

TRPV1在脑缺血及其并发症中的作用

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摘要 瞬时受体电位香草醛1型(transient receptor potential vanilloid subtype1, TRPV1)又称辣椒素受体, 是一种配体门控的非选择性钙离子渗透性阳离子通道, 广泛分布于感觉神经元等多种细胞的细胞膜上。TRPV1受体可通过炎症反应、氧化应激与钙超载、低温调控、血管舒张等多种途径在脑缺血过程中发挥作用。该文从TRPV1的结构、分布、病理生理功能等方面进行综述, 并重点探讨其在脑缺血及其并发症中的作用。

关键词 TRPV1; 脑缺血; 卒中后焦虑; 神经保护

The Role of TRPV1 in Cerebral Ischemia and Its Complications

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Abstract TRPV1 (transient receptor potential vanilloid subtype1) is known as capsaicin receptor, which a ligand-gated, non-selective calcium-permeable cation channels. The TRPV1 is widely distributed on the cell membrane of sensory neurons and other cells, and is involved in the regulation of various physiological functions after being activated, and plays a role in many diseases. In order to fully understand TRPV1, this article will review the mechanism, distribution, pathophysiological function of TRPV1, and mainly focus on the role of TRPV1 in cerebral ischemia and its complications.

Keywords TRPV1; cerebral ischemia; post-stroke anxiety; neuroprotection

脑缺血是由于脑血流中断或脑血管阻塞导致局部脑组织或全脑组织损伤的一种疾病^[1-2], 是全世界常见的致死和致残原因之一^[3-4]。急性脑缺血可触发一系列细胞级联反应生成自由基, 血液不同程度再灌注后引起的氧化应激、炎症反应激活等导致血脑屏障通透性改变, 从而造成暂时或永久性神经功能障碍^[5]。目前在我国临床上治疗脑缺血最常用的是静脉溶栓术及血栓切除术, 但静脉溶栓治疗有导致脑出血和血管性水肿等风险, 且时间窗狭窄导致临床获益不高^[6], 血栓切除也存在较大的手术操作

风险^[7]。保护大脑组织免受缺血和再灌注损伤, 进一步改善患者生存质量, 开发针对脑缺血及卒中后遗症的有效治疗药物具有重要的临床价值和社会意义。

瞬时受体电位香草醛1型(transient receptor potential vanilloid subtype1, TRPV1)又称辣椒素受体, 是一种配体门控的非选择性钙离子渗透性阳离子通道^[8]。最近的研究表明, TRPV1参与了脑缺血的病理生理学过程^[9]。为了充分了解TRPV1与脑缺血的关系, 本文从TRPV1的结构功能入手, 总结了近年来

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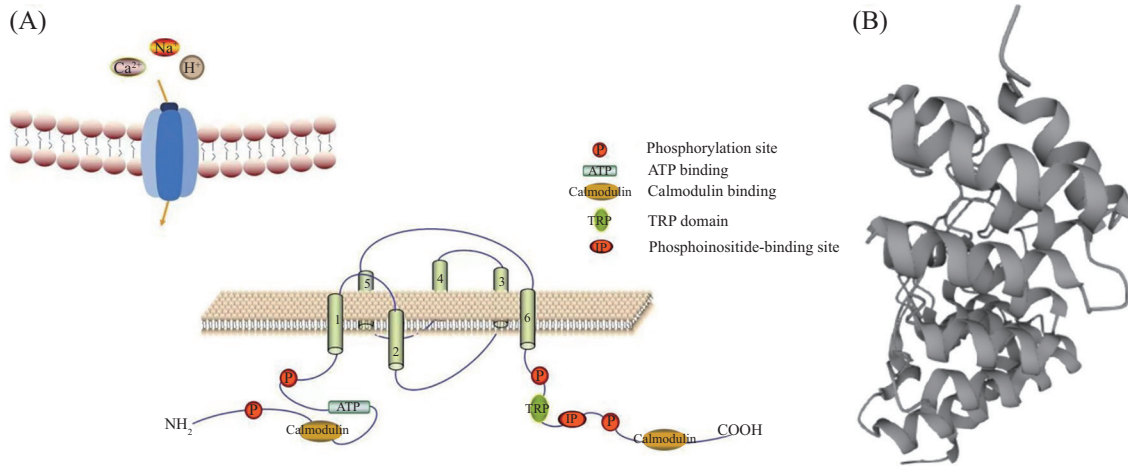
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A: TRPV1结构示意图(根据参考文献[13]修改); B: TRPV1的X射线晶体衍射结构(来源于UniProt数据库)。

