

U II /UT系统在肝硬化门脉高压症中的研究进展

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■背景资料

肝硬化门脉高压症形成的机制主要是肝内阻力增加和门脉血流量增多。血管活性物质在其中发挥重要作用, 尾加压素 II 是有效的血管活性物质, 在肝硬化门脉高压症病理生理改变中起重要作用。

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Advances in understanding the role of the U II/UT system in the pathogenesis of portal hypertension

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Abstract

Urotensin II (UII), a vasoactive peptide with structural similarity to somatostatin, is the most potent vasoconstrictor known in systemic resistance vessels and has multiple biological effects related to a variety of human diseases. Numerous studies have found that UII and its receptor (UT) play an important role in the pathogenesis of portal hypertension. This paper reviews the recent advances in understanding the role of the UII/UT system in the pathogenesis of portal hypertension.

Key Words: Urotensin II; Urotensin II receptor; Cirrhosis; Portal hypertension

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摘要

尾加压素 II (urotensin II, UII) 是一种生长抑

素样环肽, 是目前发现的最强的缩血管物质, 其生物学作用多样, 与多种疾病密切相关。越来越多的研究发现 UII 及其受体 (urotensin II receptor, UT) 系统与肝硬化门脉高压症密切相关, 本研究就 UII/UT 系统在肝硬化门脉高压症中的研究进展作一总结。

关键词: 尾加压素 II; 尾加压素 II 受体; 肝硬化; 门脉高压症

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0 引言

肝硬化门脉高压症形成的机制主要是肝内阻力增加和门脉血流量增多。肝内阻力增加是始动因素, 其原因主要分机械性和动力性因素, 机械性因素是不可逆的, 而动力性因素是可逆的^[1,2]。血管活性物质可以解除或是减弱这种可逆性的因素^[3]。尾加压素 II (urotensin II, UII) 是有效的血管活性物质, 在肝硬化门脉高压症病理生理改变中起重要作用^[4]。UII 需与其受体 (urotensin II receptor, UT) 结合才能发挥各种生物学作用^[5]。近来研究发现 UII/UT 系统参与肝硬化门脉高压症的发病并可能成为新的潜在的治疗靶点^[6]。

1 UII 的化学结构及生物学活性

1.1 UII 的化学结构及分布 UII 最早是 1985 年自硬骨鱼的脊髓尾部神经分泌系统分离出来的一种生长抑素样环肽, 属于神经肽范围, 是迄今发现的体内最强缩血管活性物质^[7]。人类 UII 由 11 个氨基酸组成, 相对分子质量为 1 388, 编码 UII 的基因位于 1p36, 有 5 个外显子^[8]。1999 年 Ames 等首次报道人体内一种孤儿 G 蛋白偶联受体 14 (G protein coupled receptor, GPR14) 是 UII 的特异性受体, 后更名为 UT。UII 与 UT 结合后导致细胞内钙离子浓度升高, 引起多种生物学作用^[9-11]。UII/UT 主要分布于心血管和神经系统^[12,13], 随着研究深入, 还发现其分布广泛、生物学活性多样, 它能够作用于多系统、多器官, 发挥多种生物学效应^[14]。

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1.2 U II 的生物学活性 U II 的生物学作用多样, 与心血管疾病^[15-18]、糖尿病^[19,20]、肾脏疾病^[18,21,22]等多种疾病密切相关. 最近研究发现其在肝硬化门脉高压症中起重要作用. U II 参与肝硬化门脉高压症的生物学作用主要包括血管活性作用、丝裂原活性及纤维化作用, 其中血管活性性质研究最多, 资料最充分. 近年来其丝裂原活性及纤维化作用越来越受到人们重视.

1.2.1 血管活性功能: U II 的血管活性作用分为收缩血管作用及舒张血管作用, 由GPR14介导, 经Rho-A/Rho-kinase途径激活平滑肌细胞导致血管收缩^[23,24], 经内皮型一氧化氮合酶(endothelial constitutive NO synthase, eNOS)信号通路激活内皮细胞导致血管舒张^[11]. U II 的血管活性作用因种属、解剖位置、血管大小不同, 其生理作用可出现相反的结果, 其机制仍待进一步研究. 如U II 可引起全身阻力血管收缩, 其缩血管作用为内皮素的10余倍^[5], 而U II 对大鼠肠系膜血管、人腹部阻力血管是舒张作用^[25,26]. U II 可引起啮齿类动物大静脉收缩, 而对人肺静脉是舒张作用^[26]. 离子渗透方法发现U II 可引起健康人血管舒张, 而引起高血压和慢性心衰患者血管收缩. 这种差异可能与上述患者内皮细胞损伤, 不能产生舒张血管的物质有关^[27]. 肝硬化门脉高压患者肝窦内皮细胞受损, 窦周系统不能产生舒张血管物质一氧化氮(nitric oxide, NO)导致窦周阻力增加, 而肝硬化时肝内阻力的增加主要来源于肝窦^[28-31].

