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·综述·

昼夜节律在口腔疾病中的作用及防治新策略

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【摘要】昼夜节律是一种由下丘脑视交叉上核调控的生物内源性过程，将光信号传递给外周时钟，并通过昼夜节律基因的平衡表达使机体与外界环境相同步。夜班、睡眠障碍及人造光的使用会导致昼夜节律紊乱及其基因失衡，已有大量研究表明昼夜节律在自身免疫性疾病及神经退行性疾病的治疗中发挥作用，且在口腔疾病中的影响受到日益关注。昼夜节律紊乱主要通过下丘脑-垂体-肾上腺轴(hypothalamic-pituitary-adrena axis，HPA axis)、脑和肌肉ARNT样蛋白1(brain and muscle ARNT-like 1，BMAL1)-脑源性神经营养因子(brain-derived neurotrophic factor，BDNF)及BMAL1-核因子κB(nuclear factor kappa-B，NF-κB)影响心理-神经-免疫机制、氧化应激、口腔微生物菌群，这可能影响口腔疾病进展。一些药物(如褪黑素、维生素D、川陈皮素、异丙酚等)通过上调BMAL1的表达来调控机体情绪障碍、免疫功能及睡眠-觉醒周期，从而缓解昼夜节律紊乱；非药物治疗(睡眠管理、心理治疗及日光疗法等)也通过HPA轴来影响上述过程。目前，昼夜节律调控BDNF、T细胞亚群及炎症信号等通路来影响口腔疾病的发病及相关治疗的具体机制尚未阐明。在未来应探讨昼夜节律在口腔疾病中作用的分子机制及其治疗靶点，同时开展多学科合作对于昼夜节律的调控将有助于口腔疾病的防治。

【关键词】昼夜节律基因；口腔疾病；睡眠障碍；心理神经免疫学；氧化应激；口腔微生物菌群；睡眠管理
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The role of circadian rhythm and its new strategies for prevention and treatment in oral diseases

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【Abstract】Circadian rhythm is a biological endogenous process regulated by the suprachiasmatic nucleus of the hypothalamus, which transmits light signals to peripheral clocks and synchronizes the body with the external environment through balanced expression of circadian rhythm genes. Working the night shift, sleep disorders, and exposure to artificial light can lead to disturbances in circadian rhythm and genetic imbalances. A substantial body of research has demonstrated that circadian rhythm plays a significant role in the treatment of autoimmune diseases and neurodegenerative disorders, with increasing attention being directed toward their impact on oral health. Disturbances in circadian rhythm

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primarily affect psycho - neuro - immune mechanisms, oxidative stress responses, and oral microflora through pathways such as the hypothalamic - pituitary - adrenal axis (HPA axis), brain and muscle ARNT-like 1 (BMAL1)-brain-derived neurotrophic factor (BDNF) signaling, and BMAL1-nuclear factor kappa-B (NF-κB) interactions. These disruptions may influence the progression of oral diseases. Certain pharmacological agents (e.g., melatonin, vitamin D, nobiletin, and propofol) have been shown to regulate mood disorders, immune function, and sleep - wake cycles by upregulating BMAL1 expression, thus alleviating disturbances in circadian rhythm. In addition, non-pharmacological interventions, such as sleep management strategies, psychotherapy approaches, and light therapy, also modulate these processes through HPA axis regulation. Currently, the specific mechanisms by which circadian rhythm regulates BDNF levels, T cell subsets, and inflammatory signals—thereby influencing both pathogenesis and treatment outcomes for oral diseases—remain unclear. Future research should focus on elucidating these molecular mechanisms as well as identifying therapeutic targets related to circadian rhythm within the oral health context. Further, multidisciplinary collaboration encompassing pharmacy, sleep behavior studies, and psychology will be instrumental in advancing prevention strategies and treatments for oral diseases.

【Key words】 circadian rhythm genes; oral diseases; sleep disorder; psychoneuroimmunology; oxidative stress; oral microbiota; sleep management

