *et al*. (31) compared salivary and gingival crevicular fluid melatonin levels in four groups of patients, i.e. those with a healthy periodontium, plaque-induced gingivitis, chronic periodontitis or aggressive periodontitis. The measured values were inversely related to the severity of the oral pathology. Thus, lower melatonin levels were found in patients with chronic or aggressive periodontitis than in subjects who had a healthy periodontium or simple gingivitis (without plaque formation) in both the saliva and crevicular fluid. Given that salivary (and probably crevicular fluid) levels of melatonin correlate with serum levels of the indoleamine, it could be assumed that patients with advanced periodontitis probably also had depressed serum levels of melatonin. Conversely, the diminished concentrations may have been a consequence of the more rapid utilization of melatonin as it functioned in the detoxification of free radicals whose production is elevated during inflammation. Finally, the melatonin measurements were done on daytime-collected fluid samples. During the day, these values are normally near their minimal concentrations. Had group differences been apparent in the elevated nocturnal melatonin levels, they perhaps would have been a more reliable predictor of the severity of periodontal disease.

Additional information regarding the physiology of melatonin in oral cavity fluid was provided when it was observed that the normally depressed daytime salivary melatonin levels in patients with periodontitis were restored after non-surgical periodontal therapy, which was not accompanied by a change in serum melatonin levels (32). This suggests that lower melatonin concentrations in saliva may be a result of its greater utilization as a free radical scavenger as inflammation generates elevated levels of ROS (33).

Severe periodontitis also causes negative changes in cells far from the oral cavity, e.g. in the lungs, kidney, liver, etc., due to the escape of lipopolysaccharide (LPS) into the blood vascular system from its original site in the mouth (34). By limiting the severity of periodontitis, melatonin would also protect other organs from oxidative damage.

Melatonin receptor-mediated and receptor-independent actions in the oral cavity

Membrane receptors for melatonin exist on most, if not all, cells (2). These receptors, designated MT1 and MT2, are members of the family of G protein-coupled receptors and have the characteristic seven transmembrane domains. Activation of these receptors leads to the modulation of any of several intracellular signals, including adenylate cyclase, guanylyl cyclase, phospholipase A_2 and C and changes in calcium and potassium channels.

Pharmacologically, melatonin receptors have been tentatively identified in the parotid gland. Luzindole, a melatonin receptor antagonist, blocked melatonin-mediated protein synthesis in the rat parotid gland consistent with the presence of MT1 and MT2 receptors in this organ (35). Only the MT1 receptor has been identified in the mucosal cells of the oral cavity (12). It is presumed that the squamous lining cells of the oral cavity may be equipped with all the receptors typical of other stratified squamous epithelium.

The lamina propria of the gingiva and periodontium often contains numerous immunocompetent cells. Melatonin, a well-known promoter of the immune system (18,36), as well as its metabolites N^1-acetyl-N^2-formyl-5-methoxykynuramine and N^1-acetyl-5-methoxykynuramine (37), have significant anti-inflammatory actions. Immunocompetent cells also produce their own melatonin (38), and the indole is believed to act in an intracrine, autocrine or paracrine manner in these cells. Considering that inflammation is a major determinant of oral health, orally available melatonin could have a role in reducing gingival inflammation.

Melatonin, as well as several of its metabolites that are formed when melatonin neutralizes toxic free radicals, are highly effective in reducing oxidative damage to tissues via receptor-independent actions (39). Because of these combined reactions, which have come to be known as melatonin's antioxidant cascade, melatonin is highly efficient at detoxifying a number of reactive species and thereby reducing the cellular and molecular damage meted out by partially reduced oxygen species (40). This has many implications for tissues of the oral cavity where oxidative stress is common.

Evidence supporting the function and use of melatonin in the oral cavity

The diversity of functions of melatonin has been recognized for at least two decades and recent research has further emphasized the ubiquitous actions of this ancient indoleamine (41). In view of this, to assume that melatonin does not have functions in the tissues of the oral cavity, as in other organs, would be an error.

