



钠尿肽受体C与心血管疾病研究进展

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摘要 钠尿肽是调节机体水盐平衡以及维持心血管等器官功能稳态的一组多肽, 包括心房钠尿肽(atrial natriuretic peptide, ANP)、脑钠肽(brain natriuretic peptide, BNP)和C型钠尿肽(C-Type natriuretic peptide, CNP)等, 均可与钠尿肽受体C(natriuretic peptide receptor C, NPR-C)结合. 传统观点认为NPR-C具有清除并降解钠尿肽的作用, 然而越来越多的证据表明, NPR-C胞内结构域与抑制性G蛋白(inhibitory G protein, Gi)偶联介导许多生物学效应, 参与调控高血压、动脉粥样硬化、冠心病、心律失常、肺动脉高压、心功能不全等多种心血管疾病. 本文将重点阐述NPR-C及其相关信号通路在高血压等心血管疾病中的研究进展.

关键词 钠尿肽受体C, 钠尿肽, 高血压, 血管平滑肌细胞, 心肌纤维化

钠尿肽是调节机体水盐平衡以及维持心血管等器官功能稳态的一组多肽, 主要包括心房钠尿肽(atrial natriuretic peptide, ANP)、脑钠肽(brain natriuretic peptide, BNP)和C型钠尿肽(C-Type natriuretic peptide, CNP). 钠尿肽受体C(natriuretic peptide receptor C, NPR-C)能分别与ANP, BNP和CNP结合发挥不同的生物学作用. 研究发现, NPR-C在心脏、血管、肾脏、脂肪和骨骼等组织中广泛表达, 并且在多种疾病状态下表达异常, 因此本文着重阐述NPR-C及其信号通路在高血压等心血管疾病中的研究进展.

1 NPR-C及其信号通路

钠尿肽受体除了NPR-C, 还包括钠尿肽受体A(natriuretic peptide A receptor, NPR-A)和钠尿肽受体B

(natriuretic peptide B receptor, NPR-B). 其中, ANP与BNP主要与NPR-A结合, CNP主要与NPR-B结合, 但三种钠尿肽均可与NPR-C结合. NPR-A和NPR-B为鸟苷酸环化酶(guanylate cyclase, GC)偶联受体, 因此也被称为GC-A和GC-B, 分别由细胞外配体结合区、跨膜区、细胞内蛋白激酶样区和鸟苷酸环化酶区组成. 钠尿肽与NPR-A和NPR-B结合后, 激活鸟苷酸环化酶产生环磷酸鸟苷(cyclic guanosine monophosphate, cGMP), 从而激活下游信号通路^[1].

NPR-C与NPR-A, NPR-B具有相似的胞外结构, 但胞内结构域的氨基酸数量较少, 仅为NPR-A和NPR-B的1/2, 由37个氨基酸组成, 因此没有鸟苷酸环化酶活性. 最初研究表明, NPR-C具有清除并降解钠尿肽的作用, 钠尿肽与NPR-C结合后通过受体介导的内化被细胞内溶酶体降解. 然而, 近年来有研究表明, NPR-C的

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胞内结构域与抑制性G蛋白(inhibitory guanine nucleotide regulatory protein, Gi)偶联,通过Gi的 α 亚型抑制腺苷酸环化酶(adenylyl cyclase, AC)活性,降低胞内环磷酸腺苷(cyclic adenosine monophosphate, cAMP)水平,且该作用可被百日咳毒素(pertussis toxin, PTX)拮抗^[2].此外, Gi的 α 亚型还可激活细胞外信号调节激酶1/2(extracellular signal regulated kinase 1/2, ERK1/2)与磷脂酰肌醇-3-羟激酶(phosphatidylinositol 3-hydroxy kinase, PI3K);而Gi的 $\beta\gamma$ 亚型则可激活磷脂酶C(phospholipase C, PLC)等调控细胞功能^[3].因此, NPR-C介导不同下游信号通路在多种心血管疾病中发挥重要作用.