A: schematic representation of TRPV1 (modified from reference [13]); B: X-ray crystal structure of TRPV1 (UniProt database).

图1 TRPV1的结构

Fig.1 The structure of TRPV1

国内外关于TRPV1在脑缺血中的作用研究,着重阐述其在脑缺血及其并发症中的作用,以期对脑缺血的靶向治疗提供坚实的理论基础。

1 TRPV1概述

1.1 TRPV1的结构

瞬时受体电位(transient receptor potential, TRP)家族是一组位于细胞膜上的非选择性阳离子通道。根据氨基酸同源性,TRP家族可分为七个亚家族:TRPC(transient receptor potential canonical)、TRPM(transient receptor potential melastatin)、TRPV(transient receptor potential vanilloid)、TRPA(transient receptor potential ankyrin)、TRPP(transient receptor potential polycystin)、TRPML(transient receptor potential mucolipin)、TRPN(transient receptor potential non-polar C-like)^[10]。其中TRPV亚家族有六个成员(TRPV1~TRPV6),TRPV1是TRP家族第一个被发现、克隆的成员^[11],也是TRP家族中最具特征的成员之一^[12]。

TRPV1是一种六通道跨膜蛋白,其整体结构分为上部和下部,分别对应着通道的跨膜和细胞内区域^[12]。每个亚单位的第五跨膜蛋白区和第六跨膜蛋白区域聚集在一起形成TRPV1通道的孔区,第一至第四跨膜蛋白对称分布在孔区域的四个角,TRPV1的N-端和C-端都在细胞内,N-端有三个锚定蛋白和多个磷酸化结合位点,可结合钙调素和ATP;C-端细胞内区域包含TRP结构域、钙调素结合位点和磷酸

肌醇结合位点(图1)^[13]。TRPV1广泛分布于感觉神经元等多种细胞的细胞膜上,是非选择性阳离子通道,对Ca²⁺、Na⁺、K⁺、Li⁺、Cs⁺和Rb⁺均具有通透性^[14]。

1.2 TRPV1的分布

TRPV1在感觉神经元中高度表达^[15],存在于各种脑区(包括下丘脑、小脑、大脑皮层、纹状体、中脑、嗅球、脑桥、髓质、海马、丘脑和黑质等)中。在非神经元组织中,TRPV1在表皮角质形成细胞、膀胱尿路上皮细胞、平滑肌细胞、肝脏细胞、多形核粒细胞、肥大细胞和巨噬细胞中表达^[16]。

1.3 TRPV1的病理生理功能

TRPV1可直接或间接地被多种物理、化学因素和炎症介质激活或敏化,如机械刺激、乙醇、炎症介质、组织损伤、高温、酸性环境(pH<6.0)、细胞外渗透压变化、细胞外氧化还原状态和前列腺素等^[17]。TRPV1的激活导致细胞外Ca²⁺内流,而细胞内钙的浓度增加使细胞去极化以产生动作电位,并将伤害性信号沿着感觉神经纤维传递到神经中枢,或通过激活细胞中的一系列信号通路,触发广泛的细胞反应^[13],如调控细胞递质的释放、肌肉收缩、细胞增殖、细胞凋亡以及基因转录等,TRPV1的激活还参与多种生理功能的调节,如体内炎症介质的释放、胃肠运动和温度调节(图2)^[18]。

