生命的化学, 2023, 43(9): 1375-1388 www.life.ac.cn doi: 10.13488/j.smhx.20230418

综述

硫化氢对血管重构作用及机制的研究进展

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摘要：硫化氢(H_2S)被认为是一种无色具有臭鸡蛋气味的有毒气体，大量吸入可导致多种组织器官的损害，严重者可导致死亡。但近年来的研究表明，H_2S在心血管系统具有多种生理和病理调节作用，是心血管功能调节的第三种气体信号分子，主要由酶促反应生成，受多种代谢途径调节。作为一种生理性血管调节因子，H_2S具有抑制血管细胞增殖、凋亡和自噬，并调控血管张力的作用。H_2S通路的下调参与了多种血管疾病的发病，如高血压、肺动脉高压、动脉粥样硬化等，并且可以通过补充H_2S来调节血管张力，抑制血管炎症，防止血管细胞钙化、氧化应激和增殖以及调节血管细胞凋亡及焦亡，进而极大地帮助防治血管疾病，这一结论已在动物和细胞实验，甚至临床研究中得到验证。本文主要论述H_2S在血管生理和病理生理中的作用及作用机制的研究现状，旨在为多种血管疾病的防治提供新的思路和启发。

关键词：H_2S；生成代谢；高血压；肺动脉高压

Research progress on the effect and mechanism of hydrogen sulfide on vascular remodeling

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Abstract: Hydrogen sulfide (H_2S) is considered to be a colorless toxic gas with a rotten egg odor that can cause damage to a variety of tissues and organs when inhaled in large quantities and can lead to death. However, recent studies have shown that H_2S has a variety of physiological and pathological regulatory effects in the cardiovascular system, and is the third gas signaling molecule in the regulation of cardiovascular function, which is mainly enzymatically promoted and regulated by a variety of metabolic pathways. As a physiological vascular regulatory factor, H_2S can inhibit vascular cell proliferation, apoptosis, and autophagy, and regulate vascular tension. A large number of studies have shown that the downregulation of the H_2S pathway is involved in the pathogenesis of a variety of vascular diseases, such as hypertension, pulmonary hypertension, atherosclerosis, etc. In addition, H_2S supplementation can regulate vascular tension, inhibit vascular inflammation, prevent vascular cell calcification, oxidative stress, and proliferation, and regulate vascular cell apoptosis and pyrodeath, thus greatly help to prevent and treat vascular diseases. This conclusion has been verified in animal and cell experiments and even clinical studies. This paper mainly discusses the role and mechanism of H_2S in vascular physiology and pathophysiology, aiming to provide new ideas and

收稿日期：2023-05-23

基金项目：黑龙江省自然科学基金项目(YQ2022H020)； 国家自然科学基金项目(82204792)； 中国博士后科学基金会项目(2022M711089)；黑龙江省博士后资助经费(LBH-Z21080)； 黑龙江省卫生健康委员会项目(20210202010178)

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inspiration for the prevention and treatment of various vascular diseases.

Key Words: H_2S; generative metabolism; high blood pressure; pulmonary hypertension

硫化氢(hydrogen sulfide，H_2S)是一种无色、可燃的水溶性气体，在体内主要以硫氢化钠的形式存在，辅以游离的气体分子状态，是继一氧化氮(nitric oxide，NO)和一氧化碳(carbon monoxide，CO)之后发现的第三种气体信号分子。H_2S作为一种新型的气体信号分子广泛参与了人体多个系统的调节[1]。此外，H_2S在调节血管的结构和功能方面也引起了广泛的关注[2]。研究已经证明，H_2S在血管细胞炎症、凋亡、细胞周期以及线粒体代谢功能等方面发挥了重要作用[3]。在血管系统中，H_2S调节血管张力、抑制血管细胞增殖，并对血管平滑肌细胞(vascular smooth muscle cells，VSMCs)的凋亡和自噬发挥双向调节作用[4]。此外，许多与血管重塑相关的疾病，如高血压和肺动脉高压等，均与H_2S生成受损关系密切[5]。因此，了解H_2S的内源性生成，及其对血管生理病理的调控，进而可以阐明血管疾病的发病机制，为血管疾病的防治提供全新的治疗思路。

