

肝肾综合征肾血管收缩机制的研究进展

郭莲怡, 刘沛

■背景资料

肝肾综合征是在严重肝功能失代偿的基础上, 由多种因素所致的进行性、功能性肾衰竭, 肾脏本身并无明显的器质性损伤。目前认为肾血管收缩是其主要原因, 具体机制不十分清楚。

郭莲怡, 刘沛, 中国医科大学第一临床学院传染科 辽宁省沈阳市 110011

作者贡献分布: 郭莲怡与刘沛对此文所作贡献两均等。

通讯作者: 刘沛, 110011, 辽宁省沈阳市, 中国医科大学第一临床学院传染科. syliupeit@yahoo.com.cn

电话: 024-81606823 传真: 024-81606823

收稿日期: 2007-11-26 修回日期: 2008-02-25

Research progress in the mechanism of renal vasoconstriction in hepatorenal syndrome

Lian-Yi Guo, Pei Liu

Lian-Yi Guo, Pei Liu, Department of Infectious Diseases, the First Affiliated Hospital of China Medical University, Shenyang 110001, Liaoning Province, China

Correspondence to: Dr. Pei Liu, Department of Infectious Diseases, the First Affiliated Hospital of China Medical University, Shenyang 110001, Liaoning Province, China. syliupeit@yahoo.com.cn

Received: 2007-11-26 Revised: 2008-02-25

Abstract

Hepatorenal syndrome (HRS) is defined as the development of renal failure in patients with severe liver disease in the absence of any other identifiable cause of renal pathology. The hallmark of HRS is renal vasoconstriction. The cause of renal vasoconstriction may involve several factors: activation of renal nervous system, imbalance of renal vasoactive mediators and molecular mechanism. In this review, we summarize the above progress.

Key Words: Hepatorenal syndrome; Renal vessel; Contraction

Guo LY, Liu P. Research progress in the mechanism of renal vasoconstriction in hepatorenal syndrome. *Shijie Huaren Xiaohua Zazhi* 2008; 16(9): 982-986

摘要

肝肾综合征(hepatorenal syndrome, HRS)是肝病晚期并发的肾功衰竭综合征, 肾脏本身无器质性病变, 肾血管收缩是其病理生理标志。目前肾血管收缩的可能机制为肾脏神经体液系

统激活, 肾血管活性物质失衡, 引起肾血管收缩的细胞内分子信息传递机制。本文就其相关研究进展进行综述。

关键词: 肝肾综合征; 肾血管; 收缩

郭莲怡, 刘沛. 肝肾综合征肾血管收缩机制的研究进展. *世界华人消化杂志* 2008; 16(9): 982-986

<http://www.wjgnet.com/1009-3079/16/982.asp>

0 引言

肝肾综合征(hepatorenal syndrome, HRS)是肝病晚期并发的肾功衰竭综合征, 肾脏本身无器质性病变, 肾血管收缩是其病理生理标志^[1]。目前肾血管收缩的机制尚不完全清楚, 可能与肾脏神经体液系统激活以及肾血管活性物质失衡有关, 另外, 引起肾血管收缩的细胞内分子信息传递机制也愈发受到关注。现就其相关研究进展作一综述。

1 神经体液系统激活

HRS时, 由于内脏及体循环血管舒张, 几种神经体液反应系统明显激活^[2], 以维持动脉血压, 但也诱导了肾血管收缩, 肾血流减少。

1.1 交感神经系统 由于HRS患者有效动脉血容量不足, 动脉压下降, 刺激颈动脉压力感受器, 交感神经系统高度激活, 引起肾血管收缩, 钠潴留增加。研究表明肾脏和内脏血管床儿茶酚胺分泌是增加的, 此外肝肾神经反射也起了重要作用。Kostreva *et al*观察到肝内压增加可导致肾脏传出交感肾上腺系统活性增强, 引起肾入球动脉收缩及肾小管钠、水重吸收增加^[3]; 而麻醉阻滞腰交感神经后肾交感神经活性降低, 可部分逆转HRS患者的肾衰竭。HRS时肾交感神经兴奋是恢复血容量的一种代偿机制^[4], 然而其引起的肾血流减少和肾血流重新分布, 可能是HRS发生的病理基础。

