·专家笔谈·

酸敏感离子通道3在颅颌面疼痛中分子调控机制研究进展

杨虹　林佳雨　肖韬穆　戴静桃　刘楚峰
南方医科大学口腔医院正畸科,广州　510280
通信作者:刘楚峰,Email:xyzmmok@163.com

刘楚峰

【摘要】 口颌面部疼痛被定义为头颈部、口腔颜面部或各种口腔组织来源疼痛的总称,是口腔常见病症。酸敏感离子通道3(ASIC3)主要分布在外周感觉神经元,参与伤害性感受、机械感觉和化学感觉,是疼痛相关的组织酸中毒的分子决定因素。研究ASIC3在口颌面部疼痛中的作用对研究疼痛机理有重要意义。本文系统梳理了近年来ASIC3在口颌面部疼痛中的作用及其镇痛作用的研究进展,以期为临床治疗和药物研制提供新思路,为口颌面部疼痛的精准治疗开辟新路径。

【关键词】 酸敏感离子通道;　面部疼痛;　牙齿移动;　三叉神经节

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Research progress on the molecular regulatory mechanism of acid-sensing ion channel 3 in craniofacial pain

Yang Hong, Lin Jiayu, Xiao Yaomu, Dai Jingtao, Liu Chufeng
Department of Orthodontics, Stomatological Hospital, Southern Medical University, Guangzhou 510280, China
Corresponding author: Liu Chufeng, Email: xyzmmok@163.com

【**Abstract**】 Oral and maxillofacial pain, defined as the pain originating from the head and neck, oral and facial regions or various oral tissues, is a common oral condition. Acid-sensing ion channel 3 (ASIC3), mainly distributed in peripheral sensory neurons, participates in nociception, mechanosensation and chemosensation, and is a molecular determinant of tissue acidosis-related pain. Studying the role of ASIC3 in oral and maxillofacial pain is of great significance for understanding the mechanism of pain. This article reviews the research progress on the role of ASIC3 in oral and maxillofacial pain and its analgesic effect in recent years.

【**Key words**】 Acid sensing ion channels;　Facial pain;　Tooth movement;　Trigeminal ganglion

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疼痛是一种与实际或潜在的组织损伤相关的不愉快感觉和情绪体验[1],国际疼痛学会(International Association for the Study of Pain,IASP)国际疾病分类第十一次修订本(International Classification of Diseases 11th Revision,ICD-11)疼痛分类标准将慢性疼痛分为7个亚类,包括慢性原发性疼痛、慢性癌症相关性疼痛、慢性术后疼痛和创伤后疼痛、慢性神经病理性疼痛、慢性头痛和颌面痛、慢性内脏痛及慢性肌肉骨骼疼痛[1]。Okeson[2]进一步将口颌面部疼痛又分为生理性和心理性疼痛。生理性疼痛包括肌肉骨骼疼痛(如咀嚼肌和颈椎)、神经性疼痛[间歇性(如三叉神经痛)和持续性(外周神经病理性疼痛和中枢敏化)疼痛、神经血管紊乱(如偏头痛)]及炎性疼痛(如正畸疼痛、癌性疼痛等)。心理性疼痛包括情绪和焦虑症[3-4]。本文集中于生理性口颌面部疼痛的相关论证。有效治疗颌面部疼痛不仅关乎患者个体的生活质量,还对医疗体系优化和社会健康水平提升具有重要意义。

研究发现,酸敏感离子通道3(acid sensing ion channel 3,ASIC3)广泛参与伤害性感觉、机械感受和化学感受[5],是疼痛传导的关键受体之一。目前,口颌面部疼痛治疗主要为治疗原发病的同时给予抗疼痛的对症治疗,尚缺乏针对口颌面部疼痛治疗的靶向药物。本文旨在总结ASIC3在口颌面部疼痛中的作用,以期为临床治疗和药物研制提供新思

