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文献综述 REVIEW

内皮素系统与门静脉高压症的病理生理和临床治疗

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■背景资料
门静脉高压症是一种常见的临床综合征, 关于内皮素系统与门静脉高压症已有诸多报道. 应用内皮素受体拮抗剂治疗门静脉高压症在部分动物模型和患者中显示出满意的效果. 因此全面认识内皮素系统在门静脉高压症病理生理学中的作用, 从调控ET-1受体功能角度开发治疗PHT的药物具有现实意义.

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Pathophysiology and clinical practice analysis on endothelin system and portal hypertension

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Abstract
Portal hypertension (PHT) is a common clinical syndrome which leads to various severe, even lethal complications. The concentration of endothelin-1 (ET-1) in plasma is increased both in human body and PHT animal model. The effect of ET-1 depends on the kind of tissue and the expression of ET-1 receptor in this tissue. However, the expression of ET-1 receptor is not identical even in the same tissue at different PHT phases. This review aims to give an update on the endothelin syetem in PHT and elucidate a potential novel strategy.

Key Words: Portal hypertension; Endothelin-1; Endothelin receptor

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摘要
门静脉高压症(portal hypertension, PHT)是一种常见的临床综合征, 且引起很多严重并发症. 人体和动物实验都证实PHT时血浆和肝组织中内皮素-1(ET-1)浓度显著升高. ET-1在某种组织表现出的作用取决于在该组织ET-1受体的分布情况, 而在PHT的不同阶段, 即使同一组织内皮素受体的分布也不相同. ET-1参与PHT时多种病变, 因此以内皮素系统作为靶点可能是治疗PHT的一项新的策略.

关键词: 门静脉高压症; 内皮素-1; 内皮素受体

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0 引言
门静脉高压症(portal hypertension, PHT)是一种常见的临床综合征, 其特点是由于门静脉系统血流障碍引起门静脉压力病理性升高. 根据欧姆定律, 门静脉压力与血流量和血流阻力有关. 人体和动物实验都证实, 肝纤维化患者或动物模型的血浆和肝组织中内皮素-1(ET-1)表达显著增加, 纤维化肝组织内皮素受体和内皮素转化酶的表达增强[1-5]. 肝纤维化时ET-1与其受体结合参与了肝组织结构改变以及血液动力学失常, 对影响门静脉压力升高的两个主要因素有重要的调节作用[6-11]. ET-1还参与了肝纤维化时由于肝血窦毛细血管化引起的物质交换功能障碍[12]. 因此内皮素(ET)系统在PHT的病理过程中有重要意义.

1 ET与肝脏血流调节
ET、ET受体(ETR)、ET转化酶(ECE)是内皮素系统的主要成员. ET家族包含3种由21个氨基酸组成的结构和功能相似的异构体肽, 即ET-1、ET-2和ET-3. ETR有ETAR和ETBR两种类型, 他们都属于G-蛋白偶联受体[13]. ETBR又有ETB1和ETB2两种亚型[14-16]. 3种ET与ETAR的亲和力为: ET-1的亲和力最大, 其次是ET-2, ET-3的亲和

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力最小, 其中ET-1与ETAR的亲和力超过ET-3与ETAR亲和力的100倍. ETBR与ET的3种异构体均具有相同的亲和力[13].

生理情况下, ET-1与分布在血管平滑肌上的ETAR结合, 平滑肌收缩维持血管的基础张力. ET-1与ETBR结合究竟是产生舒张作用还是收缩作用部分取决于其作用的细胞类型. ET-1与内皮细胞上的ETB1结合诱导内皮细胞产生NO导致血管舒张, ET-1与血管平滑肌细胞上的ETB2结合导致血管收缩[14], 这也部分解释了ET-1与ETBR结合产生作用的多样性. 肝星状细胞(hepatic stellate cells, HSCs)位于肝窦内皮细胞的周围, 属于肝非实质细胞的一种. 肝损伤以后HSCs活化并且成为合成ET的主要细胞[17-18]. ET-1与HSCs上的ETR结合, 表达平滑肌样蛋白的HSCs收缩使肝血窦管径变小, 肝内血管阻力增加, 门静脉压力升高[19]. ET-1还参与了肝损伤时的纤维生成过程[20-21]. 研究表明纤维化大鼠长期给予ETAR和ETBR的混和型拮抗剂TAK-044, 免疫组化证明肝组织α-肌动蛋白(α-SMA)阳性细胞数减少[3], 体外实验表明ET-1促进培养的HSCs增殖, 细胞外基质蛋白和平滑肌α-SMA表达增加[22].

