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文献综述 REVIEW

肠屏障和肝屏障损伤及保护在减体积肝移植术后小肝综合征中的研究进展

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Injury of the hepatic barrier and intestinal barrier in patients with small-for-size graft syndrome after partial liver transplantation: mechanisms and protective measures

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Abstract

The intestinal barrier can resist the invasion of pathogens and prevent harmful substances from going into blood circulation to maintain the stability of internal environment, while the hepatic barrier is a vital structure that can protect liver function and prevent endotoxin and virus from entering the liver to damage hepatocytes. Both the two barrier structures are most vulnerable to damage after partial liver transplantation due to the occurrence of postoperative 'small-for-size graft syndrome'. The pathogenesis of 'small-for-size graft syndrome' is associated with postoperative portal hypertension and hyperperfusion. How to effectively control the occurrence of 'small-for-size graft syndrome' and to protect the intestinal barrier and hepatic barrier postoperatively are key to the maintenance of intestinal and hepatic functions. The primary aim of this paper is to review the mechanisms underlying the development of injury of the hepatic barrier and intestinal barrier in patients with small-for-size graft syndrome after partial liver transplantation and to propose the corresponding protective measures.

Key Words: Partial liver transplantation; Hepatic barrier; Intestinal barrier; Tight junction; Inflammatory factor

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摘要

肠屏障可以抵抗病原体的侵袭, 阻止有害物质进入血液循环, 从而保持机体内环境的稳定. 肝屏障对于维护肝脏正常功能有重要意义, 其可阻止内毒素、病毒等进入肝脏损伤肝细胞. 肠屏障和肝屏障是减体积肝移植术后最易受到损伤的2个结构, 其损伤的原因与术后"小肝综合征"的发生有关. "小肝综合征"的发病机制与肝移植术后门静脉高压、门静脉过度灌注等有关. 如何有效地控制"小肝综合征"的发生, 保护术后的肠屏障和肝屏障, 是维持肠道和肝脏功能的关键点. 本文主要阐述肠屏障和肝屏障的概念, 分析其功能和结构破坏的原因以及相应的保护措施.

关键词: 减体积肝移植; 肝屏障; 肠屏障; 紧密连接; 炎性因子

严笑鹏, 仇毓东. 肠屏障和肝屏障损伤及保护在减体积肝移植术

■背景资料
肝脏移植是治疗终末期肝病最有效的手段, 挽救了大量患者的生命. 然而, 术后"小肝综合征"的发生是引起肠屏障和肝屏障损伤的重要原因. 因此, 保护这2个屏障是促进病人术后顺利康复的重要措施.

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■研发前沿
目前对于肝屏障的报道较少, 如何保护术后的肝屏障及具体作用机制仍是下一步研究的热点.

后小肝综合征中的研究进展. 世界华人消化杂志 2012; 20(1): 47-52
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0 引言

肝脏移植目前已经成为全世界公认的治疗终末期肝病最有效的手段, 但手术例数的不断增加也使供体短缺的问题日益严重. 以劈离式和活体肝脏移植为代表的部分肝移植技术的成功, 为解决供肝短缺矛盾开辟了新的道路, 目前已得到日益广泛的应用. 部分肝移植的广泛应用也带来一系列的问题, 研究表明, 小体积移植肝所承受的缺血再灌注损伤比全肝移植更重, 可能会导致肝再生和肝功能需求量增加之间平衡的破坏; 再加上免疫应答等多种损伤因素, 如果超过了小体积移植肝的耐受限度, 将出现一系列肝功能不全的表现, 进一步诱发脓毒血症、消化道出血等并发症, 继而引起一系列的临床综合征, 即称为“小肝综合征”[1, 2]. 小肝综合征的发病机制与肝移植术后门静脉高压、门静脉过度灌注等有关[3]. 本综述将从肠屏障和肝屏障2个方面来具体阐述其在小肝综合征中的功能变化的原因和可能的保护机制, 并分析2个屏障之间可能存在的联系.

