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文献综述 REVIEW

重症急性胰腺炎中肠屏障功能障碍机制的研究进展

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摘要

重症急性胰腺炎(severe acute pancreatitis, SAP)常伴随肠屏障功能障碍的发生, 使肠道通透性增加, 继而引起细菌和内毒素移位, 导致严重感染和多器官功能损害, 加剧了SAP的病程. 肠道微循环障碍、缺血再灌注损伤、炎症介质过度释放以及细胞凋亡、菌群失调等多种因素共同作用可能是肠屏障损伤的机制. 探讨SAP中肠屏障功能障碍的发生机制, 对治疗SAP具有重要的指导意义.

背景资料

重症急性胰腺炎(severe acute pancreatitis, SAP)属于急性胰腺炎的特殊类型, 是一种病情险恶、并发症多、病死率较高的急腹症. 以往研究认为胰腺坏死组织继发感染是SAP患者并发症和死亡的主要原因之一, 而肠屏障功能障碍和随之发生的肠源性细菌移位在胰腺坏死组织继发感染起关键作用. 本文通过探讨SAP肠屏障功能障碍的发生机制, 为防治SAP提供理论依据.

Mechanism of gut barrier failure associated with severe acute pancreatitis

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Abstract

Gut barrier failure is often present in severe acute pancreatitis (SAP), and it increases the gut permeability, leads to translocation of bacteria or endotoxin, causes severe infection and multiple organ dysfunction syndrome, and worsens the course of the disease. The injury of gut barrier may result from the interactions among microcirculation disturbance, ischemia-reperfusion injury, excessive release of inflammatory mediators, apoptosis, flora imbalance and so on. The research on the mechanism of gut barrier failure caused by SAP is of important significance for the treatment of SAP.

Key Words: Severe acute pancreatitis; Gut barrier failure; Mechanism

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同行评议者

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研发前沿
近年来, 肠道微循环障碍、缺血再灌注损伤、炎症介质过度释放以及细胞凋亡、菌群失调等一直是SAP肠屏障功能障碍发生机制的研究重点, 但仍有待更具体深入的研究.

关键词: 重症急性胰腺炎; 肠屏障功能障碍; 发生机制

核心提示: 重症急性胰腺炎常伴随肠屏障功能障碍的发生, 继而引起细菌和内毒素移位, 导致严重感染和多器官功能损害. 肠道微循环障碍、缺血再灌注损伤、炎症介质过度释放以及细胞凋亡、菌群失调等多种因素共同作用可能是肠屏障损伤的机制.

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0 引言

重症急性胰腺炎(severe acute pancreatitis, SAP)属于急性胰腺炎的特殊类型, 是一种病情险恶、并发症多、病死率较高的急腹症, 占整个急性胰腺炎的10%-20%[1,2]. 而胰腺坏死组织继发感染是SAP患者发生并发症和死亡的主要原因之一, 研究认为肠屏障功能障碍和随之发生的肠源性细菌移位在胰腺坏死组织继发感染起关键作用[3,4]. 本文将从肠屏障功能障碍的病理生理变化方面对其在SAP中的发生机制研究进展作一综述.