路,为口颌面部疼痛的精准治疗开辟新路径。

一、口颌面部疼痛信号的传导

游离的神经末梢是痛觉的感受器,广泛分布于皮肤、黏膜和血管旁结缔组织等处。痛觉冲动由Aδ或C型纤维传导[6],多终止于三叉神经脊束核尾侧亚核(caudal subnucleus of spinal trigeminal nucleus, Vc)的Ⅰ、Ⅱ层[7]。疼痛信号一旦被口颌面部感觉末梢接收,就会通过神经纤维经三叉神经节(trigeminal ganglion, TG)、Vc和腹后核传递,最终到达疼痛感知的感觉皮层[8]。第一级神经元是TG中的三叉神经细胞,它是假单极神经元,具有外周突起和中枢突起,TG中的神经肽和受体在正畸疼痛的调节中起重要作用。Guo等[9]用瞬态感受器电位阳离子通道(transient receptor potential vanilloid-1, TRPV1) shRNA序列的慢病毒抑制TG中TRPV1的表达,正畸疼痛随之缓解。Zhou等[10]的研究表明,随着正畸牙移动,TG中降钙素基因相关肽(calcitonin-gene-related peptide, CGRP)表达增加,大鼠疼痛增加,而辣椒素能减少TG中CGRP表达,同时降低疼痛水平。Bai等[11]的研究发现,相比于野生大鼠,肿瘤坏死因子α(TNF-α)基因敲除的大鼠中,炎性颞下颌关节痛明显减弱。三叉神经脊束核尾侧核和腹后核是位于延髓内的第二级神经元,直接接受痛觉纤维传导的信息,且密布着痛觉特异神经元,同样在颌面部疼痛中发挥重要作用。Liu等[12]发现,下行的A11神经核-三叉神经脊束核尾侧多巴胺投射对于三叉神经病理性疼痛的调节至关重要。Wang等[13]用硬脑膜酸诱导致小鼠三叉神经痛,同时能诱导表达c-fos,用酸通道抑制剂APETx2能减少小鼠c-fos阳性三叉神经脊髓核尾部(caudal part of the spinal trigeminal nucleus, Sp5C)神经元数量,并减轻疼痛。Sp5C第三级神经元位于丘脑腹后区,三叉神经核发出纤维形成三叉神经丘脑束,三叉神经丘脑束交叉到对侧,并上升与丘脑腹后核形成突触。最后,丘脑将纤维发送到大脑的许多区域,包括海马、杏仁核、岛叶皮质和躯体感觉皮质,而这些脑区投射纤维又汇聚于感觉皮层并整合疼痛信息[14]。而在这些疼痛传导的关键节点上(牙周膜、TG和Vc等)都存在着ASIC3的分布(图1)。因此,研究ASIC3在口腔颌面部疼痛中的作用有着重要意义。

二、酸敏感离子通道3的基本情况

1. ASIC3的结构:ASIC是上皮钠通道/退化蛋白超家族成员[15]。ASIC有4个成员,包括ASIC1、ASIC2、ASIC3和ASIC4,构成通道的亚基都包含细胞内的N和C末端,2个疏水跨膜(transmembrane, TM)区域,以及1个大的细胞外环,其中有许多具有保守间距的半胱氨酸残基。TM区域通常被象征为TM1(克隆到N-末端)和TM2(接近C-末端)。离子选择性地从细胞外侧流入细胞质的通道的孔是由三聚体的3个TM2区域形成的[16]。其中,ASIC3主要分