1.2 肾素-血管紧张素-醛固酮系统(renin-angiotensin-aldosterone system, RAAS) 50%-80%失代偿期肝硬化患者的RAAS激活, HRS患者更

■同行评议者

黄颖秋, 教授, 本溪钢铁(集团)有限责任公司总医院消化内科

甚。血管紧张素Ⅱ(AngⅡ)对肾循环具有强有力的缩血管活性,在HRS中对肾血管起主要收缩作用^[5]。在急性实验性肾功能衰竭发生机制的研究中发现:AngⅡ具有增加入球小动脉交感神经活性的功能,引起实验动物肾血管收缩,肾血流减少,肾小球滤过率下降^[6]。AngⅡ在肾脏产生,作为局部血管收缩机制,可能通过RAAS参与肝硬化时肾血管收缩的发生。

1.3 抗利尿激素(antidiuretic hormone, ADH) HRS时,由于有效动脉血容量不足,刺激容量感受器,反射性地刺激垂体后叶释放ADH^[7]。ADH的作用^[8]:(1)正常血中ADH浓度为5 ng/L,很少参与血压的调节,主要通过V₂受体发挥抗利尿作用;(2)当血中ADH浓度达10-200 ng/L时,通过V₁受体阻断ATP敏感性钾通道(KATP)或干扰一氧化氮-环磷酸鸟苷(NO-cGMP)信号转导,引起肾血管收缩及肾小管水潴留,维持血压稳定。抑制肝硬化大鼠V₁受体可引起明显的低血压^[9]。

2 HRS时多种缩血管活性物质合成增加

2.1 内皮素(ET) ET是缩血管活性最强的多肽物质,家族成员有ET-1、ET-2和ET-3,其中ET-1具强烈的缩血管作用,ET-3可通过刺激血栓素A₂释放而间接收缩血管^[10]。急、慢性肝衰竭常伴内毒素血症,刺激ET-1和ET-3水平升高^[11]。研究表明ET含量与肌酐清除率、有效动脉血容量和血清钠水平呈显著负相关,且局部ET-1形成较循环ET-1升高更重要^[12]。

2.2 内毒素 重型肝炎肠源性内毒素血症发生率高达56%-100%^[13]。内毒素诱发HRS机制:(1)内毒素的直接毒性作用。实验表明静脉注射内毒素后3 min,肾血流量由230 mL/min降至38 mL/min,肾血管阻力增加6倍;实验动物在出现全身血流动力学改变前,已出现肾血管阻力增加和少尿^[14];(2)内毒素的毒性物质脂多糖内层的脂质A可直接引起动脉血管收缩或通过兴奋交感神经致儿茶酚胺释放^[15];(3)内毒素激活单核巨噬细胞,生成许多脂类炎症介质(如白三烯(LT)C₄、D₄,血栓素A₂(TXA₂)等)和血管活性物质,介导肾血管收缩^[16]。

2.3 肿瘤坏死因子-α(TNF-α) 重症肝病时血中TNF-α水平明显增高^[17]。TNF-α可引起血管收缩,机制如下:(1)TNF-α可通过Ⅱ型TNF受体引起ET产生增多发挥缩血管作用。当阻断ET受体后,TNF-α就不再有缩血管作用了^[18];(2)TNF-α抑制内皮依赖的NO-cGMP导致血管收缩^[19]。首

先TNF-α通过活化蛋白激酶C(PKC)抑制内皮型一氧化氮合酶(eNOS)磷酸化从而抑制eNOS的活性^[20];同时TNF-α可通过缩短eNOSmRNA的半衰期来下调eNOSmRNA^[21-22];(3)TNF-α可增强Ca²⁺依赖及非Ca²⁺依赖蛋白激酶活性,增强血管平滑肌细胞收缩^[23-25];(4)血中TNF-α水平与血中肌酐、尿素氮水平相关,抑制TNF-α合成(用PTX-己酮可可碱)可改善肾功能^[26];(5)TNF-α通过增加肾小球前小动脉平滑肌细胞的1, 4, 5-三磷酸肌醇受体(IP3R)蛋白和IP3RmRNA表达促进胞内钙释放来增加肾脏对缩血管物质的敏感性^[27]。