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昼夜节律(circadian rhythm,CR),又称睡眠—觉醒周期,是以24 h为周期的人体内源性调节过程,控制每日褪黑素分泌、免疫系统及心理状况的节律性[1]。昼夜节律内源性振荡器位于下丘脑的视交叉上核(suprachiasmatic nucleus,SCN),负责调节大脑的内部时钟并协调外周时钟。固有光敏视网膜神经节细胞接受环境中的光线并投射到SCN,后者将光信号传递给外周器官和组织的时钟,当中央时钟与外周时钟同步时,机体将适应外部环境[1]。昼夜节律分子振荡器主要包括转录因子脑和肌肉ARNT样蛋白1(brain and muscle ARNT-like 1,BMAL1)、昼夜运动输出周期蛋白(circadian locomotor output cycles kaput,CLOCK)、周期蛋白(periods,PERs)、隐花色素(cryptochromes,CRYs)、核受体亚家族1组D成员(REV-ERBα)、RAR相关的孤儿受体α(retinoic acid-related orphan receptors-α,RORα)等,这些基因通过转录—翻译反馈环共同调控生物体的昼夜节律[2]。昼夜节律主要包括两种信号通路,第一条为BMAL1和CLOCK形成异二聚体并结合启动子区的E-box元件诱导PERs和CRYs的表达,后两者负反馈调节BMAL1/CLOCK的转录。时钟基因第二条经典途径为BMAL1/CLOCK二聚体可以诱导REV-ERBα与RORα的表达,REV-ERBα可以抑制BMAL1的转录,RORα则可增强BMAL1的转录,这2条环路构成了分子钟调控节律相关基因表达的基础[2]。

夜班工作、熬夜行为及老年性睡眠障碍可导致昼夜节律紊乱,这是由昼夜节律内部系统的改变或内源性昼夜节律与外部环境之间的不同步所引起,主要表现为失眠和白天过度嗜睡[3]。昼夜节律紊乱通常会导致免疫、身心等方面障碍,并参与机体自身免疫病及神经退行性类疾病的发生发展,研究表明生物钟基因是阿尔兹海默病的潜在治疗靶点[4]。时钟基因的破坏与溃疡性结肠炎患者黏膜异常的免疫反应有关[5],且BMAL1在免疫相关疾病的靶向治疗中具有广阔的潜力[6]。目前,昼夜节律在口腔疾病发病中的作用及其应用前景也日益受到关注。

大多数昼夜节律基因存在于牙体及牙周组织、口腔黏膜上皮、颌骨、颞下颌关节及唾液腺等口腔组织内,并有序地调控各种口腔组织的发育和生长。例如,通过上调BMAL1/CLOCK的表达可促进牙齿硬组织的形成与矿化[7],BMAL1和PER2调控Wnt/β-catenin通路影响小鼠间充质干细胞的成骨分化和增殖来参与颌骨发育[8]。其次,BMAL1调节牙周组织中氧化应激与细胞凋亡参与牙周炎进展[9]。同时,控制唾液分泌的钙通道蛋白也受BMAL1水平影响[10]。昼夜节律调节下颌髁

突软骨细胞中糖原合成酶激酶3β(glycogen synthase kinase 3 beta,GSK3β)/β-catenin参与颞下颌关节骨关节炎的进展[11]。此外,昼夜节律还影响小鼠体内口腔鳞状细胞的细胞周期、增殖及凋亡,如生物钟基因PER1会通过改变肿瘤细胞增殖与凋亡来参与口腔鳞状细胞癌的发生[12],昼夜节律可能也通过上述过程维持人体口腔上皮的稳态。当昼夜节律失衡时会影响上述过程导致牙齿发育异常、颌面畸形、牙周炎、唾液腺功能障碍、口腔黏膜病及口腔鳞状细胞癌的发生发展[13]。本文主要概括了昼夜节律对口腔疾病发病机制如心理神经免疫学、氧化应激及口腔微生物群的影响基于昼夜节律在口腔疾病发病中的作用,总结药物及非药物疗法对昼夜节律紊乱的具体防治策略。

1　昼夜节律影响口腔疾病的机制

1.1　昼夜节律与心理神经免疫学

心理神经免疫学(psychoneuroimmunology,PNI)作为一个跨学科的研究领域,包含心理因素、神经内分泌系统和免疫反应,近年来,三者之间错综复杂的相互作用在口腔疾病中引发了越来越多的关注[14]。昼夜节律也可通过影响三者来参与口腔疾病发生发展。

1.1.1　昼夜节律与心理因素　昼夜节律通过下丘脑—垂体—肾上腺轴(hypothalamic-pituitary-adrenal axis,HPA axis)影响情绪,也可直接影响大脑神经元兴奋性、神经细胞炎症及神经递质的释放来调节情绪。昼夜节律紊乱通过HPA轴失调触发皮质醇的释放,后者作为压力的重要标志物参与精神障碍的发生[15]。昼夜节律不同步导致控制情绪的生物钟基因节律失调,如PER1和REV-ERBα表达显著增加,而正时钟调节因子BMAL1和RORα的水平降低,使前额叶皮层锥体神经元的兴奋性下降[16-17]。其次,夜晚时间型与较高的焦虑与抑郁症状相关[18-19],长期人造光照射会降低大鼠BMAL1表达,激活M1极化并上调IL-6、TNF-α、IL-1β表达,从而诱发小鼠炎症[20-21]。此外,昼夜节律核受体REV-ERBα增加小鼠大脑中缝背侧色氨酸羟化酶2(tryptophan hydroxylase 2,Tph2)的水平,并控制5-羟色胺(5-hydroxytryptamine,5-HT)的合成进而减轻抑郁症状[22]。

