ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 9, Issue, 8(D), pp. 28518-28523, August, 2018

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Review Article

MELATONIN AND PERIODONTIUM

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DOI: http://dx.doi.org/10.24327/ijrsr.2018.0908.2473

ARTICLE INFO

Article History:
Received 6th May, 2018
Received in revised form 10th June, 2018
Accepted 24th July, 2018
Published online 28th August, 2018

ABSTRACT

Melatonin (*N*-acetyl-5-methoxy tryptamine) is a substance secreted by multiple organs including the pineal gland, retina, bone marrow, the gastro-intestinal track, and the immune system. Its main function is the regulation of the circadian rhythm (day-night cycles). It plays an antiinflammatory, antioncotic, and immunomodulatory role by scavenging free-radicals and via interactions with cell membrane and intracellular proteins. Melatonin is capable of entering the oral cavity by diffusing into the saliva from blood. As the majority of the melatonin remains bound to serum albumin, the amount of melatonin in saliva is approximately one third of that present in the blood . Melatonin mainly exerts antioxidant effects by interacting with melatonin receptor 1 (MT1) and melatonin receptor 2 (MT2) receptors on cells. Perhaps, a potent antiinflammatory property of melatonin is linked to its ability to act as a scavenger of exogenous and endogenous reactive oxygen species (ROS) and reactive nitrogen species (RNS). In addition, both ROS and RNS have been associated with DNA mutations leading to carcinogenesis. The existence of MT1 receptors on healthy and cancerous oral mucosal cells is suggestive that melatonin may act as an antiinflammatory or antioncotic agent in the oral cavity; for example, its antiinflammatory effects have been reported on human gingival fibroblasts. Furthermore, intraperitoneal melatonin has been reported to reduce periodontitis in diabetic rats. Similarly, topical application of melatonin in diabetic patients has diminished the progression of periodontal bone loss as evident by the down-regulation of proinflammatory factors. Hence, it has been suggested that melatonin may be used in the management of periodontitis and antioncotic agents for oral cancer cells. The aim of this review is to critically analyze and summarize the research focusing on the potential of melatonin in the fields of oral medicine and periodontology.

INTRODUCTION

Periodontal disease is an oral inflammatory disorder of the periodontium that affects the supporting tissues of the teeth (alveolar bone, gums, and periodontal ligament), leading to progressive destruction of connective tissue attachment and alveolar bone. A consequence is the severe loss of supporting periodontal tissues and teeth, seen prevalently among adults and older people. Current information indicates that bacterial infection and accumulations on the teeth may be the primary causative agent of PD.[1,2] Nowadays, PD represents one of the most commonly reported chronic inflammatory adult conditions. Approximately 48% of U.S. adults have chronic PD, and similar or higher rates (up to 70%) have been reported in other populations[3]. PD incidence is increased by several risk factors; in general, all those conditions that provide the anaerobes ample time to survive in periodontal tissue or any medical conditions (e.g., HIV infections) that trigger host antibacterial defense mechanisms will likely promote PDs[4].

The severity of periodontitis is characterized by the degree of marginal bone loss, depth of periodontal pockets, degree of attachment loss, and number of teeth with furcation development[5]. In diagnosing PD, the probing depth is a good indicator of the advance of the disease. In a healthy periodontium, there is no loss of epithelial attachment or pocket formation and the periodontal pocket is less than 2 mm deep[6]. The disease state ranges from gingivitis to periodontitis and advanced periodontitis. Gingivitis, the most prevalent and mild form of PD, is characterized by the inflammation of the gums caused by plaque deposits, with possible bleeding when brushed or probed[5].Periodontitis can be identified by the