1 内源性H_2S的生成及代谢

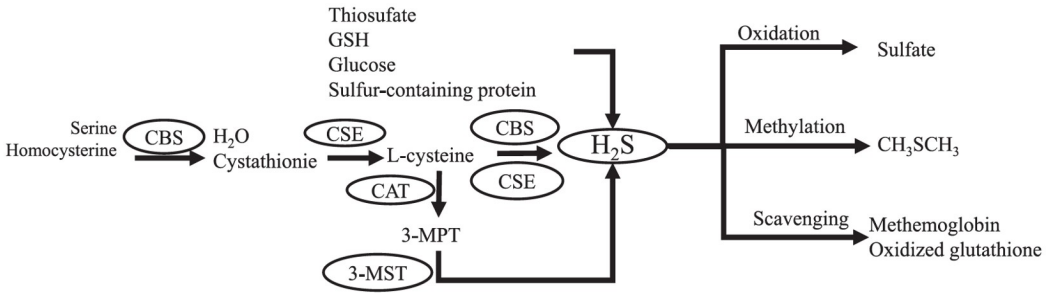
内源性H_2S大多由酶催化产生，只有小部分通过非酶途径产生[6,7]。催化H_2S产生的酶主要有胱硫醚-β-合成酶(cystathionine β-synthase，CBS)、胱硫醚-γ-裂解酶(cystathionine γ-lyase，CSE)、3-丙酮酸巯基转硫酶(3-mercaptopyruvate sulfurtransferase，3-MST)和半胱氨酸氨基转移酶(cysteine aminotransferase，CAT)[8]，而合成酶的缺失会导致人体多个系统疾病的产生[9,10]。H_2S主要催化底物L-半胱氨酸，CBS和CSE作为其生产的主要酶[11]，具有组织特异性。CBS主要分布在脑、肝、肾中，并在子宫动脉、肠系膜动脉、颈动脉球中也有少量表达[12]；CSE则主要分布在肝脏、回肠、门静脉、胸主动脉和非脉管系统中[13]；3-MST则分布在中枢和周围神经系统、血管内皮和其他组织中[14]，并催化3-巯基丙酮酸(3-mercaptopyruvate，3-MPT)在体内产生H_2S和丙酮酸。在这三种酶中，CBS通过β-消除反应催化底物半胱氨酸生成H_2S和丝氨酸，或通过α、β-消除反应催化胱氨酸生成过硫半胱氨酸，再生成H_2S；CBS还可以通过β-置换反应催化缩合两个半胱氨酸分子，或γ-置换反应催化同型半胱氨酸和半胱氨酸反应生成H_2S。CSE除了能像CBS那样完成相同的消除反应和置换反应外，还可以通过α-消除反应直接生成H_2S。另外，CSE可以单独以同型半胱氨酸为底物，通过α、γ消除或γ置换生成H_2S。3-MST则与CAT共同作用生成H_2S。具体步骤如下：首先，CAT催化α-酮戊二酸和半胱氨酸生成3-MPT和谷氨酸；其次，MST与其3-MPT底物之间的相互作用在Cys248处产生酶结合的半胱氨酸过硫化物中间体，并伴随着丙酮酸的释放；最后，内源性还原剂硫氧还蛋白和二氢硫辛酸与MST过硫化物中间体结合产生H_2S[15]。

与酶促反应相反，H_2S生成的非酶促反应大部分以半胱氨酸为底物，由VitB6和铁的协同活性催化，多发生在脾脏、心脏、肺、肌肉、骨髓和血浆中，尤其是红细胞中[16]。此外，研究还表明，主动脉、尾动脉、肠系膜动脉、肺动脉和胸主动脉等多种不同动脉的H_2S生产速率也不尽相同[17,18]。为了维持体内H_2S的生理平衡，形成了3种途径进行分解代谢[19]，(1)氧化途径：H_2S在线粒体中氧化代谢生成硫酸盐和硫代硫酸盐经尿排出；(2)甲基化途径：H_2S通过硫醇S-甲基转移酶催化的甲基化反应产生甲硫醇和二甲硫醚[20]；(3)清除途径：H_2S与高铁血红蛋白结合生成含硫血红蛋白而被降解(图1)。

2 H_2S对血管的生理、病理性调节

2.1 H_2S对血管张力的影响

H_2S对血管张力具有双向调节作用[21]。有研究表明，H_2S在血管系统中发挥舒张作用的主要机制为钙调素蛋白激活CSE，在*CSE*基因敲除小鼠体内H_2S水平较低，血压异常升高，内皮依赖性血管舒张功能丧失，直接证明了H_2S对维持血管功能的重要性，在不同部位其血管扩张能力各有不同[22,23]。此外，与H_2S相比，氢多硫化物包含更多的硅烷硫



CBS：胱硫醚-β-合成酶；CSE：胱硫醚-γ-裂解酶；3-MST：3-丙酮酸巯基转硫酶；CAT：半胱氨酸氨基转移酶；3-MPT：3-巯基丙酮酸；Serine：丝氨酸；Homocysterine：同型半胱氨酸；H_2O：水；Cystathionie：胱硫醚；L-cysteine：L-半胱氨酸；Oxidation：氧化；Methylation：甲基化；Scavenging：清除；Sulfate：硫酸盐；CH_3SCH_3：二甲硫醚；Methemoglobin：高氧血红蛋白；Oxidized glutathione：氧化型谷胱甘肽；Thiosufate：硫代硫酸盐；GSH：谷胱甘肽；Glucose：葡萄糖；Sulfur-containing protein：含硫蛋白质

图1　H_2S的生成及代谢

原子，同样具有松弛VSMCs降低血压的作用[24]。H_2S在某些条件下也具有收缩血管的作用，硫氢化钠(sodium hydrosulfide，NaHS)能在特定的浓度范围内收缩VSMCs[25]。Ping等[26]的研究也证实了这一点，浓度在10~300 μmol/L的NaHS可以诱导大鼠冠状动脉收缩。因此，H_2S对血管张力的调节是双向的。

