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Biological functions of melatonin in relation to pathogenesis of oral lichen planus

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ABSTRACT

Oral lichen planus (OLP) is considered as a chronic inflammatory immune-mediated disease causing oral mucosal damage and ulcerations. Accumulated data support the involvement of cell-mediated immune dysfunction in the development of OLP. However, the connection between neuroendocrine system and oral immune response in OLP patients has never been clarified. Melatonin is considered as a major chronobiotic hormone produced mainly by the pineal gland. This gland is recognized as a regulator of circadian rhythm and a sensor in the immune response through the NF-kB transduction pathway. It was suggested that pineal-derived melatonin and extra-pineal melatonin synthesized at the site of inflamed lesion might play a role in inflammatory response. According to our immunohistochemical study, expression of melatonin could be detected in human oral mucosa. In addition, increased levels of melatonin were observed in inflamed oral mucosa of OLP patients. We hypothesize that chronic inflammation possibly induces the local biosynthesis of melatonin in inflamed oral mucosa. We also speculate that melatonin in oral mucosa may play a cytoprotective role through its anti-oxidative and anti-inflammatory properties. Moreover, melatonin may play an immunomodulatory role in relation to pathogenesis of OLP. Our hypothesis provides a new implication for upcoming research on the connection between circadian neuroendocrine network and immune response in oral mucosal compartments.

Background

Oral lichen planus (OLP) is a chronic inflammatory immune-mediated disease of oral mucosa, and usually found in middle-aged women [1]. Clinical manifestations of OLP consist of erythema and white lines on oral mucosa called Wickham striae with various appearances including reticular, papular, plaque, atrophic, erosive, and bullous [2,3]. Atrophic or erosive type of OLP (Fig. 1) can cause symptoms ranging from burning sensation to severe pain that affect the patients' quality-of-life [4,5]. Histopathological characteristics of OLP consist of degeneration of basal keratinocytes, epithelial basement membrane disruption, and intense subepithelial infiltration of T-lymphocytes (Fig. 2). Our previous study demonstrated an increase in 8-oxodG and 8-nitroquanine, known as biomarkers for oxidative and nitrative DNA damage, in OLP lesions [6]. OLP has been considered as a potentially malignant disorder associated with an increased risk for oral cancer [7]. The exact etiology of OLP remains unclear. Accumulated data support the involvement of cell-mediated immune dysfunction in the development of OLP [8–10]. Several studies reported the increased level of NF-kB and pro-inflammatory cytokine signaling molecules in inflamed oral mucosal tissues of OLP patients [11–13]. However, the connection between immune response in oral mucosal compartments and neuroendocrine system has never been investigated.

Previous studies demonstrated a crosstalk between circadian signals and outputs of systemic immune response [14–17]. The pineal gland is generally accepted to be a transducer of photoperi-

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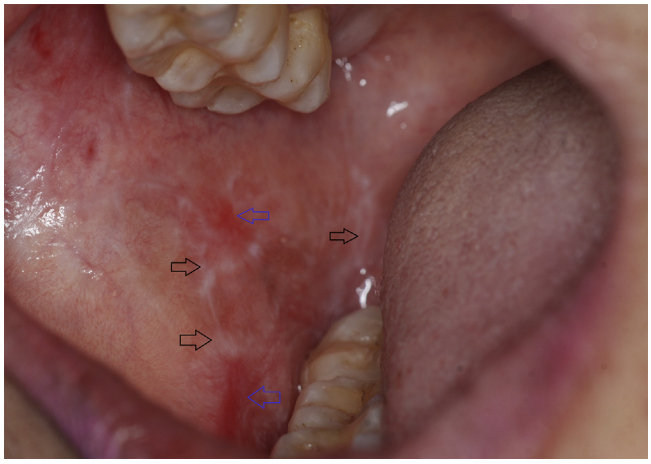

Fig. 1. Clinical manifestations of oral lichen planus (OLP) consist of white striation (black arrows), and atrophic lesions (blue arrows) on oral mucosa. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