2 TRPV1与脑缺血

脑缺血的病理生理过程较复杂,兴奋性毒性神经递质谷氨酸的释放^[19]、炎症反应^[20]、神经元凋亡^[21]、

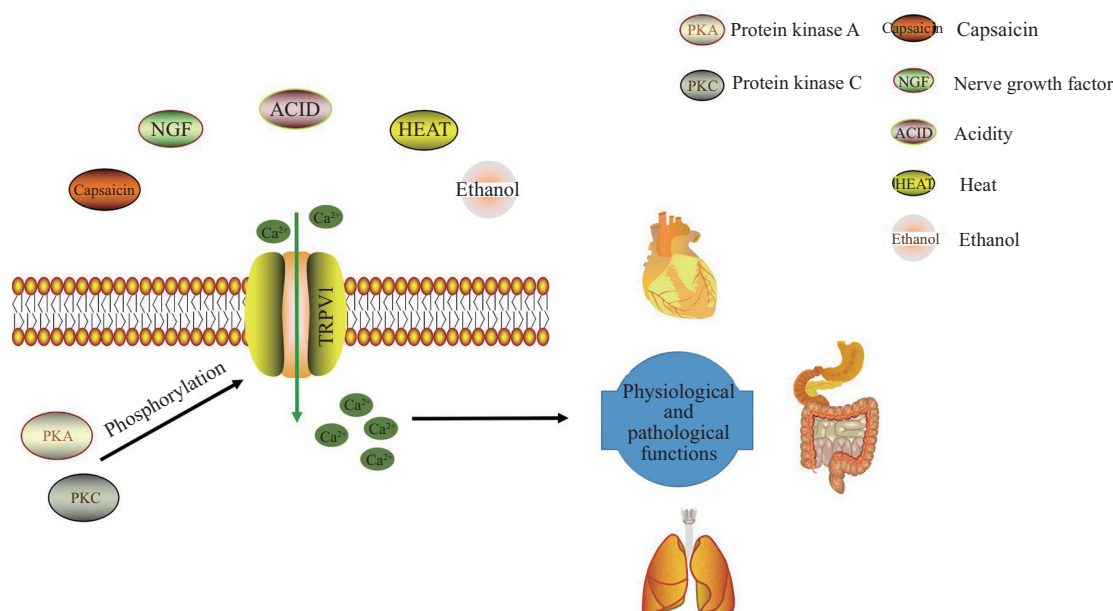


图2 TRPV1通道激活及其在哺乳动物细胞中的功能(根据参考文献[13]修改)

Fig.2 TRPV1 channel activation and its function in mammalian cell (modified from reference [13])

钙超载^[22]、氧化应激^[23]等均参与了脑缺血及再灌注损伤的发展。这些过程触发了一系列病理事件,如脂质过氧化、血脑屏障破坏和脑水肿^[24]。TRPV1在各脑区内参与神经调节,如在体温调节^[25]、疼痛调节^[26]、抑制肿瘤增殖^[27]、促进海马突触可塑性和空间记忆^[28]、调节神经炎症^[29]以及脑缺血再灌注损伤等方面发挥重要作用^[30]。

MIYANO HARAHARA等^[9]建立大脑中动脉闭塞模型(middle cerebral artery occlusion, MCAO)探讨TRPV1是否参与脑缺血损伤,发现TRPV1-KO小鼠的神经和运动缺陷以及梗死体积低于野生型小鼠,与其结果一致的是,在缺血开始前30 min,侧脑室注射TRPV1拮抗剂capsazepine可以减轻神经和运动缺陷,减小脑梗死体积。然而在这项研究中,capsazepine对TRPV1-KO小鼠的保护作用并不明显,这也表明capsazepine通过特异性调节TRPV1减轻缺血性脑损伤。除此之外,TRPV1在缺血中的作用也在永久性MCAO模型中得到证实,与对照组相比,TRPV1拮抗剂(AMG9810)显著减小了梗死体积,降低了神经功能缺损评分^[31]。综上所述,TRPV1参与缺血性脑损伤的形成和脑缺血导致的神经功能障碍。