2.4 其他 LT C₄, D₄, TXA₂, 在肾缺血及脂质过氧化增强时产生,是强烈的肾血管收缩因子^[28]。HRS时合成均增加,是引起肾血流灌注和肾功能紊乱的重要介质^[29]。

3 舒血管物质参与血流动力学改变

3.1 一氧化氮(NO) NO由内皮细胞、血管平滑肌细胞合成,是最早发现的血管扩张因子^[30]。其作用机制^[31]:(1)通过cGMP来活化cGMP依赖的蛋白激酶,使肌球蛋白轻链磷酸酶活化,介导血管舒张;(2)NO通过钙离子依赖性钾通道(K_{ca})活化血管平滑肌细胞,介导血管舒张。肝硬化时NO内生量增高^[32]。TNF-α等内毒素相关细胞因子的增加可诱导NO合成。利用离体肠系膜血管研究其对缩血管物质的反应,发现血管反应性降低且为内皮依赖的^[33],而抑制NOS可完全或部分恢复血管反应性。在动物模型或肝病患者的在体实验研究中也得到同样的结果^[34]。此外,NO在不同部位血管床的活性不同。内脏、体循环中NO活性高,可致内脏动脉扩张及平均动脉压下降;肝内NO合成减少,肝内循环NO活性低,可使肝内血流阻力上升,加重门脉高压;肾脏中NO活性高,对维持肝硬化时的肾灌注至关重要^[35-36]。

3.2 胰高血糖素 肝硬化时胰高血糖素增加。胰高血糖素可降低全身血管阻力,但对门静脉有收缩作用,是肝硬化时全身高动力状态和门脉高压形成的原因之一^[37]。生理剂量的胰高血糖素即可引起血管舒张。其作用机制^[38]:(1)与内毒素协同诱导NO合成,使VSMC释放NO,使肝硬化时NO产生增加;(2)促进环磷酸腺苷(cAMP)产生:肝细胞膜上的胰高血糖素不仅能刺激胞内cAMP聚积,还可诱导肝细胞产生cAMP,使血中cAMP水平升高。cAMP可与胰高血糖素协同,改善肾脏血流动力学,使肾小球滤过率(GFR)增

■研究前沿

肾血管收缩是肝肾综合征时肾血流减少的主要原因,其发生机制除与肾脏神经体液系统以及肾血管活性物质有关外,引起肾血管收缩的细胞内分子信息传递机制也成为目前研究的热点。

■创新盘点

目前的研究主要集中在神经体液因素及肾血管活性物质对血流动力学的影响方面上, 本文从分子水平对肝肾综合征时肾血管收缩机制, 发病机制及胞内信号转导作了深入阐述。

加。但重症肝病时, 肝脏cAMP产生不足, 且肾脏近曲小管对cAMP产生抵抗, 故血中胰高血糖素水平虽增高, 却不能使GFR增加^[39]。

3.3 前列腺素(PGs) 前列腺素是花生四烯酸在肾内通过环氧化酶等途径的主要代谢产物, 包括PGE、F、I等型, 具有舒张血管和抑制钠、水重吸收作用^[40]。肾脏PGs在脱水, 充血性心衰, 休克或代偿期肝病等情况下, 对于肾功能的维持具有重要作用, PGs可拮抗去甲肾上腺素、Ang II对肾血管的收缩作用, 降低入球小动脉阻力和抑制抗利尿激素作用^[41]。代偿期肝硬化患者若使用消炎痛(PGs合成酶抑制剂), 可发现肾血流量下降甚而发生HRS。HRS时肾髓质PGs合成酶减少, 尿中PGE₂与PGI₂排泄量显著减低, 提示肾脏合成PGs减少^[42]。