1 肠屏障功能破坏的原因

肠屏障主要包括4种屏障, 即机械屏障, 生物屏障, 化学屏障和免疫屏障. 在机体受到创伤、应激、缺血缺氧、微生物及其产生的有害代谢产物损害时, 肠黏膜这4种屏障可以抵抗病原体的侵袭, 阻止有害物质进入血液循环, 从而保持机体内环境的稳定[4]. 部分肝移植术后, 在小肝综合征的发生过程中, 肠屏障功能也受到损伤. 肠黏膜屏障功能的破坏是引起细菌移位的基本病理生理因素. 研究表明, 移植后1 wk菌血症、肠道细菌移位等表现同胆汁淤积、腹水等小肝综合征表现相关, 同时与门静脉压力增高呈正相关[5]. 在发生小肝综合征的病例中约有50%受体会在移植后的4-6 wk内发生细菌移位引起的脓毒血症[6]. 因此, 研究小肝综合征发生过程中肠黏膜屏障功能的改变及其损伤机制近年来备受关注, 尤以肠屏障中机械屏障(即紧密连接)的破坏最为引人注意, 其损伤可能是肠屏障功能破坏最重要的原因.

1.1 紧密连接的破坏 肠黏膜上皮细胞间的连接, 从顶端到基膜依次为紧密连接、黏附连接、桥粒和缝隙连接. 其中紧密连接(tight junction, TJ)是构成上皮机械屏障功能最重要的结构, 由一些跨膜蛋白组成, 包括occludin, claudin[7,8], JAM, ZOs[9,10]等, 其功能是允许离子及小分子可溶性物质通过, 而不允许毒性大分子及微生物通过, 这对维护肠道屏障功能起到举足轻重的作用[11-14].

部分肝移植术后小肝综合征的产生和一系列的病理生理变化可导致肠黏膜机械屏障功能受损. Such等研究发现门静脉高压破坏肠黏膜屏障, 主要表现为肠黏膜上皮细胞间紧密连接部的破坏[15,16]. 肠上皮细胞的紧密连接部维持上皮细胞间的渗透性, 限制膜脂肪和膜蛋白的侧向扩散以维持细胞的极性, 是调节肠黏膜屏障功能的关键部位. Lambert等[17]研究认为TJ是具有一定特殊结构的细胞膜微区域(即为不溶于detergent的raft膜微区域), 区域内富含糖脂、鞘磷脂和胆固醇, 通过改变该区域的detergent可溶性或糖脂、鞘磷脂组成可以破坏紧密连接. 用蔗糖密度梯度超速冷冻离心法可以从极性肠上皮细胞株(T84细胞)中分离TJ的膜微区域等, 同时发现紧密连接部特异性蛋白occludin和ZO-1分布在紧密连接膜微区域中. 免疫沉淀结果确定occludin与raft特异蛋白caveolin-1在相同的紧密连接膜微区域中[18]. 另外, 在炎性肠病的研究中, 学者发现在肠黏膜通透性增高的同时, 作为机械屏障的紧密连接和其临近的连接结构会发生变化, 具体包括claudin-2分布异常, occludin的表达降低和重新分布以及ZO-1的表达分布异常等. 而这些变化与一系列的炎性因子的表达增加有关, 比如TNF-α, IFN-γ等[19]. 因此, 在肠黏膜上皮紧密连接膜微区域中, 紧密连接结构蛋白的改变可能是小肝综合征中肠黏膜屏障功能改变的分子基础, 而炎性因子可能是导致紧密连接结构蛋白改变的最重要的原因.

1.2 炎性因子的释放和作用 供肝缺血-再灌注损伤可以促进肠上皮细胞表达TNF-α, IFN-γ, IL-6等细胞因子,增加肠黏膜的通透性[20]. 而肝脏Kupffer细胞受损, 肝脏清除内毒素能力下降, 并诱导Kupffer细胞释放大量炎症细胞因子, 包括TNF-α, IL-1β, IL-6[21,22]. 实验研究表明, 多种炎症介质均可引起肠黏膜通透性增高[23,24]. 其中TNF-α和IFN-γ增加肠上皮通透性可能是通过破坏细胞间紧密连接的结构, 降低紧密连接蛋白的表达而实现的, 并且两者还具有协同效应[25,26]. 而在白介素(interleukin, IL)中, IL-1通过降低occludin的表达水平, 进而增加肠上皮通透性; IL-4

通过降低ZO-1和occludin的表达水平, 增加肠道通透性; IL-6则通过改变ZO-1的分布来增加肠黏膜通透性; IL-13也可降低ZO-1的表达来实现增加肠上皮的通透性[27]. 因此, TNF-α, IFN-γ, IL等炎性因子可能是通过影响紧密连接膜微区域中结构蛋白分布, 改变细胞间紧密连接结构, 从而增加肠黏膜屏障的通透性, 破坏肠黏膜屏障功能.