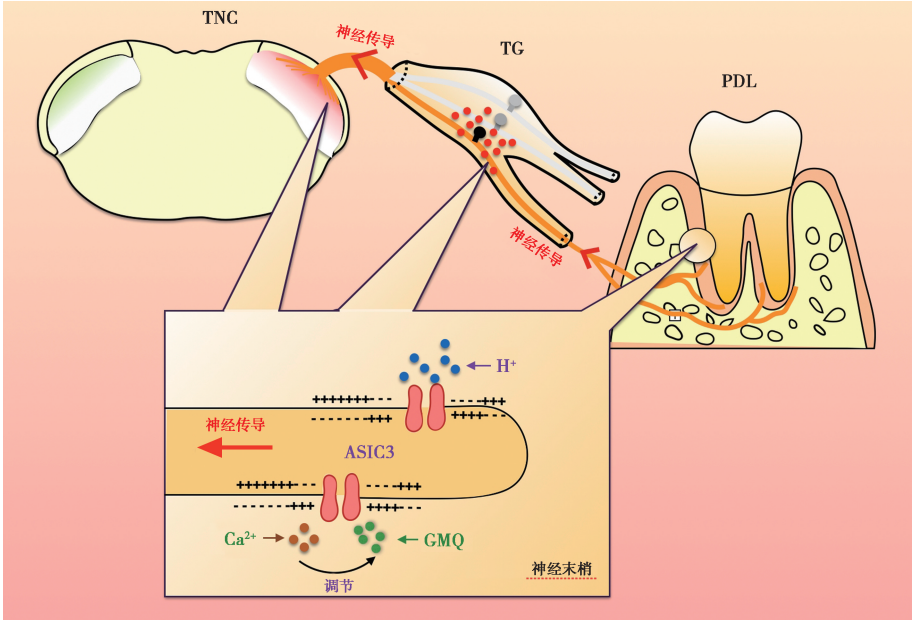

图1 酸敏感离子通道3(ASIC3)参与颌面部疼痛调控相关的分子机制图 口腔颌面部疼痛传导经外周神经传入三叉神经节(TG)、三叉神经尾侧核(TNC)。ASIC3分布于传导通路上,质子(H^+)或2-胍-4-甲基喹唑啉(GMQ)可以激活ASIC3,其中GMQ对钙离子(Ca^{2+})敏感,降低Ca^{2+}浓度将增强GMQ诱导的电流。PDL:牙周膜;红箭头示神经传导。

布在外周感觉神经元,ASIC3孔顶部为高亲和力Ca^{2+}位点,并以Ca^{2+}作为变构调节剂和通道阻断剂,进而感知细胞外酸度的变化[17],这也是其参与感受调节的结构基础之一。

2. ASIC3的受体结合特性

(1) ASIC3的质子配体(H^+)敏感区:ASIC3对胞外质子显示出高敏感性[16],且激活阈值刚好低于生理pH值(pH=7.2)[18]。轻度酸中毒(即pH=7.0)会导致相当大的峰值电流,然后是持续的脱敏电流。极端酸中毒(即pH=5.0)会导致更大的峰值电流和更小的持续电流[19]。最初的瞬时去极化成分可被阿米洛利(anthopleura elegantissima x2, APETx2)阻断,而持续成分可通过去除溶液中的K^+消除或被阿南达胺和奎尼丁等阻断剂部分阻断[20]。许多炎性刺激如三磷酸腺苷(ATP)[21]、乳酸[22]、花生四烯酸[23]、胍丁胺和5-羟色胺[15]被报道能增强质子诱导的ASIC3电流。研究表明,酸性溶液广泛参与ASIC3介导的疼痛相关行为,而施加正畸力就将导致牙周酸性微环境,从而诱发正畸痛[9-10,24-25]。用中等酸性(pH=6.6)激活角膜感觉神经元的ASIC样电流后,眨眼、用前爪抚眼等大鼠对伤害性刺激的伤害性反应增加[26];重复肌内注射酸性0.9%氯化钠溶液(pH=4)可产生长时间的机械性痛觉过敏等[5]。