Oral herpes infections

Herpes simplex lesions (fever blisters, cold sores) of the mucosa of the lips and oral cavity are often painful and unsightly. Boga and colleagues (42) recently reviewed the published literature related to the antagonistic actions of melatonin on viral infections. These results support the idea that melatonin would likely ameliorate the symptoms of at least some viral infections. These infections are frequently exacerbated by a weakened immune system and the resulting molecular damage is often because of free radicals (43). Melatonin stimulates both the innate and adaptive immune responses and the indoleamine differentially modulates enzymes with pro-inflammatory actions while limiting the production of inflammatory mediators, including cytokines and leukotrienes. These actions, coupled with the free radical scavenging capabilities of melatonin and its by-products, are

consistent with its ability to resist viral infections, although it may not kill the viruses. While the literature related to the ability of melatonin to resist viral infections generally is quite extensive (42), data on its relation to herpes infections of the oral cavity are limited, with only a single incomplete report being published (30). If, in fact, melatonin would be proven as an effective treatment for oral herpes infections, it would have implications for genital herpes as well. The results would also be of interest given that the usual prescription drugs taken for herpes infections have untoward side effects. In addition, a combination of melatonin with these drugs, e.g. acyclovir, may also prove of value given that melatonin has been shown to decrease the toxicity of many medications.

Gingivitis and periodontitis

Gingivitis and periodontitis are common inflammatory conditions that affect soft tissues of the oral cavity (Fig. 1). Advanced periodontitis can eventually destroy the periodontal ligament and erode alveolar bone thereby leading to tooth loss. Severe inflammatory responses are associated with massive free radical generation. Thus, the actions of melatonin as an anti-inflammatory and antioxidative agent could be beneficial, particularly when placed directly in the mouth, to abate the severity of inflammation of the gingiva and periodontium.

As the current review was being compiled, a number of studies relating to melatonin use as a treatment for periodontitis were published. To test this association, Kara *et al.* (44) placed a ligature in a subgingival position on the mandibular first molar teeth in rats; this is a commonly used method to promote plaque accumulation and the associated inflammatory response (45). After 4 wk, the ligatures were removed and the animals were given intraperitoneal placebo or melatonin (15 mg/kg) daily for 15 d. The authors claimed that melatonin treatment led to reduced serum levels of the proinflammatory cytokines, interleukin-1B and tumor necrosis factor-alpha, and lowered the amount of 8-hydroxy-2′-deoxyguanaine (an oxidatively damaged DNA product) in the gingival muscle tissue. Additionally, melatonin stimulated the production of glutathione, an important intracellular antioxidant, in the same tissues and preserved the histomorphological appearance of the gingival mucosa as evidenced by the reduction in inflammatory cell recruitment to the affected oral tissues.

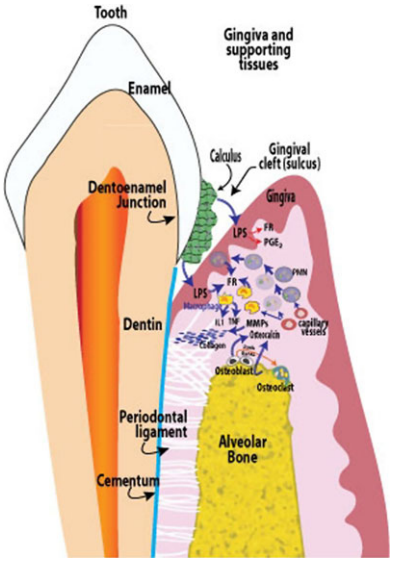

Fig. 1. Mechanisms of gingivitis, periodontitis and alveolar bone loss. Gram-negative bacteria in calculus, often located in the gingival cleft (sulcus) release toxic LPS leading to the production and discharge of cytokines, e.g. IL-1 and TNF-α, and the generation of FR. The resulting oxidative stress stimulates the activity of MMPs, which break down intracellular tissues, including collagen in the periodontal ligament leading to its disintegration. PMN leukocytes migrate from blood vessels to the inflammatory site. They, along with macrophages, PGE_2 and LPS generate additional FR that destroy tissue. Stimulation of osteoclastic activity dissolves alveolar bone by processes that also involve FR. The dissolution of the periodontal ligament and associated bone loss causes loosening of the tooth and potential tooth loss. Melatonin works at several sites to limit inflammation and tissue damage. Melatonin does this by: (i) limiting recruitment of PMN to the site; (ii) reducing the toxicity of LPS; (iii) inhibiting MMPs; (iv) suppressing osteoclastic activity; and (v) stimulating osteoblastic activity. Further discussion and associated references can be found in the text. FR, free radicals; IL, interleukin; LPS, lipopolysaccharide; MMP, matrix metalloproteinases; PGE_2, prostaglandin E_2; PMN, polymorphonuclear; RANK, receptor activator of nuclear factor kappa B; RANKL, receptor activator of nuclear factor kappa B ligand; TNF, tumor necrosis factor.