2.1 介导药理学低温控制

低温对卒中有明显的神经保护作用^[32],药理学低温控制是缺血性脑损伤的一种强有力的保护手段。TRPV1是参与痛觉感受的热敏感离子通道之

一,在温敏神经纤维中高度表达^[33],可被高温、质子、内源性和外源性激动剂(如辣椒素和二氢辣椒素)等激活^[33]。在啮齿动物MCAO模型中,辣椒素介导的TRPV1在再灌注后被立即激活,并介导可逆性低温,从而在鼠脑梗死完全发展之前提供神经保护作用^[34]。除此之外,脑缺血后3.5 h开始的TRPV1介导的低温显著减少了脑缺血后1个月的皮层损伤(原发性损伤),并发挥了神经保护作用。除了减少原发性皮层损伤外,TRPV1介导的低温还可以远程控制丘脑损伤(继发性损伤)的发展——减小丘脑损伤体积、增加神经元数量和减少星形胶质细胞增生^[35]。继发性损伤涉及丘脑皮质神经元的逆行损伤,这些神经元大多起源于丘脑腹内核和腹后内侧核,并将投射延伸到S1/S2脑区。由于丘脑通过大脑后动脉和后交通动脉产生的小动脉接收血流,因此皮层损伤后的丘脑损伤被认为是通过丘脑-皮层特异投射系统的损伤来传递的,这些投射不仅仅是丘脑的径向延伸(即在同一冠状平面内),而且通常涉及到前额叶皮层,包括S1/S2感觉皮层和M1/M2运动皮层。

研究表明,注射25 mg/kg的Rinvanil(一种TRPV1激动剂)可诱导低温,并减轻缺血性脑损伤,但高剂量(50 mg/kg)的Rinvanil却没有显著作用,表明过度刺激TRPV1可能会对神经元存活产生不利影响^[36],由此推断低剂量的TRPV1激动剂可能通过诱导低温发挥神经保护作用,但通过激活TRPV1治疗脑缺血

可能存在引发中枢神经系统神经毒性的风险。内脏中TRPV1也参与体温调节^[37], β -肾上腺素受体拮抗剂普萘洛尔可以抑制TRPV1拮抗剂AMG9810诱导的体温过高^[38]。然而具有脑高穿透性的TRPV1拮抗剂AS1928370对体温几乎没有影响^[39]。因此, 可将TRPV1激动剂与成熟的冷却系统联合使用, 如使用不影响外周TRPV1活性的拮抗剂选择性地抑制中枢神经系统中的TRPV1的表达, 可能可以预防TRPV1介导的神经毒性。

2.2 抑制炎症反应

炎症反应是以白细胞浸润为主, 炎症介质(包括各种细胞因子、趋化因子和黏附分子)过度表达的急性炎症反应过程^[40], 其在脑缺血的病理生理学中起着关键作用^[41]。脑缺血后会有活性氧形成、组织损伤以及细胞坏死等, 这些可导致炎症细胞的激活。脑缺血发生后促炎因子如肿瘤坏死因子 α (tumor necrosis factor- α , TNF- α)、TNF- γ 表达量增加^[42-43]。这些炎性因子可导致缺血性损伤进一步加重^[44]。相反, 抗炎因子如白介素-10(interleukin-10, IL-10)在卒中后可发挥神经保护作用, 减轻缺血性再灌注损伤^[45]。实验表明, TRPV1在神经炎症中发挥关键作用^[46], 研究发现大鼠脑梗死周围区域的TRPV1表达量显著升高, 使用AMG9810抑制TRPV1可降低促炎因子TNF- α 及TNF- γ 的表达量, 并增加抗炎因子IL-10的表达水平, 减小缺血性脑卒中动物模型的梗死体积, 减轻运动和感觉功能障碍, 从而改善神经功能缺损^[46], 因此推测TRPV1与促炎介质之间存在功能上的相互作用。据报道, IL-10对TNF- α 的产生和活性有很强的抑制作用^[47], AMG9810抑制TRPV1表达后, 导致IL-10水平增加, 可能还会使TNF- α 的表达水平二次降低, 但是TRPV1对IL-10和TNF- α 表达的调节作用的细胞机制尚不清楚, 还需继续深入研究。