1 微循环障碍和缺血再灌注损伤

目前普遍认为SAP伴肠道屏障功能障碍与微循环障碍及缺血再灌注损伤有关. SAP时由于胰腺水肿、炎症反应及微血管的渗漏, 大量体液进入第三间隙, 导致机体全身血容量不足. 为了保障心脑等重要脏器的血供, 机体通过神经内分泌等机制使内脏血管收缩, 肠道黏膜血供急剧减少[5]. 且SAP时易累及肺, 造成组织缺氧[6], 肠黏膜血管痉挛, 肠道血流明显减少. 同时在一些SAP发病过程中会出现胰源性腹水, 导致腹腔内高压, 甚至引起腹腔间隔室综合征, 加重肠黏膜缺血[7]. 肠道血液灌注严重不足时会产生肠黏膜组织的酸中毒, 可能是由于ATP消耗和脂质过氧化作用, 引起肠黏膜通透性增加[8,9]. 有研究[10]表明SAP过程中内脏灌注不足会加剧肠黏膜完整性的破坏. 因此, 微循环障碍可能是造成SAP时肠道黏膜屏障功能损伤的重要原因之一. 另一方面, 肠屏障特别容易受到缺血的影响, 因为肠绒毛微循环独特的解剖特点, 即多支回流静脉围绕一根中央小动脉呈网囊状结构, 产生氧气的动静脉分流和绒毛顶端缺氧[11], 且中央小动脉呈直角发出易造成血液稀释, 从而加剧肠道缺血缺氧[12]. 另外内皮素-1的释放可能会加剧肠黏膜局部缺血, 动物研究[13,14]表明内皮素-1受体阻滞剂能增加内脏血流, 改善肠黏膜微循环障碍. 因此检测AP病程中血浆的内皮素-1水平可评估疾病的严重程度及治疗的效果[15]. 细胞间黏附分子-1(intercellular cell adhesion molecule, ICAM-1)也会加重肠道黏膜的缺血损伤, ICAM-1在稳定细胞间相互作用和促进白细胞和内皮细胞的迁移起到重要作用. 有研究[16,17]显示ICAM-1尤其是在SAP早期就出现高表达, 引起白细胞浸润和组织学变化的显著增加, 肠道和胰腺灌注减少, 而且其指标高低也可用来预测AP的严重性.

肠道在缺血的条件下进行液体复苏, 容易产生缺血再灌注损伤(ischemia-reperfusion injury, IR), 这也是导致肠屏障衰竭的常见原因[18]. 严重肠IR的特征为肠黏膜损伤, 其特征表现为广泛的上皮与绒毛分离, 上皮坏死, 固有层破损, 黏膜溃疡、出血坏死. 这导致肠道的吸收功能障碍及黏膜的通透性升高, 使大分子溶质和多种有害生物活性物质得以通过[19]. IR时, 黄嘌呤氧化酶将次黄嘌呤转化为黄嘌呤并释放超氧离子, 而超氧离子又会导致氧自由基的进一步形成, 氧自由基通过脂质过氧化作用损伤细胞膜[20]. 另一方面, 氧自由基也会趋化中性粒细胞, 伴随其他刺激[如肿瘤坏死因子-α(tumor necrosis factor α, TNF-α)、白介素(interleukin, IL)-1、IL-8、GM-CSF、干扰素-γ(interferon-γ, IFN-γ)、白三烯、血小板活化因子、ICAM-1、ELAM-1、补体C3a和C5a], 启动激活的中性粒细胞转移到缺血再灌注组织[21]. 激活的中性粒细胞的积累可能肠道损伤的主要原因, 他通过加重缺血, 释放氧自由基和蛋白酶, 增强炎症反应等介导损伤[22,23]. 因此肠道再灌注通过产生氧自由基和炎症介质导致进一步的损害. 另外, 在缺血再灌注过程中NO会被超氧自由基转化为有细胞毒性的亚硝酸盐, 最终也会导致肠道通透性的增加. 有研究[24]表明在肠道缺血-再灌注后, CD44表达明显降低, 影响肠道细胞与细

相关报道
近期研究认为肠道菌群紊乱在SAP肠屏障功能障碍中发挥了重要作用, 这为治疗SAP提供了新的思路.

胞、细胞与基质的连接, 使肠道黏膜完整性受到破坏.