1.2.2 促增殖及促纤维化作用: 随着对U II 丝裂原活性及纤维化活性的深入研究, 发现U II 是一种内源性丝裂原. 有研究报道U II 可引起血管平滑肌细胞和内皮细胞增殖分化, 加速巨噬细胞泡沫细胞的形成, 刺激心肌细胞肥大, 并上调转化生长因子 β (transforming growth factor beta, TGF β)表达而诱导心肌成纤维细胞分泌胶原^[32-34]. 我们前期结果发现肝星状细胞表达UT, U II 可以促进肝星状细胞增殖, 促进肝星状细胞 I、III型胶原的合成以及 I、III型胶原和金属蛋白酶抑制物-1(tissue inhibitor of metalloproteinase 1, TIMP-1)mRNA表达. 提示U II 可直接促进肝星状细胞增殖, 促进胶原合成, 抑制胶原降解而加速肝脏纤维化^[35].

此外, U II 还参与神经系统^[36-38]和代谢^[39,40]功能的调节, 是否参与肝硬化门脉高压症的发病还有待研究.

2 U II 与肝硬化门脉高压症的研究

U II 参与心力衰竭、高血压、糖尿病、肾脏衰竭等多种疾病的发生发展^[41-43]. 近来研究发现U II 与肝硬化门脉高压症有一定关系^[6,44-47].

最初研究U II 与肝硬化门脉高压症的关系是从临床资料开始的. Heller等^[45]研究发现肝硬化患者血浆U II 水平明显高于健康对照组, 与门脉压力呈正相关. 肝静脉U II 水平明显高于门静脉, 提示肝硬化时U II 来源于肝细胞. Kemp等^[48]发现血浆U II 水平在肝硬化患者明显升高, 且血浆U II 升高的程度与门脉压力及疾病严重程度成正比(Child-Pugh分级). U II 基线的水平可以预测肝硬化并发症的发生, 如难治性腹水及患者的存活率.

近期研究发现对正常SD大鼠经微量泵持续注入U II 评估其对肝纤维化及门脉高压的作用, 研究分为正常组, U II 低剂量组, U II 高剂量组. 结果发现U II 可以剂量依赖性的增加门脉压力, U II 还可以促进肝脏羟脯氨酸、I型胶原及纤维化细胞因子, TGF β 1、结缔组织生长因子(connective tissue growth factor, CTGF)等的表达, 提示U II 通过调节内脏血管和体循环的血管舒缩, 而介导了肝硬化门脉高压时血流动力学的失调, 此外U II 还可以诱导纤维化细胞因子分泌而促进肝纤维化^[49]. 肝星状细胞在肝纤维化过程中起重要作用, 它的活化决定肝纤维化的形成、发展与转归, 是肝纤维化的关键环节^[50,51]. U II 是一种内源性丝裂原, 具有促增殖作用. 我们研究发现U II 可以促进肝星状细胞增殖, 增加胶原合成, 抑制胶原降解, 促进细胞外基质沉积, 而发挥促纤维化作用^[35].

上述资料提示U II 在肝硬化门脉高压症患者升高, U II 还可以通过其血管活性作用、丝裂原活性、纤维化作用加速肝硬化门脉高压血流动力学的失调并促进肝纤维化进程而参与肝硬化门脉高压的病理生理学改变.

2.1 U II/UT在肝硬化门脉高压症中的肝脏表达 关于U II/UT分布的一系列研究表明, U II 只有和UT受体结合, 才能完成其生物学效应, 因此检测正常肝组织和肝硬化肝组织U II/UT表达的变化, 能进一步阐明U II 在肝硬化门脉高压中的意义. Trebicka等^[52]研究发现胆管结扎的肝硬化大鼠其肝脏表达U II/UT较正常大鼠明显升高, 且UT在肝脏表达定位于动静脉及胆管的内皮细胞、库普弗细胞. 我们前期研究也发现肝硬化门脉高压患者肝脏U II/UT基因水平较正常对照

■研发前沿

目前U II/UT系统对门脉压力及纤维化程度的影响是研究的热点、重点, U II/UT系统有望成为肝硬化门脉高压治疗的新靶点.

■相关报道

Heller等研究发现肝硬化患者血浆U II水平明显高于健康对照组,与门脉压力呈正相关。肝静脉U II水平明显高于门静脉,提示肝硬化时U II来源于肝细胞。

人群明显升高,血U II水平也显著升高且与肝脏U II mRNA水平呈正相关。此外,肝脏UT蛋白表达也明显升高,肝脏库普弗细胞、肝窦内皮细胞表达UT^[6],而这些细胞在肝硬化门脉高压中发挥重要作用,U II/UT可能通过调节这些细胞而在肝硬化门脉高压中发挥重要作用。但Leifeld等^[53]研究肝硬化及暴发性肝炎患者中U II/UT表达时,发现U II/UT的表达在肝硬化肝组织和正常肝组织表达没有明显差异,这与Trebecka及我们的研究不一致,这种差异的可能与以下因素有关:(1)所选择患者不同;(2)U II是一自分泌和旁分泌物质^[54,55],推测U II分泌后马上降解;(3)方法和敏感度不同,我们分别用基因检测U II/UT的表达,免疫组织化学和免疫荧光双标方法检测UT的细胞定位,Western blot定量分析UT蛋白表达。(4)除了病因方面的不同,我们选择的患者均证实具有门脉高压的存在。