多数口腔疾病均受心理因素影响[23],如灼口综合征、口腔扁平苔藓(oral lichen planus,OLP)、复发性阿弗他溃疡(recurrent aphthous ulcer,RAU)、唇疱疹、颞下颌关节紊乱病等[24],其中灼口综合征是一种表现为口内灼烧感的神经性病变,并具有晨轻暮重的日节律性,中老年受试者灼口综合征与焦虑障碍之间存在中度关联[25]。由此可见,昼夜节律可能通过诱发焦虑参与灼口综合征的发生。睡眠障碍、焦虑及抑郁与OLP具有较强相关性,大多数OLP患者焦虑及抑郁方面的评分高于对照组,且评分也随着疾病严重程度而增加[26],推测睡眠障碍通过昼夜节律紊乱来影响OLP患者情绪。目前对于昼夜节律紊乱如何破坏情绪来参与口腔疾病进展的机制尚不明确,还需进一步研究探索。

1.1.2　昼夜节律与神经内分泌系统　昼夜节律两个最突出的内分泌表现为糖皮质激素(glucocorticoid,GC)和褪黑素在体内的昼夜节律性。昼夜节律通过HPA轴调控GC(如皮质醇)的水平使之具有昼夜变化[27]。其次,SCN还通过调控松果体节律性分泌褪黑素并释放到血液中,也可从唾液腺的腺泡细胞释放到唾液和龈沟液中,其水平通常在天黑时开始上升,在醒来前开始下降以促进觉醒[28]。睡眠中断会使糖皮质激素及褪黑激素的释放与环境不同步,夜间蓝光以GC依赖性方式干扰前额叶皮层中的脑源性神经营养因子(brain-derived neurotrophic factor,BDNF)表达,后者参与睡眠、情绪和突触可塑性调节,且BDNF/细胞外调节蛋白激酶通路在改善抑郁样行为中起重要作用[29]。糖皮质激素及褪黑素已被证明在口腔黏膜抗炎及免疫反应中发挥关键作用[30-31],这提示昼夜节律通过神经内分泌系统调控心理因素来参与口腔疾病发生发展。

1.1.3　昼夜节律与免疫反应　生物钟基因影响机体先天性及适应性免疫功能,并调控其相关因子的表达水平。目前BMAL1被认为是昼夜节律与炎症反应的“桥梁”,其与核因子κB(nuclear factor kappa-B,NF-κB)结合调节体内炎症途径[32],昼夜节律蛋白CLOCK会影响人体外周血中的调节性B细胞功能[33]。其次,REV-ERBα负向调节辅助性Th17(T helper cell 17,Th17)细胞发育及白细胞介素-17(interleukin 17,IL-17)的表达并参与自身免疫反应[34]。Th17细胞及IL-17在OLP发病机制中起重要作用[35],这表明昼夜节律基因可能主要通过调控T细胞及其相关因子的表达参与OLP疾病进程。睡眠障碍是复发性阿弗他溃疡发作的潜在风险因素[36],而伤口愈合主要是BMAL1/PER/CRY

调控成纤维细胞肌动蛋白动力学和迁移的结果[37]，这些证据暗示昼夜节律紊乱可抑制成纤维细胞迁移、增加促炎因子的表达来阻碍RAU愈合并促进炎症发展。上述研究提示昼夜节律通过免疫反应影响口腔疾病，但对于精确调控机制值得进一步探索。

1.1.4　昼夜节律通过心理—神经—免疫系统来参与口腔疾病进展　压力、焦虑等因素引起的急性应激通过HPA轴影响皮质醇水平并抑制细胞免疫活动，包括牙周组织及伤口愈合速度变慢。其次，PNI还体现在口腔疾病与全身状况之间的相互联系。其中脑肠轴、自主神经系统通过免疫调节和炎症反应严重影响口腔疾病的发生，而牙周炎等慢性口腔疾病也可通过神经内分泌免疫途径影响心理健康并加重全身炎症状况[14]。

睡眠障碍引起的昼夜节律紊乱可诱发心理应激，后通过HPA轴导致皮质醇水平升高并抑制免疫系统，直接促进TNF-α、白细胞介素-6（interleukin-6，IL-6）、干扰素-γ和C反应蛋白等炎症因子的释放[38-39]。睡眠时间短及抑郁症均与牙周炎显著相关[40-41]，提示上述过程可能参与牙周炎的进展。昼夜节律紊乱可影响心理因素、神经内分泌系统及免疫反应，并通过三者之间相互的联系影响口腔疾病进程。