ET-1与其受体结合引起经典的G-蛋白偶联受体调节的级联反应[23]. ET-1与ETB2受体结合以后激活G-蛋白偶联受体调节的磷脂酶C-β(PLC-β). PLC-β分解磷脂酰肌醇-4, 5-二磷酸(PIP2)产生三磷酸肌醇(IP3)和甘油二酯(DAG). 在经典的信号转导通路中, IP3的作用是动员胞内钙贮池Ca^{2+}的释放. 细胞液中游离Ca^{2+}水平升高激活了Ca^{2+}/钙调素依赖的肌球蛋白轻链激酶(MLCK). MLCK磷酸化促使平滑肌收缩.

2 PHT肝组织ET系统的变化

在肝组织, ET-1主要作用于肝窦内皮细胞和HSCs. 正常肝脏, ET-1主要来源于肝窦内皮细胞, 肝损伤以后ET-1主要来源于活化的HSCs, 推测可能与内皮细胞内ECE-1减少有关[18]. Nagasue *et al*发现肝纤维化门静脉高压患者(都没有腹水)不同部位血浆ET-1的浓度是不同的. 体循环静脉、肠系膜上静脉和脾静脉血浆内皮素浓度均升高而且肠系膜上静脉和脾静脉升高更明显[17]. 肠系膜上静脉和脾静脉血汇入门静脉, 因此推测肠和脾脏也是PHT时ET的来源部位之一.

肝纤维化时, 肝组织ET-1升高的程度与肝纤维化、脾肿大的程度以及脾体重比呈正相关, 同时伴有食管静脉曲张的患者ET-1的浓度比没有食管静脉曲张的患者要更高[2,24-25]. 无论是正常还是纤维化肝组织, ET-1的受体中ETBR的分布占主要地位[26-28], PHT时ETBR在肝窦内皮细胞和HSCs表达明显增多[29]. 门静脉部分结扎(PPVL)造成的大鼠PHT模型, 肝脏ETR的总量没有变化, 但是ETAR和ETBR的比例发生变化, ETBR在蛋白和基因水平表达都上调[30]. 结合动力学实验证实培养的HSCs的激活过程伴随着ETAR的分布占优势转变为ETBR占优势, 同时HSCS转变为肌纤维母细胞[31]. 有人推测肌纤维母细胞样的HSCs上ETAR的位点占20%, ETBR的位点占80%[32]. PHT大鼠门静脉灌注ETBR的激动剂引起肝窦外血管的收缩, 肝组织灌注指数降低[30], 因此推测PHT时ET-1与ETBR结合表现的主要是收缩作用. PHT时, 肝组织ECE-1的表达也发生了变化. 纤维化大鼠肝组织ECE-1在蛋白水平增加但是转录后水平降低[33], Shao *et al* 推测原因可能是ECE-1 mRNA的稳定性增加, 在此过程中TGF-β发挥了重要作用[18]. 转录后的调节过程(包扩mRNA稳定性增加)在基因的表达中有重要意义. 大多数mRNA的稳定性是由3'端未转录区域(3' UTRs)决定的. 3' UTRs的特定部位与mRNA结合蛋白结合防止mRNA本身的脱腺苷和断裂. TGF-β作用于活化的HSCs, 3' UTRs mRNA结合蛋白增加, ECE-1 mRNA的稳定性增加[18].

3 ET系统与PHT并发症

3.1 肝肺综合征(hepatopulmonary syndrome, HPS) 是由于PHT时体循环的血管舒张物质进入肺微循环, 血管扩张导致气体交换障碍[34]. 大鼠胆总管结扎造成的HPS模型发现肺血管扩张与ETBR选择性升高有关[35-36]. 胆总管结扎2 wk后血气分析显示HPS形成, 同时肺组织eNOS和ETBR表达开始升高, 而肺组织ETAR的表达没有显著变化[37]. 免疫组化显示肺组织ETBR的表达主要集中在肺微循环. 体外实验表明, 与HPS大鼠体内相似浓度的外源性的ET-1通过ETBR引起肺血管段舒张, 并且ET-1刺激培养的肺血管内皮细胞eNOS表达增加, 活性升高. 这就为肝纤维化时ET-1通过与肺组织的ETBR结合参与HPS形成提供了直接和间接的实验证据[38].