4 胞内分子机制

4.1 酪氨酸激酶(PTK)激活 根据PTK的结构, 可分为受体型和非受体型PTK两大类。PTK可通过胞内信号转导的不同水平调节VSMC的收缩, 包括调节K⁺通道、Ca²⁺通道、胞内钙库、钙敏感性收缩装置、兴奋收缩偶联装置及细胞骨架^[43]。此外受体型PTK活化后还可通过激活腺苷酸环化酶、多种磷脂酶(如磷脂酰脂酶特异性磷脂酶C、磷脂酶A和鞘磷脂酶)等调控基因表达。抑制PTK可减少钙内流, 抑制钙库释放; ET和Ang II可激活PTK^[44]。肝硬化时血中ET和Ang II水平均明显升高, 可激活PTK介导肾血管收缩^[45]。

4.2 钙信号 高浓度Ca²⁺引起平滑肌收缩, 低浓度Ca²⁺引起平滑肌舒张^[46]。钙离子来源于胞外Ca²⁺内流(Ca²⁺通道)和胞内钙库Ca²⁺释放(IP₃R及ryanodine受体钙通道)^[47]。

L型钙通道主要调节肾小球入球动脉; T型钙通道对入球和出球动脉均有影响, 且易于活化, 轻微去极化就可引起Ca²⁺内流^[48]。钙通道阻断剂可减弱入球动脉对灌注压变化的自身调节作用。肝硬化时入球动脉自身调节活性明显降低及球管反馈机制障碍与这两型钙通道功能异常有关^[49]。IP₃R分4型, 肾血管平滑肌细胞及肾小球系膜细胞主要存在I型和III型IP₃R^[50]。肝硬化时血中高水平的Ang II、ET可通过G蛋白偶联受体激活IP₃R引起胞内钙释放介导肾血管收缩及系膜细胞收缩^[51-53]; 同时血中高水平TNF-α可通过增加血管平滑肌细胞IP₃R蛋白表达促进胞内钙释放^[27]。

4.3 钾通道活化 主要有三种类型的钾通道控制

钾离子外流^[54]。(1)三磷酸腺苷(ATP)敏感性钾通道(K_{ATP})^[55]: 正常时K_{ATP}关闭; 当ATP/ADP(二磷酸腺苷)比值下降或激动剂诱导的G蛋白依赖途径激活时, K_{ATP}活化开放引起血管舒张, 此时应用K_{ATP}抑制剂可引起血管收缩。(2)延迟调整钾通道: 当胞膜去极化时开放。(3)K_{ca}分3种即SK_{ca}、IK_{ca}、BK_{ca}, 胞内钙浓度增加或ATP/ADP比值下降时开放。K_{ca}活化可拮抗缩血管物质。钾通道活化开放后, 由于K⁺外流, 血管平滑肌细胞膜超极化, 阻止胞外Ca²⁺进入细胞, 而引起血管舒张。组织低氧、前列环素、神经肽、NO均为钾通道活化因子。SK_{ca}过表达在肝硬化时的血管舒张上有重要作用^[56], 肝硬化时高动力循环增加了管壁切变压, 内皮SK_{ca}活化, 内皮细胞超极化, 胞外Ca²⁺通过电压依赖性钙通道内流, 进而eNOS活化, NO产生增加使血管舒张, 这是内皮依赖性的^[57]。

4.4 环磷酸腺苷(cAMP)作用 cAMP为胞内第二信使^[58]。当第一信使(如肽类激素、儿茶酚胺和前列腺素)作用于细胞膜上的特异受体时, 激活胞膜内的腺苷环化酶(AC), 使细胞中的ATP转化为cAMP, cAMP激活cAMP依赖的蛋白激酶A(PKA), PKA使靶蛋白磷酸化发挥生物学效应, 如肌肉细胞的收缩与舒张、神经细胞的电位变化、腺细胞的分泌、细胞通透性变化以及各种酶反^[59]。在AC信号转导途径中存在着两种作用相反的G蛋白(Gs与Gi), 他们通过增加或抑制AC活性来调节细胞内cAMP浓度^[60]。cAMP可与胰高血糖素协同, 扩张肾血管^[37]; 而cAMP降解产生的腺苷可引起肾血流动力学障碍。肝病早期肝脏产生cAMP增多; 肝病加重时肝脏不能产生足够的cAMP, 且肾脏对cAMP产生抵抗, 主要由cAMP降解产生的腺苷发挥作用^[61]。