(2)ASIC3的非质子配体敏感区:许多H^+敏感通道需要突然和显著的pH降低才能打开,但这种变化在大多数生理和病理条件下在体内可能是不常见的[27]。可以想象,ASIC3要发挥其生理功能,除了质子之外还有其他配体直接激活ASIC3或促进其对酸的反应。研究发现了一组含有胍基和杂环的小分子,即2-胍-4-甲基喹唑啉(guanidine-4-methylquinazoline, GMQ)。GMQ是有效的ASIC3激活剂,使用GMQ作为探针,学者发现了此种配体感受器,它可能使用诱变、共价修饰分析和行为测试相结合的方法来服务于ASIC的门控功能[28]。GMQ能在生理正常pH下诱导持续电流,并对细胞外阿米洛利和Ca^{2+}阻断敏感。与酸诱导的电流不同,GMQ诱导的电流显示很少或没有脱敏,并且GMQ诱导的电流对胞外Ca^{2+}的阻断表现出更高的敏感[29]。轻度酸中毒(pH=7.3~7.5)能显著增强GMQ诱导的持续电流。此外,如上所述,GMQ诱导的电流对胞外Ca^{2+}变化高度敏感,降低细胞外Ca^{2+}显著增强GMQ诱导电流的峰值幅度,而将其增加到10 mmol/L则完全消除了GMQ电流。结果表明,细胞质子与Ca^{2+}和GMQ在调节ASIC3激活中的动态相互作用[30],GMQ能促进ASIC3介导的疼痛相关行为。

三、酸敏感离子通道3的分布

ASIC3主要在背根神经节(dorsal root ganglia, DRG)、TG和结状神经节(nodose gangilion, NG)中表达[21]。结合全细胞膜片钳记录的逆行追踪研究表明,功能性ASIC3主要表达于DRG伤害性感受器和本体感受器的传入神经元[31]。在中枢神经系统,ASIC3只在脑干区的本体感觉神经元中表达[32]。

1. ASIC3在牙周膜中的分布:Rahman等[33]报道中发现,在牙周膜中存在多种具有树枝状分支的ASIC3阳性结构,ASIC3免疫反应存在于轴浆中,但在普通雪旺细胞,包括相关的终末雪旺细胞中未见。越来越多的证据表明,ASIC在本体感受器、机械感受器和伤害性感受器的机械传导中发挥着重要作用[34-35],牙周膜ASIC3也被报道参与了牙齿的机械传导。研究发现,ASIC3存在于一些专门的神经末梢,如Meissner小体,Pilo-Ruffini神经末梢和Merkel细胞,以及表皮中的小游离神经末梢[36]。Rahman等[33]研究中标记Ruffuni小体的蛋白PGP 9.5和S-100与ASIC3共同定位于牙周膜中,表现为扩展的轴突终末的厚密的树枝状结构,表明ASIC3可能在牙周Ruffini末端作为机械感觉的分子发挥作用。Gao等[25]报道发现,ASIC3在牙周组织的压力侧和张力侧均有表达,且在实验性牙齿移动后表达增加。

2. ASIC3在外周神经系统中的分布:ASIC3主要分布于感觉神经元,包括DGR[21,37]、TG[38]、耳蜗螺旋神经节[39]和视网膜神经节[36]。Rahman等[33]对TG的观察显示,各种大小的神经元都表达ASIC3免疫反应,并通过使用特异性cRNA探针的原位杂交组织化学证实,最强的免疫阳性反应出现在中小型神经元中。Wang等[40]用免疫荧光染色检测大鼠三叉神经尾侧核(trigeminal nucleus caudails, TNC)中ASIC3蛋白表达,显示ASIC3主要表达于TNC组织中的神经元细胞膜和细胞质且ASIC3在GFAP标记的星形胶质细胞中有轻微表达。此外,P2X(3)、TRPV1和ASIC3通常在三叉神经细胞中共表达,这意味着可以形成功能性复合体,使颅面伤害性神经元对疼痛中改变的ATP和pH做出协同反应[41]。