2 肠屏障的保护研究

当肠黏膜屏障受到破坏, 就会发生细菌移位、肠源性感染, 甚至严重的脓毒血症, 严重威胁肝移植患者的预后. 因此, 保护肝移植术后的肠黏膜屏障功能显得尤为重要. ω-3多不饱和脂肪酸能调节脂类介质的合成、细胞因子的释放, 激活白细胞活性和内皮细胞活化, 进而调控机体的过度炎性反应, 从而减轻炎性反应对肠屏障功能的破坏[28]. 在炎性肠病的研究中, 证实了ω-3多不饱和脂肪酸可以防止改变紧密连接部特异性蛋白occludin和ZO-1的分布移位和破坏紧密连接部的形态, 从而维持Crohn's病患者的肠黏膜形态结构的完整性, 阻止肠道细菌的过度增殖和黏附[29]. ω-3多不饱和脂肪酸在部分肝移植中的应用目前尚无相关研究, 其是否可以从紧密连接和炎性因子2个方面产生作用, 从而对肠黏膜屏障功能起到保护作用, 值得作进一步深入研究.

3 肝屏障功能破坏的原因

肝屏障主要包括3种屏障, 即机械屏障[30], 肝细胞-血液屏障[31]和血液-胆汁屏障[32]. 在部分肝移植术后小肝综合征中, 任何一种屏障的损伤都可能是导致肝脏功能受损的机制, 并与肠黏膜功能损伤可能密切相关.

3.1 *机械屏障破坏* 肝脏的机械屏障同肠黏膜一样, 由各种连接组成, 其中最重要的就是TJ. TJ是肝细胞间连接的最重要的形式, 是维持肝脏组织形态的重要结构[33,34]. TJ中主要的屏障蛋白是occludin和claudin, 在肝脏中有特定的表达[34]. 其他组成TJ的蛋白还包括JAM, CAR等[35]. Lora等[36]研究发现在大鼠结肠炎模型中, 肝脏的紧密连接会发生变化, 导致机械屏障通透性增加; Han等[37]研究发现在小鼠模型中内毒素对肝脏紧密连接有明显损伤, 尤以ZO和occludin蛋白表达降低最为显著. 在小肝综合征中释放的炎性因子不仅对肠黏膜的TJ有损伤, 而且对肝脏的TJ亦有破坏. 由于肝脏富含TNF-α受体, 是TNF-α作用的靶器官, 因此TNF-α的释放可抑制肝脏紧密连接中ZO-1的表达, 破坏紧密连接, 损伤肝细胞; 其他炎性因子, 如IL类亦对紧密连接有损伤, 而其中IL-10对肝脏具有保护作用, 可对抗其他促炎因子如IFN-γ对紧密连接的破坏, 维持紧密连接正常形态[27]. 因此, 炎性因子可直接和间接损伤肝脏机械屏障, 即直接破坏肝脏紧密连接和通过损伤肠黏膜产生内毒素来间接破坏肝脏紧密连接.

3.2 *肝细胞-血液屏障破坏* 肝细胞-血液屏障即肝血窦, 由肝脏毛细血管组成, 其内有肝非实质细胞, 包括肝窦内皮细胞(sinusoidal endothelial cell, LSEC)和Kupffer细胞等, 而肝窦内皮细胞形成的内皮细胞网络就是肝细胞与血液之间的屏障[37-39]. 在肝移植后, 肝窦内皮细胞可能是最易受到损伤的部位, 且研究表明, 供肝缺血-再灌注后, Kupffer细胞产生多种炎性因子, 包括TNF-α, IL-8等, 并对肝窦内皮细胞造成损伤; 而小肝综合征中产生的内毒素亦能刺激Kupffer细胞释放炎性因子, 对肝窦内皮细胞产生破坏, 并进而损伤肝细胞[40-42]. 肝窦内皮细胞具有强大的清除能力和内吞噬能力[43,44], 能将机体体循环中的代谢物质和有害物质清除, 如90%的透明质酸(hyaluronic acid, HA), 通过肠道进入体循环的脂多糖(lipopolysaccharide, LPS), 病毒和其他病原体都由肝窦内皮细胞的内吞噬作用清除, 因此, 肝窦内皮细胞成为肝脏先天性免疫系统的重要组成部分[45]. 在肝移植术后早期, 缺血-再灌注损伤是肝窦内皮细胞损伤的主要原因之一[46], 而HA水平的增高则反映了肝窦内皮细胞的损伤程度, LPS的水平增高也反映了肝窦内皮细胞的清除能力的下降[45]. 而研究发现, 对肠黏膜有损伤作用的IL-1β, 可以诱导超氧化锰歧化酶(Mn-SOD)的生成, 进而减轻缺血-再灌注损伤, 促进肝窦内皮细胞的内吞噬作用[47-49]. 因此, 对肝窦内皮细胞的保护研究显得尤为重要.

