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Review

Melatonin and periodontal tissues: Molecular and clinical perspectives

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ABSTRACT

Periodontal disease is a frequent chronic inflammatory pathology that implies the destruction of the tissues supporting the teeth, which represents a high sanitary cost. It usually appears associated with other systemic conditions such as diabetes, metabolic syndrome, depression and Alzheimer disease among others. The presence of melatonin and its receptors in the oral cavity supports the hypothesis that this hormone could play a role in homeostasis of periodontal tissues. In the present review we will discuss the potential role of melatonin, a circadian synchronizing hormone, with proved antiinflammatory and antioxidant profile, in the pathogenesis and treatment of periodontitis. Particular emphasis will be placed on the role of the indolamine in the treatment of periodontal disease when this oral condition is comorbid with other pathologies that would also benefit from the therapeutic potential of melatonin and its analogs through diverse mechanisms.

Contents

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1. Introduction

Melatonin (MEL), (N-acetyl-5-methoxytryptamine) is a natural hormone produced in different organs such as retina, gastrointestinal tract, bone marrow, leukocytes, lymphocytes and skin but mainly in the pineal gland, where is synthesized in a circadian manner, showing the highest levels of secretion at night, in most species [1]. Pineal production of MEL is the result of a series of well-known reactions [2]. Circadian information related to light/dark environment is transmitted through retino-hypothalamic tract to suprachiasmatic nucleus. This central rhythm generator, in turn, sends a stimulus to the upper thoracic cord and superior cervical ganglia, and through postganglionic sympathetic fibres to the pineal gland, thus determining the polysynaptic activation of beta-adrenergic receptors [3]. Finally, this neural signal is translated into activating the endocrine MEL synthesis pathway, in which the activity of the enzyme arylalkylamine *N*-acetyltransferase (AA-NAT), a key enzyme in MEL biosynthesis, is increased from 30 to 70 times at night and it constitutes a rate-limiting step [4].

Most of MEL actions are mediated by its G protein-coupled membrane (MT1 and MT2) as well as its nuclear (RZR/ROR) receptors [5]. MT1 receptor is present in the brain, cardiovascular system, immune system, testes, ovary, skin, liver, kidney, adrenal cortex, placenta, breast, retina, pancreas and spleen [6]. MT2 receptor, 60% homologous to MT1 receptor, shares the distribution with MT1. There is a MEL-related receptor GPR50, an orphan receptor which Exhibits 45% amino acid homology to MEL receptors. Although MEL does not bind to GPR50, this receptor may heterodimerize with the MT1 receptor, inhibiting its activity [7]. All the commercialized melatoninergic drugs act on both types of receptors without significant selectivity [8]. A third receptor, MT3, with low affinity for MEL and not-coupled to G protein, has initially been found in hamsters and rabbits. It has been reported that this MT3 is analogous to human quinone reductase II and it may contribute to some antioxidant and protective effects of the indolamine [9]. MEL can also bind to nuclear retinoid orphan receptors: ROR and RZR [10]. In addition, several important effects of MEL are displayed without receptor involvement. The pineal hormone passes freely through membranes and reaches all body compartments, whereas MEL synthesized in retina, intestine and other tissue apparently acts locally, in a paracrine way [11].

This hormone regulates important physiological and pathological processes. By binding to its membrane receptors, MEL modulates seasonal and circadian rhythms, acting as an effective synchronizing agent in several situations, such as maternal-fetus entrainment [12], dissociated circadian rhythms induced by a short light–dark cycle [13], insomnia and jetlag [14]. MEL also reduces oxidative stress: directly by scavenging reactive oxygen and nitrogen species and indirectly by stimulating antioxidant enzymes while suppressing pro-oxidant ones. This action diminishes lipid and protein peroxidation [15]. The high levels of MEL in mitochondria could explain its antiapoptotic and antioxidant properties. The indolamine also contributes to protect DNA integrity by activating DNA reparation enzymes [16]. In addition, it modulates immune responses, body weight, reproduction, bone metabolism and tumor growth [17].