1.2　昼夜节律与氧化应激

在生理条件下，细胞内活性氮(reactive nitrogen species，RNS)和活性氧（reactive oxygen species，ROS）的水平与细胞抗氧化能力之间处于平衡状态。当RNS或ROS水平超过细胞的抗氧化能力时，会发生氧化应激，主要通过氧化人体内脂质、蛋白质和DNA导致细胞损伤及慢性炎症状态。过量的ROS诱导激活人体内促凋亡蛋白并诱导细胞死亡，这与口腔内牙周炎中的炎症有关[42]。

昼夜节律可调控氧化应激，其中昼夜节律基因BMAL1、CLOCK调节线粒体功能并参与控制细胞氧化状态的还原型辅酶I/还原型辅酶II的氧化还原系统，PER2-CRY参与人体中细胞应激反应，碳水化合物和脂质代谢[43]。临床研究已证明夜班工作可使机体氧化损伤标志物丙二醛（malondialdehyde，MDA）水平上升及总抗氧化能力升高[44]。Liu等[9]研究显示昼夜节律紊乱通过下调BMAL1的分子表达水平而加剧大鼠牙周组织的氧化损伤及细胞凋亡来参与牙周炎进展，其中BMAL1水平下调引起MDA及氧化性DNA损伤的生物标志物8-羟基脱氧鸟苷（8-oxo-2-deoxyguanosine，8-OHdG）表达水平升高，抗氧化酶超氧化物歧化酶1（superoxide dismutase 1，SOD1）表达水平降低，同时增加Bax及caspase-3促进牙周组织中细胞凋亡。上述证据表明昼夜节律紊乱可通过氧化应激影响口腔环境稳态。

1.3　昼夜节律与口腔微生物菌群

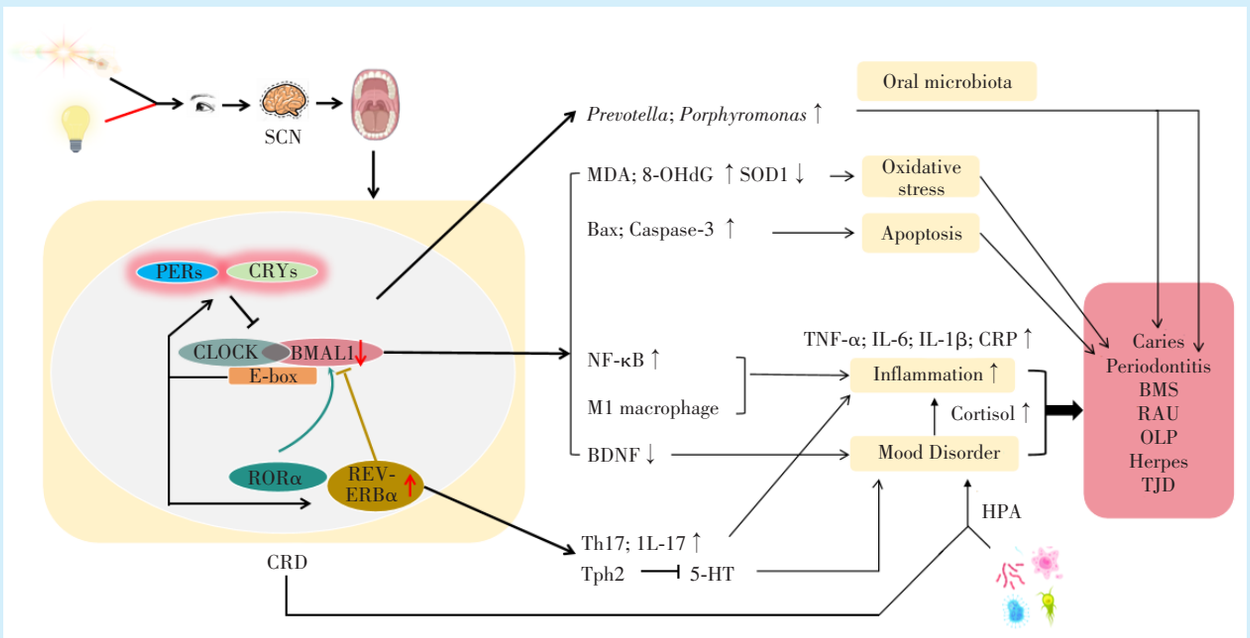
口腔微生物稳态在维持口腔黏膜上皮稳态及免疫反应中发挥重要作用[45]。人类唾液中微生物丰度和基因的表达具有昼夜节律性[46]，在口腔中普雷沃氏菌和棒状杆菌属醒来时的相对丰度都高于睡眠前[47]。炎症因子水平与口腔微生物组特定群体会表现出相同周期的节律性波动，如在白细胞介素-1β（interleukin-1β，IL-1β）和普雷沃氏菌之间以及IL-6与普雷沃氏菌、奈瑟菌和卟啉单胞菌之间存在这种现象[48]。

