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高原低压低氧环境下牙周炎与中枢神经系统炎症的相关性

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【摘要】 近年来,随着在高原和山区活动人群的增多,高海拔暴露变得越来越普遍,许多基础疾病患者受高原低压低氧环境影响,病程进一步加重甚至导致认知障碍的现象频发。牙周炎是一种常见的炎症性疾病,能诱发牙周局部炎症反应,甚至中枢神经系统炎症。在高海拔环境下,机体出现免疫力下降、组织缺氧等反应,这些反应会促进牙周炎的发生发展,甚至有可能增加牙周炎引发中枢神经系统炎症的风险。随着高原医学研究的不断深入,高原低压低氧环境下牙周炎与中枢神经系统炎症之间的关系引发越来越多的关注。本文就牙周炎与中枢神经系统炎症的研究进展进行综述,并对高原低压低氧环境下牙周炎与中枢神经系统炎症之间的相关性进行讨论。

【关键词】 高原;低压低氧;牙周炎;中枢神经系统炎症
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Correlation of periodontitis with central nervous system inflammation in hypobaric hypoxia environments at plateau

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【**Abstract**】 With the increase in human activity in plateau and mountainous areas in recent years, high-altitude exposure has become increasingly common. Many patients with underlying diseases are affected by hypobaric hypoxia in plateau environments, which further aggravates disease processes and even leads to cognitive disorders. Periodontitis is a common inflammatory disease that induces periodontal local inflammatory responses and even causes central nervous system inflammation. At high altitudes, the body suffers from decreased immunity and tissue hypoxia, which can promote the occurrence and development of periodontitis and may even increase the risk of periodontitis-induced central nervous system inflammation. As plateau medical research advances, the relationship between periodontitis and central nervous system inflammation in hypobaric hypoxia environments at plateau is attracting more and more attention. This work reviews the

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progress of research on periodontitis and central nervous system inflammation and discusses the correlation between periodontitis and central nervous system inflammation when exposed to hypobaric hypoxia in plateau environments.

【Keywords】 plateau; hypobaric hypoxia; periodontitis; central nervous system inflammation

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随着社会的进步,迁移至高海拔地区就业和居住的人不断增多,低压低氧是高原地区的主要环境特征[1],可以引发机体一系列不良反应[2-4],甚至导致高原低压低氧脑损伤[5-6]。而炎症在高原低压低氧脑损伤中发挥着重要作用[7-8],系统性炎症和局部炎症的存在会增加高原低压低氧脑损伤的风险[9-10]。牙周炎作为一种口腔局部炎症性疾病,以牙周袋壁炎症、牙槽骨吸收、牙齿松动为主要特征,高原低压低氧环境对牙周炎的病情会产生负面影响[11],尽管已有研究发现牙周炎能够引发中枢神经系统炎症导致学习与记忆障碍[12],但高原低压低氧环境下牙周炎与中枢神经系统炎症的讨论尚未见报道。因此,本文就高原低压低氧环境下牙周炎与中枢神经系统炎症的相关性进行讨论,或可为高原低压低氧环境下牙周炎和中枢神经系统炎症的预防提供思路。

1 牙周炎的现状

牙周炎是由牙周病原微生物引发的牙周组织炎症性疾病,初期牙龈轻微出血,随着时间的推移,牙菌斑生长,牙结石积聚,牙周炎症加重,最终导致牙齿脱落[13]。除了微生物因素外,环境、宿主炎症和遗传等因素也推动着牙周炎的发生和发展[14],使牙周炎在人群中广泛流行。我国第四次全国口腔疾病流行病学调查显示,牙周炎影响了一半以上中国成年人的口腔健康[15-16]。在全球范围内,约 7.43 亿人的口腔健康受牙周炎影响[17],且患病率呈上升趋势[18],牙周炎已成为全球口腔健康问题。不仅如此,研究发现牙周炎还是中枢神经系统炎症的重要危险因素之一[12]。

