•综述•

酸离子敏感通道1a在炎症性疾病中的研究进展

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摘要: 酸离子敏感通道1a (acid-sensing ion channel 1a, ASIC1a) 属于氨氯敏感配体门控离子通道, 在中枢和外周神经系统中广泛分布及表达。在生理环境下, 细胞通过H^+的多种转运方式维持细胞外和细胞内的pH值并相对稳定在7.0～7.5左右。在一些病理条件如过敏性哮喘、肾炎、关节炎、肠炎、急性肺损伤等炎症性疾病的发生过程中, 由于组织的无氧糖酵解产生乳酸和ATP水解的H^+积聚, 导致组织酸化及体液pH值急剧下降至4.0～6.0左右, 而进一步激活的ASIC1a可引起炎症性疾病病情急剧恶化。近年来, 靶向ASIC1a可能是一种潜在的治疗策略, 本文就ASIC1a在炎症性疾病中的作用做简要综述, 探讨ASIC1a在炎症性疾病中的研究进展。

关键词: 酸离子敏感通道1a; 分布; 炎症性疾病; 组织酸化; pH

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Research progress of ASIC1a in inflammatory diseases

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Abstract: Acid-sensing ion channel 1a (ASIC1a) is an ammonia-chlorine-sensitive ligand-gated ion channel, and is widely distributed and expressed in the central and peripheral nervous systems. In a physiological environment, cells maintain a stable pH value around 7.0−7.5 through various transport modes of H^+. During the occurrence of some pathological conditions such as allergic asthma, nephritis, arthritis, enteritis, acute lung injury, and other inflammatory diseases, the anaerobic glycolysis of tissue produces H^+ accumulation of lactic acid and ATP hydrolysis, resulting in tissue acidification and body fluids. The pH value drops sharply to around 4.0−6.0, which further activates ASIC1a, causing a sharp deterioration of the inflammatory disease. In recent years, targeting ASIC1a may be a potential treatment strategy. This review briefly summarizes the role of ASIC1a in inflammatory diseases and discusses the research progress of ASIC1a in inflammatory diseases.

Key words: acid ion-sensitive channel 1a; distribution; inflammatory diseases; tissue acidification; pH

酸离子敏感通道1a (acid-sensing ion channel 1a, ASIC1a) 是分布于中枢和外周神经系统的氨氯敏感配体门控的离子通道[1,2], 在炎症、癫痫等多种生理与病理疾病发生过程中, ASIC1a均发挥关键调节作用[3-6]。目前对神经系统以外的其他组织中ASIC1a的表达及功能受到越来越多的关注。在一些病理情况下, 局部组织的pH值急剧下降 (如炎症、缺血、肿瘤等), ASIC1a的酸离子敏感通道被瞬间激活[7]。

1 ASIC1a的结构、分布及表达

ASIC1a由2个疏水跨膜结构域 (trans-membrane domain, TM) 1和2、及1个富含半胱氨酸的细胞外环

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组成, 其氨基端和羧基端面向细胞内空间, ASIC1a的形成需具备四肽甲酰胺 (FMRFamide, FMRFa) 亚基、Na^+和H^+[8]。来源于德克萨斯州珊瑚蛇的珊瑚蛇毒素蛋白 (MitTx-α/β) 是一种异二聚体多肽毒素, 是ASIC1a的激动剂[9,10]。Baconguis等[11]解析了ASIC1a与MitTx-α/β的共结晶结构, 发现: 当pH值为7.5时, ASIC1a处于封闭的、不敏感状态, 在此状态下, 其细胞外前厅 (excellular vestibule) 结构采用收缩构象; 当pH值下降至4.0～6.0时, ASIC1a被激活, 其细胞外前厅结构采用扩张构象, 由拇指区 (thumb) 稳定, 其细胞外结构域与MitTx-α/β跨膜结构域相耦合, 二者形成复合物, 并使ASIC1a的构象发生旋转, 离子通道孔开放。ASIC1a−MitTx-α/β复合物的研究也进一步阐明了MitTx-α/β的作用机制, ASIC1a TM2结构域是一个不连续的α螺旋体, 其中“甘氨酸−丙氨酸−丝氨酸” (glycine-alanine-serine, Gly-Ala-Ser) 基序采用扩展的带状构象, 可选择性地将443位Gly的羰基插入MitTx-α/β跨膜结构域内, 通过相邻碱性阳离子 (Na^+) 与位于细胞质中的ASIC1a TM2结构域的1/3区域进行交换, 可形成具有3个含有羰基氧原子的三角环, 其在离子跟水分子结合生成带电微粒 (水合离子) 的过程中为其提供了能量屏障[12]。