3.2 门静脉-肺动脉高压症(PPHT) 少数门静脉高压患者肺动脉闭塞, 肺循环阻力增加, 肺动脉压力的升高, 形成PPHT. PPHT发病率很低, 但

■研发前沿
肺血管ETBR表达升高是肝肺综合征(HPS)和PPHT形成的一个原因还是病变的结果还不清楚. ETBR是否也在内脏血管系统发挥了与HPS相同的作用还不得而知.

■相关报道
有研究表明内皮素受体的拮抗剂TAK-044可以改善肝功能, 逆转纤维的形成, 同时TAK-044可以改善高动力循环, 降低门静脉压力.

■创新盘点
本文从门静脉高压症时病变的肝组织以及门静脉高压症引起的并发症两个方面详细阐述内皮素系统发挥的作用, 同时根据目前的研究提出很多未能解决的问题.

是恶性程度很高. 有报道PPHT患者在明确诊断之后的生存期限是15 mo. 严重的肺动脉高压患者肺动脉ETBR的基因表达增加, ETAR的表达没有变化[39]. 非选择性ETR的拮抗剂Bosentan能够显著降低PPHT患者的门静脉压力和肺动脉压力, 改善肺循环血液动力学[40-43]. 生理情况下, ET-1与肺动脉ETBR结合, 血管舒张. PPHT患者ET-1与肺动脉ETBR结合以后, 血管收缩. HPS和PPHT同属于PHT引起的并发症, 病变部位相同, 但是病理生理学表现却不相同, ETBR在这两种病理过程中发挥了相反的作用. 肺血管ETBR表达升高是HPS和PPHT形成的一个原因还是病变的结果还不清楚.

3.3 高动力循环 PHT后期, 体循环舒张和收缩血管的活性物质平衡被破坏, 内脏处于高动力循环状态, 门静脉的血流量增多, 成为PHT持续存在的重要因素. 高动力循环的血液动力学表现为心输出量增加, 外周循环阻力降低, 血液重新分布及体循环平均动脉压(MAP)降低. PHT大鼠肠系膜上动脉ETAR和ETBR表达增加[47]. 早期肝纤维化患者和PHT动物模型, 应用ETBR的拮抗剂能够升高体循环动脉压力, ETAR的拮抗剂不能改善MAP, 推测ET-1与ETBR结合引起的血管舒张参与了体循环低血压的形成[7,47-48]. 但是现在还没有实验证据表明具体是哪一个或者是哪些部位的ETBR表达改变与高动力循环形成有关. HPS和高动力循环的相似点是肺组织和内脏血管都有扩张, 血管收缩性下降. ETBR是否也在内脏血管系统发挥了与HPS相同的作用还不得而知.

3.4 其他 PHT大鼠食管黏膜下静脉ET-1及其受体ETAR、ETBR在蛋白和基因水平都表达增加, 并且参与黏膜下静脉的扩张及破裂[46]. Chan *et al*发现ET-1通过ETAR对侧支循环血管有直接收缩作用[47-48]. 早期肝纤维化患者阻断ETAR降低肺循环平均肺动脉压和肺血管阻力指数, ETBR的受体拮抗剂对肺循环血液动力学没有影响[4], 说明肝纤维化早期肺循环中ETAR受体的作用占优势.

已经有学者提出PHT体循环和内脏血管收缩性下降的原因不仅包括血管收缩物质受体表达改变同时还存在血管收缩物质发挥作用的信号转导通路发生障碍[49-53]. 很多血管收缩物质(如ET-1、ATⅡ等)的受体属于G蛋白偶联受体[54]. 纤维化大鼠胸主动脉对ATⅡ反应性下降, G蛋白偶联受体激酶(GRK)和细胞内的β-arrestin在此过程中起了重要作用[55]. β-arrestin是细胞内一种可溶性蛋白, 对细胞信号转导起抑制作用. GRK结合并且磷酸化与G蛋白偶联的血管紧张素Ⅱ1型受体(AT1R), 磷酸化的AT1R与β-arrestin结合增加, 受体失敏, 不能与配体结合因而不能充分发挥收缩血管的作用. 同时血管收缩物质信号转导通路障碍还影响平滑肌细胞内钙离子敏化蛋白的活性, 这是血管收缩性下降的另外一个重要原因[56]. 高动力循环时ET-1的信号转导通路是否发生改变还不清楚, 内脏血管ET受体是否也存在磷酸化增加, 从而失敏还需要进一步的实验证据.