2 牙周炎对中枢神经系统炎症的影响

长期以来,中枢神经系统炎症是中枢神经系统疾病的重要病理机制[19],牙周炎作为一种局部炎症与中枢神经系统炎症密切相关[20-21]。而牙周炎引发中枢神经系统炎症的主要病因一方面是牙周病原微生物及其产物[20],包括牙龈卟啉单胞菌(*Porphyromonas gingivalis*, Pg)[22]、齿垢密螺旋体(*Treponema denticola*, Td)[23]、具核梭杆菌(*Fusobacterium nucleatum*, Fn)[24]等,这些病原微生物进入脑内能引发免疫反应,还能产生多种毒力因子激活脑内免疫细胞,如脂多糖(lipopolysaccharide, LPS)[25-26]、牙龈蛋白酶[27-28]、荚膜[29]、外膜囊泡(outer membrane vesicle, OMV)[30]、新型鞘脂[31]。另一方面,牙周炎症状态时释放的炎症因子一旦进入大脑,不仅会增加炎症因子的数量,也会刺激神经胶质细胞产生额外的炎症因子,引发脑内炎症反应[32]。这些致炎物质从牙周组织出发,通过多种途径进入脑内(图 1),主要分为以下 4 种途径:

(1)血液循环途径:研究显示,牙龈卟啉单胞菌通过牙周袋渗漏进入血液循环,一旦进入脑血管,可能会通过多种方式诱导血脑屏障(blood brain barrier, BBB)的破坏,使 Pg 经血脑屏障进入脑内[32-33]。牙周炎症部位还能释放炎症因子进入血液循环,炎症因子穿过血脑屏障进入脑内[34]。不仅如此,脑室周围器官(circumventricular organs, CVO)缺乏连续的血脑屏障,当牙周病原微生物和炎症因子进入血液后可能经此位置进入大脑[35]。另外,大脑表面蛛网膜与软脑膜间的蛛网膜下腔含丰富的血管[36],Pg-LPS 经血液循环到达脑血管后能使外周巨噬细胞产生炎症因子,软脑膜细胞能够将外周巨噬细胞炎症信号转导到脑内[37],炎症因子还能与脑血管内皮细胞(endothelial cells, EC)上的炎症因子受体结合,激活血管周围巨噬细胞与小胶质细胞间的通讯,使小胶质细胞分泌炎症因子,导致神经炎症[38]。

(2)神经旁路途径:齿垢密螺旋体是牙周炎的病原微生物之一[39],能通过三叉神经进入大脑到达三叉神经中脑核和海马体[40-41],也能沿着嗅神经进入大脑[35]。牙龈卟啉单胞菌细胞外囊泡(extracellular vesicles, EVs)能通过三叉神经进入大脑,诱发神经炎症[42]。此外,外周炎症因子还能刺激周围神经传入纤维,激活迷走神经将信号传入大脑,导致脑内炎症因子水平升高[43]。

(3)口腔微生物-肠-脑轴途径:研究发现,肠道微生物通过肠-脑轴影响其宿主的大脑功能,涉及神经、内分泌和免疫途径[44],而口腔菌群变化会引起肠道菌群的改变[45]。因此,口腔微生物通过影响