小胶质细胞是一种神经胶质细胞, 与外周巨噬细胞一样, 参与构成中枢神经最强大的免疫防御系统, 在引发和维持神经炎症的过程中发挥着重要作用, 缺血性脑卒中后小胶质细胞介导的炎症反应是脑组织损伤的主要原因^[48]。LIN等^[49]采用小胶质细胞在体外构建了糖氧剥夺/再灌注损伤(oxygen-glucose deprivation/reperfusion, OGD/R)模型, 发现TRPV1可能通过促进自噬抑制OGD/R诱导的小胶质细胞炎症, 并抑制NLRP3炎症小体及其下游分子Caspase-1的表达。后续研究发现6-姜酚(6-gingerol)

在脑缺血再灌注损伤期间通过促进TRPV1/FAF1复合物解离从而促进自噬, 发挥抗细胞凋亡和抗炎作用^[50]。Toll样受体(Toll-like receptors, TLRs)是一组炎症免疫细胞识别跨膜受体, 可以通过激活NLRP3炎症小体加重炎症反应, 尤其是TLR2和TLR4介导各种生理性脑功能以及炎症等病理状况^[51]。HAKIMIZADEH等^[31]研究发现, TRPV1拮抗剂AMG9810可以通过抑制TLR2和TLR4表达抑制炎症反应。因此, TRPV1介导的脑缺血后炎症反应和自噬平衡的调节可能是预防和治疗脑缺血损伤的一种新措施, 但是还需要探讨TRPV1介导的炎症和缺血后自噬与再灌注损伤严重程度的相关性。

2.3 调控钙超载

氧化应激源于活细胞中促氧化剂和抗氧化剂之间的不平衡, 是造成神经元损伤的关键因素之一^[52], 缺血再灌注损伤可诱导活性氧(reactive oxygen species, ROS)过度形成, 导致神经元损伤和死亡^[23]。脑缺血时三磷酸腺苷(adenosine triphosphate, ATP)生成障碍导致钙泵衰竭, Ca^{2+} 无法重新泵回钙池, Ca^{2+} 大量堆积在细胞中, 导致 Ca^{2+} 超载, 继而触发了一系列反应而导致细胞凋亡^[53]。先前的体外研究表明, 辣椒素(capsaicin, 一种TRPV1激动剂)可减少皮层神经元兴奋性毒性和谷氨酸诱导的 Ca^{2+} 内流, 从而减小脑缺血再灌注大鼠的梗死体积, 改善神经行为评分和运动协调性^[54]。然而进一步的研究证实非特异性的TRPV1阻断剂可抑制 Ca^{2+} 超载和神经毒性, 防止 Ca^{2+} 超载介导的氧化应激, 减轻脑水肿, 抑制细胞凋亡, 改善脑缺血再灌注损伤后的短期和长期神经功能, 发挥神经保护作用^[55], 以上结果均说明TRPV1参与脑缺血后的 Ca^{2+} 超载, 但归因于TRPV1被激活还是被抑制从而保护脑损伤这一矛盾还需进一步探究, 产生以上矛盾可能是由于脑缺血的发病机制极其复杂, 并且缺乏关于TRPV1在脑缺血机制中作用的细节导致。

2.4 促进血管舒张

内皮一氧化氮合酶(endothelial nitric oxide synthase, NOS)是负责调节心血管稳态的关键酶, 在生理条件下, 组成型eNOS活性和内皮一氧化氮(nitric oxide, NO)的产生发挥着重要的神经血管保护功能。eNOS以脉动的方式合成NO, 当细胞内 Ca^{2+} 升高时, eNOS活性显著增加^[56-57]。研究表明, TRPV1的活化诱导NO生成造成血管舒张^[58-60]。在易中风的自发