H_2S诱导的血管舒张的潜在机制目前尚不明确。有研究表明，血管的舒张作用与铁通道的激活相关，表明H_2S通过开放VSMCs中三磷酸腺苷(adenosine triphosphate，ATP)敏感的钾通道(K_{ATP}通道)来发挥血管舒张作用[27,28]，H_2S还介导了一种对氧化还原敏感的新型蛋白质翻译后修饰，即巯基化[29]，更详细地说，是H_2S引起Kir6.1中半胱氨酸-43的巯基化反应，导致Kir6.1与ATP结合能力降低，与磷脂酰肌醇二磷酸(phosphatidylinositol diphosphate，PIP2)结合的能力增强，最终导致K_{ATP}通道开放和VSMCs松弛[30]。除了K_{ATP}通道之外，钙化钾通道(K_{Ca}通道)也被H_2S激活[31]。H_2S通过增加平滑肌Ca^{2+}放电活性，激活内皮大电导钙激活的钾通道(BK_{Ca}通道)[32]，同时瞬时受体电位阳离子通道Ⅴ亚家族成员4(transient receptor potential cation channel subfamily Ⅴ member 4，TRPV4)也通过巯基化被H_2S改变，随后激活并打开TRPV4依赖的Ca^{2+}内部流动和内皮BK_{Ca}通道，并导致血管舒张[33]。此外，H_2S通过巯基化修饰作用也能激活SK_{Ca}通道的α-亚单位异构体$SK_{2.3}$[34]，其对电压敏感钾通道(K_V通道)和Kv7.4电压门控钾通道的激活是发挥血管张力作用的关键[35]。

H_2S是否通过调节环鸟苷单磷酸(cyclic guanosine monophosphate，cGMP)途径来发挥血管舒张作用仍存在不同看法。研究表明，H_2S发挥血管舒张作用主要通过激活内皮一氧化氮合酶(endothelial nitric oxide synthase，eNOS)和抑制cGMP降解来实现[36]，具体机制如下：H_2S直接与NO反应产生硝基氧基(HNO)，从而激活硝基氧基-瞬时受体电位锚定蛋白1-降钙素基因相关肽(HNO-TRPA1-CGRP)通路调节血管张力[37]；H_2S通过减少cGMP降解和促进cGMP信号传导来抑制磷酸二酯酶5(phosphodiesterase 5，PDE5)的活性，随后激活cGMP依赖性蛋白激酶(protein kinase G，PKG)对血管扩张剂刺激的磷蛋白(vasodilator-stimulated phosphoprotein，VASP)的磷酸化，最终导致血管舒张[38]。此外，Sun等[39]认为，H_2S通过巯基化修饰相关的磷酸二酯酶5A(phosphodiesterase 5A，PDE5A)二聚体来发挥血管舒张功能。H_2S通过促进$eNOS^{S1177}$磷酸化，使得eNOS偶联增加，进而减轻氧化应激[40,41]。H_2S还可以通过降低可溶性鸟苷酸环化酶(soluble guanylate cyclase，sGC)中血红素Fe这一方式，增强sGC与NO的反应[36,42]，从而达到促进NO调节的细胞信号传导过程的目的[43]。然而，对于H_2S的舒张血管作用仍存在分歧。Zhao等[44]认为，特定的sGC抑制剂增强了血管舒张，但H_2S不依赖于cGMP途径发挥血管舒张作用。同样，在大鼠冠状动脉中，NaHS诱导的松弛不受ODQ(sGC抑制剂)的影响[45]。综上所述，H_2S的血管舒张作用在不同的物种和细胞类型中差异很大，这可能解释了H_2S舒张血管与收缩血管相互矛

盾的结果[42]。

H_2S舒张血管的作用与抑制线粒体复合物Ⅰ和Ⅲ有关。有研究表明，NaHS(100~1 000 μmol/L)抑制线粒体电子传递，从而在大鼠肠系膜小动脉中发挥血管舒张作用，这种效应能被复合物Ⅰ和复合物Ⅲ的激动剂抑制[31]。血管周围脂肪组织(perivascular adipose tissue，PVAT)中的H_2S在调节血管张力方面同样发挥重要作用，其作用机制主要是脂肪细胞衍生的松弛因子所诱导[46]。另外，Schleifenbaum等[47]认为，H_2S可能是调节血管张力的松弛因子，其机制可能与激活K_{ATP}和(或)电压敏感的K_{CNQ}钾通道有关[48]，对血管H_2S-K_{CNQ}途径的研究很有可能是改善血管功能障碍新的突破点。综上所述，H_2S通过激活铁通道、与NO-cGMP信号相互作用、抑制线粒体复合物Ⅰ和Ⅲ以及H_2S作为松弛因子的方式来实现血管舒张的作用，为心血管疾病治疗药物的研究与开发提供新思路。然而，在某些条件下，H_2S同样具有收缩血管的作用，这主要与H_2S激活Na^+-K^+-$2Cl^-$-共转运蛋白和电压门控钙离子通道有关[25]。

2.2 H_2S对血管平滑肌细胞增殖和凋亡的影响

作为VSMCs增殖的抑制剂，研究表明，H_2S在*CSE*基因敲除小鼠中的VSMCs增殖率显著提高，而内源性H_2S能显著抑制*CSE*基因敲除小鼠平滑肌细胞的增殖[49]。同样，作为常用的H_2S供体，NaHS也能剂量依赖性地抑制VSMCs的增殖。H_2S抑制VSMCs增殖的潜在机制，与H_2S抑制丝裂原活化蛋白激酶(mitogen activated protein kinase，MAPK)的活性密切相关[50]。内源性CSE/H_2S途径可以抑制丝裂原活化蛋白激酶/硫氧还蛋白相互作用蛋白(MAPK/TXNIP)信号的级联传导[51]，从而保护内皮功能。此外，H_2S通过抑制*Brg1*基因的转录和表达，减少增殖基因启动子区域的募集，从而抑制VSMCs的增殖[52]。另一方面，外源性H_2S能阻止丙酮酸脱氢酶复合物-E1(pyruvate dehydrogenase complex-E1，PDC-E1)的核易位，抑制糖尿病状态下血管平滑肌细胞增殖[53]。此外，Wang等[54]证明，钙敏感受体(CaSR)能通过钙-钙调素信号途径促进H_2S的内源性生成，同样达到抑制VSMCs增殖的目的。本实验室之前的研究也表明，H_2S通过抑制叉头框蛋白O1(Forkhead box O1，FOXO1)的磷酸化发挥抑制平滑肌细胞增殖的作用[4]。综上所述，H_2S可以通过调控多个路径，如基因、分子和信号通路等方式，达到抑制VSMCs增殖的目的。