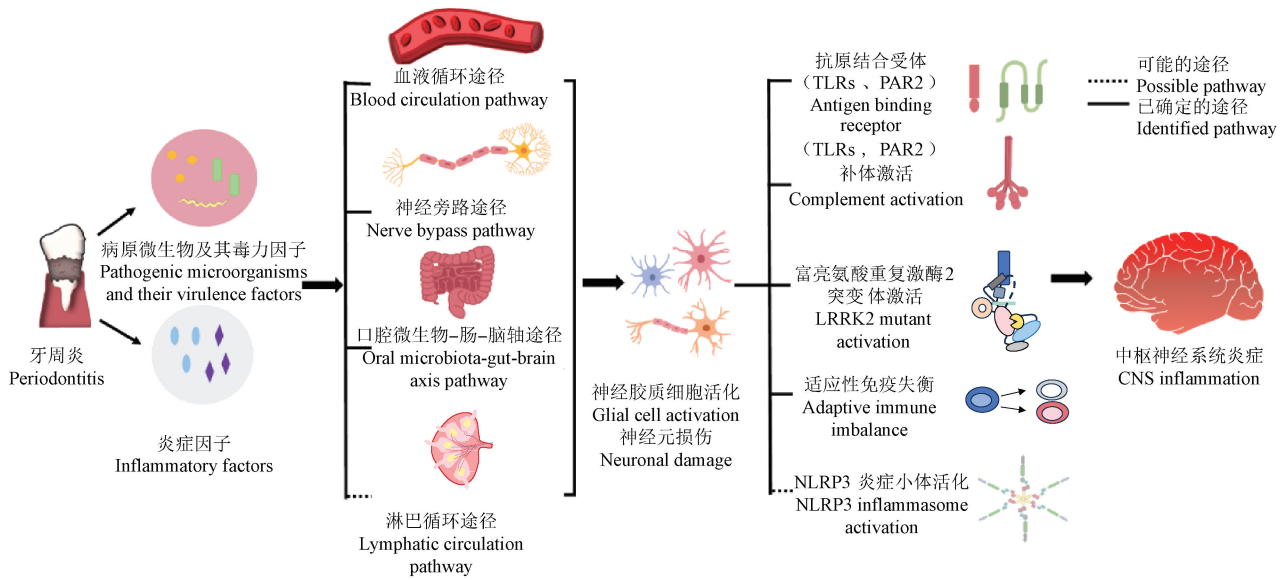

图 1　牙周炎影响中枢神经系统炎症的途径

Figure 1　Pathways of periodontitis affecting CNS inflammation

肠-脑轴从而影响中枢神经系统炎症发生是有可能的。在小鼠模型中，牙周炎相关唾液微生物群的持续灌胃损害认知功能，导致脑内神经炎症[46]。Xue 等[47]发现小鼠慢性牙周炎诱导口腔微生物-肠-脑轴紊乱导致中枢神经系统炎症与认知障碍也为此途径提供了直接证据。

（4）淋巴循环途径：淋巴管中含有大量抗原呈递细胞，能识别抗原并呈递至区域淋巴结进行处理[48]，其中第三和第四脑室与颈部中深淋巴结相连[49-50]，口腔区域淋巴也与颈部中深淋巴结相连[32]，虽然目前没有证据表明它是将口腔细菌传播到大脑的通路，但是一种可能的途径。

以上研究表明，牙周病原微生物及其产物和炎症因子能通过多种方式侵入脑内，引发中枢神经系统炎症。而作为脑内的主要免疫细胞，小胶质细胞和星形胶质细胞在大脑中有调节神经炎症的作用，是脑内炎症因子的重要来源[51]。在牙周炎与中枢神经系统炎症的联系中，小胶质细胞和星形胶质细胞的活化占据重要地位。根据文献报道，牙周病原微生物及其产物和炎症因子使小胶质细胞和星形胶质细胞活化，引发神经元损伤，导致脑内神经炎症的具体机制包括以下 5 点：

（1）抗原结合受体：研究发现，Pg-LPS 能通过结合细胞膜上的 Toll 样受体，激活 NF-κB/STAT3 信号通路，上调炎症因子表达，活化小胶质细胞和星形胶质细胞[25,52]。此外，Pg 产生的牙龈蛋白酶能与蛋白酶激活受体 2（proteinase activated receptor-2，PAR2）结合，激活 PI3K/AKT 信号通路和 ERK 信号通路，使小胶质细胞释放 IL-6 和 TNF-α[28]。

（2）补体激活：在阿尔茨海默病（Alzheimer's disease，AD）小鼠中，Pg 能够穿过血脑屏障进入脑内，激活小胶质细胞产生炎症因子，并且还能够诱导补体成分 1q（complement component 1q，C1q）过表达，使小胶质细胞进一步活化，加剧中枢神经系统炎症[53]。

（3）富亮氨酸重复激酶 2（leucine-rich repeat kinase 2，LRRK2）突变体激活：富亮氨酸重复激酶 2 突变体是帕金森病发病机制中最常见的遗传因素[54]。研究发现，Pg 能激活 LRRK2 突变体，使小胶质细胞活化，诱导的神经变性具有 LRRK2 突变依赖性[55]。

（4）适应性免疫失衡：适应性免疫的主要参与者是 $CD4^+$T 细胞，通过分化为辅助性 T 细胞（helper T cell，Th）和调节性 T 细胞（regulatory T cell，Treg），可以调控脑内神经炎症[56]。研究发现，在 Pg-LPS 诱导的牙周炎小鼠中，Th17 相关促炎细胞因子在血液和大脑中的表达增加，而 Treg 相关抗炎细胞因子的表达降低，神经元凋亡加剧[57]。