3. ASIC3在中枢神经系统中的分布:Wu等[42]的研究表明,*ASIC3* mRNA在小鼠大脑中的表达较低或检测不到。只有脑干表达低水平的全长*ASIC3*

mRNA,而在海马中几乎检测不到。研究表明,ASIC3免疫阳性反应在下丘脑广泛分布,以室旁核、视上核、视交叉上核、弓状核、背内侧核、正中视前核、腹内侧视前核和背侧结节乳头状核密度最高[43]。

四、酸敏感离子通道3参与口颌面部疼痛调节机制

1. ASIC3与口腔颌面部炎性疼痛:炎症过程中ASIC3的升高与神经元的兴奋性增强相平行且ASIC3直接被非甾体抗炎药抑制[44]。这提示ASIC3在口腔颌面部炎性疼痛中也将发挥作用。牙髓炎是指发生于牙髓组织的炎性病变,是口腔中最为多发和常见的疾病之一[45]。ASIC3存在于约67%的牙髓神经元中,是牙髓组织中机械刺激信号转导的关键介质。但是研究表明,炎症状态下表达ASIC3的牙髓神经元的比例并未增加[46]。ASIC3对牙髓炎疼痛的影响有待更多的研究。

正畸痛是临床常见的正畸治疗并发症,对正畸患者的生活质量有显著影响[47]。一旦施加正畸力后出现牙周酸性微环境,牙周感觉末梢上丰富的局部H^+结合到ASIC3上,并通过三级神经元传导,引发痛觉[48]。此外,ASIC3在正畸疼痛中可能存在双重作用。据报道,ASIC3在牙周组织中的机械感受器(Ruffini小体)中表达,提示ASIC3在感受正畸力的机械感受器中起作用[33]。牙周膜中神经冲动一旦传递到TG的三叉神经元,将刺激三叉神经元释放中枢(TG、Vc和腹后核)和外周(牙周组织)的几种神经源性介质,如CGRP和P物质(substance P,SP)等[21,49],在正反馈环路中放大了正畸疼痛(图1)。

2. ASIC3与口颌面部神经病理性疼痛:口腔颌面部神经病理性疼痛与神经损伤相关,在普通人群的患病率估计在7%~10%[50]。口颌面部常见的神经病理性疼痛有三叉神经痛、带状疹后遗神经痛和偏头痛等。研究表明,选择性抑制ASIC1a和ASIC3,可以逆转大鼠炎性和神经病理性痛敏[51]。ASIC3在TG中表达(图1),其反应被一氧化氮增强,一氧化氮可触发偏头痛发作。据报道,ASIC3阻滞剂APETx2能抑制一氧化氮诱导的大鼠三叉神经伤害性反应的敏化[52]。而在中枢神经系统,ASIC1a调节脊髓背角的中枢敏感化,ASIC3主要在外周参与炎症性疼痛、缺血性疼痛和机械性疼痛[53]。

3. ASIC3与颞下颌关节紊乱诱发疼痛:颞下颌关节紊乱综合征(temporomandibular disorders,TMD)是指累及颞下颌关节和(或)咀嚼肌系统的,具有相关临床问题(如疼痛、弹响和开口受限等)的一组疾病的总称,是口腔颌面部常见疾病之一。TMD病因不明,研究表明ASIC3分布于头面部肌肉传入神经上,与肌肉疼痛密切相关[54]。Xu等[55]建立了一种实验性咬合干扰的大鼠模型,持续地诱导颌肌机械性痛觉过敏,双侧三叉神经节中ASIC3的基因表达和蛋白水平均上调。由此可见,ASIC3参与介导病理条件下的肌肉痛敏反应。相较于肌肉组织,ASIC3在颞下颌关节中的调控机制更为复杂,因此颞下颌关节炎中的酸性微环境调控的痛觉信号通路知之甚少[56]。由此可见,靶向ASIC3可能成为同时干预肌肉与关节痛的双重策略。探究三叉神经伤害性感受器的酸效应,有助于口面部肌肉痛和TMD相关疼痛的治疗。