ASIC1a是酸离子敏感通道家族的重要成员, 具有广泛表达谱, 其在中枢神经系统 (central nervous system, CNS) 的大脑皮质、海马等部位含量丰富[13], 也存在于大部分脑区、脊髓、背根神经节 (dorsal root ganglion, DRG) 和螺旋神经节 (spiral ganglion, SG) 的周围神经系统 (peripheral nervous system, PNS) 中。ASIC1a参与调节大脑神经活动, 并参与检测有害酸中毒介导的神经元损伤及细胞死亡[14]。除神经系统外, ASIC1a也在外周组织中表达, 包括动脉、骨髓、肠、舌和膀胱[15]。研究发现, 在星形胶质细胞[16]、NG2胶质细胞[17]、少突胶质细胞[18]、树突状细胞[19]和血管平滑肌细胞[20]均发现有ASIC1a表达。在酸离子敏感通道家族的所有成员中, ASIC1a是唯一可介导Ca^{2+}运输的成员[21]。作者前期结果显示, 在大鼠急性肺损伤模型的肺组织中, ASIC1a存在高表达[22], 其在糖尿病肝纤维化双模型肝组织中也高表达, 并且在高糖环境下重组小鼠血小板衍生生长因子 (platelet-derived growth factor BB, PDGF-BB) 诱导的肝星状细胞中也存在高表达, 并通过升高细胞内Ca^{2+}水平而促进肝纤维化的发生发展[23]。

2 ASIC1a与炎症性疾病

2.1 过敏性哮喘 过敏性哮喘属于慢性炎症, 主要特征是气道高反应性、气道重塑、大量嗜酸性粒细胞浸润和杯状细胞粘液分泌增加。ASIC1a在小鼠呼吸道高表达, 主要分布于呼吸道黏膜[24]。Ca^{2+}、K^+和Na^+通道多表达于呼吸道黏膜组织。而ASIC1a作为唯一介导Ca^{2+}透过的酸离子敏感通道参与了气管细胞的凋亡、气道的重塑等气道慢性炎症过程[25,26]。研究发现[24], 细胞外酸化刺激可显著增加牛胚气管细胞的凋亡, 而使用ASIC1a特异性阻断剂 (psalmotoxin 1, PcTx1) 后, 可显著抑制该过程, 提示牛胚气管细胞的过度凋亡可能有ASIC1a的参与。另有研究表明[27], 气道高反应性 (airway hyper reactivity, AHR) 的过度气道狭窄是哮喘的标志性特征, 而卵圆蛋白致敏的小鼠体内ASIC1a的缺失则可在不减少气道炎症的情况下预防气道高反应性的发生。Faisy等[28]发现ASIC1a参与了pH诱导的豚鼠气道的基础张力作用, ASIC1a阻断剂阿米洛利 (amiloride) 阻断ASIC1a表达后, 导致豚鼠气道基础张力松弛, 可减轻哮喘发作症状。综上, ASIC1a在过敏性哮喘疾病中发挥重要调节作用。

2.2 类风湿性关节炎 类风湿性关节炎是侵犯关节的、以慢性炎症为主要特点的一种多系统性自身免疫疾病, 以关节变形为最终状态, 引起关节功能的丧失。研究表明[29-31], ASIC1a在大鼠的关节软骨细胞中的表达被显著上调, 提示在炎症环境下ASIC1a可被瞬间激活。由于PcTx1可明显降低细胞内钙离子的浓度 (intracellular calcium ion concentration, $[Ca^{2+}]i$), 大鼠关节软骨细胞损伤被抑制, 表明$[Ca^{2+}]i$增加是由ASIC1a介导的。ASIC1a通过Ca^{2+}/Rac1 (Rac family small GTPase 1) 信号激活类风湿关节炎成纤维样滑膜细胞的侵袭及迁移, 促进滑膜对软骨的侵袭性破坏。另有研究发现[32], ASIC1a通过抑制Ca^{2+}依赖p38 MAPK (microtubule associated protein kinase)/c-jun和ERK (extracellular regulated protein kinases)/c-fos (cellular oncogene fos) 信号通路, 抑制基质金属蛋白酶-2/9和甘油氨基聚糖、羟脯氨酸、基质金属蛋白酶组织抑制因子-1/2的表达, 导致关节软骨细胞损伤, 抑制基质合成, 造成关节软骨结构和功能丧失。进一步研究证实[33], 在佐剂性关节炎大鼠关节软骨细胞的动物模型中, 小分子RNA沉默ASIC1a表达后, 可上调胶原 (II型) 与蛋白聚糖的表达量, 提示佐剂性关节炎大鼠的关节软骨细胞在过度凋亡过程中有ASIC1a的参与。另有研究发现[34], amiloride可能通过阻断ASIC1a抑制Ca^{2+}超载进而抑制软骨细胞凋亡, 而其通过调节B淋巴细胞瘤-2 (B-cell lymphoma-2, Bcl-2) 家族、人细胞色素C (cytochrome-C, cyt-C)、含半胱氨酸的天冬氨酸蛋白水解酶 (cysteinyl aspartate specific proteinase, caspase) 等凋亡基因的表达, 可对线粒体的功能进行保护, 实现保护关节的作用。另有研究发现[35,36], 在白细胞介