总之, HRS时肾血管的收缩是肾脏神经体液系统、肾血管活性物质以及引起肾血管收缩的细胞内分子信息传递机制等多因素、多途径共同作用的结果, 并非单一因素独立起作用, 上述因素在不同个体之间既各有侧重又密切相关。随着我们对HRS时肾血管收缩发生机制认识的逐渐深入, 进一步研究其胞内信号转导机制, 对于将来我们在临床上预防和治疗HRS取得一些突破性进展大有裨益。

5 参考文献

- 1 Wadei HM, Mai ML, Ahsan N, Gonwa TA. Hepatorenal syndrome: pathophysiology and management. *Clin J Am Soc Nephrol* 2006; 1: 1066-1079
- 2 Lee RF, Glenn TK, Lee SS. Cardiac dysfunction in

- cirrhosis. *Best Pract Res Clin Gastroenterol* 2007; 21: 125-140
- 3 Kostreva DR, Pontus SP. Hepatic vein, hepatic parenchymal, and inferior vena caval mechanoreceptors with phrenic afferents. *Am J Physiol* 1993; 265: G15-G20
- 4 Cassinello C, Moreno E, Gozalo A, Ortuño B, Cuenca B, Solís-Herruzo JA. Effects of orthotopic liver transplantation on vasoactive systems and renal function in patients with advanced liver cirrhosis. *Dig Dis Sci* 2003; 48: 179-186
- 5 Arroyo V. Review article: hepatorenal syndrome-how to assess response to treatment and nonpharmacological therapy. *Aliment Pharmacol Ther* 2004; 20 Suppl 3: 49-54; discussion 55-56
- 6 Basile DP, Donohoe DL, Phillips SA, Frisbee JC. Enhanced skeletal muscle arteriolar reactivity to ANG II after recovery from ischemic acute renal failure. *Am J Physiol Regul Integr Comp Physiol* 2005; 289: R1770-R1776
- 7 Schmidt LE, Ring-Larsen H. Vasoconstrictor therapy for hepatorenal syndrome in liver cirrhosis. *Curr Pharm Des* 2006; 12: 4637-4647
- 8 Salerno F, Gerbes A, Ginès P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut* 2007; 56: 1310-1318
- 9 Chan CC, Wang SS, Lee FY, Chang FY, Lin HC, Hou MC, Huang HC, Lee SD. Effects of vasopressin on portal-systemic collaterals of cirrhotic rats. *Scand J Gastroenterol* 2005; 40: 83-89
- 10 Aulakh GK, Sodhi RK, Singh M. An update on non-peptide angiotensin receptor antagonists and related RAAS modulators. *Life Sci* 2007; 81: 615-639
- 11 Palmes D, Skawran S, Stratmann U, Armann B, Minin E, Herbst H, Spiegel HU. Amelioration of microcirculatory damage by an endothelin A receptor antagonist in a rat model of reversible acute liver failure. *J Hepatol* 2005; 42: 350-357
- 12 Neuhofer W, Pittrow D. Role of endothelin and endothelin receptor antagonists in renal disease. *Eur J Clin Invest* 2006; 36 Suppl 3: 78-88
- 13 Han DW. Intestinal endotoxemia as a pathogenetic mechanism in liver failure. *World J Gastroenterol* 2002; 8: 961-965
- 14 Boffa JJ, Arendshorst WJ. Maintenance of renal vascular reactivity contributes to acute renal failure during endotoxemic shock. *J Am Soc Nephrol* 2005; 16: 117-124
- 15 Birnbaum J, Lehmann C, Stauss HM, Weber M, Georgiew A, Lorenz B, Pulletz S, Gründling M, Pavlovic D, Wendt M, Kox WJ. Sympathetic modulation of intestinal microvascular blood flow oscillations in experimental endotoxemia. *Clin Hemorheol Microcirc* 2003; 28: 209-220
- 16 Yamaguchi N, Jesmin S, Zaedi S, Shimojo N, Maeda S, Gando S, Koyama A, Miyauchi T. Time-dependent expression of renal vaso-regulatory molecules in LPS-induced endotoxemia in rat. *Peptides* 2006; 27: 2258-2270
- 17 Zhang HY, Han DW, Wang XG, Zhao YC, Zhou X, Zhao HZ. Experimental study on the role of endotoxin in the development of hepatopulmonary syndrome. *World J Gastroenterol* 2005; 11: 567-572