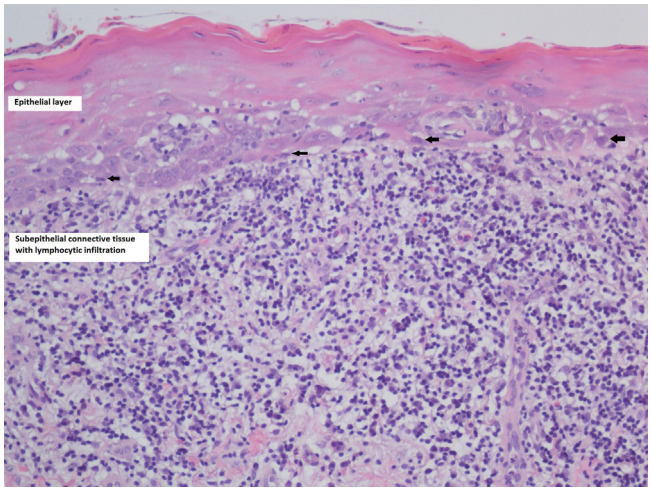

Fig. 2. Histopathological characteristics of oral lichen planus (OLP) consist of degeneration of basal keratinocytes (black arrows), and subepithelial lymphocytic infiltration.

odic information and a regulator of circadian rhythm via the production of melatonin (N-acetyl-5-methoxytryptamine). Moreover, the pineal gland was also recognized as a sensor in the immune response through the NF-kB transduction pathway [18,19]. The biosynthesis of pineal derived melatonin is regulated by the suprachiasmatic nuclei-driven sympathetic innervation of the pineal gland, leading to the activation of arylalkylamine-N-acetyl transferase (AANAT) which is a rate-limiting enzyme in the melatonin biosynthesis [20]. Melatonin has two major mechanisms of actions: receptor-mediated and receptor-independent pathways [21]. There are two membrane-bound G-protein related melatonin receptors: MT1 and MT2 [22]. Besides its influence on circadian regulation, melatonin has other biological functions such as anti-inflammatory activity [23]; anti-oxidant activity [24]; and immunomodulatory activity [25]. It was suggested that melatonin produced by the activated immune cells at the site of inflamed lesion might play an immunomodulatory role [26]. The role of pineal and extra-pineal melatonin in the innate and acquired immune response was addressed in several review articles [27,28]. Melatonin has been investigated in several chronic inflammatory diseases such as multiple sclerosis [29]; systemic lupus erythematosus [30]; rheumatoid arthritis [31]; and inflammatory bowel diseases [32]. Physiological and pathological implications of melatonin in the oral cavity were addressed [33]. However, data of melatonin in relation to chronic inflammatory oral mucosal diseases are limited [34].

According to our immunohistochemical study, the presence of melatonin was observed in human oral mucosa (Fig. 3). Our previous investigation demonstrated that the levels of AANAT, melatonin, and MT1in inflamed oral mucosa of OLP patients were significantly higher than those in normal oral mucosa of control subjects [34]. These findings suggest that chronic inflammation possibly induces the local biosynthesis of melatonin in inflamed oral mucosa via AANAT, and enhances the action of melatonin via MT1 [34]. The presence of extra-pineal melatonin might help to protect the mucosa cells against an oxidative and inflammatory damage (for a review, see [35]). Accumulated data demonstrated that melatonin produced in extra-pineal tissues might act in autocrine, paracrine, and/or intracrine manner [36], and had a variety of functions depending on organ localization and physiological context [37]. It was also reported that extra-pineal melatonin might have a cytoprotective role through its antioxidant actions [38,39]. In some pathological conditions such as cell injury and malignancy, melatonin can enhance pro-oxidant actions [40,41]. Nevertheless, the biologic functions of melatonin in human oral mucosa have not been clarified. Thus, further investigations of the relationship between the systemic and local melatonin production and its function in oral compartments would be of importance.

