Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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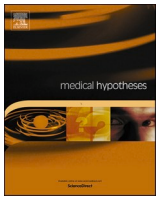

Role of NLRP3 inflammasome in COVID-19 and periodontitis: Possible protective effect of melatonin

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ABSTRACT

Daily new information emerges regarding the COVID-19, infection of SARS-CoV-2, which is considered a global pandemic. Angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) are required to complete the viral invasion pathway and are present in the oral mucosa, gingiva and periodontal pocket. Thus, increasing the likelihood of periodontitis and gingivitis caused by COVID-19. The cytokine storm during COVID-19 similarly arises during periodontal inflammation. Studies have reported that NOD-Like Receptor family pyrin domain-containing 3 (NLRP3) inflammasome is significant in the cytokine storm. Recently, the course of the COVID-19 has been related to the melatonin levels in both COVID-19 and periodontal diseases. It is known that melatonin prevents the activation of NLRP3 inflammasome. In light of these findings, we think that melatonin treatment during COVID-19 or periodontal diseases may prevent the damage seen in periodontal tissues by preventing the activation of NLRP3 inflammasome.

Introduction

COVID-19, an infection of SARS-CoV-2, which emerged in Wuhan, China in December 2019, has become a global pandemic, with the daily levels of mortality and morbidity continuing and increasing [1].

The oral cavity serves as an important reservoir for pathogens, through the continuous microbial communication between the environment and the human body. Since SARS-CoV-2 is being harboured in the oral cavity, and abundantly present in saliva, these saliva samples are at the forefront of COVID-19 diagnoses using PCR based methods [2]. SARS-CoV-2 requires angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) receptors for entry into cells. ACE2 and TMPRSS2 were abundantly expressed in the oral mucosa, gingiva, periodontal pocket and dorsal surface of the tongue [2,3].

Although the SARS-COV-2 invasion is mediated through the ACE2 receptors, ACE2 activity decreases after virus replication which involves the activation of ACE1 enzyme. It leads to increased infiltration of neutrophils, with a rise in levels of reactive oxygen species, nuclear factor-κB (NF-κB), and NLRP3 inflammasome [4,5]. Smell and taste disturbances caused by cytokine storm are involved in this syndrome's pathogenesis [6]. Activation of NLRP3 inflammasome leads to an increase in cytokine levels, which results in caspase-mediated inflammatory cell death (pyroptosis) and tissue loss [7].

The hypothesis

The elevation in cytokine expression in COVID-19 infection can cause disease in periodontal tissues or worsening of the COVID-19 prognosis is possible in people with periodontal disease. During COVID-19 infection, modulation of the immune system can prevent inflammation, especially in periodontal tissues. Likewise, suppression of periodontal inflammation can be expected in patients with periodontal disease who are also exposed to COVID-19. Since melatonin is an immunomodulator with a pleiotropic effect, we think it can suppress the synergistic effect between COVID-19 and periodontal diseases.

Evaluation of the hypothesis

Microorganisms mediate inflammation and tissue injury in periodontal diseases. Periodontal tissues are also likely to be affected by

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COVID-19, which has become widespread and distressing throughout the world [8]. The fact that ACE2 and TMPRSS, which play a crucial role in the invasion of SARS-CoV-2, are also localized in the mouth. Thus, the virus may also influence inflammation in the periodontal tissues and cytokine storm [9,10].

The pineal gland synthesizes melatonin, N-acetyl-5-methoxytryptamine, a powerful antioxidant and immunomodulator, and its activities such as regulating the seasonal reproductive cycles and circadian rhythm. Melatonin has been reported to have scavenging effects with direct action against free radicals [11,12]. Moreover, it enhances the antioxidant defence system by increasing endogenous antioxidants; such as superoxide dismutase, glutathione peroxidase, and catalase [13]. Additionally, melatonin possesses a pleiotropic effect on the modulation of the immune system [14,15]. This process occurs under both physiological and physiopathological conditions [16,17], where melatonin has been shown to elevate antibody levels in cases where the immune system is weakened and inhibits cytokine expression in pathological events where the immune system has become over-activated [18,19].