Cutando *et al.* (46), who are major advocates of research on the use of melatonin in suppressing periodontal disease, recently published two reports that begin to describe the mechanisms by which the indoleamine operates in these situations. They selected patients with diabetes for the study, as they are predisposed to periodontitis. Before melatonin treatment, patients with diabetes had significantly elevated salivary levels of alkaline and acid phosphatase as well as higher values of osteopontin (bone sialoprotein) and osteocalcin compared to these values in non-diabetic control subjects. Following the topical application of melatonin (1% orabase cream formula) to the gingiva once daily for 20 d there were significant reductions in each of these four parameters. Moreover, the gingival index and pocket depth were reduced because of melatonin use.

In their second published report, Cutando and colleagues (47) again studied patients diagnosed with diabetes who also had periodontitis and they estimated several salivary and serum parameters that affect the health of oral cavity tissues. After the initial measurement of salivary RANKL and osteoprotegerin (OPG) and both salivary and serum melatonin levels, the patients applied melatonin gel (as in the previous study) (46) to their gingiva for 20 d. Relative to those in healthy controls, patients with diabetes initially displayed elevated levels of RANKL in their saliva as well as depressed OPG in the salivary samples and diminished melatonin in both saliva and serum. Following melatonin treatment, the patients with diabetes had statistically significant reductions in their gingival index pocket depth and RANKL levels as well as higher OPG concentrations

in their saliva and melatonin levels in both fluids. The augmented OPG values correlated significantly with the changes in the gingival index and pocket depth.

Collectively, several of the indices evaluated by Cutando *et al.* (46,47) are consistent with melatonin promoting the health of alveolar bone by reducing osteoclastic activity. These findings are compatible with the actions of melatonin on osseous tissue throughout the body where the indoleamine has been shown to maintain and restore bone health. As the other studies showed that melatonin also reduces the severity of the inflammatory response of periodontitis (48), the implication is that melatonin may be of use as an agent to preserve periodontal health, particularly in people who smoke, use methamphetamines, in the aged when endogenous melatonin levels diminish and in many other situations.

Oxidative damage and inflammation

The continued destruction of cellular lipids is believed to be a major event that occurs during the progression of the inflammatory response in the periodontium (Fig. 1) (49). LPS discharged from the bacteria recruits neutrophils and macrophages to this tissue; the associated respiratory burst by these inflammatory cells produces free radicals in excess of what endogenous antioxidative system can overcome and molecular damage and cell death ensues. The molecular destruction comes in the form of altered lipids, disfigured DNA and protein destruction. Melatonin and its metabolites have repeatedly been shown to protect each of the categories of molecules from oxidative damage (3,39). These actions of melatonin, coupled with anti-inflammatory effects (18), are probably highly capable of resisting tissue destruction associated with periodontitis (50).

Mechanistically, melatonin has well characterized anti-inflammatory actions, but its ability specifically to influence experimental periodontitis was only recently examined. In the initial study in this field (51), RAW264.7 cells were challenged with *Prevotella intermedia*-derived LPS. *P. intermedia* is a major contributor to inflammation of the periodontium. Melatonin interfered with actions of LPS by limiting NF-κB signaling; thus, it reduced the translocation of NF-κB p50 subunit into the nucleus and its binding to DNA thereby suppressing STAT1 signaling. These findings are consistent with the known actions of melatonin on inflammatory responses (18,52). As *P. intermedia* are abundant in the oral cavity, the observed actions of melatonin in this study could aid in alleviating gingivitis/periodontitis.

Prosthodontic benefits

Breakdown of the periodontal ligament and alveolar bone resorption, which can lead to tooth loss, is believed to involve activation of matrix metalloproteinases, which destroy the supporting tissues of the tooth (53). Given that melatonin prevents activation of metalloproteinase-9 (54), which contributes to periodontal membrane disintegration and erosion of the supporting bone, the indole would also be expected to reduce tooth loss in cases of severe periodontitis (Fig. 1).

There is a significant amount of experimental data showing that melatonin promotes the differentiation of mesenchymal stem cells into osteoblasts and enhances bone formation (55). Additionally, melatonin boosts type I collagen synthesis by human osteoblasts and elevates the expression of bone sialoprotein as well as other bone protein markers. Finally, melatonin under the conditions of one study, reduced the normal period of osteoblast differentiation from 21 to 12 d (56). In general, the evidence is compelling that melatonin has a positive impact in bone health.