Hypothesis

We propose our new hypothesis modified from the "pineal-immune axis" concept by Markus et al. [26] for consideration as follows (Fig. 4). Under physiological conditions, melatonin produced in the pineal gland in a rhythmical manner is released into the circulation. Melatonin enters oral mucosal compartments and helps to maintain the homeostasis by controlling the migration of leukocytes from the blood stream, thereby avoiding unwanted oral mucosal inflammatory response [26]. According to our observations [34], melatonin produced locally in the oral mucosal tissue may help to restore the homeostasis by eliminating the excessive free radical and other oxidative stress molecules. At the early phase in OLP, danger signals from exogenous and/or endogenous stimuli trigger inflammatory response in oral mucosal tissue through an activation of dendritic cells [42,43], leading to the production of inflammatory mediators. These signaling molecules such as TNF-α and NF-kB [12,13] suppress synthesis of the pineal melatonin, favoring the migration of immune cells from the blood stream into the connective tissue of oral mucosa [26]. Activated oral epithelial cells and infiltrated immune cells produce local melatonin to modulate oral inflammatory response. At the chronic phase in OLP, dysregulation of the oral immune response caused by continuity of danger signals [43] in the oral mucosal environment enhances accumulation of free radical and oxidative stress molecules [6], contributing to the oral mucosal damage. According to our immunohistochemical findings [34], increased melatonin and MT1 in oral epithelial cells of OLP patients may play a cytoprotective role through its anti-oxidative and anti-inflammatory properties, and to rescue the injured oral epithelial cells from undergoing apoptosis. Production of melatonin by the infiltrated immune cells in oral mucosa may play an immunomodulatory role by enhancement of phagocytosis and reduction of inflammatory response. In addition, changes in biosynthesis of melatonin and its receptors in the oral mucosa during chronic inflammation may affect the oral epithelial cell permeability and cell integrity [44], resulting in a variety of OLP manifestations.

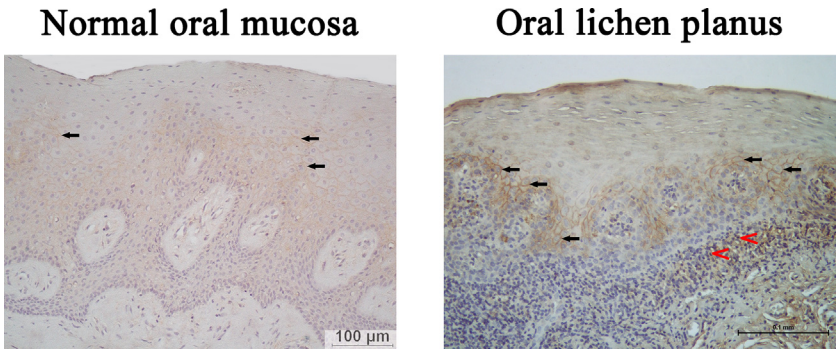

Fig. 3. Photomicrographs of representative samples for immunohistochemical staining with antibodies against melatonin in normal oral mucosa, and oral lichen planus (OLP). A stronger melatonin immunoreactivity is observed in oral epithelium (black arrows) and infiltrated lymphocytes (red arrowheads) of OLP as compared with normal oral mucosa. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