- 18 Tang C, Wu AH, Xue HL, Wang YJ. Tanshinone IIA inhibits endothelin-1 production in TNF-alpha-induced brain microvascular endothelial cells through suppression of endothelin-converting enzyme-1 synthesis. *Acta Pharmacol Sin* 2007; 28: 1116-1122
- 19 Elahi M, Asopa S, Matata B. NO-cGMP and TNF-alpha counter regulatory system in blood: understanding the mechanisms leading to myocardial dysfunction and failure. *Biochim Biophys Acta* 2007; 1772: 5-14
- 20 Michell BJ, Chen Zp, Tiganis T, Stapleton D, Katsis F, Power DA, Sim AT, Kemp BE. Coordinated control of endothelial nitric-oxide synthase phosphorylation by protein kinase C and the cAMP-dependent protein kinase. *J Biol Chem* 2001; 276: 17625-17628
- 21 Alonso J, Sanchez de Miguel L, Monton M, Casado S, Lopez-Farre A. Endothelial cytosolic proteins bind to the 3' untranslated region of endothelial nitric oxide synthase mRNA: regulation by tumor necrosis factor alpha. *Mol Cell Biol* 1997; 17: 5719-5726
- 22 Yoshizumi M, Perrella MA, Burnett JC Jr, Lee ME. Tumor necrosis factor downregulates an endothelial nitric oxide synthase mRNA by shortening its half-life. *Circ Res* 1993; 73: 205-209
- 23 Hunter I, Nixon GF. Spatial compartmentalization of tumor necrosis factor (TNF) receptor 1-dependent signaling pathways in human airway smooth muscle cells. Lipid rafts are essential for TNF-alpha-mediated activation of RhoA but dispensable for the activation of the NF-kappaB and MAPK pathways. *J Biol Chem* 2006; 281: 34705-34715
- 24 Hsu YM, Chiu CT, Wang CC, Chien CS, Luo SF, Hsiao LD, Liang KY, Yang CM. Tumour necrosis factor-alpha enhances bradykinin-induced signal transduction via activation of Ras/Raf/MEK/MAPK in canine tracheal smooth muscle cells. *Cell Signal* 2001; 13: 633-643
- 25 Parris JR, Cobban HJ, Littlejohn AF, MacEwan DJ, Nixon GF. Tumour necrosis factor-alpha activates a calcium sensitization pathway in guinea-pig bronchial smooth muscle. *J Physiol* 1999; 518 (Pt 2): 561-569
- 26 Akriadiadis E, Botla R, Briggs W, Han S, Reynolds T, Shakil O. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000; 119: 1637-1648
- 27 Wang J, Sun J, Lu S, Liu P. Tumor necrosis factor-alpha enhances type I inositol 1, 4, 5-triphosphate receptor expression in rat glomerular afferent arterioles smooth muscle cells. *Zhonghua Neike Zazhi* 2002; 41: 86-89
- 28 Boffa JJ, Just A, Coffman TM, Arendshorst WJ. Thromboxane receptor mediates renal vasoconstriction and contributes to acute renal failure in endotoxemic mice. *J Am Soc Nephrol* 2004; 15: 2358-2365
- 29 Laffi G, La Villa G, Pinzani M, Marra F, Gentilini P. Arachidonic acid derivatives and renal function in liver cirrhosis. *Semin Nephrol* 1997; 17: 530-548
- 30 Erusalimsky JD, Moncada S. Nitric oxide and mitochondrial signaling: from physiology to pathophysiology. *Arterioscler Thromb Vasc Biol* 2007; 27: 2524-2531
- 31 Turkay C, Yonem O, Arikan O, Baskin E. Nitric oxide and renal functions in liver cirrhosis. *Turk J Gastroenterol* 2004; 15: 73-76
- 32 Genesca J, Segura R, Gonzalez A, Catalan R, Marti R, Torregrosa M, Cereto F, Martinez M, Esteban R, Guardia J. Nitric oxide may contribute to nocturnal hemodynamic changes in cirrhotic patients. *Am J*