Various inflammation models have established melatonin's crucial role in reducing NLRP3 inflammasome levels, mainly via its immunosuppressant effect. Thus, melatonin exerts a protective effect by preventing the cytokine and pyroptosis cascade such as NLRP3/Caspase-1/IL-1β [20,21]. The abundance of ACE2 and TMRPSS enzymes plays a vital role in COVID-19′s virus invasion into oral tissues. In the later period, with virus replication, ACE1 is activated, and this causes cytokine expression. This inflammatory process coincides with the mechanism of inflammatory dental diseases such as periodontitis, caused by an increase in NLPR3 inflammasome.

COVID-19 and NLRP3

SARS-CoV-2 invasion causes NLRP3 activation in cells and cytokine secretion and disruption of tissue integrity (Fig. 1) [5]. The viral genome expresses three ion channel proteins: open reading frame (ORF) 3a (ORF3a), ORF8a and E [22,23]. ORF3a and E are required for both replication and virulence. These proteins act as NLRP3 agonists [24,25] and possibly mediates the pathogenesis of inflammation, the formation of reactive oxygen species and caspase 1 activation in COVID-19 [26,27].

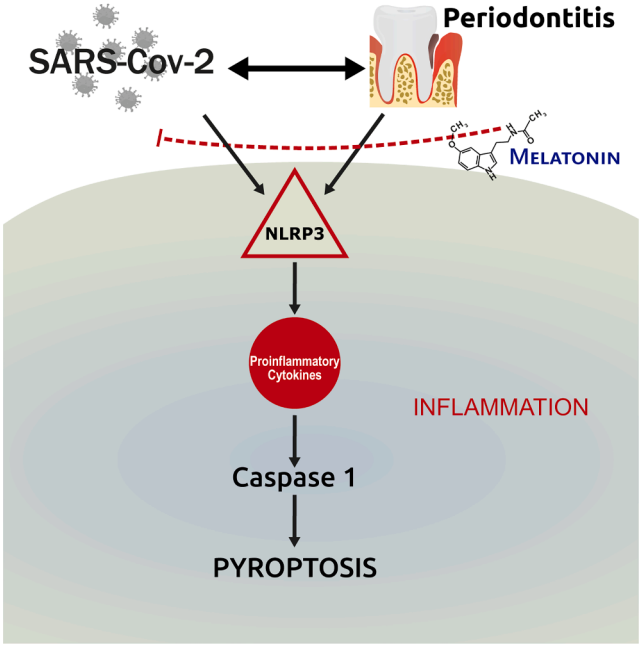

Fig. 1. SARS-CoV-2 and Periodontitis promote expression of NLRP3 inflammasome and thus leads to a cytokine response and pyroptosis. Melatonin may act an inhibitory effect on reducing NLRP3.

Periodontitis and NLRP3

Chronic periodontitis, which influences most of the adult population, is a biofilm-induced chronic inflammatory disease that affects the connective tissue and the alveolar bone between tooth and results in the slow progressive destruction of periodontium, pathological periodontal pocket formation, gingival recession and tooth loss [28]. The pathogenesis of chronic periodontitis is complex and multifactorial. Although the disease's aetiology is the colonization of subgingival bacteria, called periodontopathogen, that forms the biofilm, it is the host inflammatory response that determines the progression and pattern of the disease [29]. Periodontal health refers to the maintenance of the host-microorganism balance in the periodontium, also called homeostasis. High resistant biofilm, changes in the host's immunoinflammatory state, and various predisposing factors cause this balance to change in favour of the microorganisms, also known as dysbiosis and initiates inflammatory changes [30].

Periodontal diseases are infections caused by bacterial species complex. This ensures inflammatory cytokines secretion [31]. The red complex consists of *Treponema denticola, Porphyromonas gingivalis* and *Tannerella forsythia*, which are later involved in biofilm development and are considered to induce and progress periodontitis. These bacterial strains are prominent in adult periodontitis cases and sites with deeper pockets or more advanced lesions [32]. Of these species, *Porphyromonas gingivalis* is primarily responsible in the development of chronic periodontitis [33].