4. ASIC3与口颌面部癌性疼痛:癌症相关疼痛是指肿瘤直接引起的疼痛或是特殊治疗带来的疼痛。癌症相关性疼痛是增加发病率、降低生活质量和影响生存的主要原因[57]。ASIC3的表达变化是癌性骨痛的相关因素之一,也是癌症疼痛治疗的潜在靶点[58-59]。Hiasa等[60]在人多发性骨髓瘤细胞的小鼠异种移植模型中发现,破骨细胞和多发性骨髓瘤协同诱导酸性骨微环境,通过上调ASIC的表达而导致痛觉过敏从而激发重度骨痛,且单次注射选择性ASIC3拮抗剂APETx2可显著降低模型中的骨痛。

五、酸敏感离子通道3在颌面部疼痛方面的临床应用和展望

1. ASIC3抑制剂的运用:APETx2是一种由42个氨基酸组成的海葵肽,能有效地抑制ASIC3介导的电流[61]。大量研究表明,运用ASIC3抑制剂能减轻疼痛[62]:在大鼠局部组织给予APETx2,可以减轻过敏性结膜炎模型中轻度酸性溶液介导的急性疼痛,以及炎性疼痛[26];皮下注射APETx2可显著逆转利血平诱导的纤维肌痛痛觉过敏[63];单次注射选择性ASIC3拮抗剂APETx2可显著降低多发性骨髓瘤小鼠模型中的重度骨痛[60];牙周应用APETx2可减轻正畸痛等[25]。由此可见,阻断ASIC3的活动或抑制ASIC3在外周的表达,可以减少疼痛行为。

2. 基因治疗:在反复肌内注射引起慢性广泛性肌肉痛的小鼠模型中,野生型小鼠和*Asic1a*基因敲除(*Asic1a*$^{-/-}$)小鼠出现了持久的机械性痛觉过敏,但*Asic3*$^{-/-}$型小鼠完全消除了这种痛觉过敏,不能通过向肌肉中重复注射酸来诱发继发性痛觉敏[64]。除此之外,靶向基因传递是治疗口颌面疼痛的一种很有

前途的治疗选择。许多病毒基因载体可用于基因传递,包括腺病毒载体、腺相关病毒载体和慢病毒载体[65]。使用小分子干扰RNA(small interference RNA,siRNA)或微小核糖核酸(microRNA,miRNA)对*ASIC3*表达进行基因沉默或使用*ASIC3*基因敲除小鼠进行的实验中,疼痛过敏也被有效降低了[66]。由此可见,构造*Asic3*$^{-/-}$型小鼠或者使用特定的siRNA敲除体内的*ASIC3*对原发性炎症诱导的痛觉过敏具有有效的镇痛作用。因此,针对ASIC3的靶向基因治疗对口颌面疼痛有重要意义,也是未来研究的重点。

总之,ASIC3在口腔面部疼痛痛觉过敏的发展中起着至关重要的作用。ASIC3的特异性抑制剂和针对ASIC3的靶向基因治疗对口颌面部炎性疼痛具有显著的镇痛作用,为颌面部疼痛的治疗提供了新思路。当然,现在的ASIC3相关研究更多的为动物模型试验和神经电生理研究,药物的临床转化有赖于更多的机制研究和临床试验。机制研究方面,未来可关注ASIC3与其他离子通道的交互作用,以及ASIC3是否参与胶质细胞调控神经病理性疼痛的相关过程,从而系统性揭示其网络调控关系。临床转化方面亦前景广阔,未来研究可重点关注ASIC3在个体化医疗中的应用潜力,如ASIC3靶点药物的临床试验,结合人工智能辅助药物设计或基因编辑技术,优化ASIC3靶向治疗的精准性与安全性等。从而探索出更广泛接受的衡量及控制疼痛的方法,减少患者在正畸治疗过程中的痛苦,提高患者的生活质量,从而实现舒适化正畸治疗,增强患者的合作性,改善临床医疗环境。

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