（5）NLRP3 炎症小体活化：NOD 样受体热蛋白结构域相关蛋白 3（NOD-like receptor thermal protein domain associated protein 3，NLRP3）炎症小体是先天免疫系统的关键部分，在多种炎症性疾病中起重要作用[58]。Gong 等[30]研究发现，口服饲喂小鼠牙龈卟啉单胞菌外膜囊泡后，可在海马体和皮层中检测

到外膜囊泡,星形胶质细胞和小胶质细胞活化,IL-1β 水平增加,海马体中 NLRP3 炎症小体相关蛋白的表达上调,表明外膜囊泡能激活脑内免疫细胞进而引发中枢神经系统炎症,NLRP3 炎症小体激活是一种可能的机制。这些研究进一步证明牙周炎是中枢神经系统炎症的重要危险因素之一。

3 高原低压低氧环境下牙周炎与中枢神经系统炎症的关系

随着高原医学研究的深入,科学家们开始探索高原低压低氧环境下牙周炎与中枢神经系统炎症之间的可能关联。目前关于这方面的研究,杜灿等[59]讨论了高原慢性低氧环境慢性牙周炎与阿尔茨海默病的相关性,提出了相关见解,但高原低压低氧环境下牙周炎与中枢神经系统炎症的研究目前仍未见报道。因此,接下来围绕以下两个部分对高原低压低氧环境下牙周炎与中枢神经系统炎症相关关系进行讨论,为进一步的实验研究提供思路。

3.1 高原低压低氧环境对牙周炎的影响

近年来,高原低压低氧环境对牙周炎的影响引发关注。根据我国口腔流行病学调查统计,平原地区生活人群牙结石、牙龈出血检出率分别为 53.5%、18.8%,而西藏地区的高原移民检出率为 68.6%、30.4%[60]。不仅如此,在一项针对中国西部地区青少年牙龈状况与海拔的相关性分析中发现,64.09%和 77.15%的青少年分别患有牙龈出血和牙结石,高原地区青少年患病率显著高于平原地区青少年[61]。以上研究均表明,高原环境下牙周炎的发病率明显高于平原地区。此外,一项对空军部队的口腔健康状况调查分析也显示,驻高原空军官兵牙周炎患病率显著高于平原空军官兵,且随高原驻军时间延长,牙周炎逐渐加重[62],这提示高原环境与牙周炎发病率和病情发展相关。

首先,在人群研究中发现,高原牙周炎患者血清中内脂素(visfatin,VF)水平升高,促炎作用增强,导致牙周组织损伤加重[63]。此外,在牙周炎兔模型中,低压低氧后血清和牙龈组织中细胞间黏附分子-1(soluble intercellular adhesion molecule-1,sICAM-1)、可溶性血管黏附分子-1(soluble vascular cell adhesionmolecule-1,sVCAM-1)显著上调[64],提示血管通透性增加;超氧化物歧化酶(superoxide dismutase,SOD)活力降低,超氧自由基(superoxide radical,SR)增多,炎症加剧[65]。而在牙周炎大鼠模型中,低压低氧后牙周组织炎症因子水平显著上升[66],龈沟液中 C-反应蛋白(C-reactive protein,CRP)水平增加[67],血清中基质金属蛋白酶-2(matrixmetalloproteinase-2,MMP-2)和基质金属蛋白-3(matrixmetalloproteinase-3,MMP-3)表达上调[68-69],增强牙周组织细胞外基质的降解,使炎症进一步发展。以上人群和实验动物模型的研究结果均表明低压低氧能够加速牙周炎的发生发展,而高原低压低氧加重牙周炎症的主要原因可能涉及以下 4 个方面:

(1)低压低氧使牙周病原微生物增多

牙周病原微生物是导致牙周炎的主要因素,黄镜静等[70]研究发现牙周炎兔模型低压低氧后龈下菌斑中牙龈卟啉单胞菌水平相比其余各组显著升高。李淼等[71]采用高通量测序检测菌群,发现高原牙周炎人群口腔菌群中齿垢密螺旋体等专性厌氧菌增多,表明低压低氧有利于牙周病原微生物生长。而牙周病原微生物能产生多种毒力成分[72],使口腔微生物生态失调,诱发牙周组织炎症。

