

# 胃黏膜保护的基础与临床研究进展

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## 摘要

长期以来胃黏膜保护一直是基础和临床研究的重点与热点。近年来人们对胃黏膜保护的细胞和分子机制已有了全面深入的认识, 发现具有胃黏膜细胞保护作用的物质有很多种, 具有细胞保护作用的器官和组织也不仅仅限于胃黏膜, 在胰腺、肝脏、肾脏、心脏和脑等都发现有类似现象。因此细胞保护概念的内涵和外延都有拓展。我们对三叶因子、氧自由基、幽门螺杆菌、酒精、非甾体类抗炎药及细胞因子等研究热点与胃黏膜保护相互作用的机制进行初步的探讨。

**关键词:** 胃黏膜; 保护; 基础与临床研究

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## 0 引言

1975年美国密歇根Upjohn药厂Andre Robert发现前列腺素(prostaglandins, PGs)可明显防止或减轻皮质类固醇、非甾体类抗炎药(non-steroidal anti-inflammatory drugs, NSAIDs)、酸化阿司匹林、酸化牛磺酸盐、沸水、应激、结扎幽门(Shay大鼠)等对胃黏膜的损伤, 其效果呈剂量依赖性, 与抑制胃酸分泌无关。据此Andre Robert提出细胞保护(cytoprotection)的概念。很多现象提示其在胃黏膜保护的病理生理过程中居主导地位。

胃黏膜保护是指黏膜能耐受经常接触的各种损伤因子包括大幅度pH、渗透压和温度变化, 以及具有去垢作用的物质或能引起全身或局部炎性反应的细菌代谢产物及抗原等, 而结构与功能不受明显伤害的现象。胃黏膜并不是不受食物或自身分泌的内源性因子损伤, 而是经常发生损伤, 但胃黏膜能快速地修复损伤, 使损伤发生在上皮最表浅层, 阻止有害因子进入黏膜组织或体循环。当胃黏膜受刺激后, 黏膜的抵御能力相

应增强, 即出现适应性细胞保护现象, 提示胃黏膜细胞保护是动态过程而非静态过程。

胃黏膜保护作用由多种因素介导, 这些因素相互联系、相互作用, 形成复杂的网络体系, 并受全身和局部神经、体液及腔内物质的调节。从解剖结构上可将这些因素分为五个层次。第一层次由分泌入胃腔的成分组成, 包括酸、碱、黏液、免疫球蛋白和其它抗菌成分(如乳铁蛋白)、表面活性磷脂(surface active phospholipid, SAPL)等。第二层次是上皮层, 具有显著的抗酸损伤功能并形成紧密连接防止被动扩散。如果上皮层连续性破坏, 能够快速修复。第三层次由黏膜微循环与黏膜、黏膜下感觉传入神经组成。酸或其它损伤因子逆流流入黏膜引起神经介导的胃黏膜血流(gastric mucosal blood flow, GMBF)升高, 这对限制损伤和促进修复有重要意义。第四层次由黏膜免疫细胞构成, 包括肥大细胞、巨噬细胞, 可感受进入黏膜的异物成分, 形成适当的炎性反应。第五层次即胃黏膜自身修复机能包括胃腺的生长和重建、外来和内在神经系统的再生、微循环的重建, 许多生长因子在其中的重要意义已经被认识。现将近年来胃黏膜保护的基础与临床方面研究进展综述如下:

## 1 三叶因子与胃黏膜保护

三叶因子家族(trefoil factor family, TFF)是一群主要由胃肠道黏液细胞分泌的小分子多肽。目前在哺乳动物体内发现的三叶肽(trefoil peptide)有3种, 即乳癌相关肽(pS2或TFF1)、解痉多肽(SP或TFF2)和肠三叶因子(ITF或TFF3)。其共同特征为均含一特殊结构——P结构域, 由一段38-39个氨基酸序列通过6个高度保守的半胱氨酸残基经由3个分子内的二硫键(Cys1-Cys5, Cys2-Cys4, Cys3-Cys6)相互联接, 使整个肽链扭曲、折叠形成三叶状结构, 由此命名。这种三叶形结构的稳定性使TFFs具有明显的抗蛋白酶水解、酸消化及耐热特性, 因而能在消化道复杂的环境中保持生物活性。在哺乳动物体内, 三叶肽具有肿瘤抑制、信号传导、诱导细胞凋亡以及减轻各种理化因素引起的胃黏膜损伤并促进黏膜修复等功能, 但其发挥功能的具体机制尚不明<sup>[1-13]</sup>。

国外已有大量的实验证明, 三叶肽在胃肠道黏膜保护中发挥了重要的作用。其作用机制目前有2种假

说: (1)物理方式, 与黏液中的糖蛋白结合形成稳定的凝胶复合物, 加强黏液凝胶层, 减少胃表面有害物质及机械应力等因素对黏膜的损伤; (2)生物化学方式, 三叶肽可能通过与其受体或转运蛋白结合而发挥生理功能, 但具体的受体或结合蛋白并未明确确定. 除保护作用外, 研究结果证明三叶肽参与了损伤组织的修复过程, 可增强受损黏膜周围完好的上皮细胞向损伤黏膜表面迁移覆盖, 促进损伤黏膜的重建. 三叶肽是一种快速反应肽, 在黏膜损伤后30 min内即可见表达上调. 体外实验显示, 无论是重组TFF3或重组TFF2, 都能刺激肠道上皮细胞的迁移, 促进伤口愈合, 改变上皮细胞钙黏蛋白(E-cadherin)的表达和细胞定位.