2 细胞因子和炎症介质的过度释放

研究[25,26]表明SAP早期即有大量活化的白细胞, 从而引起细胞因子和炎症介质如TNF-α、IL-1、IL-6、IL-8的过度释放, 这些细胞因子间又相互诱导刺激, 最终形成级联反应. 首先TNF-α在介导肠屏障损害中起了重要作用, 一方面TNF-α对细胞有直接杀伤或抑制作用, 他能通过改变肠上皮紧密连接的脂质组成来诱导肠上皮通透性的增加[27], IFN-γ对此具有协同作用[28]. 另一方面TNF-α促进中性粒细胞黏附至内皮细胞, 从而促进局部炎症反应. 此外TNF-α还可作用于内皮细胞, 使血管损伤和血栓形成, 加重肠黏膜缺血. Surbatovic等[29]则认为TNF-α可用来评估急性胰腺炎的严重性和结局. 磷脂酶A2(phospholipase A2, PLA2), 被发现在肠黏膜中具有高浓度, 临床研究[30]发现PLA2是SAP发生一系列严重并发症的早期标志物, 与SAP的发展密切相关, 基因敲除PLA2可减轻急性胰腺炎的严重性. PLA2在肠缺血及脓毒症条件下被过度激活, 并在TNF-α控制下释放, 产生促炎性介质如血小板活化因子, 刺激内皮细胞及中性粒细胞, 增强中性粒细胞介导的组织损伤. 中性粒细胞通过分泌多种介质增强炎症反应, 当他们被激活后将释放大量的促炎症细胞因子如IL-1、IL-6、IL-8、TNF-α、IFN-β, 并且可激活血小板和凝血级联反应, 抑制纤维蛋白溶解, 引起血栓形成. 而IL-1与IL-6均可通过不同的分子机制增加肠上皮紧密连接的通透性[31,32]. 血清高迁移率族蛋白B1(high mobility group box-1 protein, HMGB1)是一种重要的晚期致炎因子, Xu等[33]发现HMGB1在SAP中出现高表达, 并介导了肠黏膜屏障的损伤. 此外, SAP时常伴发生肠源性内毒素血症, 内毒素可促进TNF-α、IL-1等多种炎症介质的释放, 进一步损伤肠黏膜屏障, 导致更多的内毒素入血, 形成恶性循环.

3 细胞凋亡

研究发现急性坏死型胰腺炎(acute necrotizing pancreatitis, ANP)大鼠早期肠黏膜上皮细胞凋亡为细胞死亡的主要形式[34], 肠上皮细胞凋亡在ANP早期肠屏障功能障碍过程中可能起重要作用. SAP时肠上皮细胞凋亡可能与下列因素有关: (1)肠黏膜缺血缺氧, 氧自由基大量产生和钙超载[35]; (2)细胞因子和炎症介质的过度释放, 如TNF-α、NO等诱导和调控肠上皮细胞凋亡[36]; (3)细胞黏附分子表达异常, 致使上皮细胞与细胞基质间连接破坏[37]; (4)肠内营养严重缺乏[38]. 上述因素通过复杂的调控共同作用诱导和加速肠上皮细胞凋亡. 而田瑞等[39]研究认为SAP发生后, TNF-α等炎症因子瀑布样释放, 引起肠黏膜IR, 形成严重的氧化应激反应, 从而激活Caspase3通路, 导致了肠黏膜细胞凋亡增加. 最近研究[40]还发现FaS和FasL的表达与感染性并发症的发生和SAP的严重程度成正相关, 由于他们的过度表达促进了淋巴细胞的凋亡, 使机体免疫低下和肠道免疫功能受损.

4 肠道营养缺乏

SAP时机体处于高分解状态, 加上长期禁食、持续胃肠减压、全胃肠外营养等原因, 使肠黏膜营养供给障碍. 谷氨酰胺作为肠黏膜上皮及肠道相关淋巴组织的特需氨基酸, 是肠黏膜细胞生长的主要能量来源. 在SAP时血液及组织中谷氨酰胺含量降低, 肠上皮合成生长因子减少, 导致肠黏膜上皮萎缩变薄, 细胞间连接破坏, 使肠道通透性增加, 淋巴细胞、巨噬细胞调节功能障碍[38,41]. Alhan等[42]实验发现单独给予谷氨酰胺能有效改善ANP的进程. 此外SAP时缺乏食物对消化的刺激, 胃酸、胆汁、消化酶、溶菌酶等产生减少, 肠道杀菌能力减弱, 导致肠道内致病菌大量繁殖, 加重SAP的病理生理过程. Vieira等[43]临床试验发现, 与肠外营养相比, 给予肠内营养的SAP患者预后更好, 感染性并发症更少. 且肠内营养能有效地调节促炎症反应和抗炎反应之间的平衡[44].