龋病及牙周炎发病始于牙齿表面由微生物构成的生物膜[45]，例如牙龈卟啉单胞菌是牙周炎的关键病原体，通过牙龈蛋白酶等毒力因子并增加了IL-1β等促炎介质的分泌，导致牙龈组织和牙周韧带的破坏[49]。在患有严重（Ⅲ-Ⅳ期）牙周炎的患者中，卟啉单胞菌属水平较正常对照组高出四倍[50]。昼夜节律紊乱（如在轮班工作及因跨时区而导致昼夜节律紊乱的人群中）严重改变了口腔微生物群景观，显著增加致病菌导致口腔内菌群及其相关炎症因子失调[46]，这会直接参与龋病及牙周病进展，同时加重牙体、牙周组织乃至整个口腔中的炎症及免疫反应。由此得出，昼夜节律紊乱可调控口腔微生物菌群失调来直接参与口腔疾病进展。此外，口腔病原菌数量的增多也会导致HPA轴失调从而加重抑郁症状[51]，这表明生物钟紊乱可能通过口腔菌群稳态的破坏影响情绪障碍，进而参与口腔疾病发展。见图1。

2　昼夜节律调控在口腔疾病防治中的新策略

2.1　药物疗法

褪黑素作为一种外周生物钟蛋白，在调控昼夜节律周期中发挥重要作用，外源性褪黑激素可降低轮班工人的昼夜节律错位，且在早晨型中作用更加明显[52]，高剂量褪黑素增加老年人深度睡眠时间、提高睡眠质量[53]。其次，褪黑素还可通过调节生物钟基因的表达来治疗抑郁症状及免疫功能。褪黑激素治疗逆转了大鼠海马区由昼夜节律紊乱诱导的BMAL1/CLOCK表达下调并改善认知



The light signal is transmitted through the eye to the suprachiasmatic nucleus (SCN), which then relays this signal to oral tissues, synchronizing the oral biological clock with environmental cues. The use of artificial light at night downregulates the expression of BMAL1 while upregulating REV-ERBα. Downregulation of BMAL1 reduces brain-derived neurotrophic factor (BDNF) levels, leading to mood disorders, activating inflammatory pathways, and promoting oxidative stress and cell apoptosis. Upregulation of REV-ERBα increases the expression of Tph2 and elevates Th17 cell levels. Disruption of the circadian rhythm can cause partial dysbiosis of the oral microbiome, promoting the progression of dental caries and periodontal disease. Circadian disruption can also induce psychological stress via the hypothalamic-pituitary-adrenal (HPA) axis, increasing cortisol levels, which in turn elevate levels of inflammatory markers. This contributes to the pathogenesis and progression of periodontitis, BMS, RAU, OLP, herpes, and TJD. CRD: circadian rhythm disorder; MDA: malondialdehyde; 8-OHdG: 8-Oxo-2-Deoxyguanosine; SOD1: superoxide dismutase 1; Tph2: tryptophan hydroxylase 2; 5-HT: 5-hydroxytryptamine; BMS: burning mouth syndrome; RAU: recurrent aphthous ulcers; OLP: oral lichen planus; TJD: temporomandibular joint disorders.

Figure 1　The role of circadian rhythm and its genes in the pathogenesis of oral diseases

图 1　昼夜节律及其基因在口腔疾病发病中的作用

障碍[54]，还可抑制 PER2 的异常表达来维持星形胶质细胞水通道蛋白 4（aquaporin-4，AQP4）极化，进而缓解小鼠抑郁症状并恢复淋巴系统功能[55]。此外，补充褪黑激素逆转了夜间人造光（artificial light at night，ALAN）导致的大鼠氧化还原稳态破坏[41]，同时可增加抑郁症患者中 BDNF 的水平[56]。腹腔注射人重组 rhBmal1 蛋白缓解睡眠剥夺诱导的焦虑和认知障碍，恢复 BMAL1 和 BDNF 水平，降低小鼠海马氧化应激[57]。因此，褪黑素可能通过上调 BMAL1 表达来增加 BDNF 水平并减轻氧化应激水平。褪黑素可以局部或全身给药，其通过清除自由基、维持线粒体稳态及减少牙槽骨吸收来治疗牙周炎[58]，有效地保护口腔健康免受炎症的影响，同时其免疫调节属性可降低疱疹病毒的感染[31]。褪黑素可能通过影响昼夜节律及其基因的表达在口腔中发挥调节情绪、抗炎及抗氧化作用，这将为治疗口腔疾病提供新思路，但其口服剂量应进一步研究证实。