Cytokine secretion is activated by inflammatory cells against bacterial infection. Cytokines are initially protective in eliminating infectious bacteria. However, overproduction of inflammatory cytokines is related to periodontal degradation, including collagen destruction, alveolar bone resorption and the loss of periodontal attachment [34].

Inflammasomes are reported to be responsible for the maturation of proinflammatory cytokines and pyroptosis. They are the key components in the pathogenesis of inflammatory diseases. In particular, the function of NLRP3 has been demonstrated in COVID-19 during cytokine storm and has been shown to increase cytokine expression in periodontitis (Fig. 1) [35,36].

Melatonin and NLRP3

Melatonin, an immunomodulator, prevents activation of NLRP3 during inflammation. It has also been detected that melatonin prevents NLRP3 activation during sepsis, thus exhibiting an anti-inflammatory effect (Fig. 1) [37]. Likewise, Cao et al.'s [38] study found that melatonin suppresses NLRP3 inflammasome in cadmium toxicity, lowering the level of proinflammatory cytokines and preventing caspase 1 mediated pyroptosis. Besides, the role of NLRP3 inflammasome in neurodegenerative disorders has been shown, and melatonin has been reported to slow down the progression of neurodegenerative diseases, through the suppression of NLPR3 inflammasome activation [39].

COVID-19 and melatonin

It has previously been observed that melatonin has indirect antiviral effects due to its antioxidant, immunomodulatory and anti-inflammatory properties [40]. It has been suggested that during COVID-19, melatonin can prevent cytokine storm with its immunomodulatory effect and thus have a protective effect [41]. It has been reported in these studies that melatonin may be a potential agent by suppressing the CD 147 protein that causes virus invasion during COVID-19, preventing toll-like receptor activation, and blocking inflammatory pathways [15,42].

Periodontitis and melatonin

Periodontitis has been identified as the sixth most prevalent condition worldwide, as stated in the Global Burden of Disease 2010 Study [43]. Periodontal disease contributes to the inflammatory burden of oral diseases, shares common risk factors with various chronic diseases, resulting in a poorer prognosis. The World Health Organization recently emphasized the importance of strengthening periodontal diseases since periodontal diseases contribute significantly to the global burden of chronic diseases [44].

Melatonin, which is secreted in various tissues other than the pineal gland, is present in the oral epithelium, salivary gland ducts, maxillary alveolar bone osteoblasts among other oral cells and fibroblasts of the mucosal lamina propria [45]. It has been shown that reactive oxygen species and increased cytokine expression cause alveolar tissue loss in periodontitis [46]. In the study of Almughrabi et al., it was found that salivary melatonin levels from patients suffered from gingivitis and periodontitis were lower than healthy ones [47]. Cutando et al. has also reported a positive correlation between saliva melatonin levels and periodontitis [48]. Melatonin has been shown to reduce periodontal damage in experimental periodontitis studies in animals [49,50].

Consequences of the hypothesis and discussion

There is a possibility of periodontal diseases during COVID-19, as the enzymes ACE2 and TMRPSS, which are required for SARS-COV-2 invasion, are also present in tissues such as the tongue and periodontal pocket. Likewise, increased NLRP3 activation and cytokine expression during periodontitis may further exacerbate COVID-19. NLRP3 provides the ability to further increase the cytokine storm during both COVID-19 and periodontitis. This increases the likelihood that damage to periodontal tissues, and the effects on entire systems will be more severe. Therefore, modulation of the immune system is important for the protection of both oral and other tissues. Melatonin, along with its antioxidant and anti-inflammatory properties, is thought to reduce COVID-19 and periodontal damage by preventing NLRP3 activation and cytokine expression and pyroptosis.

Declarations

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Availability of data and material (data transparency): Yes.

Code availability (software application or custom code): None applicable.

Ethics Approval: Not applicable.

Author Contribution Statement

All authors have made substantial contributions to conception and design of the study. AÖŞ, UA, RBKÜ and SS have been involved in literature search, data analysis, and drafting the manuscript. AÖŞ critically revised the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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