应用要点

本文全面综述肝肾综合征时肾血管收缩的相关机制,对进一步开展肝肾综合征发生机制的相关研究有一定的参考价值。

■同行评价

本文综述全面,层次清楚,可读性较好,引用文献较新,对进一步认识肝肾综合征的病理生理学机制有一定参考价值。

- 33 Atucha NM, Shah V, Garcia-Cardena G, Sessa WE, Groszmann RJ. Role of endothelium in the abnormal response of mesenteric vessels in rats with portal hypertension and liver cirrhosis. *Gastroenterology* 1996; 111: 1627-1632
- 34 Goh BJ, Tan BT, Hon WM, Lee KH, Khoo HE. Nitric oxide synthase and heme oxygenase expressions in human liver cirrhosis. *World J Gastroenterol* 2006; 12: 588-594
- 35 Graebe M, Brond L, Christensen S, Nielsen S, Olsen NV, Jonassen TE. Chronic nitric oxide synthase inhibition exacerbates renal dysfunction in cirrhotic rats. *Am J Physiol Renal Physiol* 2004; 286: F288-F297
- 36 Sherman DS, Fish DN, Teitelbaum I. Assessing renal function in cirrhotic patients: problems and pitfalls. *Am J Kidney Dis* 2003; 41: 269-278
- 37 Yang YY, Lin HC, Huang YT, Hou MC, Lee FY, Chang FY, Lee SD. Inhibition of glucagon improves splanchnic hyporesponse to terlipressin in cirrhotic rats with blood retention in the gastric lumen. *J Hepatol* 2005; 42: 652-658
- 38 Fierbinteanu-Braticevici C, Udeanu M, Usvat R, Andronescu D. The role of octreotide on renal function in patients with advanced cirrhosis. *Rom J Intern Med* 2004; 42: 173-181
- 39 Bankir L, Ahloulay M, Devreotes PN, Parent CA. Extracellular cAMP inhibits proximal reabsorption: are plasma membrane cAMP receptors involved? *Am J Physiol Renal Physiol* 2002; 282: F376-F392
- 40 Ejaz P, Bhojani K, Joshi VR. NSAIDs and kidney. *J Assoc Physicians India* 2004; 52: 632-640
- 41 Ruiz-del-Arbol L, Monescillo A, Arocena C, Valer P, Ginès P, Moreira V, Milicua JM, Jiménez W, Arroyo V. Circulatory function and hepatorenal syndrome in cirrhosis. *Hepatology* 2005; 42: 439-447
- 42 Kamisako T, Miyawaki S, Gabazza EC, Ishihara T, Kamei A, Kawamura N, Adachi Y. Polyethylene glycol-modified bilirubin oxidase improves hepatic energy charge and urinary prostaglandin levels in rats with obstructive jaundice. *J Hepatol* 1998; 29: 424-429
- 43 Salomonsson M, Arendshorst WJ. Effect of tyrosine kinase blockade on norepinephrine-induced cytosolic calcium response in rat afferent arterioles. *Am J Physiol Renal Physiol* 2004; 286: F866-F874
- 44 Shah BH, Baukal AJ, Chen HD, Shah AB, Catt KJ. Mechanisms of endothelin-1-induced MAP kinase activation in adrenal glomerulosa cells. *J Steroid Biochem Mol Biol* 2006; 102: 79-88
- 45 François H, Placier S, Flamant M, Tharaux PL, Chansel D, Dussaule JC, Chatziantoniou C. Prevention of renal vascular and glomerular fibrosis by epidermal growth factor receptor inhibition. *FASEB J* 2004; 18: 926-928
- 46 Hirota S, Helli P, Janssen LJ. Ionic mechanisms and Ca²⁺ handling in airway smooth muscle. *Eur Respir J* 2007; 30: 114-133