维生素 D（vitamin D，VD）在日光条件下由紫外线参与合成，可能通过人体皮肤中的黑视蛋白—光敏系统调控睡眠及昼夜节律，足够水平的 VD 可改善睡眠质量、减少夜间觉醒的次数[59]。睡眠时间短时，血清中 VD 低水平与昼夜节律紊乱之间显著关联[60]。其次，VD 补充剂可改善 VD 缺乏症患者的焦虑症状[61]。此外，VD 在口腔疾病中具有重要的抗炎、抗氧化作用。例如，VD 可抑制 OLP 患者中 IFN-γ 水平，作为 OLP 的辅助疗法具有重要的防治作用[62]，VD 补充剂可减少氧化应激和炎症，并在治疗糖尿病相关牙周炎中具有重要潜力[63]。以上证据提示补充外源性 VD 可改善睡眠—觉醒周期紊乱及心理健康，但上述机制如何影响口腔疾病仍需深入探索。

川陈皮素是一种来自柑橘的膳食类多酚及天然的昼夜节律增强剂，通过川陈皮素和SR8278可恢复Ⅰ型单纯疱疹病毒（herpes simplex virus 1，HSV-1）感染引起的昼夜节律紊乱。衰老皮肤的昼夜节律因子BMAL1和CLOCK水平降低，川陈皮素和SR8278可恢复以BMAL1/CLOCK为基础的负反馈方式来增强抗病毒肽（antiviral peptide，AVP）的表达，从而减少人皮肤角质形成细胞中HSV-1的感染，这可能有助于减轻唇部及口周皮肤单纯疱疹的严重程度[64]。

药物可调节生物钟基因的表达来缓解精神障碍，如抗抑郁药氯胺酮调控CLOCK/BMAL1启动子的募集及CLOCK基因转录，直接上调抑郁症小鼠模型内侧前额叶皮层中RORα的表达并降低了PER2、CRY1、CRY2和REV-ERBα的表达水平，从而改善抑郁症状[17]。其次，异丙酚也可用于睡眠及精神障碍的治疗，主要通过上调BMAL1表达和抑制小胶质细胞M1极化来降低神经元炎症，从而改善睡眠剥夺诱导的昼夜节律破坏和认知障碍[65]。上述药物可能通过调控昼夜节律基因改善心理因素来进而缓解口腔疾病进展，这为治疗口腔疾病提供新的思路。

2.2　非药物治疗

2.2.1　睡眠管理　睡眠障碍与昼夜节律紊乱密切相关，可影响免疫功能及心理健康。睡眠时间≤5小时的个体，昼夜节律会发生紊乱[66]。夜班的间歇有利于HPA轴的恢复，早晨时间型是抑郁症的保护因素，同时优质的睡眠防止认知功能下降来改善抑郁症程度[18,67]。抑制夜间蓝光可阻断大鼠中应激诱导的BDNF信号传导，并减少大鼠的负面情绪[68]。夜间暴露于人造光会导致褪黑素分泌减少，而保持规律健康的睡眠习惯可调节褪黑素水平来维持生物钟稳态[69]。睡眠充足组的学龄儿童和青少年龈沟液中过氧化氢和MDA含量明显低于睡眠不足（< 7 h）组[41]，通过提高睡眠质量也会降低口腔溃疡的患病率[70]。根据上述研究，充足的睡眠及其质量的增强有助于减轻口内炎症因子水平并维持氧化还原平衡。

由此可见，睡眠管理可能通过改善行为和睡眠习惯来改善昼夜节律，建议包括睡眠时间达到7～9 h、保持一致的睡眠/清醒时间表、减少睡前人造蓝光的暴露，这将有利于口腔乃至机体内昼夜节律稳态的维持。

2.2.2　时辰疗法　时辰疗法是指根据人体内细胞增殖、细胞周期、DNA合成、药物代谢酶活性等昼夜节律的波动规律，调整给药时间来优化药物疗效并最大限度地减少副作用[71]。

目前，生物节律性在口腔疾病的时辰治疗中已得到较多的应用，大多数肿瘤细胞DNA合成高峰期与正常细胞相反，把握好肿瘤药物服用或放化疗时间，可以最大程度上抑制肿瘤细胞的生长，同时也可将放化疗药物对正常细胞的杀伤副作用降到最低[71]。目前顺铂、奥沙利铂、紫杉醇等化疗药物在口腔鳞状细胞癌中的适用疗法已有明确研究。例如，顺铂触发的DNA损伤及细胞凋亡受昼夜节律控制[72]。PER2可以通过抑制人口腔鳞状细胞癌中肿瘤细胞的DNA核抗体修复，从而增强奥沙利铂的细胞毒性并促进细胞凋亡，这提示与PER2表达高峰一致的时间给药可增强奥沙利铂的疗效[73]。此外，BMAL 1与紫杉醇在最佳时间范围内协同作用，可提高舌部鳞状细胞癌对紫杉醇的敏感性[74]。

