

TRPV1通道调节血管平滑肌改善 高血压作用的研究进展

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摘要 瞬时受体电位香草酸亚型1(transient receptor potential vanilloid 1, TRPV1)通道是一种非选择性阳离子通道, 可以被辣椒素、高温等多种刺激因素激活。近年来多项研究表明, TRPV1通道在心血管疾病中发挥重要作用。该文旨在综述现阶段TRPV1通道在调节血管平滑肌细胞(vascular smooth muscle cell, VSMC)功能和降低高血压等相关疾病作用的研究进展。

关键词 TRPV1; 高血压; 血管平滑肌细胞; 神经递质; 钙离子

The Role of TRPV1 in Modulating VSMC Function and Attenuating Hypertension

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Abstract The transient receptor potential vanilloid type 1 (TRPV1) channel is a non-selective cation channel that can be activated by multiple stimuli, including capsaicin and heat. In recent years, several studies have shown that TRPV1 channels play an important role in cardiovascular diseases. This review focuses on the current knowledge of the role of TRPV1 channel in modulating vascular smooth muscle cell (VSMC) function and attenuating hypertension.

Keywords TRPV1; hypertension; VSMC; neurotransmitters; Ca^{2+}

高血压是危害人类健康的重大慢性病之一, 也是冠心病、中风和心肾功能衰竭等严重心脑血管疾病的主要病因。血管重构是引起高血压靶器官损伤的病理基础, 而血管平滑肌细胞(vascular smooth muscle cell, VSMC)异常增殖是血管重构发生、发展过程中非常重要的病理机制。瞬时受体电位香草酸亚型1(transient receptor potential vanilloid 1, TRPV1)通道是瞬时受体电位(transient receptor potential, TRP)超家族的一种非选择性阳离子通道。

大量研究表明, TRPV1通道表达于VSMC, 在高血压疾病中起到保护性作用。本文将对目前TRPV1通道在调节VSMC功能以及改善高血压疾病作用的研究现状进行总结和讨论。

1 VSMC与高血压

高血压主要表现为外周血管张力持续性升高, 血管舒缩性异常, 并常伴有血管重塑和血管阻力增加, 而这些病变很大程度上都是由VSMC增殖、迁

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移和肥大所导致的。VSMC位于血管中膜,是维持血管张力的主要细胞组成成分。在机体正常生理条件下,VSMC通过适度收缩来维持血管壁的张力^[1]。正常成熟的VSMC是收缩型,处于分化状态^[2]。在高血压等病理情况下,VSMC表型可转化为去分化的VSMC,此时其收缩能力明显降低。在体循环高压时,阻力血管VSMC转变成成肌型,向内膜处迁移并增殖,造成血管壁肥厚、管腔减小,同时还因其合成分泌功能增强,使得血管中膜胶原的含量显著增加,I型胶原的比例增加,使得血管顺应性下降^[3]。由此可见,VSMC增殖、迁移及表型转化等的改变与高血压的发生发展有着密切联系^[4]。

神经-内分泌系统在维持外周血管张力及调节正常生理血压中也发挥着重要作用。大量证据表明,辣椒素敏感的感觉神经细胞及其激活促进神经递质的释放与高血压的发病机制密切相关。支配心脏和血管活动的神经纤维中的TRPV1通道受各种刺激因素激活后,可以释放多种神经活性肽,参与外周血管舒缩功能的调节,其中以降钙素基因相关肽(calcitonin gene-related peptid, CGRP)为主,通过激活一些相关信号通路来抑制VSMC增殖,发挥心血管活性作用^[5]。目前,TRPV1通道作为高血压及其相关疾病的靶分子受到了广泛关注,但是其精确的细胞学调节机制研究仍知之甚少。

2 TRPV1通道

1997年,Caterina等^[6]成功地在感觉神经细胞上分离克隆了TRPV1通道。TRPV1是TRPV亚家族第一个被克隆的通道蛋白质,属于瞬时受体电位通道(transient receptor potential channels, TRP)家族,因其可被辣椒素激活又被称为辣椒素受体。TRPV亚家族有6个成员,分别为TRPV1~TRPV6。其中,TRPV1通道是TRPV亚家族中最早被发现,也是研究最为充分的一个。TRPV1通道是由838个氨基酸组成的蛋白质,相对分子量为95 kDa,该蛋白质通常以同四聚体的形式构成非选择性阳离子通道,基本结构包括6个跨膜结构及1个位于第5和第6跨膜区之间的孔型区域^[7]。

TRPV1通道在体内高表达于背根神经节、三叉神经节的中小型神经细胞以及小型无髓鞘C感觉神经纤维或中等大小的A δ 神经感觉神经纤维^[6,8]。此外,TRPV1在一些非神经组织如角质细胞、上皮细胞、内皮细胞及VSMC中均有表达^[7]。TRPV1通