MEL synchronizing properties, its anti-inflammatory and antioxidant effects and its immune modulation capacities together with its pharmacokinetic and pharmacodynamic profiles are key characteristics that justify the therapeutic use of this hormone as well as some synthetic analogs for the treatment of various conditions such as diabetes, metabolic and cardiovascular diseases, sleep disorders, Parkinson, affective disorders, chronic inflammatory diseases and cancer among others, be it as monotherapy or as an add-on drug together with other pharmacological agents [18]. In the present article we review the relationship between MEL and different conditions affecting the oral cavity, be it primarily or secondary to other diseases such as diabetes and psychiatric disease among others, discussing the potential benefits of its therapeutic use.

2. Melatonin in the oral cavity and periodontal diseases

Ubiquitious MEL is also present in oral cavity. MEL level in saliva is one-fourth to one-third of the level in blood circulation and ranges from 1 to 5 pg/ml during daytime to 50 pg/ml after midnight peak [19]. Salivary MEL is believed to derive from the unbound melatonin present in systemic circulation which, being a lipophilic molecule, passively enters the cells of the major salivary glands. However, Shimozuma et al. [20] have recently identified the expression of AA-NAT in major salivary rodent and human glands, which suggests that MEL could also be synthesized locally in this tissue. The presence of both MT1 and MT2 receptors in salivary gland ducts and acini, oral epithelium, fibroblasts of the mucosal lamina propria and osteoblasts of maxilar alveolar bone among other oral cells, has been confirmed in different studies [5,21,22]. The importance of MEL in salivary fluid and its precise effects in oral cavity remain to be studied in depth.

Periodontal disease is one of the most common oral infectious conditions among humans, gingivitis and periodontitis being the two major forms of this pathology. It implies the destruction of the tissues supporting the teeth (gingiva, periodontal ligament, radicular cement and alveolar bone) due to the accumulation and maturation of oral bacteria as well as the subsequent immune response displayed by the host [23]. According to Chapple [24], periodontitis is defined as a "complex heterogenic biological phenomenon, derived from the interaction between genetic and epigenetic factors together with environmental determinants that lead to a dysbalance of oral microbiome homeostasis and an inadequate imunitary response". This condition is aggravated by an overproduction of reactive oxygen species (ROS) that leads to peroxidation of membranes, damaging cellular structures [25]. Once established, this condition evolves with reduction of collagen fibres, loss of the attachment to the radicular surface and resorption of alveolar bone [26], eventually causing teeth loss.

There are evidences that MEL could improve periodontal status. Almughrabi et al. [18] examined the association between daytime salivary MEL levels and the severity of the inflammatory status in 70 subjects with periodontal disease. Patients with chronic and aggressive periodontitis had lower levels of MEL both in gingival crevicular fluid and saliva than patients with mild gingivitis and healthy subjects. Similar results were obtained by Bertl et al. [27], who also found that non surgical periodontal therapy resulted in a recovery of the decreased salivary MEL levels in patients with periodontitis. Cutando et al. [28] reported an inverse correlation between plasma and salivary MEL levels and the severity of periodontitis, suggesting that MEL is consumed when scavenging free radicals generated by inflammation. Interestingly, Lodhi et al. [29] found opposite results, being MEL higher in those patients with the most severe inflammatory status. These elevated salivary levels could be the result of compensatory protective mechanism to fight inflammation of the gingiva. More studies including wider populations to assess this variable would be welcome. In any case, salivary MEL could act as a diagnostic biomarker in periodontal disease [30]. Analogous results were reached in animal models. Kara et al. [31] found an improvement of periodontal status with reduced inflammatory cytokines, lower oxidative stress parameters and less periodontal destruction, in rats treated with MEL after periodontitis induction. Similarly, Köse et al. [32] demonstrated a recovery of oxidative stress after inflammation triggered by radiotherapy (Fig. 1).