时辰疗法不仅应用于口腔鳞状细胞癌的化疗药物，还体现在其他治疗口腔疾病的药物中。例如，长期口服糖皮质激素使得外源性GC抑制HPA轴和促肾上腺皮质激素水平，清晨给药与内源性GC峰值相一致，可降低发生肾上腺皮质功能减退症的风险[30]。口腔微生物群中致病菌也具有明显的昼夜节律性[46]，提示抗生素在最佳时间使用可使致病菌作用最大化，对有益菌副作用最小化。时辰疗法对多种治疗口腔疾病的药物具有重要意义，但未来仍需探索并完善时辰疗法在口腔疾病中的应用。

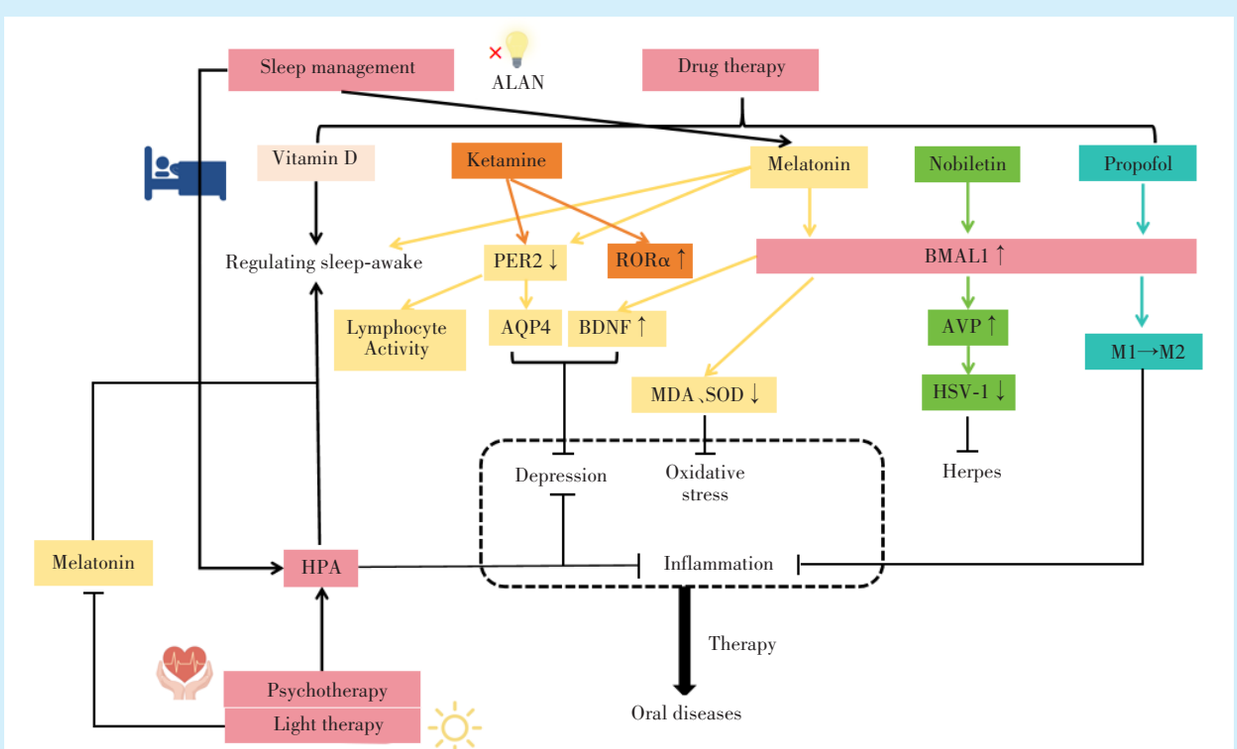
2.2.3　心理疗法　昼夜节律紊乱导致HPA轴失调，以皮质醇水平异常为指标，认知行为疗法（cognitive behavioral therapy for insomnia，CBT）与正念可作为压力管理训练的方法增强HPA轴的恢复[75]。治疗失眠的认知行为疗法（cognitive behavioral therapy for insomnia，CBT-I）是以睡眠为重点的指导性心理治疗方法，旨在指导患者改变睡眠相关行为和思维模式，减少无益的信念，减少患者消极行为及消极情绪与睡眠的联系来改善抑郁症状[76]，其中睡眠限制疗法减少睡前觉醒并巩固睡眠来改善睡眠－觉醒模式的规律性[77]，并可降低体内皮质醇及IL-6、TNF-α的表达水平[78-79]。CBT-I在治疗轮班所导致的失眠中有较好疗效，其可减轻轮班工作护士的睡眠障碍，改善失眠的严重程度并促进心理健康[80]。CBT对某些口腔颌面部疾病