H_2S具有促进或抑制血管细胞凋亡的作用[55]。对于H_2S促进细胞凋亡的观点[4]，有实验研究表明，H_2S可以通过激活细胞外信号调节蛋白激酶/含半胱氨酸的天冬氨酸蛋白水解酶-3(ERK/Caspase-3)途径，促进人主动脉平滑肌细胞的凋亡[56]。过表达CSE或补充外源性H_2S的方式，可以刺激ERK1/2、p38MAPK和$p21^{Cip/WAK-1}$的表达，抑制细胞周期蛋白D1的表达，从而促进细胞凋亡[46,56]。相反，对于H_2S抑制细胞凋亡的观点，H_2S能激活Kelch样环氧氯丙烷相关蛋白1-核红细胞2相关因子2(keap1-Nrf2)信号通路，从而抑制细胞凋亡[57]。还有研究表明，NaHS通过下调与内质网应激(endoplasmic reticulum stress，ERS)相关的Caspase-12、C/EBP同源蛋白(C/EBP homologous protein，CHOP)和葡萄糖调节蛋白78(glucose-regulating protein 78，GRP78)的表达来抑制细胞凋亡，从而保护血管内皮功能[58]。因此，H_2S促进细胞凋亡主要是以MAPK介导的信号通路为主，抑制细胞凋亡则与内质网应激相关因子密切相关。在不同的条件下，H_2S促进或抑制细胞凋亡，具有双向调控的作用。

2.3 H_2S对血管自噬的影响

在细胞分化和程序性死亡、降解入侵病原体以及向免疫系统提供抗原等过程中，自噬发挥了至关重要的作用[59,60]。在不同的病理过程中，H_2S可以促进或抑制自噬[61]。研究表明，NaHS可以促进大鼠主动脉内皮细胞中线粒体的自噬[62]，具体表现为NaHS首先激活被PTEN诱导性激酶1(PTEN induced putative kinase 1，PINK1)募集的Parkin，然后使丝裂菌素2(mitofusin 2，Mfn2)泛素化，最后达到增强线粒体自噬的目的。外源性H_2S还可以通过上调大鼠沉默信息调节因子1-PTEN诱导性激酶蛋白1-E3泛素连接酶(SIRT1-PINK1-parkin)通路增加线粒体自噬[63]。与此同时，一些研究还表明，补充H_2S或者过表达H_2S的合成酶能抑制线粒体自噬[64]。一方面，H_2S能抑制与自噬相关的AMP活化蛋白激酶-哺乳动物雷帕霉素(AMPK-mTOR)通路[65]；另一方面，微管相关蛋白1A/1B轻链3(1A/

1B-LC3)-Ⅱ与LC3-Ⅰ的比值作为自噬的指标，在补充H_2S之后，LC3AⅠ/Ⅱ的比值能明显降低[64]。NaHS还可以通过激活磷脂酰肌醇激酶/蛋白激酶B/哺乳动物雷帕霉素(PI3K/PKB/mTOR)信号通路的方式来抑制过度自噬[66]。综上所述，H_2S能对血管自噬进行双向调控，在不同的疾病过程中发挥切实有效的治疗作用。

2.4 H_2S对血管钙化的影响

血管钙化(vascular calcifification，VC)在糖尿病、慢性肾脏病及心血管疾病等疾病中是一种较为常见的病理过程[67]。研究表明，补充外源性H_2S能够延缓VC的发展进程[68,69]，作为诱导VC发生的有效刺激物[70]。Sikura等[69]在无机磷酸盐和氯化钙诱导的VIC钙化模型中，分别加入硫化物盐(如NaHS)和新型的缓释硫化物供体(如AP72)，发现两种供体均以剂量依赖性的方式降低钙的积累；与此同时，骨钙素(osteocalcin，OC)和碱性磷酸酶(alkaline phosphatase，ALP)表达均增加。同样，在离体条件下高磷刺激载脂蛋白E缺陷小鼠瓣膜组织，予以4-甲氧基苯基哌啶基膦二硫酸(AP72)处理也可以明显减弱高磷导致的钙化[71]。关于H_2S改善血管钙化的潜在机制，Zavaczki等[72]发现，H_2S分别在50 mmol/L和100 mmol/L的浓度下能最大程度地抑制磷的吸收，缓解钙沉积和VSMCs的成骨转分化。Yang等[73]发现，在维生素D3加尼古丁(VDN)模型中，H_2S减轻了VC和VSMCs的表型转化，同时还能抑制主动脉组织的内质网应激(endoplasmic reticulum stress，ERS)。Éva Sikura等[71]发现，在载脂蛋白E缺陷小鼠中，在通过腹腔注射AP72增加外源性H_2S之后，能显著抑制高脂饮食造成的主动脉瓣增厚以及炎症因子白细胞介素-1β(interleukin-1β，IL-1β)和肿瘤坏死因子-α(tumor necrosis factor-α，TNF-α)的高表达，从而实现改善血管钙化的目的。一些研究还表明，改善VC与抗氧化应激密切相关[74]。综上所述，H_2S可以通过调节矿物质稳态、缓解内质网应激、抗炎、抗氧化应激等途径实现改善VC的作用。