2 NPR-C与高血压

高血压是最常见的心血管疾病,是脑卒中、心肌梗死和心力衰竭等严重致死致残性疾病最重要的危险因素^[4].高血压的病因复杂,归根结底在于高血压是基因与多种环境因素相互作用的结果.本课题组前期在东亚人群全基因组关联研究(genome-wide association studies, GWAS)中发现5个东亚人群中特有的与血压调节相关的遗传位点,其中就包括NPR-C^[5].进一步研究发现NPR-C基因的几个高度连锁的变异位点(rs2270915, rs700923, rs2292026)与尿钠排泄以及血压显著相关^[6,7],提示NPR-C是调控高血压的关键基因.Matsukawa等人^[8]发现, NPR-C基因敲除(*NPR-C*^{-/-})小鼠血压低于正常小鼠,尿液浓缩能力下降.但*NPR-C*^{-/-}小鼠血浆ANP和BNP水平与野生型(wild-type, WT)小鼠相比并无明显升高,实际上还略低于正常小鼠.显然, *NPR-C*^{-/-}小鼠的轻度利尿特征并非血液循环中ANP或BNP升高所致,而是NPR-C信号通路直接参与了血压调控.

为进一步探索*NPR-C*^{-/-}小鼠的降压机制,本课题组^[9]在血管紧张素II(angiotensin, Ang II)诱导的高血压模型上发现敲除NPR-C可明显改善Ang II诱导的水钠潴留,从而抑制血压升高. Ang II可激活无赖氨酸激酶(with-no-lysine kinase 4, WNK4)及其下游信号STE20相关脯氨酸/丙氨酸丰富激酶(Ste20 related proline/alanine rich kinase, SPAK),使肾远曲小管细胞钠氯共转运蛋白(sodium chloride co-transporter, NCC)表达及活性增加从而导致水钠潴留^[10].本课题组^[9]还发现,敲除NPR-C后可抑制Ang II诱导的PKC激活,从而逆

转远曲小管细胞WNK4/SPAK/NCC通路激活,促进水钠排泄降低血压.因此,本课题组的研究提示, NPR-C调控肾小管上皮钠离子通道激活是水盐代谢紊乱诱导高血压的关键机制.

然而,另有研究表明NPR-C通过调控血管功能参与血压调节^[11],反映出NPR-C组织特异性以及信号通路复杂性.一氧化氮是维持血管收缩舒张的重要生理调节因子,主要由内皮型一氧化氮合酶(endothelial NO synthase, eNOS)生成.研究表明, NPR-C可与eNOS偶联产生一氧化氮(nitric oxide, NO)^[12].然而在eNOS敲除小鼠心脏和肾脏组织中NPR-C mRNA的表达水平更高^[13],在NO信号通路减少或丢失的情况下,可能存在增强的NPR-C介导的血管舒张作用^[1].此外, Del Ry等人^[14]发现,内皮功能降低的人群NPR-C mRNA表达水平显著升高.这些研究提示在心血管系统中, NPR-C和NO信号通路具有互补保护作用,一条信号通路缺失可以通过上调另一条信号通路来弥补.另有研究发现NPR-C对血压的调控作用还受性别影响, *NPR-C*^{-/-}雌鼠血压稍高于WT小鼠,而*NPR-C*^{-/-}雄鼠的血压则低于WT小鼠^[9,15]. Moyes等人^[15]认为是NPR-C调节阻力血管的舒张功能有性别差异所致,因为在*NPR-C*^{-/-}雌鼠血管中观察到内皮功能障碍,而在*NPR-C*^{-/-}雄性小鼠中没有观察到.

C-心钠素(ANP)4-23,一种ANP的环缺失类似物,被认为是NPR-C的特异激动剂.研究表明C-ANP₄₋₂₃减轻Ang II诱导主动脉平滑肌细胞氧化应激和过度增殖^[16].在Dahl大鼠中, C-ANP₄₋₂₃通过减少足细胞中的损伤线粒体和增加抗氧化功能参与盐敏感性高血压^[17]. Li等人^[18]进一步发现, C-ANP₄₋₂₃显著降低自发性高血压大鼠(spontaneously hypertensive rat, SHR)的血压,其主要通过抑制血管Gi α 蛋白表达和氧化应激发挥降压作用.本课题组近期研究发现, C-ANP₄₋₂₃抑制DOCA-盐诱导血压升高以及肾小管上皮间充质转化,从而改善肾纤维化(尚未发表).