各种原因导致的PHT, 血浆ET-1浓度升高, 活化的HSCs收缩, 肝内血管阻力升高. ET-1引起HSCs收缩的原因有两个方面: (1)ET-1与ETAR结合导致HSCs收缩; (2)ET-1与HSCs上的ETBR结合以后收缩作用大于舒张作用导致HSCs收缩[57-60]. 肝损伤以后ETBR浓度升高有两种作用: 一是ET-1与ETBR结合调节血管张力, 另外就是扮演ET-1的“清除受体”角色. PHT时肝外组织ET受体的分布也不尽相同, 在肝纤维化早期肺组织ETAR的收缩作用占优势而在肝肺综合症和体循环低血压中ETBR的舒张作用占优势. ET-1表现出的作用取决于其作用的组织以及在该组织ET-1受体分布情况. PHT时ET-1作用的多样性不仅体现在ET-1与受体结合之后有舒张和收缩两种作用, 同时还表现为在PHT的不同阶段, 即使同一组织ET受体的分布也是不同的[61]. ET-1参与了PHT多种病变, 主要体现在调节血管张力和纤维生成两个方面.

4 应用ET受体拮抗剂治疗PHT

ET系统参与PHT的多个病理环节, 因此以ET系统作为靶点可能是治疗PHT一项新的策略. 运用单纯的ETAR的拮抗剂, 肝内血管阻力降低但是内脏血管扩张门静脉血流量增加, 使已经升高的的门静脉压力更加恶化[7]. 应用ETBR的拮抗剂调节肝内血管张力并且改善了体循环低血压, 但是与ETBR清除ET-1的作用矛盾. 应用ETAR-ETBR的混合型拮抗剂产生的结果也不一致. 门静脉短期灌注ETAR-ETBR的混合型拮抗剂SB 209670, 门静脉压力降低[62]并且缓解了内毒素引起的肝损伤[63]. ETAR和ETBR混合型拮抗剂Bosentan改善肝内血管阻力, 降低肝纤维化大鼠门静脉压力并且能够显著改善CCl_4大鼠肝血窦的物质交换功能. 但是Bosentan降低肝动脉血流

量加重了体循环低血压[18], 并且高剂量的Bosentan引起转氨酶升高, 加重了纤维化患者的肝功能损害, 这也是Bosentan不能应用于临床的一个重要原因. 肝纤维化大鼠长期给予ETAR-ETBR的混合型拮抗剂TAK-044, 8 wk和12 wk门静脉压力分别降低58%和60%, 减慢纤维生成到纤维化的进程, 改善了体循环低血压状况[3]. 纤维化大鼠急性灌注TAK-044, 门脉压力降低20%[64]. 长时间应用ET受体拮抗剂降低门脉压力通过两方面机制: 促进纤维溶解和抑制参与血管收缩的细胞成分(HSCs), 急性用药只是对收缩细胞有影响[65-67]. 这就说明应用ET混合型受体拮抗剂产生的效应与给药方式和用药时间有关.

ET-1是目前发现的强烈收缩血管的物质之一, ET系统在PHT肝组织以及PHT并发症中发挥的作用已经有很多研究. 应用混和型ET受体拮抗剂在部分PHT动物模型取得了比较满意的效果, 但是能否适用于肝纤维化患者还需要进一步的实验证据. 由于PHT时ET-1对血管作用的复杂性和多样性, 应用ET受体拮抗剂应该达到一种最合适的平衡. 既要关注药物有益的方面, 更要充分考虑药物在不同系统可能产生的副作用. 当然, 从调控ET-1受体功能角度开发治疗PHT的药物将更具有现实意义.

■应用要点
本文对于从内皮素角度出发开发治疗门静脉高压症的药物有一定的指导作用.

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■名词解释
1 肝肺综合征(HPS): 由门静脉高压症引起的高动力循环, 体循环收缩和舒张血管的活性物质平衡破坏, 血管舒张物质进入肺微循环, 肺血管扩张导致气体交换障碍, 称为肝肺综合征.
2 门静脉-肺动脉高压症(PPHT): 少数门静脉高压症患者肺动脉闭塞, 肺循环阻力增加, 肺动脉压力升高, 形成门静脉-肺动脉高压症.

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