道是一种伤害感受器信号分子,可以被多种刺激因素激活,包括内源性及外源性化学物质、机械压力以及温度。在pH为7.4时,激活TRPV1通道的最低热阈为43 °C,同样在正常生理温度(37 °C)下,低pH值也会引起TRPV1通道激活^[9]。除辣椒素外,TRPV1通道还可被N-花生四烯酸乙醇胺和大麻素激活^[10]。有报道称,N-花生四烯酸乙醇胺激活TRPV1通道,可抑制高盐膳食引起的血压升高^[11]。大麻素是强效血管扩张剂,可同时作用于大麻素受体和TRPV1通道起到降血压作用^[12]。

近期有研究表明,过表达VSMC上的TRPV1通道可以激活AMPK[adenosine 5'-monophosphate (AMP)-activated protein kinase]信号通路,抑制平滑肌细胞泡沫化^[13]。膳食辣椒素长时间激活TRPV1通道能够改善内皮细胞功能,降低血压,抑制动脉粥样硬化。TRPV1通道还可以加速损伤血管再内皮化,抑制新生内膜的过度增生,在小鼠血管损伤再狭窄中起到保护性作用^[14]。TRPV1通道在代谢综合征的发生发展中起到关键作用,敲除TRPV1通道基因不会影响高脂饮食小鼠体重,但是可以预防小鼠由肥胖引起的高血压,抑制低级别炎症反应,改善葡萄糖的耐受性等^[15]。此外,心肌缺血时,TRPV1通道被激活,不仅诱导TRPV1通道阳性感觉神经细胞应对多种缺血性代谢产物,从而引起胸痛,而且还诱导一些能够保护心肌损伤的神经递质释放^[16]。

3 TRPV1通道调节VSMC增殖和迁移

TRPV1通道为非选择性阳离子通道,具有Ca²⁺和Na⁺通透性,可介导阳离子顺其电化学梯度进行跨膜流动,从而使细胞内的Ca²⁺、Na⁺浓度升高,细胞内膜去极化^[13]。TRPV1通道除了能够介导细胞外Ca²⁺内流进入胞内,还可以介导Ca²⁺从细胞器中释放进入胞质,从而进一步改变细胞内Ca²⁺浓度^[17]。Ca²⁺是细胞内重要的功能调节分子,在VSMC的收缩、增殖迁移、基因表达以及表型转化中起着关键作用^[18]。然而,目前关于TRPV1通道在调节VSMC增殖迁移和高血压中作用的研究结论并不一致,一部分研究发现,抑制TRPV1通道可抑制平滑肌细胞增殖迁移,对高血压有保护作用,如:在慢性低氧状态下,人肺动脉VSMC上TRPV1通道基因表达和蛋白质水平升高,引起细胞内静息Ca²⁺浓度显著增加,导致细胞增殖、迁移明显^[19-20]。而TRPV1通道抑制剂辣椒平可

部分抑制低氧引发的人肺动脉VSMC容积性 Ca^{2+} 内流,进而抑制低氧引发的细胞增殖和迁移,在低氧引发的人肺动脉VSMC增殖产生高血压过程中起到重要的保护性作用^[21]。激活TRPV1通道可引起大鼠肺动脉VSMC细胞内 Ca^{2+} 浓度增加,进而促进增殖,抑制凋亡,引起肺动脉收缩性增加,最终导致肺动脉高压^[20]。另一部分研究发现,激活TRPV1通道可抑制平滑肌细胞增殖迁移,对高血压有保护作用,如自发性高血压大鼠主动脉VSMC中TRPV1通道表达水平显著降低,增殖能力显著升高^[22]。应用TRPV1通道激动剂辣椒素可显著上调VSMC中TRPV1通道的表达,且呈剂量依赖性地抑制自发性高血压大鼠主动脉VSMC的增殖,但对正常大鼠VSMC增殖的抑制作用并不显著^[23]。TRPV1通道被激活后可以诱导细胞内 Ca^{2+} 浓度显著增加,进而激活AMPK信号通路可以抑制VSMC的增殖和迁移,改善血管重构,延缓高血压的发生发展^[13,24-25]。上述结果提示,高血压导致的VSMC增殖活跃可能与TRPV1通道的表达改变有关,TRPV1通道在VSMC增殖迁移和高血压疾病过程中起到重要的调控作用。但是其介导细胞增殖和迁移对高血压疾病的影响作用情况及机制却尚不清楚,需要进一步深入研究。