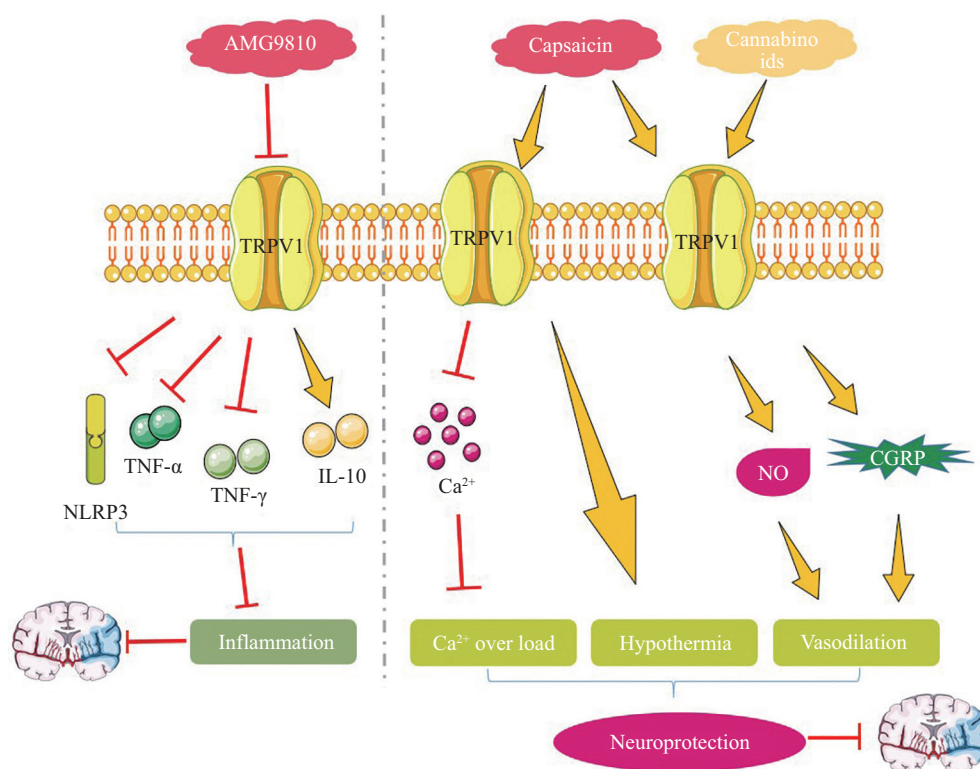


图3 TRPV1与脑缺血

Fig.3 TRPV1 and cerebral ischemia

性高血压大鼠中,发现TRPV1通道和eNOS共表达,慢性饮食辣椒素可通过激活TRPV1通道显著放松基底动脉,抑制颅内动脉肥大,并诱导eNOS磷酸化,辣椒素通过激活脑动脉中的TRPV1通道,显著延缓了中风的发生,并延长了易中风的自发性高血压大鼠的生存时间^[61]。后续也发现血管中的TRPV1可介导内皮依赖性和非依赖性血管舒张,并参与脑血流量的调节^[62],从而减少缺血和缺氧神经元损伤。另一项研究表明,大麻素(cannabinoids)可以激活神经元末端的TRPV1受体,从而导致降钙素基因相关肽(calcitonin gene related peptide, CGRP)的产生,进一步促进平滑肌细胞的超极化以激活钾离子通道和血管舒张^[63]。除此之外,长期激活TRPV1可能还有助于降低中风风险,这可能归因于氧化应激对脑缺血具有长期保护作用^[64]。以上研究提示TRPV1是预防中风的潜在靶点。

TRPV1的激活或抑制通过正反馈和负反馈调节缺血性脑损伤,促进神经保护作用。其中TRPV1的激活触发自主神经反应,导致下丘脑的热量损失以及体温和氧代谢降低,血氧饱和度升高,从而缓解神经损伤,但要注意激活剂剂量的使用,防止造成二