NPR-C除了分布在血管和肾脏,也在脂肪组织中表达.研究表明, *NPR-C*^{-/-}小鼠的白色及棕色脂肪量均减少,但产热基因和棕色脂肪细胞特征蛋白表达则升高^[19].此外, *NPR-C*^{-/-}小鼠白色脂肪组织中棕色脂肪细胞增加,抵抗饮食诱导的肥胖以及增强胰岛素敏感性^[20]. Wu等人^[21]进一步利用NPR-C脂肪细胞特异性敲除小鼠研究,发现该小鼠对高脂饮食诱导的肥胖

具有抵抗力, 主要表现为能量消耗增加, 胰岛素敏感性提高, 葡萄糖吸收增加, 肝脂肪变性和内脏脂肪炎症改善等。敲除NPR-C促进胰岛素刺激脂肪细胞对葡萄糖的摄取, 并增强新生脂肪的生成^[22]。因此, 在肥胖合并高血压患者的脂肪组织中, NPR-C基因表达高于肥胖但血压正常者^[23], 而禁食诱导的减肥可导致血压下降, 脂肪细胞NPR-C表达显著下调^[24]。这些结果提示, 抑制NPR-C信号通路是肥胖患者降压的靶标。

总之, 近年来的研究表明NPR-C与血压的关系复杂, 尤其涉及不同NPR-C下游信号通路的激活, 从而调控肾脏、血管等靶器官功能, 发挥不同的血压调节作用。

3 NPR-C与动脉粥样硬化

动脉粥样硬化是冠心病、脑梗死、外周血管病的主要原因, 其发病机制涉及血管内皮细胞和平滑肌细胞等血管细胞功能的改变, 从而导致动脉壁增厚变硬、血管腔狭窄。研究发现, NPR-C在血管内膜及中膜表达较高, 且NPR-C表达与血管病变严重程度呈正相关^[25]。NPR-C可以直接调节血管细胞的增殖、迁移等, 维持血管稳态平衡。有研究报道NPR-C可通过调控下游ERK1/2信号激活, 增强内皮细胞增殖的同时抑制血管平滑肌细胞(vascular smooth muscle cell, VSMC)生长, 这提示NPR-C在不同血管细胞中的作用不同^[26]。Bubb等人^[27]利用内皮细胞特异性NPR-C敲除小鼠, 发现NPR-C信号激活参与调控内皮细胞新生, 敲除NPR-C抑制下肢缺血后血流的恢复, 并促进损伤诱导新生内膜的形成, 其机制主要依赖于Gi, ERK1/2和PI3K γ /Akt通路的激活。内皮细胞特异性CNP敲除小鼠的动脉瘤、动脉粥样硬化的发生率均明显增加, 而CNP对血管稳态的维持必须依赖其受体NPR-C^[15]。此外, NPR-C在颈动脉易损斑块内膜区表达较高, 提示NPR-C是颈动脉斑块进展和破裂的潜在生物标志物^[28]。

4 NPR-C与冠心病

冠心病的主要病理基础是冠状动脉粥样斑块形成。2016年我国开展的一项GWAS研究表明, 在校正冠心病常见危险因素(年龄、性别、吸烟、高血压、糖尿病和血脂异常等)后, NPR-C单核苷酸多态性(single-

nucleotide polymorphisms, SNPs)与冠心病关联仍然显著, 提示NPR-C基因SNPs与冠心病的遗传易感性有关^[29]。Casco等人^[30]发现, 不同程度的动脉粥样硬化病变患者冠状动脉内膜和中层内侧均有NPR-C的表达。经皮冠状动脉介入治疗(percutaneous coronary intervention, PCI)后NPR-C在新生内膜中表达增加^[31]。

临床研究表明, 心脏外膜脂肪组织(epicardial adipose tissue, EAT)与冠心病的发病、进展或严重程度有关^[32,33]。与稳定型冠心病患者或冠脉造影结果正常者相比, 急性冠脉综合征患者心脏外膜脂肪组织NPR-C的表达均较低^[34]。尽管EAT在冠心病发病中的潜在病理生理机制还不完全清楚, 但有证据表明, EAT中低水平的NPR-C表达导致心脏外膜脂肪功能失调, 从而促进冠心病发展。此外, Hobbs等人^[35]研究发现NPR-C参与调节冠状动脉血流, NPR-C信号在冠心病缺血再灌注损伤中是一种保护机制, 包括减少梗死面积, 维持冠状动脉灌注压和左心室压等。