4 TRPV1通道促进神经递质释放调节血压

有研究发现,激活TRPV1通道可以通过促进神经递质释放改变血管张力调节血压^[26]。心血管

系统中广泛分布有TRPV1通道阳性感觉神经细胞,大麻素或辣椒素激活TRPV1通道后,可促使感觉神经细胞释放多种神经活性肽,如降钙素基因相关肽(calcitonin gene-related peptid, CGRP)和P物质(substance p, SP),从而引起血管舒张、血压降低^[27-29]。TRPV1通道在遗传性盐敏感型高血压大鼠模型中也有类似的降压作用^[30]。CGRP、SP分别与CGRP受体和NK1受体结合后(图1),一方面,可通过激活内皮细胞腺苷酸环化酶引起环腺苷酸(cyclic adenosine monophosphate, cAMP, cAMP)升高,继而引起一氧化氮和前列环素释放增加,一氧化氮和前列腺素具有强烈的血管舒张作用;另一方面,能够激活VSMC上的 K_{ATP} 通道导致VSMC超极化,引起血管舒张^[31]。另有研究表明,外周血管释放的CGRP通过激活ERK1/2信号通路抑制VSMC的增殖,因此可以阻碍动脉粥样硬化和血管狭窄的形成^[32]。在血管损伤时,内源性的CGRP大幅抑制氧化应激反应及VSMC增殖和迁移,在CGRP基因敲出的小鼠中,血管损伤能够引起氧化应激反应,并且诱导VSMC增殖和迁移^[5]。cAMP/PKA(protein kinase A)通路可能介导了CGRP抑制主动脉和肺动脉血管平滑肌增殖作用^[33]。此外,也有证据证实,激活TRPV1通道可以增加肾小球的滤过率,促进尿钠排泄,从而降低肾血管阻力,这可能与肾脏中TRPV1通道阳性感觉神经细胞释放的CGRP和SP有关^[34]。

在外周神经系统中, CGRP和SP常共同作用于

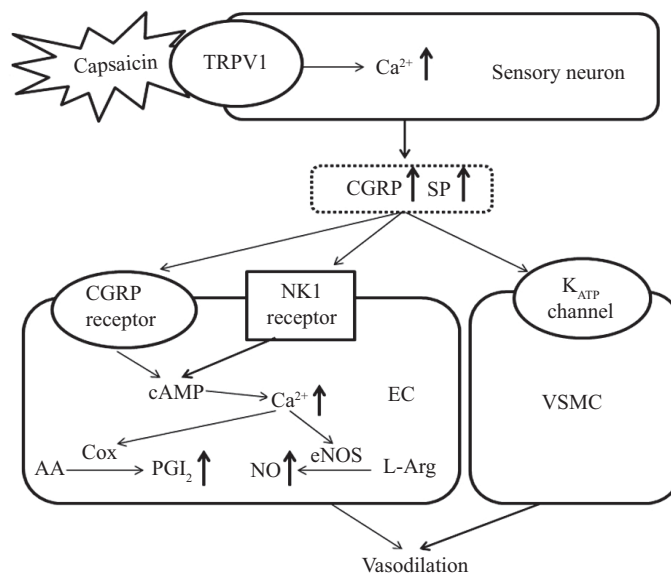


图1 TRPV1通道介导神经递质释放引起血管舒张的作用

Fig.1 The role of neurotransmitter release mediated by TRPV1 in vasodilation

血管床产生舒血管效应^[35-36]。肾上腺髓质激素是由血管内皮细胞和VSMC产生的可降低血压和抑制VSMC增殖的活性肽, SP可通过调节细胞内cAMP的浓度来促进肾上腺髓质激素的产生, 进而诱导血管舒张、尿钠排泄以及血压调节^[18,37]。TRPV1通道被内源性配体花生四烯酸乙醇胺激活后, 也可产生类似辣椒素降压效果。此外, 人脑动脉内皮细胞中2-花生四烯酸甘油可激活TRPV1通道, 增加细胞Ca²⁺内流, 引起血管舒张, 并能促进磷蛋白(vasodilator-stimulated phosphoprotein, VASP)磷酸化, 这种磷蛋白是蛋白激酶PKG(protein kinase G)和PKA的底物, 而PKG和PKA在血管扩张中具有重要作用^[38]。研究还发现, 长期给予高血压大鼠辣椒素膳食激活内皮细胞TRPV1通道, 能够引起细胞内Ca²⁺增加, 增加PKA的磷酸化和内源性一氧化氮合酶的活性以及一氧化氮代谢产物, 进而引起内皮依赖性血管舒张, 产生降压效果^[39]。

综上所述, TRPV1通道能够通过调节细胞内Ca²⁺浓度、血管平滑肌增殖迁移及神经递质释放等来调节VSMC功能和高血压等相关疾病。TRPV1通道可能是预防高血压发生发展的一个有效靶点。

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