次伤害;而TRPV1的阻断可以减轻钙超载,并抑制炎症反应,从而减小脑梗死面积,改善神经功能(图3)。因此关于TRPV1在脑缺血机制中作用的细节还有待深究。

3 TRPV1与卒中并发症

3.1 卒中后焦虑

焦虑是一种高度觉醒和警觉相关的恐惧状态,其有助于更好地应对未来的威胁,但过度焦虑则会导致神经精神功能障碍和慢性致残性疾病^[65-66]。卒中发生后患者表现出的焦虑情绪障碍被称为卒中后焦虑(post-stroke anxiety, PSA)^[67]。临床上,卒中后PSA患病率在18.0%~52.9%。此外,超过一半的卒中患者会在某个时间点出现PSA,其对神经功能恢复产生了不利影响^[68]。PSA可持续5年及以上,导致患者的生活质量明显下降,身体恢复延迟,长期功能恶化则进一步增加卒中的死亡率^[2]。PSA已成为当今的社会难题,也是导致残疾的主要原因^[68]。

3.1.1 TRPV1与MAPK 丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)属于丝氨酸/苏氨酸(Ser/Thr)蛋白激酶,MAPK家族包括三个主要成

员:氨基末端激酶(Jun N-terminal kinase, JNK)、p38 丝裂原活化蛋白激酶(p38 mitogen-activated protein kinase, p38 MAPK)、细胞外信号调节蛋白激酶(extracellular regulated protein kinases, ERK)。这三者分别介导三条并行的MAPK信号通路,并参与了缺血性脑损伤的生理病理过程^[69-70]。有研究表明, JNK和p38 MAPK信号通路在焦虑样行为调控以及脑缺血后细胞损伤进程中发挥着重要的作用^[71-72]。张震等^[73]研究发现,在小鼠MCAO模型中,抑制TRPV1可干扰JNK及p38 MAPK信号通路,减轻小鼠脑缺血后杏仁核区脑血管损伤及组织水肿;此外,高架十字迷宫实验显示,抑制TRPV1可使小鼠脑缺血后焦虑样行为明显减少,这表明抑制TRPV1可通过MAPK信号通路减轻小鼠缺血再灌注后焦虑样行为^[73]。

3.1.2 TRPV1与 γ -氨基丁酸 γ -氨基丁酸(γ -aminobutyric acid, GABA)作为大脑中最丰富的抑制性神经递质之一,参与焦虑的发生发展^[74]。GABA主要通过GABAA和GABAB受体发挥作用。TRPV1在初级传入纤维可通过刺激脊髓中的抑制性神经元,进而引起GABA分泌增多,有研究表明,通过鞘内注射选择性消融感觉神经末梢上的TRPV1,可抑制脊髓GABA系统和增强肾交感神经兴奋反应,从而导致大鼠血压升高,这表明TRPV1可对GABA分泌产生影响^[75]。另有研究表明,将GABA或GABA受体激动剂注入杏仁核可降低动物的恐惧和焦虑程度, GABA拮抗剂的注入具有致焦虑效应,表示GABA神经元在杏仁核与焦虑相关的信息门控中发挥关键调节作用^[74],而抑制TRPV1可通过刺激脊髓中的抑制性神经元而促进GABA分泌,降低焦虑程度。

3.1.3 TRPV1与谷氨酸 谷氨酸(glutamate, Glu)是中枢神经系统中主要的兴奋性递质之一,它调控突触功能、细胞死亡和存活、运动功能、学习和记忆。有研究表明,在脑缺血中谷氨酸水平升高发挥兴奋性毒性作用,加重脑缺血及再灌注损伤^[76]。Glu受体包括离子型和代谢型两大类,离子型受体对 Ca^{2+} 具有高渗透性。Glu在海马中也发挥着重要作用,并影响焦虑和记忆相关过程的发病机制^[77]。研究表明,辣椒素可激活孤束中的一个神经元亚群,促进内向电流和神经元自发活动,促进Glu的释放^[78]。与此不太一致的是, YU等^[75]发现辣椒素还能够刺激海马神经末梢的TRPV1,激活钙调神经磷酸酶,进而降低钙离