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hardening of plaque to form calculus, causing gum recession. This results in the formation of pockets between 3.5 and 5.5 mm between the tooth surface and the gum[7]. The symptoms are similar to those of gingivitis but are more severe due to higher accumulation of bacteria and stronger inflammatory responses. Advanced forms of periodontitis are also prevalent, affecting approximately 10%-30% of the adult population in the United States.[8] Advanced periodontitis is distinguished by excessive tissue loss of gingiva and alveolar bone and pockets greater than 5.5 mm in depth. This condition often leads to tooth exfoliation due to the destruction of the tooth connective ligaments.[9] The etiology and pathogenesis of PD are not completely clear. Human gingivitis and periodontitis are the results of an imbalance in the bacterial species that colonize the oral cavity and are characterized by complex interactions between pathogenic bacteria and the host's immunoinflammatory responses[11,12]. In the past three decades, marked advances have occurred in our understanding of the infectious agents of PD. There are more than 300 distinct species of bacteria present in the gingival area of the mouth, most of which exist in a commensal relationship with the host. However, three Gram-negative, anaerobic, or microaerophilic bacteria species, known as periodontal pathogens (Actinobacillus actinomycetemcomitans, Bacteroides forsythus, and Porphyromonas gingivalis), have been identified as being ubiquitous in periodontal plaque formations[9,10,12]. Moreover, within the past years, various herpes viruses, such as human cytomegalovirus and Epstein-Barr virus, have also emerged as pathogens in the destructive PD.[13] As reported above, the damage of periodontal tissues results both from a direct effect of the toxic products released by the bacteria and from the action of the immune system that, if stimulated by bacterial infection, produces and releases mediators that induce the effectors of connective tissue breakdown.[14,15] Numerous studies have showed that the destruction of periodontal tissue in PD is mainly due to host-derived mediators and free radicals[16,17]. Different mechanisms, including DNA damage, lipid peroxidation, protein damage, oxidation of important enzymes, and stimulation of proinflammatory cytokine release, have been implicated as causes of tissue damage by an increase in both ROS and reactive nitrogen species (RNS)[18,19]. An inverse relationship between peroxidation products and antioxidant molecules or enzymes in spontaneous or in experimental PD has been stressed[20-22]. Chapple *et al*[9]. reported that total antioxidant activity is reduced in saliva of patients with periodontitis relative to that in nonperiodontitis subjects. The imbalance between oxidative stress induced by ROS and the concentrations (or activity) of the antioxidants may lead to a further oxidative attack and substantial deterioration of the periodontal tissues,[23,24] resulting in tissue damage[25,26]. Microbial components, especially lipopolysaccharide (LPS), have the capacity to induce an initial infiltrate of inflammatory cells. Activated macrophages synthesize and secrete a variety of proinflammatory molecules, including some interleukins (IL-1α, IL-β, IL-6, and IL-8), tumor necrosis factor α (TNF-α), prostaglandins (PGE2), and hydrolytic enzymes[27]. These cytokines recruit polymorphonuclear leukocytes (PMN) to the site of infection[10]. PMN play a relevant role in the etiology of PD, as they are the predominant host immune response to oral bacterial infection. Upon stimulation by bacterial antigens, cytokines promote the PMN to express adhesion molecules and move out of the circulation to the site of infection[28]. When PMN arrive here, they can induce an autoamplification effect producing IL-8 to attract more PMN into the infection site. This is exacerbated by the ability of P. gingivalis to modulate the mobility and function of PMN within the site of infection:[10] a reduction of IL-8 secretion in epithelial cells, mediated by the bacterium, inhibits the recruitment of PMN to the infected area. At the site of infection, PMN produce proteolytic enzymes (e.g., elastase), but also ROS. Indeed, PMN in periodontal patients display an increased number, adhesion, and oxidative activity[29]. As the release of ROS is not target-specific, damage to host tissue also occurs. Gingival epithelial cells are highly susceptible to attack by PMN-derived oxidants;[30] human PMN produce in vitro desquamation (as a consequence of the digestion of extracellular matrix constituents by PMN neutral proteases) and lysis of gingival epithelial cells (caused by PMN oxidants generated by myeloperoxidase). In PD, a number of proteases that degrade collagen and extracellular matrix (ECM) play key roles in periodontal tissue breakdown.[31] A particular subgroup of matrix metalloproteinases (MMPs), called collagenases, is the major group of enzymes responsible for degradation of ECM and for collagen destruction in periodontitis. These latent collagenolytic enzymes are activated by ROS in the inflammatory environment, giving rise to elevated levels of interstitial collagenase in inflamed gingival tissue.[32] The attachment loss deepens the sulcus, creating a periodontal pocket. This pocket provides a microbial niche that can harbor on the order of 100 bacterial cells[33]. This event marks the transition from gingivitis to periodontitis. PD is clearly an important and potentially life-threatening condition, often underestimated by health professionals and the general population. The available evidence implicating inflammatory mediators and cells in the disease process suggests that local antioxidant status may be of importance in determining susceptibility to the disease and its progression following initial bacterial colonization.