5 NPR-C与心律失常

研究表明, NPR-C通过影响心肌细胞离子电流、心肌组织重构、调节交感神经等机制参与心脏节律调控。NPR-C可选择性抑制牛蛙心房心肌细胞L-型钙离子通道($I_{Ca,L}$), CNP和C-ANP₄₋₂₃通过NPR-C显著减少小鼠心肌细胞内 $I_{Ca,L}$ 的电压从而控制心率^[36]。NPR-C激动剂C-ANP₄₋₂₃也可控制异丙肾上腺素刺激的心率增快, 这与NPR-C激活后房室传导减慢有关^[37]。此外, NPR-C缺失可导致窦房结(sinoatrial node, SAN)功能障碍, SAN恢复时间延长, 心房颤动的风险增加^[38]。

NPR-C通路的激活具有强大的抗心肌纤维化和抗心肌成纤维细胞增殖作用^[39], $NPR-C^{-/-}$ 小鼠在基础水平即可表现出心房纤维化, 这是导致异常SAN传导的原因^[40]。在Ang II诱导房颤模型中, $NPR-C^{-/-}$ 小鼠与WT小鼠相比, 左心房收缩Vmax降低、动作电位延长, 表明缺失NPR-C加重了Ang II诱导的心肌组织电重塑; $NPR-C^{-/-}$ 小鼠心房心肌纤维化更加明显, 表明缺失NPR-C加剧了Ang II诱导的心房重塑; 给予NPR-C激动剂C-ANP₄₋₂₃可以降低房颤与心房结构异常的发生率^[40]。房颤常与窦房结疾病并存, 尤其常见于心力衰竭。因此, Ang II刺激的 $NPR-C^{-/-}$ 小鼠更易发生房颤, 射血分数下降更明显, 窦房结功能下降与心力衰竭

的严重程度一致^[41]。此外, 钠尿肽及其受体对自主神经功能也有影响。NPR-C^{-/-}小鼠心率较快、昼夜变化较小, 窦性停搏增多, 心率变异性下降, 表明交感神经的活动明显增强^[42]。

6 NPR-C与肺动脉高压

肺动脉高压(pulmonary arterial hypertension, PAH)指肺动脉压力升高超过一定阈值的一种血流动力学和病理状态, 可导致右心衰竭。在对NPR-C^{-/-}小鼠进行心脏超声检查时, 可观察到右心房扩大、右心室游离壁肥厚、三尖瓣反流以及右心室压力负荷增大等表现, 这些都是肺动脉高压的典型临床表现^[43], 提示NPR-C信号通路在PAH的发生发展过程中起重要作用。研究发现在缺氧诱导的PAH动物模型中, 肺组织中NPR-C表达下降^[44]。在人肌成纤维细胞上, NPR-C介导CNP的抗纤维化^[39]以及BNP与CNP的抗增殖作用^[45]。因此, NPR-C激活后的抗增殖作用是其预防PAH的主要机制。此外, 体外培养肺动脉血管平滑肌细胞在缺氧条件下, 成纤维细胞生长因子(fibroblast growth factor, FGF)和血小板源性生长因子(platelet-derived growth factor, PDGF)刺激诱导NPR-C mRNA表达下降^[46]。激活NPR-C信号可通过丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)和PI3K途径抑制血管活性物质诱导的VSMC过度增殖^[47]。因此, NPR-C信号通路的激活受损可能导致NPR-C在肺血管系统中的抗增殖作用消失, 进而导致血管性肺损伤, 包括内皮功能和血管平滑肌功能障碍、细胞外基质变化、血小板和炎症细胞激活^[1]。虽然NPR-C信号通路的激活受损可能会导致PAH, 但C-ANP₄₋₂₃可降低右心室收缩压和肺动脉收缩压, 并增强心脏功能, 包括左心室肌力, 从而改善PAH^[48]。因此, NPR-C通路有望成为预防或治疗肺动脉高压的新靶点。

7 NPR-C与心功能不全

与本课题组^[6,7]在高血压候选基因研究中的结果相似, Pereira等人^[49]在以美国人群为对象的遗传学研究发现, NPR-C rs2270915 A/G变异(N521D氨基酸替换)GG纯合子心脏舒张功能异常的患病率比A/G杂合子和A/A野生型高出15%。这一结果提示, NPR-C基