3.3 *血液-胆汁屏障破坏* 在肝脏内, 紧密连接不仅存在于肝细胞间, 还分布于胆小管上[50], 构成血液-胆汁屏障, 使胆汁在胆小管内与血液循环分离开来, 并对于细胞间的通透性, 胆汁的分泌和细胞的极性起到了重要的作用[51-53]. 有研究表明, 紧密连接在信号传导网络中也是一个重要的组成部分, 尤其表现在血液-胆汁屏障中. 不同连接之间具有相互作用和联系, Cx32的表达可以导致TJ的形成, 包括occludin, claudin-1和ZO-1的诱导表达[51]. 一些炎性细胞因子, 如IL-

■相关报道
Such等研究发现门静脉高压破坏肠黏膜屏障, 主要表现为肠黏膜上皮细胞间紧密连接的破坏; Takashi等研究了肝脏中血液和胆汁之间的屏障作用, 包括肝细胞之间的紧密连接.

■创新盘点

本文综述了肝屏障和肠屏障的具体组成, 探讨其功能状态, 分析屏障在部分肝移植后受到损伤的机制及可能保护屏障功能的对策, 重点介绍了肝屏障的损伤原因及保护研究, 在其他文献中较少有对其的报道.

1β, 可通过信号传导途径引起Cx32和Claudin-1的减量调节或Claudin-2的增量调节, 如细胞分裂素活化蛋白激酶(MAP)、P38MAP激酶、磷酸肌醇3激酶(PI3), 因此, 紧密连接可能通过此途径被炎性因子作用, 继而发生改变, 引起肝屏障功能的破坏[54-61].

4 肝屏障的保护研究

当肝屏障受到破坏后, 肝细胞会发生凋亡, 胆汁血液互通, 毒素或病原体等无法被清除, 导致进入体循环, 引起脓毒血症. 因此, 肝移植术后对肝屏障的保护亦很重要, 对术后移植肝的功能有极大的影响. 对肠屏障功能具有保护作用的ω-3多不饱和脂肪酸对肝屏障也具有保护作用. ω-3多不饱和脂肪酸可以减少炎性因子的释放, 如TNF-α, IFN-γ, IL-1, IL-6等, 进而减少肝细胞的凋亡[61]. 尤其对于TNF-α而言, ω-3多不饱和脂肪酸可以降低他的炎性应答, 从而保护肝脏[62]. 而ω-3多不饱和脂肪酸还可以抑制花生四烯酸来源的介质的生成, 调控黏附分子的表达[63,64]. 研究表明, ω-3多不饱和脂肪酸可以极大程度的提高肝脏组织中EPA, DHA和DPA的浓度, 继而影响肝脏中ω-3多不饱和脂肪酸与ω-6多不饱和脂肪酸之间的比例, 而这种变化在肝脏缺血-再灌注损伤中减少了二联类前列腺素的生成, 抑制了炎性因子的激活, 从而起到了保护肝脏的作用[65]. 因此, ω-3多不饱和脂肪酸在肝移植后同样会对肝脏起到一定的保护作用.

5 结论

在减体积肝移植术后会出现一系列的临床变化, 这与移植肝体积过小而使肝缺血-再灌注损伤加重, 引起小肝综合征有关. 无论对于肠屏障还是肝屏障的功能来说, 诸多的改变引起屏障的破坏都与炎性因子的释放与紧密连接的破坏有关, 并且两者之间存在着许多联系, 这2个重要因素将肠屏障与肝屏障紧密联系在了一起. 为了术后患者的顺利康复, 对于这两个屏障的功能保护就显得尤为重要. ω-3多不饱和脂肪酸可以抑制炎性因子的释放, 保护紧密连接蛋白的形态, 在理论上对肠屏障和肝屏障都能起到保护作用. 初步的体外实验和动物实验证实了其有效性, 而具体的作用机制和临床应用还有待进一步研究.

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■应用要点
本文对肝屏障和肠屏障的结构、功能、损伤机制及保护措施进行了全面的论述, 对于临床肝移植工作具有一定借鉴和指导意义.

■同行评价
本文创新性较好, 同时综述内容较全面, 逻辑层次清晰, 科学性也较好, 对于临床肝移植工作具有一定借鉴和指导意义.

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• 消息 •

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