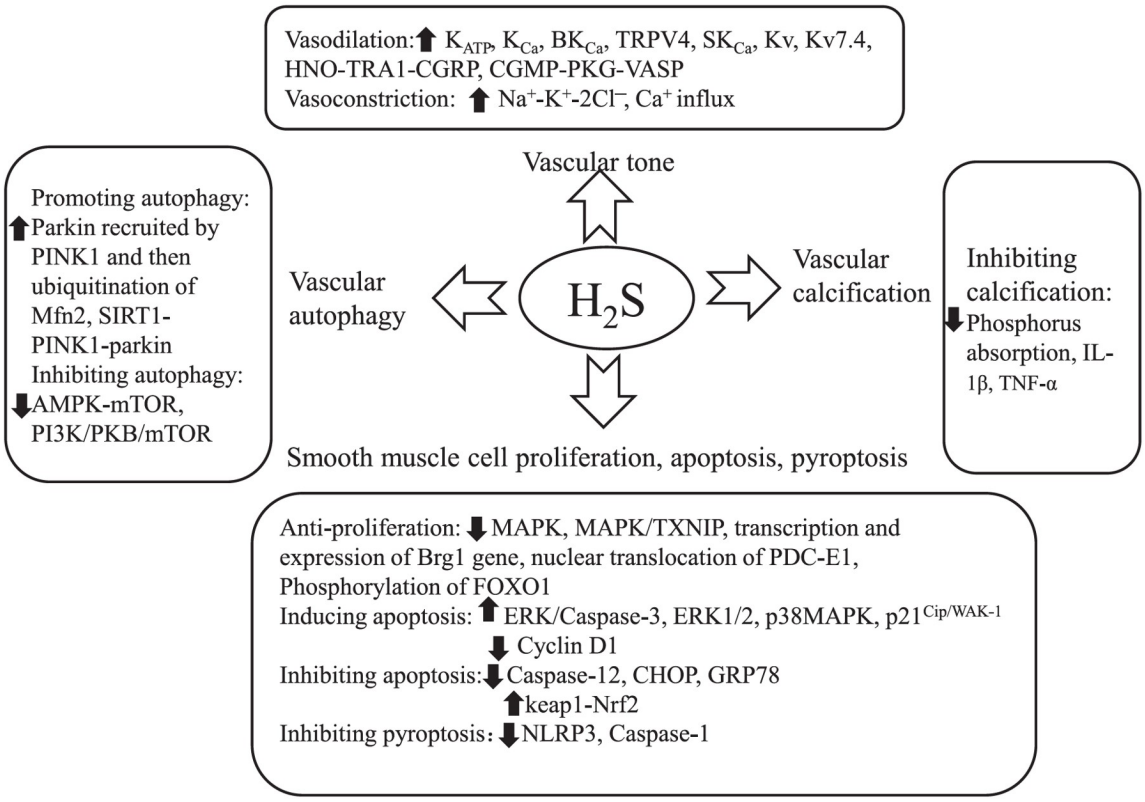
2.5 H_2S对血管细胞焦亡的影响

细胞焦亡(pyroptosis)是一种由炎症应答引起的新型程序性细胞死亡[75]，该过程包含多种细胞因子的激活与降解，表现为细胞内炎症小体被激活，进而激活Caspase-1促进成熟的白介素-1β和白介素-18(interleukin-18，IL-18)形成，同时切割消皮素D(gasdermin D，GSDMD)在细胞膜上打孔，促使炎症因子释放，最终诱发炎症反应[76]。核苷酸结合寡聚结构域样受体蛋白3(nucleotide-binding oligo-merization domain-like receptor protein 3，NLRP3)/Caspase-1则为介导细胞焦亡的关键信号通路[77]。研究表明，H_2S通过抑制NLRP3炎性小体来减少细胞焦亡，主要通过调控NLRP3/Caspase-1通路来实现[78]。与此同时，H_2S或其供体均通过抑制细胞焦亡信号通路标志蛋白(NLRP3、Caspase-1)的表达而发挥治疗急性肾损伤[79]、抗炎[80]及抗高血压[81]作用。综上所述，H_2S对血管细胞焦亡的调控作用主要与炎性小体及NLRP3、Caspase-1等蛋白质表达水平密切相关(图2)。

3 H_2S对血管疾病的调节

3.1 H_2S与高血压

高血压是心血管系统的常见病，以动脉血压升高、造成心肌负荷过重代偿性肥厚为特征。有研究表明，高血压与H_2S减少之间存在密切关系，内源性H_2S合成和H_2S依赖血管舒张的减少能导致高血压患者的微血管功能障碍[82]。CBS、CSE和3-MST作为H_2S的主要生成酶在高血压患者中的表达明显降低[83]，表明H_2S生成途径可能与高血压的发病机制有关。类似的结果在动物研究中也有所显示，在自发性高血压大鼠(spontaneously hypertensive rats，SHRs)的生长过程中，其主动脉中内源性H_2S含量降低[84]，在使用DL-炔丙基甘氨酸(DL-propargylglycine，PPG，一种CSE的抑制剂)之后可显著增强正常大鼠血管阻力，增加血供压，提示H_2S参与了血管舒张的调节[85]。与SHRs相似，在盐敏感的Dahl大鼠中CBS/H_2S途径也被下调[86]。在病理情况下，H_2S对血压调节起着至关重要的作用。Sun等[87]研究发现，NaHS能降低SHRs的尾动脉压力，延缓从高血压前期到高血压状态的转变，改善肾血管性高血压大鼠的内皮功能，改善受损的内皮依赖性收缩和内皮依赖性舒张功能[88]。此外，下丘脑室旁核(hypothalamic paraventricular nucleus，PVN)内源性H_2S也可以通过Nrf2介导的抗氧化和抗炎作用达到调控高血压的目的[89]。