In addition to its promotional effect on osteoblast-mediated bone formation, another possible target of melatonin to influence bone mass is the osteoclast. These cells incite bone resorption via a process involving free radicals and, as melatonin neutralizes these toxic brigands, the indole interferes with the capacity of osteoclasts to break down bone (57). Which of the actions of melatonin, i.e. promotion of bone formation or reduction of bone resorption, is most important in terms of the indole maintaining bone health is debated. However, both processes would be beneficial.

Concurrent with the studies related to bone formation and dissolution, the influence of melatonin on the thoroughness of osteointegration after placement of dental implants was examined. After tooth extraction from the mandible of beagle dogs, 1.2 mg lyophilized melatonin powder was added directly into the bone cavity before implant placement (58). When the implant sites were examined 2 wk later, the amount of bone in contact with the metal implants was significantly greater in the melatonin-treated sockets than in the controls. This was assessed by measuring the amount of bone in direct contact with the implant, the improved density of the bone and amount of new bone formed. The beneficial effects of locally applied melatonin in terms of bone-to-implant contact and peri-implant bone were still apparent 5 and 8 wk after implant placement (59). When melatonin and growth hormone, both applied directly into the evacuated sockets after tooth extraction, were used, synergistic effects were seen in terms of osseointegration of the dental implants (60). Additional studies using melatonin combined with collagenized porcine bone to accelerate the osteointegration of the rough discrete calcium deposit, surface implants in dogs also had a positive outcome (61). Again, melatonin promoted all aspects of bone growth and stabilized the implants.

Tooth extraction is commonly associated with extensive polymorphonuclear leukocyte infiltration to the site with massive ROS/reactive nitrogen species generation leading to elevated oxidative stress, including DNA damage. Cutando *et al.* (62) showed that topically applied melatonin into the evacuated sockets following tooth removal of the maxillary and mandibular premolars and molars from beagle

dogs significantly reduced all parameters of oxidative stress in the associated tissues. By limiting the tissue damage, melatonin would curb the negative consequences of tooth removal and encourage more rapid healing of the wound.

Methacrylate toxicity

Monomers of methacrylates are in common use in restorative and aesthetic dentistry. They have proven highly useful as their polymers have excellent mechanical properties and they have a high affinity for enamel and dentin. In the event of incomplete polymerization of the monomers, however, some free monomers may be released into the oral cavity after which they could exhibit toxicity either locally or at distant sites. The methacrylates may also be degraded by salivary enzymes and/or due to shearing forces associated with chewing. In particular, if the restoration is near the dentinoenamel junction or invades the dentin, monomers could also enter dentinal tubules and be transported to the dental pulp where they would have access to the systemic circulation.

Whether methacrylate monomers possess cytotoxicity or genotoxicity has been extensively debated with opinions differing as to the level of toxicity. The exposure of human gingival fibroblasts to methacrylate monomers reportedly induces DNA double-strand breaks (63); such breaks are of particular concern when they do not undergo repair. The basis of the DNA damage by methacrylate monomers is likely the oxygen and/or nitrogen-based reactants that are generated. Schweikl *et al*. (64) claimed that the production of ROS in human fibroblasts occurs when these cells are incubated in a solution of triethylene glycol dimethacrylate.

Against this background, Blasiak *et al*. (65) tested whether the antioxidant melatonin would afford protection against DNA damage and repair mechanisms in human gingival fibroblasts after their exposure to a dental adhesive containing 45% 2-hydroxyethyl methacrylate and 55% bisphenol A-diglycidyl dimethacrylate. The neutral comet assay was used to evaluate DNA double-strand breaks. Melatonin reduced DNA double-strand breaks and fibroblast apoptosis resulting from methacrylate exposure. Likewise, the slowed DNA repair was improved in the presence of melatonin. These findings imply that oxidative processes may account for the DNA damage caused by methacrylate exposure. One implication of the results is that methacrylates leached from dental fillings may cause DNA damage *in vivo* and the regular use of sublingual melatonin, in particular, may reduce these lesions and any consequences thereof (66).

Chlorhexidine toxicity

Chlorhexidine (CHX) is a disinfectant commonly used to limit subgingival plaque formation (67). This dicationic biguanide has both bacteriostatic and bactericidal properties (68). CHX is not only destructive to bacteria, however, it is also damaging to other oral cavity cells such that its useful concentration is limited by its toxicity (69). CHX has also been proposed as a potentially effective agent to support periodontal bone regeneration (70). As with many drugs, the destructive actions of CHX on normal tissues, including osteoblasts, is related to excessive free radical generation (71). Given that melatonin, due to its free radical scavenging activities and antioxidative actions (3,16,17,39), has been repeatedly shown to reduce the destructive side effects of many agents, it is predicted that melatonin would also limit the toxicity of CHX thereby making it a more effective agent for use in preserving oral health.