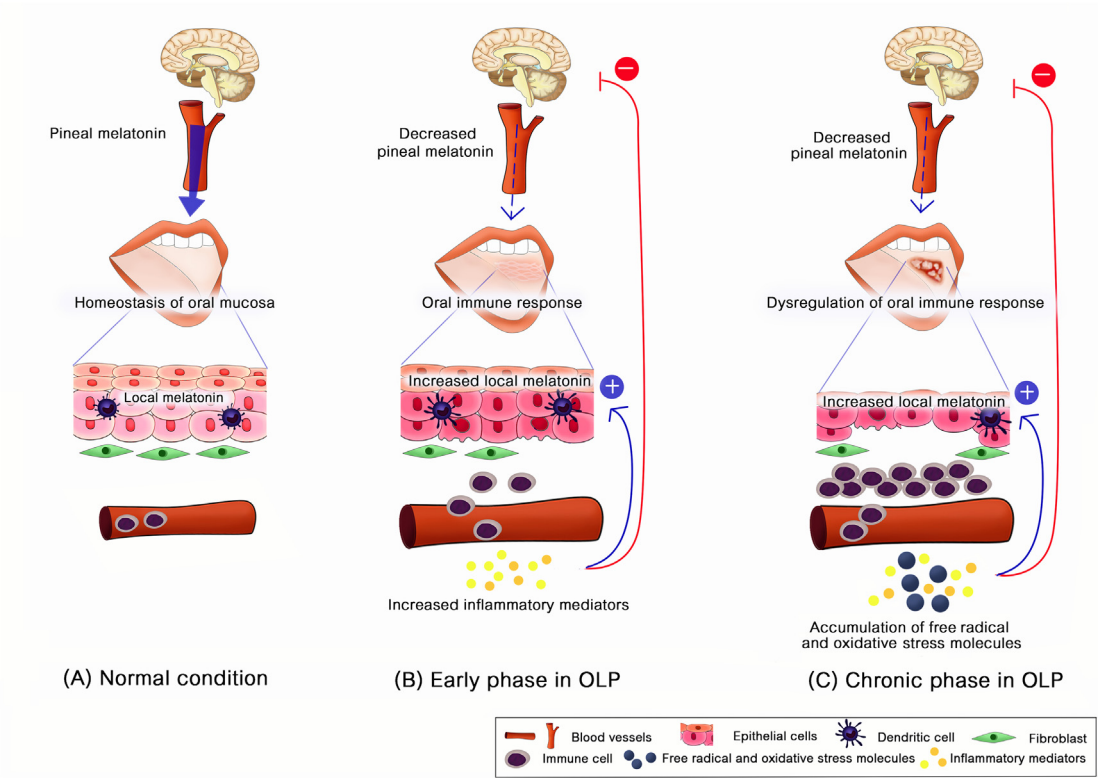

Fig. 4. A new hypothesis of melatonin in association with pathogenesis of oral lichen planus (OLP). (A) Under the physiological condition, melatonin from the pineal gland is released into the circulation. Pineal melatonin enters oral mucosal compartments and helps to maintain the homeostasis by controlling the migration of leukocytes from the blood stream, avoiding unwanted oral inflammatory response (Markus et al., 2013 [26]). Local melatonin produced in oral epithelium and connective tissue helps to maintain the homeostasis by eliminating unwanted free radical and oxidative stress molecules. (B) At the early phase in OLP, danger signals from exogenous and/or endogenous stimuli (Gallo et al., 2013 [43]) trigger oral inflammatory response, leading to production of inflammatory mediators. These mediators such as TNF-α and NF-kB signaling molecules reduce synthesis of pineal melatonin, favoring the migration of immune cells from the blood stream into the connective tissue of oral mucosa (Markus et al., 2013 [26]). Activated oral epithelial cells and infiltrated immune cells produce local melatonin to modulate immune response in oral mucosa. (C) At the chronic phase in OLP, dysregulation of oral immune response caused by continuity of danger signals in the oral mucosal environment enhances accumulation of free radical and oxidative stress molecules, contributing to oral mucosal damage. Injured oral epithelial cells and activated immune cells enhance production of local melatonin to resolve oxidative and inflammatory damage.

Discussion

Very little is known about the role of melatonin and its receptors in the oral mucosal tissue under physiological and pathological conditions. According to previous investigations [26] combined with recent observations [34], our hypothesis provides a new implication for upcoming research on the connection between immune response in oral mucosal compartments and circadian neuroendocrine network. However, this hypothesis has several research gaps that tremendously require further experimental and clinical validations. It is important to underline that lacking in supportive evidences concerning association between biological functions of melatonin and immunopathogenesis of OLP is mainly due to unavailability of a well-established animal model for OLP. Therefore, development of animal model for OLP is essentially needed. It is important to verify the association between the role of melatonin in oral epithelial cell integrity and clinical manifestations of OLP patients. Moreover, therapeutic effects of melatonin

on OLP lesions should be validated for the treatment of patients with OLP.

Compliance with ethical Standards

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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