总之,目前研究提示肝硬化门脉高压时肝脏表达U II/UT明显升高,阻断U II/UT的作用有望成为治疗肝硬化门脉高压症的新靶点。

2.2 UT拮抗剂在肝硬化门脉高压中的研究 研究特异性受体拮抗剂在理解U II/UT的生理作用以及揭示其治疗潜力方面非常重要。如同血管紧张素II(angiotensin II, Ang II)受体拮抗剂^[2,56-58]和内皮素受体拮抗剂^[31,59-63]能够用于门脉高压的治疗,尾加压素受体拮抗剂不久将可能为这种疾病治疗的提供另一种选择^[54]。

2002年, Behm等^[65,66]首先发现生长激素释放抑制因子(somatostatin, SST)拮抗剂SB-710411,在离体的大鼠主动脉,10 $\mu\text{mol/L}$ 的SB-710411能显著地抑制hU II引起的收缩反应,但却没有抑制Ang II、氯化钾、苯肾上腺素引起的收缩作用。随后Patacchini等^[67]又发现新的人类U II受体拮抗剂,命名为Urantide,在离体的大鼠主动脉研究中发现,其拮抗人类U II的作用比其他任何化学物的50-100倍。该拮抗剂能与人类U II受体高选择性结合,极低水平时可能产生激动效能。Palosuran(ACT-058362)^[68]是一种新合成的非肽类U II受体拮抗剂,具有高度特异性,Clozel等证实其能以剂量依赖的方式抑制U II引起的兔主动脉环收缩,与人类U II受体的结合能力明显高于兔U II受体^[69,70]。

关于UT拮抗剂在肝硬化门脉高压症中的作用已成为国内外研究的热点。研究发现UT拮抗剂SB-710411预防给药可以改善CCl₄肝硬化大鼠模型的高动力循环状态,降低肝硬化大鼠

的肝纤维化评分、肝组织中羟脯氨酸含量、肝纤维化指标透明质酸和层粘连蛋白水平,下调大鼠肝脏的I型胶原、III型胶原以及TIMP-1 mRNA表达,从而改善肝脏纤维化^[35]。提示UT拮抗剂SB-710411可以预防肝纤维化,改善门脉高压的血流动力学紊乱,可用于预防肝硬化门脉高压的发生发展。Trebecka等^[52]研究Palosuran对胆管结扎肝硬化大鼠血流动力学的影响,结果发现Palosuran可以增加内脏血管阻力,降低门脉血流,而降低门脉压力,其机制与上调肠系膜血管RhoA/Rho-kinase,增加Rho-kinase活性,降低一氧化氮/环磷酸鸟苷(nitric oxide/cyclic guanosine monophosphate, NO/cGMP)信号通路,导致血管收缩有关。此外Palosuran可以增加胆管结扎肝硬化大鼠的肾小球率过滤,促进水钠排泄。有研究发现Urantide对心肌缺血具有保护作用^[71],但目前尚无Urantide与肝硬化门脉高压的研究报道。

近来肝硬化门脉高压的治疗取得了重大进展,但目前尚无有效的治疗肝硬化门脉高压的药物,上述研究提示UT拮抗剂可以降低肝硬化门脉高压症的门脉压力,降低纤维化指标,并促进水钠排泄,因而在肝硬化门脉高压症方面具有潜在治疗作用。

3 结论

肝硬化门脉高压症时U II/UT水平表达增加,U II可加速肝硬化门脉高压血流动力学的失调并促进肝纤维化进程。随着研究的深入,UT拮抗剂可能成为防治肝硬化门脉高压症的重要治疗工具,尤其是Palosuran作为一种新合成的特异性高、与人类UT结合能力强的非肽类化合物,理化特性稳定,用药途径简单,且已在二期临床用于治疗糖尿病、肾病,安全性高,可用来进一步研究U II的生理病理特性,并为肝硬化门脉高压症的药物治疗提供新的思路。

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■创新盘点

U II/UT系统与肝硬化门脉高压的关系是国外研究的热点,但国内文献报道较少,且未有人进行详细总结。本文对其研究进展进行详细总结,并结合本实验室的研究成果,对读者可以起到很好的参考作用。

■应用要点

U II/UT与肝硬化门脉高压症密切相关。在肝硬化门脉高压中发挥重要作用, UT拮抗剂可能成为防治肝硬化门脉高压症的重要治疗工具, 为肝硬化门脉高压症的药物治疗提供新的思路。

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■同行评价
本文选题恰当, 新颖性较好, 具有一定的参考作用.

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