Oral cancer

Melatonin displays a wide variety of mechanisms by which it inhibits cancer in many organs. However, studies on the effects of melatonin on oral cancer are still rare (72). Relative to precancerous oral diseases, leukoplakia (73) and lichen planus (74) should be examined in reference to melatonin as ROS are involved in their pathogenesis. Recently, the above-mentioned melatonin-containing pharmaceutical gel (patent number, P201191400001816), when applied in the oral cavity, was found to virtually eliminate the mucositis and mucosal lesions resulting from radiotherapy (G. Escames, unpublished). At the cellular level, the protective actions of melatonin were particularly obvious in terms of reducing mitochondrial damage in the mucosal cells.

A common treatment for cancer of the head and neck is ionizing radiation, which often leads to mucosal lesions of the oral cavity. The beneficial actions of melatonin in limiting molecular damage to mitochondria resulting from ionizing radiation during oral mucositis are not unexpected. Melatonin is a known protector against ionizing radiation. The ulcerated and inflammatory lesions characteristic of mucositis (75) are a result of massive oxidative damage and the release of toxic cytokines. As mentioned above, melatonin has both potent antioxidant (16,39,69) and anti-inflammatory activity (18). In light of these data, it would seem important to test melatonin more extensively, alone or in combination with other agents, as a protector against radiotherapy- and chemotherapy-mediated mucositis.

Dental caries

Finally, considering the reported antibacterial properties of melatonin (76,77), its ability to reduce dental caries, which are often related to *Streptococcus mutans* (78,79) as well as other bacteria should be examined. Individuals who use sublingual melatonin on a regular basis may have reduced tooth decay. Here again, melatonin-enriched toothpastes, mouth washes and dental gels may prove of value.

Conclusions and perspectives

The data summarized in this report highlight the publications related to the potential utility of melatonin to treat oral disorders and pathologies.

Of particular note are the likely benefits of melatonin as a treatment to reduce inflammatory responses in the gingiva and periodontium and as an aid in preserving and promoting alveolar bone growth. In addition, other potential applications for melatonin are summarized.

While research related to the range of functions of melatonin in the oral cavity is in its early stages, it already seems obvious that melatonin acts on these tissues as it does on others. Certainly, given the antioxidant and anti-inflammatory capabilities of melatonin and its by-products, these molecules may reduce pathogenetic processes associated with a variety of oral afflictions including, for example, candidiasis, leukoplakia, recurrent aphthous ulceration and lichen planus. Each of these conditions has a free radical component. This is in addition to the more obvious benefit melatonin would be expected to have in quelling inflammation and tissue damage in the periodontium and reducing the likelihood of certain types of oral cancer.

There are other situations in which melatonin may protect tissues of the oral cavity from harm. For example, methamphetamine use is devastatingly damaging to the soft and hard tissues of the oral cavity (so-called meth mouth). These lesions involve, among other processes, free radical damage and in other tissues melatonin has been shown to reduce methamphetamine-mediated molecular destruction. Perhaps the common use of oral melatonin products by individuals who abuse this toxic drug would help preserve the integrity of the oral tissues. This may also be the case for individuals who smoke, chew tobacco products, use "betel nut" or dip snuff. These bad habits normally seriously compromise good oral health. Finally, individuals who have chronic systemic diseases, e.g. diabetes, which influence the integrity of tissues in the oral cavity may also benefit from the regular oral use of melatonin.

It may prove interesting to examine the association of the circadian melatonin rhythm to the incremental growth lines in the enamel (lines of Retzius). These increments reportedly mark periods of growth and no growth over a 24 h interval.

Melatonin deposited directly into the oral cavity would have the highest expectation of improving the health of associated tissues. In this regard, sublingual melatonin tablets and oral melatonin sprays are currently available and should be examined relative to their ability to reduce oral pathologies described in this review. Additionally, the already patented melatonin-containing toothpastes, mouthwashes and pharmaceutical gel should be investigated more thoroughly as to their potential aid in improving oral health.

Conflict of interest

None of the authors received research funds for the studies reviewed in this article. GE holds the patent on the melatonin-containing pharmaceutical gel. There are no other conflicts of interest.

Author contributions

All co-authors were actively engaged in the discussions of data and the writing of the review. The initial draft was written by RJR but all co-authors made substantial suggestions for revision of the report. All co-authors have read and approve the final submitted version of the paper.

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