向上箭头代表促进, 向下箭头代表抑制。Vascular tone：血管张力；Vascular calcification：血管钙化；Smooth muscle cell proliferation, apoptosis, pyroptosis：平滑肌细胞增殖、凋亡、焦亡；Vascular autophagy：血管细胞自噬

图2 H_2S对血管的生理、病理性调节

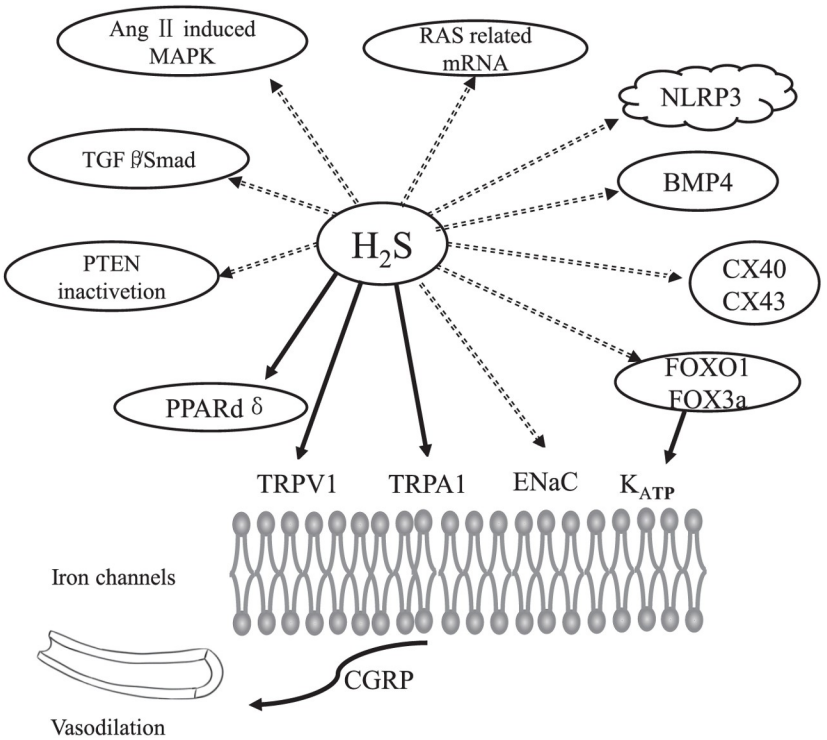
关于H_2S对高血压的调控作用及其潜在机制的探究，有研究表明，H_2S供体NaHS能显著抑制SHRs中的NOD样受体3(NLRP3)、炎症小体和氧化应激[88,90]。此外，H_2S通过对骨形态发生蛋白4(bone morphogenetic protein 4，BMP4)及其下游信号分子的抑制，使过量的内皮依赖性收缩功能得到改善[91]。NaHS还可以通过激活过氧化物酶体增殖物激活受体δ(peroxisome proliferator-activated receptor δ，PPARδ)的方式来保护内皮细胞并改善内皮功能[92]。除了改善血管内皮之外，NaHS还可以通过下调SHRs中连接蛋白40/连接蛋白43(Cx40/Cx43)T淋巴细胞的表达逆转SHRs中多种T淋巴细胞亚型的变化来调节免疫功能[93]，这正是H_2S的抗炎作用。除此之外，离子通道的调控也是H_2S发挥降压作用的关键。Sun等[87]表明，H_2S能激活K_{ATP}通道，从而引起血管扩张。此外，H_2S可以通过抑制FOXO1和叉头框蛋白O3a(forkhead box O3a，FOXO3a)的磷酸化来激活K_{ATP}通道，随后诱导它们与SUR2B和kir6.1的核结合。除了对K_{ATP}通道的调控外，H_2S还可以通过巯基化激活瞬时受体电位阳离子通道V亚家族成员1(transient receptor potential cation channel subfamily Ⅴ member 1，TRPV1)离子通道，增加SHRs中颈动脉窦压力受体的敏感性[94]。与此同时，TRPA1也被H_2S激活，诱导降钙素基因相关肽(calcitonin gene-related peptide，CGRP)释放并促进血管舒张[95]。另一方面，H_2S还通过下调SHRs肾脏中RAS相关mRNA的表达，从而阻断了RAS系统，达到抑制SHRs的病理状态和发挥血管舒张作用的目的[96]，其作用机制主要与抑制胶原蛋白沉积有关。在模型SHRs中，H_2S剂量依赖性地抑制由血管紧张素Ⅱ诱导的MAPK的激活，下调血管紧张素Ⅱ 1型(AT1)的亲和力，抑制转化生长因子-β/Smad信号通路，最终抑制SHRs中的血管重塑和胶原沉积[97,98]。关于H_2S调节高盐Dahl大鼠血压的机制，Liang等[99]表明，H_2S能下调高盐Dahl大鼠室旁核的氧化应激反应，减弱交感神