Gold Standard Therapies in PD

Due the minimal symptoms of gingival bleeding and attachment loss, many individuals neglect to treat their disease. Left untreated, gingivitis may progress to irreversible periodontitis, resulting in tooth loss. Periodontal research has provided sufficient evidence indicating that, once diagnosed, chronic PD is successfully treatable[34]. The first therapeutic goal in treatment of PD is to alter or eliminate the origin of the microbes as well as the contributing risk factors. The majority of periodontal treatment modalities, however, attempt to arrest the progression of periodontal destruction in order to avoid tooth loss and preserve the healthy state of the periodontium[35]. Furthermore, in severe cases, regeneration of the periodontal attachments must be attempted[36]. The first nonsurgical step of PD treatment involves special cleaning called scaling and root planing. Supplemental treatment may include antiseptic mouth medications, either to aid the healing process or to further control the bacterial infection. Often, antibiotics may be administered, which may offer an effective alternative. Doxycycline, a wide-spectrum antibiotic, and other tetracyclines are frequently used in dental treatments for soft tissue and bone regeneration after PD because of their strong activity against periodontal pathogens; they are able to inhibit the activity of human MMPs and reduce the severity and

progression of PDs in animal models and humans[37]. Along with antibiotic therapy, if the periodontal pockets are not reduced or further loss of alveolar bone is observed, surgical treatment may therefore be beneficial to PD patients to prevent bone loss. If the PD has caused excessive loss of gum tissue or bone, then soft-tissue grafts or bone grafts may be performed to reduce further gum recession and bone loss.