素-1β (interleukin-1β, IL-1β) 和 (tumor necrosis factor-α, TNF-α) 诱导的关节软骨细胞中, 被激活的 (nuclear factor kappa-B protein 65, NF-κB p65) 迅速转移至细胞核内, 与核内ASIC1a启动子结合并激活靶基因转录, 吡咯烷二硫代氨基甲酸盐 (pyrrolidine dithiocarbamate, PDTC) (NF-κB p65抑制剂) 预处理可以逆转该作用。这些结果提示, IL-1β和TNF-α可通过激活NF-κB p65上调ASIC1a的表达增强酸诱导的软骨细胞凋亡, 促进类风湿性关节炎的发生。进一步机制研究发现[37], ASIC1a对自噬的调节在类风湿关节炎发生过程中也起了重要作用, 在体外培养的大鼠关节软骨细胞中, 自噬及自噬小体蛋白表达均被上调, 而PcTx1作用后可使自噬及自噬小体数量显著下调, 提示ASIC1a可通过调节关节软骨细胞的自噬, 参与由自噬引起的类风湿关节炎疾病的发生发展过程。因此, ASIC1a可能成为类风湿关节炎治疗的干预靶点。

2.3 过敏性紫癜肾炎 过敏性紫癜 (henoch schnlein purpura, HSP) 是儿童中最常见的系统性血管炎, 涉及皮肤、关节、肠道和肾脏的小血管发炎。有30%～60%的HSP患儿在发病后的4～6周内发展为肾炎, 常伴有蛋白尿、血尿、管型尿等并发症, 称紫癜性肾炎 (henoch schnlein purpura nephritis, HSPN)[38]。有研究发现[39,40], 过敏性紫癜患者的ASIC1a高表达于皮肤小血管, 用患儿的血清刺激血管内皮细胞可引起ASIC1a表达增高, 皮肤血管损伤加重。而当ASIC1a的高表达被甲泼尼龙抑制时, 皮肤血管的损伤可减轻, 提示在皮肤血管损伤过程中, ASIC1a可能发挥关键作用。在HSP急性发作期的直接或者间接刺激可使在血管内皮细胞中的ASIC1a表达显著上调, 进而加重血管内皮细胞损伤[41,42]。肾小管远曲小管的作用是重吸收H_2O分子和Na^+离子, 并同时向肾小管腔内分泌H^+和K^+离子, 进而维持人体血液的酸碱平衡。当炎症反应发生时, 肾小管受到损伤, 人体酸碱平衡被破坏, 肾小管细胞内的pH值不断降低, 而由于ASIC1a是酸离子敏感通道蛋白, 当pH值降低时, 其被瞬间激活, 并导致肾小管损伤的进一步加重[43,44]。因此, 研究在HSPN患儿肾小管损伤的发生发展中ASIC1a发挥的关键调节作用, 可为进一步探讨ASIC1a作为HSPN治疗靶点及是否具有潜在临床应用价值提供参考。

2.4 过敏性肠道综合征 过敏性肠道综合征, 别名肠易激综合征 (irritable bowel syndrome, IBS), 是以腹痛、腹泻、排便习惯改变、大便形态、色泽异常等为特征的一种与特发性结肠过敏 (idiopathic colonic hypersensitivity, CHS) 相关的功能性胃肠疾病。Matricon等[45]发现ASIC1a的过表达多为小直径背根神经节胞体特异性表达, 增强结肠传入纤维的敏感性, 神经生长因子通过调节结肠的伤害性肽能神经元中ASIC1a的表达, 阻止CHS的发生。Amiloride可以阻断短链脂肪酸丁酸盐直肠灌肠诱导IBS大鼠模型的CHS的症状。

2.5 神经元损伤 神经元损伤指局限性的神经传导通路上的部分神经元受损。在大脑动脉闭塞导致的缺血模型中, 通过脑室注射amiloride和PcTx1可以减小梗死面积, 并且敲除*Asic1a*也能减轻由缺血引起的神经元损伤[46]。在脑缺血过程中, ASIC1a被酸激活后, 可引起细胞内的Ca^{2+}超载, 进一步导致脑损伤面积增大, 而ASIC1a通道被阻断后, 脑损伤面积随之减少[47]。Quintana等[48]发现α-氨基-3-羟基-5-甲基-4-异恶唑丙酸 (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid, AMPA) 受体的可塑性变化受到海马CA1区神经元上的ASIC1a调节, 可引起长时程增强和Ca^{2+}通透的AMPA受体分布增多。这些都表明, ASIC1a可能参与脑缺血损伤, ASIC1a有望作为治疗脑缺血导致的神经元损伤的新靶点, 其抑制剂有望作为治疗缺血性脑卒中的潜在药物。