经活性，促进抗炎因子的分泌，从而抑制炎症反应。而上皮钠通道(ENaC)对钠的重吸收能加速盐敏感性高血压的进展，H_2S则可以通过抑制ENaC来调节血压。研究表明，过氧化氢通过上调磷脂酰肌醇3,4,5-三磷酸能增加钠的重吸收，H_2S则可以完全阻断由过量的过氧化氢引起的ENaC的异常激活[100]。此外，H_2S也能显著抑制由过氧化氢引起的磷酸酶基因(*PTEN*)失活，从而降低氧化应激。综上所述，H_2S抑制高血压的机制十分复杂，主要与减少氧化应激和炎症反应、调控免疫功能和离子通道、抑制胶原沉积和血管重塑等密切相关(图3)。

3.2 H_2S与肺动脉高压

肺动脉高压(pulmonary hypertension，PH)是指心脏通向肺部的血管压力过高而形成的一组以肺血管管腔肥厚、肺血管阻力持续升高为特征的临床疾病，主要由低氧性肺动脉高压(hypoxic pulmonary hypertension，HPH)和高肺血流量引起的PH等构成。关于H_2S与PH的关系，研究表明，在HPH期间，肺组织中CSE的表达下调，内源性H_2S的生成途径受到抑制[101]。此外，Turhan等[102]也发现，在野百合碱(monocrotaline，MCT)诱导的PH模型中，大鼠肺组织中H_2S的含量下降，在补充外源性H_2S之后能提高血浆中H_2S的含量，并减轻HPH引起的肺动脉重构。

H_2S对PH调控机制有抗炎[103]、抗内质网应激[104]、诱导凋亡[105]、抗增殖[106,107]和上调CO/HO途径[108]等，具体内容如下。(1) H_2S抗炎。各种炎症介质能激发肺血管级联式炎症反应，促进肺动脉重塑继而导致PH。实验研究表明，H_2S通过抑制核因子-κB(nuclear factor-kappa-B，NF-κB)信号通路减轻肺动脉内皮炎症[109]。此外，H_2S还能通过抑制NADPH氧化酶4(NADPH oxidase 4，Nox4)的表达以及ERS相关分子标记物GRP78和CHOP的表达来减轻[58,104]。(2) H_2S诱导肺动脉平滑肌细胞(pulmonary artery smooth muscle cells，PASMC)凋亡。Li等[105]认为，在PH大鼠中，H_2S通过抑制PASMCs的B淋巴细胞瘤-2基因(B-cell lymphoma-2，*Bcl-2*)、激活Fas信号通路诱导细胞凋亡。(3) H_2S显著抑制增殖细胞核抗原和尿囊素Ⅱ的表达[110]。H_2S实现抗增殖这一作用主要与环氧化酶-2/前列环素I2(COX-2/PGI2)信号通路的上调有关[106,107]。



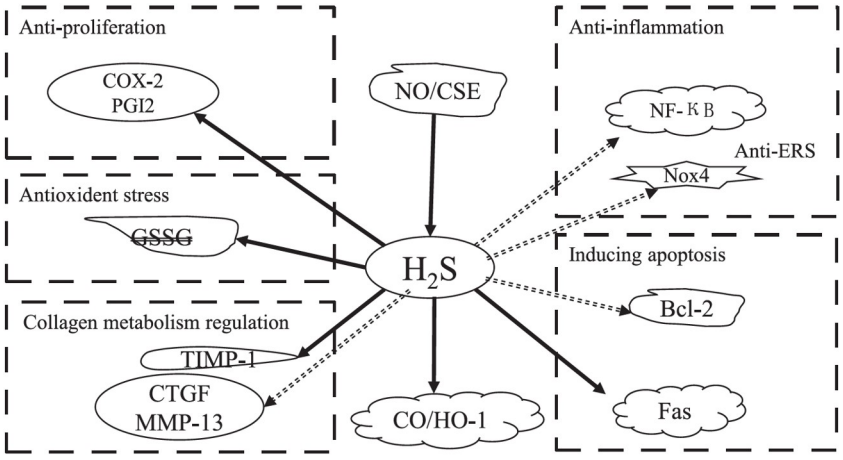
实线箭头代表促进，虚线箭头代表抑制。Iron channels：离子通道；Vasodilation：血管舒张

图3 H_2S对高血压的作用

(4)H_2S发挥抗氧化应激作用。H_2S通过清除氧化性谷胱甘肽(oxidized glutathione，GSSG)继而提高谷胱甘肽/氧谷胱甘肽(GSH/GSSG)的比率，从而在HPH中发挥抗氧化能力[111]，抑制肺血管重塑。在应用CSE抑制剂PPG之后，结缔组织生长因子(connective tissue growth factor，CTGF)、基质金属蛋白酶-13(matrix metalloproteinase-13，MMP-13)表达增强，金属蛋白酶组织抑制剂-1(recombinant human tissue inhibitor of metalloproteinases-1，TIMP-1)的表达明显下降，以上结果均表明，H_2S可以减轻氧化应激，从而实现抑制肺血管重塑的作用[112]。(5) H_2S上调一氧化碳/血红素氧合酶-1(CO/HO-1)通路，与NO共同发挥作用[113]。此外，在HPH动物模型上也证实了CO和H_2S之间的相互协同作用。Zhang等[108]证实，H_2S可以通过激活HO-1来调节HPH的发病机制，但调控CO/HO通路的具体机制尚不明确。现有的证据也表明，NO信号传导的缺失能加速PH的进展[114]。在高血流量性PH中，NO底物L-精氨酸可上调CSE/H_2S信号传导[115]。因此，H_2S通过与其他两种气体信号分子NO和CO的相互作用来保护肺血管结构。综上所述，H_2S通过抗炎、诱导细胞凋亡、抗增殖、抗氧化应激以及调节CO和NO信号通路等多种作用机制实现拮抗PH的目的(图4)。