New Perspectives in PD Treatment: Melatonin Supplementation

In recent years, the role of ROS, lipid peroxidation products, and antioxidant systems in the pathology of PD have been well clarified. It is now of importance to determine the possible contribution of diet to salivary antioxidant status because the use of antioxidant supplementation in the treatment or prevention of these chronic diseases of the oral cavity can be an excellent chance for preventing them. Recent medical and dental research in this area is geared toward the prevention of free radical-mediated diseases by using specific nutrient antioxidants supplementation. Melatonin was found to be released with saliva into the oral cavity and to be implicated in various dental and PDs: for this reason, it is one of the more prominent antioxidants used for this purpose. In particular, melatonin possesses two functions of great interest to dental professionals: first of all, its capacity to scavenge free radicals, thereby exerting antioxidative action[38,39] and second, the cell protective effect exerted by melatonin in situations of inflammation[40]. Nowadays, it is well known that melatonin not only would stimulate the immune system through the plasma fraction of the hormone but would also afford local protection though the salivary melatonin fraction[41] to better protect the cell populations affected by the periodontal process from the ROS generated by the inflammatory process. Saliva antioxidant capacity was significantly lower in diseased patients compared with controls. In addition, the ratio between saliva and serum antioxidants was also significantly lower in the diseased patients. It was proposed that the reduction in antioxidant capacity was either a direct causal factor in the PD patients or that the reduction was due to a reduction in scavenging antioxidants mediated through an increase in oxidative stress due to the pathogenesis of the disease. Cutando *et al*.[41] emphasized the physiological impact of melatonin in saliva: this little amine displays noticeable antioxidant activity in saliva[42] and helps protect the oral cavity from tissue damage due to oxidative stress. In a recent study, it was indirectly shown that nitric oxide (NO) production was elevated in the diseased periodontium. In ligature-induced periodontitis in rats, inducible nitric oxide synthase (iNOS) was expressed at higher concentrations at the ligated sites than at the nonligated sites.[43] The diseased tissue biopsies from periodontitis patients demonstrated a greater level of iNOS expression than the healthy tissue biopsies from the clinically nonperiodontitis patients. In particular, the basal layers of epithelium and macrophages, lymphocytes, and neutrophils in the connective tissue were found to stain positively for iNOS, only in diseased patients.[44] Recent evidence suggests that the pineal hormone melatonin, acting as a potent free radical scavenger, plays an important acute and chronic role in reducing or eliminating the oxidant damage produced by NO.[45] Based on a number of studies, it is estimated that melatonin inhibits the activity of NOS,[46,47] in particular iNOS, which produces excessive amounts of NO, thus contributing to the pathophysiology of inflammation and increasing the oxidative stress[48]. Furthermore, in PDs, the increase in free radical production coexists with a decrease in antioxidant defense. Besides its direct action as a free radical scavenger, melatonin influences the oxidative stress status indirectly by stabilizing the inner mitochondrial membrane and improving the electron transport chain located there[49]. It has been demonstrated that melatonin is a broad-spectrum antioxidant:[50,51] in pharmacological and physiological doses, it increases gene expression and activity of endogenous antioxidants, which are important in maintaining the integrity of vasculature and other tissues[52,53]. These antioxidant properties of melatonin could turn out very beneficial for treatment of the local inflammatory lesions and for accelerating the healing process (e.g., after tooth extration and other surgical procedures in the oral cavity). Recently, Cutando *et al*.[54] have shown the favorable effects of the local melatonin administration to the alveolar sockets after molar or premolar extraction in dogs. The animals without melatonin regimen showed an increase in lipid peroxidation, nitrite plus nitrate levels in plasma, and glutathione disulfide/glutathione ratio. Dogs who were administered 2 mg melatonin to the extration socket just after extraction did not show this stress diseases of the oral cavity including denture-induced stomatitis, gingivitis, healing of lesions, and ulcerations caused by tooth extration (alveolitis). Moreover, these studies indicate that topically applied melatonin to the oral mucosa in the area of damage or inflammation is effective in combating the inflammatory processes and acceleration of the healing of erosions and ulcerations in the oral cavity. Furthermore, melatonin seems to also have a direct effect above the cell populations of the immune system. It is known, for instance, that the metabolic products of periodontopathic bacteria decrease cytokine production including IL-2.[56,57] IL-2 regulates a series of processes in different cells of the immune system. A relationship between IL-2 and melatonin was described when it was found that melatonin stimulates the production of IL-2 by T lymphocytes.[58] On the other end, IL-2 can modulate the synthesis of melatonin at the level of the pineal gland[59]. Without doubt, this reciprocal modulation has important consequences at the time of treatment of periodontal patients who have, in one way or another, an altered immunological system. Thus, it was of interest to study the changes in the relationship between melatonin and IL-2 during periodontal pathologies. Moreover, earlier studies [60,61] showed that an increase in salivary and plasma melatonin resulted in stimulation of the CD4+ T cells, which possess membrane and nuclear receptors for the hormone.[58] This would stimulate the other immune cell populations via cytokine secretion (e.g., CD3+, CD19+, CD8+ cells), thereby facilitating the host reaction to an existing oral infection[62]. Such beneficial effects of melatonin could open new perspectives for the treatment of oral inflammatory processes,[41,42] suggesting that this indole hormone could have a protective function in fighting periodontal infection. However, the relationship between PDs and melatonin level remains to be better understood.

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How to cite this article:

Raheja.R *et al.,*2018, Melatonin and Periodontium. *Int J Recent Sci Res.* 9(8), pp.28518-28523.
DOI: http://dx.doi.org/10.24327/ijrsr.2018.0908.2473

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