（如灼口综合征、颞下颌关节紊乱）的心理方面具有积极疗效，主要通过减轻患者焦虑及抑郁状态来缓解疼痛[81]。其次，正念减压疗法也可显著提高了睡眠质量、免疫力和心理健康，是改善睡眠障碍的有效治疗方法。例如，短暂的正念练习可以减轻皮质醇水平、减轻焦虑，还可降低机体促炎细胞因子IL-6和白细胞介素-8（interleukin-8，IL-8）的水平[82]。

CBT-I及正念减压疗法作为新的、有效的非药物干预措施，可恢复HPA轴失调、降低皮质醇水平来改善心理因素及免疫功能，同时医疗成本低、易推广，为未来拓宽昼夜紊乱及口腔疾病心理疗法奠定基础。

2.2.4　光照疗法　光照疗法是一种利用自然光和人造光的疗法，其中光通过SCN减少睡眠中断，并经HPA轴调节褪黑素及皮质醇水平，从而达到治疗效果[83]。临床证据支持日光疗法对多种疾病的有益效果，包括抑郁症、睡眠障碍。间歇性暴露在强光下治疗轮班工作者的昼夜节律失调，并缓解其环境适应不良[84]。亮光疗法可增加主观睡眠时间并改善抑郁症情绪及认知功能[85]，定制照明干预可改善痴呆老年人的睡眠－觉醒周期及情绪[86]。光生物调节疗法通过刺激昼夜节律系统的黑视蛋白细胞并对帕金森病患者睡眠指标显示良好的疗效[87]。此外，该疗法可减轻牙周组织中的炎症并促进受损组织的愈合[88]，并对正畸诱导的炎性根吸收有良好的疗效[89]。

基于上述证据，光照疗法有可能通过调控机体昼夜节律来减轻口内炎症并促进口内组织的修复。见图2。



By inhibiting the exposure to artificial light at night, the secretion of melatonin can be maintained.Vitamin D and melatonin can improve the circadian rhythm by regulating the sleep-wake cycle, melatonin down-regulates PER2, polarizes AQP4, and up-regulates the level of BMAL1 to increase the molecular expression of BDNF, alleviates oxidative stress, which achieve anti-depression, anti-inflammatory and antioxidant effects. Nobiletin up-regulatesthe expression of BMAL1 to increase the level of AVP, thus resisting HSV-1 infection. Ketamine upregulates RORα and decreases PER2 expression to achieve antidepressant effect. Propofol also caused microglia phenotype to change from inflammatory M1 type to anti-inflammatory M2 type by upregulation of BMAL1. In addition, sleep management, light therapy, and psychotherapy inhibit inflammation and promote mental health by regulating the HPA axis and sleep-wake cycle. ALAN: artificial light at night; AQP4: aquaporin-4; AVP:antiviral peptide; HSV-1:herpes simplex virus

Figure 2　Mechanism of action of drug and non-drug therapies on circadian rhythm disturbance in oral diseases

图2　在口腔疾病中药物及非药物疗法对昼夜节律紊乱的作用机制

3　总结与展望

目前，对于昼夜节律如何影响心理神经免疫学的具体机制尚不明确，且在口腔疾病中昼夜节律基因BMAL1、REV-VRBα与BDNF、T细胞亚群、NF-κB通路之间的联系需要进一步研究证明。其次，在口腔疾病的治疗中，靶向昼夜节律基因尚未应用于临床实践中。未来可以开发靶向作用于昼夜节律基因的药物，同时完善时辰疗法、光照疗法等在口腔疾病治疗中的应用。此外，今后需开展大规模的临床研究以验证昼夜节律基因在口腔疾病诊断、治疗和预后评估中的应用价值。改善昼夜节律紊乱加强口腔科、睡眠科、精神科在内的多学科团队之间的密切合作，以评估多种因素并为口腔疾病患者提供个性化治疗。总之，昼夜节律与口腔疾病之间存在广阔的研究前景，通过深入研究昼夜节律在口腔疾病发病因素中的作用机制及其防治策略，不仅可以为揭示口腔疾病的发病机理提供新的视角，还有望为口腔疾病的预防、诊断和治疗提供新的方法。

【Author contributions】 Wang YJ designed the structure of article and wrote the article. Zhang L, Cheng C and Xing WM draw the figures and collected the references. Ge XJ and Cheng FL revised and reviewed the article. Zhang F designed the structure of article and reviewed the article. All authors read and approved the final manuscript as submitted.

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