3.3 H_2S和其他心血管疾病

缺血性心脏病(ischemic heart disease，IHD)及左心功能不全的发病与内源性H_2S生成途径的异常密切相关[116]，过表达CSE或补充H_2S供体能显著改善心脏功能和结构性病变[117,118]。H_2S对IHD和左心室功能障碍的改善作用可能涉及以下机制。(1)抑制氧化应激。H_2S能增强缺血/再灌注(ischemia/reperfusion，IR)小鼠心脏组织中超氧化物歧化酶(SOD)、过氧化氢酶(CAT)和GSH的表达[119,120]。在左冠状动脉闭塞和再灌注的小鼠心脏模型中，经过7 d H_2S供体治疗能促进Nrf2的核转录，Nrf2作为调节抗氧化基因的重要转录因子，有助于增加抗氧化酶表达[117]。此外，在缺血性心肌细胞H9c2细胞中，H_2S通过上调节律基因*Bmal1*表达来实现抗氧化作用[121]。(2)抑制细胞凋亡和自噬。H_2S通过上调*Bcl-2*的表达、抑制凋亡基因*Bax*和Caspase-3的表达实现降低心力衰竭小鼠心肌中凋亡细胞比例的目标[118]。另一项研究也表明，外源性H_2S能通过胞内磷脂酰肌醇激酶/血清/糖皮质激素调节激酶1/糖原合成酶激酶-3(PI3K/SGK1/GSK3β)信号通路抑制自噬[122]。(3)调控巨噬细胞相关的心脏炎症反应。对于野生型和*CSE*基因敲除型小鼠，H_2S能通过加速整合素β1的内化和激活下游Src-FAK/Pyk2-Rac途径达到控制巨噬细胞迁移的目的，进而实现抗心肌梗死的作用[123]。在心肌梗死小鼠中，巨噬细胞极化也受H_2S控制。有研究表明，NaHS诱导的M2极化是通过增强线粒体生物发生和脂肪酸氧化来实现的，同时还能增加M2极化巨噬细胞的数量[124]。(4)与其他生物活性分子的相互作用。之前的研究发现，H_2S和NO之间的相互作用能调节血



实线箭头代表促进，虚线箭头代表抑制，=代表清除。Anti-proliferation：抗增殖；Antioxident stress：抗氧化应激；Collagen metabolism regulation：胶原代谢调节；Anti-inflammation：抗炎；Anti-ERS：抗内质网应激；Inducing apoptosis：诱导凋亡

图4 H_2S对肺动脉高压的作用

管[125]。同样，在IR大鼠的心脏组织中，H_2S通过上调eNOS和nNOS的mRNA水平，降低iNOS的mRNA水平可以提高内源性NO的生成[126]。(5)线粒体保护。在HF大鼠中，H_2S通过恢复*Bcl-2*/*Bax*的平衡，减少线粒体依赖性凋亡来维持线粒体稳态[118]，并改善HF小鼠离体心脏中的线粒体呼吸及ATP合成[117]。此外，mitoK$_{ATP}$通道的阻断剂5-HD能完全阻断H_2S供体对离体IR大鼠心脏的保护作用，表明H_2S对心脏线粒体的调节作用与mitoK$_{ATP}$通道的开放密切相关[127]。

4 讨论

综上所述，H_2S参与血管系统生理和病理性的调节，机制复杂多样。H_2S扩张血管的作用主要通过激活铁通道、与NO-cGMP信号相互作用、抑制线粒体复合物Ⅰ和Ⅲ，并充当舒张因子来实现。H_2S抑制VSMCs增殖的作用与MAPK/TXNIP、Brg1、ERK1/2、PDC-E1及CaSR的信号传导密切相关。H_2S对血管细胞凋亡和自噬的调控是双向的，在不同的病理过程，它可以促进或抑制自噬和凋亡。H_2S改善血管钙化的情况，主要通过抑制磷的吸收、缓解内质网应激、抗炎、抗氧化应激等途径实现。对于细胞焦亡，H_2S主要通过调控NLRP3、Caspase-1等蛋白质的表达水平来实现。对于心血管疾病，如高血压、肺动脉高压等，H_2S可以通过调节血管张力、抗炎、抗氧化、抑制VSMCs的增殖、调节VSMCs的凋亡等方式进行调控。因此，调节H_2S水平将为心血管疾病提供一种全新的治疗方法。所以，进一步了解H_2S在心血管系统中的作用，着重研究多种气体信号分子之间的协同作用，探索其在高血压和肺动脉高压等疾病中的作用具有重要的临床意义[128]。H_2S发挥的积极治疗作用，与H_2S供体种类、实验动物或细胞的类型以及有效浓度密切相关，不同的供体在不同的实验对象上会得出不一样的实验结果，差异较大，所以对于供体的优化及其作用机制的探讨显得尤为重要，应积极地将基础研究成果应用于临床，为广大心血管系统疾病患者拓宽临床治疗途径。

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