子通道的活性并减少Glu的释放量。

虽然现有的研究已表明TRPV1与PSA有关,但是关于TRPV1减轻PSA的作用机制的研究尚缺乏。全面了解TRPV1在PSA中的作用,不仅可以丰富我们对PSA病理生理学的认识,还可提供新的治疗靶点。

3.2 卒中后吞咽困难

吞咽困难是急性卒中后常见的并发症。据估计, 37%~78%的中风幸存者患有吞咽困难^[79]。轻度吞咽困难的患者可能会出现饮水呛咳、进食困难和反复发热^[80];严重的患者容易发生窒息、吸入性肺炎及营养不良,这严重影响患者的生活质量,甚至危及生命^[81]。

一项纳入69名住院的脑卒中患者的随机、双盲实验发现长期使用天然辣椒素可以促进脑卒中吞咽困难患者吞咽功能的恢复,脑卒中吞咽困难患者在进食评估和标准化吞咽评估中的得分均大幅度下降^[82]。这可能是由于辣椒素的弱酸性可以使TRPV1通道敏化,触发口咽中表达其他感觉受体,从而起到调控吞咽困难的作用^[83]。同时NASCIMENTO等^[84]研究发现,采用TRPV1激动剂强刺激后,卒中后吞咽困难的患者的吞咽频率和吞咽幅度明显升高。后续的一项荟萃研究分析也显示辣椒素可以改善吞咽功能^[81]。综合以上研究可以推测TRPV1受体参与卒中后患者的吞咽反射控制,将为卒中后吞咽困难患者的康复提供新的证据。但是关于通过调节TRPV1改善卒中后吞咽功能的基础研究较少,需进行更多的研究分析改善吞咽障碍的作用机制。而且目前的研究也未能指出用于改善脑卒中患者吞咽功能所需的TRPV1激动剂的浓度、剂量、作用时间,还需要进行循证方法或多中心大样本的研究,分析用于患者的最佳治疗方案。

4 总结与展望

综上所述, TRPV1可通过调节炎症反应、氧化应激与钙超载、低温调控和血管舒张等多种途径在脑缺血过程中发挥作用,并可能通过介导GABA的分泌、谷氨酸释放及MAPK信号通路等途径参与PSA;除此之外, TRPV1还参与了卒中后患者的吞咽反射控制,但是具体机制还有待研究。亚低温对卒中也有明显的神经保护作用,是缺血性脑损伤的一种强有力的保护手段,但由于目前的降温策略有不

副作用, 因此限制了临床应用。越来越多的研究集中在使用药物调节体温, 以实现精准靶向冷却, 减少不良反应上。TRPV1可以在清醒的啮齿动物中诱导快速和持续的低温, 减轻脑缺血再灌注损伤并发挥神经保护作用, 是治疗脑缺血的潜在靶点, 也是迫切需要继续深入研究的蛋白之一。由于TRPV1参与脑缺血的调控是一个极其复杂的病理生理过程, 还需要额外的体内和体外实验来严格评估TRPV1在脑缺血后神经损伤中的作用。

除此之外, TRPV1还在心血管和肿瘤疾病、阿尔茨海默病、帕金森病和抑郁症中发挥有益作用^[85]; 目前更是已经提出了TRPV1在癫痫动物模型中的促癫痫和抗癫痫作用。在未来的研究中, 以TRPV1为靶点, 设计并合成安全有效的TRPV1调节剂, 希望在针对急性脑缺血提供脑保护的同时, 还可以有效缓解合并的焦虑、疼痛、吞咽困难、情绪障碍等并发症, 甚至合并治疗其他的神经系统疾病, 如阿尔茨海默病、神经系统肿瘤和帕金森病, 从而提高卒中患者的生存质量, 降低死亡率。随着研究的深入及医学技术的进一步发展, 基于TRPV1对神经精神疾病的治疗将不断推进, 以期为新药研发及临床治疗提供合理有效的理论支撑。

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