(2)低压低氧加重牙周组织局部缺血缺氧

人在高原低压低氧条件下血氧饱和度(oxygen saturation,SaO_2)远低于正常水平[73],为保证机体供氧,人体产生更多红细胞和血红蛋白以捕捉氧气分子,从而引发小血管破裂,使局部组织缺血缺氧,引发无氧代谢,细菌大量繁殖[74]。此外,牙周组织缺氧会抑制人牙周膜细胞(human periodontal ligament cells,hPDLCs)的增殖和迁移能力[75]。同时,缺氧也会引发自由基累积,炎症因子大量释放[65-66],使牙周炎症加重。

(3)低压低氧破坏牙周组织防御功能

正常状态下,口腔中的中性粒细胞能够发挥杀灭病原微生物的作用[76],而在高原低压低氧条件下牙周炎患者产生的中性粒细胞减少,识别和清除病原微生物的效果减弱,加速牙周组织感染发炎[11]。

(4)高原环境其他特点加重牙周炎症

高原地区与平原相比风力、昼夜温差和日照强度明显增强,当上升到高原后唾液分泌无法达到正常水平,导致口腔清洁能力减弱,牙周微生物加快繁殖。此外,高原地区饮食以肉奶制品为主,蔬菜水果食用频率较低,缺乏人体所需的维生素和微量元素,易导致口腔疾病的发生。同时,高原水中丰富的矿物质易沉积在牙齿表面,导致牙结石的形成,加重牙周炎[77]。

以上研究表明高原低压低氧环境会加重牙周

局部炎症,而牙周炎症引发中枢神经系统炎症的研究已有报道,但在高原特殊环境下牙周炎与中枢神经系统炎症之间的关系更为复杂。

3.2　高原低压低氧环境下牙周炎与中枢神经系统炎症的相关性

近年来,高原低压低氧环境下牙周炎与中枢神经系统炎症的关系引发关注,赵婷婷[78]研究发现牙周炎能够导致藏族中老年人认知功能明显下降,提示慢性牙周炎有可能是高原地区认知障碍的危险因素。此外,2018 年报道了一例与海拔升高相关的牙周感染导致脑脓肿的病例,表明海拔升高后低压环境对血流动力学的长期影响会导致牙周菌群分流,从而导致脑内神经炎症的发生[79]。以上研究表明高原低压低氧环境下牙周炎与中枢神经系统炎症相关,并且高原低压低氧环境可能对牙周炎引发中枢神经系统炎症具有促进作用,虽未阐明具体机制,但为高原低压低氧环境下牙周炎与中枢神经系统炎症的研究做出了初步探索。

4　展望

目前,高原低压低氧环境下牙周炎与中枢神经系统炎症之间的研究尚有待进一步深入。虽然已有研究表明高原低压低氧能够加重牙周炎,且牙周炎与中枢神经系统炎症之间存在关联,但仅限于对平原地区牙周炎与中枢神经系统炎症的研究较多,高原地区不仅对于牙周炎的研究较少,对于牙周炎与中枢神经系统炎症的研究更少,特别是在高原低压低氧环境下的特殊变化及其变化规律,与高海拔暴露的时间的关联性等都有待深入探究。此外,牙周炎进程包含不同阶段,不同阶段牙周炎在低压低氧环境下对中枢神经系统炎症的影响是否不同,牙周炎处于何种阶段在高原低压低氧环境下会引发中枢神经系统炎症,这些问题尚待进一步的研究。另外,中枢神经系统炎症是引发神经退行性疾病的重要原因,并且在高原环境下与高原脑水肿等高原病也有关联。因此,高原环境下牙周炎与神经退行性疾病和高原病的关系均是需要进一步探讨的问题。当牙周炎与高原低压低氧两种风险因素都存在时,发生中枢神经系统炎症的风险是否增加? 是否会引发神经退行性疾病和高原病? 其中的具体机制是什么? 对这些问题的研究将阐明高原低压低氧环境下牙周炎对中枢神经系统炎症以及相关疾病发生和发展的影响,从而为高原低压低氧环境下中枢神经系统炎症的预防与治疗提供思路,为到高海拔地区的人群的健康提供有价值的建议。

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