Stankowska等[49,50]发现在实验性自身免疫性脑脊髓炎 (experimental allergic encephalomyelitis, EAE) 和视神经组织炎症损伤中, 在小鼠及人类神经元轴突中的ASIC1a表达显著上调, 轴突变性明显增强。在EAE小鼠模型中, *Asic1a*$^{-/-}$小鼠与野生型小鼠相比, 其轴突变性明显减少, 提示ASIC1a可通过增强轴突变性进一步加重EAE及视神经组织的炎症损伤。因此, 研究ASIC1a的抑制剂可能为治愈脑膜炎及眼部疾病提供新的治疗药物。研究发现[51], 脊髓背角元的兴奋性与可塑性可进一步促进胞外Ca^{2+}内流的增加, 进而参与炎性的痛觉敏化过程, 该研究提示ASIC1a可能成为诱发和维持痛觉的一种新机制并成为研究镇痛药物的新靶点。

2.6 急性肺损伤 急性肺损伤 (acute lung injury, ALI) 是一种由各种肺内、外因素所致的肺源性急性炎症性疾病, 通过激活肺组织中多种炎症细胞致肺内产生炎症级联反应, 病程发展迅速并可发展为呼吸窘迫综合征 (acute respiratory distress syndrome, ARDS)[52]。在急性肺损伤的动物模型中, 模型组肺组织ASIC1a和TNF-α的mRNA和蛋白表达量与正常组相比均显著提高, 而应用amiloride可显著降低上述蛋白的表达量, 说明ASIC1a在急性肺损伤疾病中发挥重要作用[21]。研究显示[53], 在肺泡上皮细胞 (I型和II型) 及气管黏膜上皮细胞表面有ASIC1a表达。降低肺泡内液pH值后, ASIC1a被激活, 可减轻肺组织的含水量, 进而发挥清除肺水肿液体的作用。另有研究表明[54], ASIC1a可

增加肺微血管内皮细胞的屏障功能, 引起肺炎相关的通透性水肿、肺泡充血和致命的低氧血症等症状的减轻。因此, ASIC1a 在肺微血管内皮细胞上的激活作用有可能可作为改善肺炎期间毛细血管内皮屏障功能的新方法加以研究。

3 结语与展望

炎症性疾病是当机体接触到内、外源性有害因子时, 引起的各组织和器官功能受损等一系列的机体病理变化。胞外酸化激活 ASIC1a 可促进炎性细胞释放多种炎性因子, 导致机体损伤加重。炎症致病因素复杂, 与多种因素有关, 因此对炎症性疾病的诊断、预防及临床治疗是目前面临的主要难题。ASIC1a 作为酸离子敏感通道蛋白, 在多种炎症的病理及生理过程中均有重要作用, 得到广泛关注[55-66], 如在慢性疼痛的疾病中, ASIC1a 降低了雄性小鼠皮层长时程增强诱导作用和减轻炎症热痛敏的机械性异常痛的可能性。ASIC1a 通过蛋白激酶 C 介导的膜转运增加 AMPA 受体在前扣带回皮质中的调节痛相关皮质的可塑性, 结果表明, ASIC1a 可能是一个治疗慢性疼痛的镇痛靶点。在前列腺炎大鼠动物模型中, 脊髓背角神经元中 ASIC1a 的上调是神经源性炎症所致, 其促使 Ca^{2+} 信号增强, 进一步促进激活 *N*-甲基-*D*-天冬氨酸 (*N*-methyl-*D*-aspartate, NMDA) 受体, 导致丝裂原活化蛋白激酶和 Ca^{2+}/钙调素刺激的腺苷酸环化酶的激活, 最终导致活动依赖性中枢敏化, 导致前列腺疼痛。同时, 酸离子敏感通道的抑制剂被不断研发出来, 如特异性抑制剂 PcTx1 和非特异性抑制剂 amiloride, 因 PcTx1 神经毒性作用比较大, 目前不建议用于临床, 而 amiloride 在临床仅用于保钾利尿剂使用。因此, 可以用于临床治疗的抑制剂仍较少, 需进一步进行动物及临床实验验证。目前, ASIC1a 在炎症性疾病中的研究仍处于萌芽阶段, 其对治疗炎症性疾病的意义及其运用等仍需深入的实验研究和探索。

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