5 胃肠动力障碍

正常的胃肠动力是维持肠道功能的关键因素之一. 胃肠动力障碍也会导致和加重SAP肠屏障功能障碍. 王强等[45]实验发现SAP时大鼠存在胃肠激素的紊乱, 与假手术组比较, SAP组胃动素(motilin, MTL)明显下降、血管活性肽(vasoactive intestinal peptide, VIP)明显升高, 且SAP组消化间期移行性复合肌电活动

创新盘点

SAP肠屏障功能障碍是由多种复杂因素引起的, 他们之间又相互作用、相互影响, 共同介导了肠屏障功能障碍的发生. 本文比较全面的总结了其发生机制.

应用要点
本文较系统的阐述了SAP肠屏障功能障碍的发生机制, 对临床治疗和改善SAP预后具有一定的指导意义.

(interdigestive myoelectric complex, IMC)周期以及Ⅰ、Ⅱ相时间延长, Ⅲ相时间缩短. 关于SAP的研究中发现胃肠兴奋性激素升高、抑制性激素减少[46], 胃肠激素通过影响胃肠平滑肌的电活动而导致胃肠动力障碍. NO对胃肠的电机械活动起着重要的抑制性调节作用. 近年研究[47]表明在SAP中一氧化氮合酶(nitric oxide synthase, NOS)表达及活性增加, 导致产生了更多的NO, 从而介导了胃肠动力障碍. 胰源性腹水在胃肠动力障碍中也起了重要作用, 一方面其中所含毒性物质、炎症因子加剧胃肠动力障碍甚至导致肠麻痹, 另一面他会介导产生NO, 抑制胃肠运动[48]. 此外, 肠道Cajal间质细胞(interstitial cells of Cajal, ICCs)的功能对胃肠动力的正常运行至关重要. 最新研究[49]发现, 在SAP中ICCs数量减少, 伴随肠道神经功能紊乱, 且ICCs和平滑肌受损, 影响了胃肠动力功能.

6 肠道菌群紊乱

正常人体中的肠道菌群不仅在肠屏障结构和功能中起重要作用, 同时有利于维持肠相关淋巴系统的功能[50]. SAP发生后常常伴有肠道菌群变化, 肠道菌群失调可能也参与了肠屏障功能障碍. 以往的研究[51,52]表明肠道菌群失调与SAP患者中肠屏障障碍和高死亡率密切相关. 研究[53]发现SAP时肠道菌群发生了很大变化, 原本占优势的专性厌氧菌群显著减少, 而兼性或需氧菌群如肠杆菌、肠球菌则过度繁殖, 易造成大量内毒素产生和细菌移位, 破坏肠道微生态平衡, 引起继发感染等并发症. 基于此, Rychter等[54]实验造模, 给SAP小鼠提前给予益生菌治疗, 结果证明能有效改善肠屏障功能. 因此在治疗SAP过程中, 通过恢复肠道菌群稳态来维护肠屏障功能被认为是一个重要的目标. 微生态制剂将是一种很有前景的治疗方法.

7 结论

SAP肠屏障功能障碍是由多种复杂因素引起的, 他们之间又相互作用、相互影响, 共同介导了肠屏障功能障碍的发生. 肠屏障功能的正常维持对SAP发病进展和预后起了重要作用. 目前对其发病机制的研究虽有了一定的进展, 但仍有待更具体深入的研究, 这将对采取相应的治疗措施、改善SAP患者预后具有重要影响.

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名词解释

胰源性腹水：急性坏死性胰腺炎常产生大量的胰腺炎相关性腹水，其中的弹性蛋白酶和腹膜巨噬细胞产生多种毒性细胞因子，可经腹膜吸收入血，通过不同的分子机制参与急性坏死性胰腺炎胰外多脏器的损害.

同行评价

本文较全面综述了SAP中肠屏障功能障碍机制的研究进展, 文字顺畅, 层次清楚, 逻辑性强, 对临床诊治指导性强.

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