因变异与心功能不全的发病相关。Moyes等人^[50]利用NPR-C^{-/-}小鼠发现, 缺失NPR-C后冠状动脉对内皮依赖性和血流介导扩张的反应性受损, 并且缺血导致该小鼠的梗死面积增大, 功能恢复减弱。此外, NPR-C^{-/-}小鼠在压力超负荷和交感过度激活诱导的心衰中更严重, 并且NPR-C信号在心衰病人中也受到损伤^[50]。因此, NPR-C基因变异调节心功能的机制涉及心肌成纤维细胞和心肌细胞的功能障碍, 从而导致心肌纤维化和心脏舒张功能受损^[50]。

8 展望

尽管NPR-C长期以来被认为是介导钠尿肽清除的受体, 但近年来越来越多的证据显示, NPR-C通过与Gi偶联介导各种生物学效应, 参与维持心血管功能稳态。

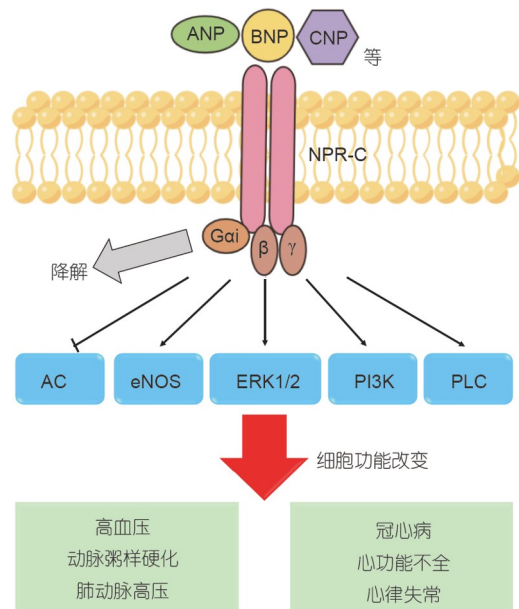


图1 钠尿肽受体C及其信号通路调控心血管疾病。心房钠尿肽、脑钠肽和C型钠尿肽等与NPR-C结合通过受体介导的内化被细胞内溶酶体降解。NPR-C的胞内结构域与抑制性G蛋白偶联, 抑制腺苷酸环化酶活性, 激活一氧化氮合酶、细胞外信号调节激酶1/2磷脂酰肌醇-3-羟激酶、磷脂酶C等信号通路调控细胞功能, 从而参与各种心血管疾病的发生发展过程

Figure 1 NPR-C and its signaling pathway in the regulation of cardiovascular diseases. ANP, BNP and CNP bind to NPR-C and are degraded by intracellular lysosomes through receptor-mediated internalization. The intracellular domain of NPR-C is coupled with Gi, which inhibits the activity of AC, activates eNOS, ERK1/2, PI3K, PLC and other signal pathways regulate cell function, and participates in the pathogenesis and development of various cardiovascular diseases

此外, NPR-C广泛表达在心脏、血管、肾脏、脂肪和骨骼等组织, 在高血压、动脉粥样硬化、心律失常、肺动脉高压、心功能不全等多种心血管疾病中表达异常, 并通过不同的信号通路发挥不同甚至相反作用, 提

示NPR-C信号通路具有组织特异性(图1)。因此, 未来研究方向在于系统阐明NPR-C信号通路在各种心血管疾病发生发展中的不同作用, 并尝试利用靶向干预方式针对不同疾病进行精准治疗, 实现临床转化。

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Research progress in natriuretic peptide receptor C and cardiovascular disease

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Natriuretic peptide (NP) system includes a group of peptides that regulate the balance of water and salt and maintain functional homeostasis of organs of the cardiovascular and several other systems. It includes atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP), which can bind to natriuretic peptide receptor C (NPR-C). NPR-C has been traditionally considered a NP clearance receptor responsible for natriuretic peptides degradation. However, there is increasing evidence that the intracellular domain of NPR-C is coupled to inhibitory G protein (G_i) which mediates many biological effects and participates in the pathophysiology of hypertension, atherosclerosis, coronary heart disease, arrhythmia, pulmonary hypertension, cardiac insufficiency and so on. This review focuses on the research progress in NPR-C and its related signaling pathways in hypertension and other cardiovascular diseases.

natriuretic peptide receptor C, natriuretic peptide, hypertension, vascular smooth muscle cells, cardiac fibrosis

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