- 47 Akata T. Cellular and molecular mechanisms regulating vascular tone. Part 1: basic mechanisms controlling cytosolic Ca²⁺ concentration and the Ca²⁺-dependent regulation of vascular tone. *J Anesth* 2007; 21: 220-231
- 48 Feng MG, Li M, Navar LG. T-type calcium channels in the regulation of afferent and efferent arterioles in rats. *Am J Physiol Renal Physiol* 2004; 286: F331-F337
- 49 Sansoè G, Silvano S, Mengozzi G, Smedile A, Touscoz G, Rosina F, Rizzetto M. Loss of tubuloglomerular feedback in decompensated liver cirrhosis: physiopathological implications. *Dig Dis Sci* 2005; 50: 955-963
- 50 Monkawa T, Hayashi M, Miyawaki A, Sugiyama T, Yamamoto-Hino M, Hasegawa M, Furuichi T, Mikoshiba K, Saruta T. Localization of inositol 1,4,5-trisphosphate receptors in the rat kidney. *Kidney Int* 1998; 53: 296-301
- 51 Wang JY, Liu HY, Liu P. Expression of type I inositol 1,4,5-triphosphate receptor on rat glomerular and afferent arterioles in a model of liver cirrhosis. *Zhonghua Ganzangbing Zazhi* 2004; 12: 609-611
- 52 Wei YH, Jun L, Qiang CJ. Effect of losartan, an angiotensin II antagonist, on hepatic fibrosis induced by CCl₄ in rats. *Dig Dis Sci* 2004; 49: 1589-1594
- 53 Dellis O, Dedos SG, Tovey SC, Taufiq-Ur-Rahman, Dubel SJ, Taylor CW. Ca²⁺ entry through plasma membrane IP₃ receptors. *Science* 2006; 313: 229-233
- 54 Glab M, Lojek A, Wrzosek A, Dołowy K, Szewczyk A. Endothelial mitochondria as a possible target for potassium channel modulators. *Pharmacol Rep* 2006; 58 Suppl: 89-95
- 55 Teramoto N. Pharmacological Profile of U-37883A, a Channel Blocker of Smooth Muscle-Type ATP-Sensitive K Channels. *Cardiovasc Drug Rev* 2006; 24: 25-32
- 56 Barriere E, Tazi KA, Pessione F, Heller J, Poirel O, Lebrec D, Moreau R. Role of small-conductance Ca²⁺-dependent K⁺ channels in in vitro nitric oxide-mediated aortic hyporeactivity to alpha-adrenergic vasoconstriction in rats with cirrhosis. *J Hepatol* 2001; 35: 350-357
- 57 Yang YY, Lin HC, Huang YT, Lee TY, Hou MC, Wang YW, Lee FY, Lee SD. Role of Ca²⁺-dependent potassium channels in in vitro anandamide-mediated mesenteric vasorelaxation in rats with biliary cirrhosis. *Liver Int* 2007; 27: 1045-1055
- 58 Hofer AM, Lefkimiatis K. Extracellular calcium and cAMP: second messengers as "third messengers"? *Physiology (Bethesda)* 2007; 22: 320-327
- 59 Lissandron V, Zaccolo M. Compartmentalized cAMP/PKA signalling regulates cardiac excitation-contraction coupling. *J Muscle Res Cell Motil* 2006; 27: 399-403
- 60 Cooper DM. Compartmentalization of adenylate cyclase and cAMP signalling. *Biochem Soc Trans* 2005; 33: 1319-1322
- 61 Spirli C, Fabris L, Duner E, Fiorotto R, Ballardini G, Roskams T, Larusso NF, Sonzogni A, Okolicsanyi L, Strazzabosco M. Cytokine-stimulated nitric oxide production inhibits adenylyl cyclase and cAMP-dependent secretion in cholangiocytes. *Gastroenterology* 2003; 124: 737-753

编辑 程剑侠 电编 吴鹏朕