目前认为TFFs可能具有特异性受体, 是通过配体-受体或配体-结合蛋白方式传导其生物学功能的, 并且其表达受多种细胞因子或配体的调控<sup>[14-16]</sup>; 同时它本身可能也扮演着某些病原微生物受体的角色<sup>[17]</sup>. TFFs在黏膜保护及修复过程中发挥了重要的作用, 深入探讨TFFs的作用机理对于黏膜保护、溃疡治疗及肿瘤诊治等方面均有重要的意义<sup>[18-20]</sup>. 体外研究业已证实了它们能促进上皮细胞修复, 其在肿瘤生成、生长过程中所扮演的角色及与胃酸分泌、胃动力之间的关系亦不明确, 主要问题在于未能自分子水平阐明TFFs分子的作用机制, 而家族各成员与结合蛋白或受体之间的相互作用成为进一步的研究重点<sup>[21-23]</sup>. 因此, 进一步研究TFFs各成员的作用机制是目前的主要研究突破方向, 由于TFFs具有明确的调节肽功能, 研究下游的受体/结合蛋白除阐明作用机制以外, 还可能提出新的研究方向、肿瘤的生成假说或新的药物.

## 2 氧自由基与胃黏膜保护

自由基指具有未配对电子的原子、原子团或分子, 由氧分子衍生的自由基称氧自由基(oxygen free radical, OFR). 主要包括超氧自由基( $O_2^{\cdot-}$ )和羟自由基( $OH^{\cdot}$ ), 它们与过氧化氢、单线态氧( $O_1$ )统称为活性氧. 正常人体内存在清除OFR的防御系统, 使其生成量不至于达到损伤组织的程度. OFR具有杀菌、细胞毒和促进炎症渗出、水肿等重要炎症介质作用. 由于OFR作用的靶细胞和分子无特异选择性, 故OFR在参与杀菌等防御作用的同时, 也会给组织细胞造成损伤. *H. pylori*感染、NSAIDs、乙醇等坏死因子、缺血再灌注损伤、应激、幽门结扎等所致胃黏膜损伤的模型中, 均涉及OFR的作用<sup>[24-30]</sup>. 可以认为, OFR参与了绝大多数致溃疡因子的致病过程, 与慢性胃炎、急性胃黏膜损伤、胃溃疡和胃癌的形成有密切关系<sup>[31,32]</sup>.

与其他组织的炎症相似, 胃黏膜在各种损伤因子作用下发生炎症时产生大量的炎症因子, 造成中性粒

细胞浸润, 通过呼吸爆发产生OFR, 因此中性粒细胞可能是OFR的主要来源<sup>[33-36]</sup>. 胃肠黏液在化学物质作用或缺血等情况下, 可产生大量的OFR<sup>[33,37]</sup>. 缺血时, 黏膜细胞内氧化磷酸化减少, ATP生成减少. 有报道鼠出血休克15 min后, 胃黏膜内ATP减少75%, ADP减少27%, 而AMP增至50%, AMP可进一步代谢为腺苷、肌苷及次黄嘌呤. 另一方面, 细胞能量不足时, 不能维持正常的离子梯度, 细胞内 $Ca^{2+}$ 增多, 激活一种蛋白酶, 使黄嘌呤脱氢酶快速不可逆地转变成黄嘌呤氧化酶. 缺血黏膜中同时有黄嘌呤氧化酶和其底物之一(次黄嘌呤)的聚集, 当组织再灌注提供另一底物( $O_2$ )时, 就可产生大量的超氧自由基. 超氧自由基和过氧化氢通过Haber-Weiss反应可生成细胞毒性更大的羟自由基. 正常情况下, Haber-Weiss反应的速度非常缓慢. 当存在金属离子时, 特别是有铁离子存在的情况下, 反应速度显著加速, 即所谓Fenton型Haber-Weiss反应. 缺血时细胞外铁水平增加, 由此可增加羟自由基的生成. 此外, 线粒体呼吸链受损和花生四烯酸代谢中也可产生部分OFR. 在许多种系中, 胃肠道黄嘌呤脱氢酶的含量远高于其他任何组织. 故一旦有条件, 胃肠黏膜将产生大量OFR.

自从Itoh和Guth 1985年报道给予超氧化物歧化酶(SOD)和过氧化氢酶可以明显减轻缺血-再灌注引起的胃黏膜损伤以来, 进一步研究证实它们也可以减轻酒精和非甾体类抗炎药等引起的急性胃黏膜损害, 从而间接提示在急性胃黏膜损害发病过程中, 反应性氧族(ROS)起了重要作用. Alarcon *et al*<sup>[24]</sup>发现给鼠动脉灌注自由基可引起胃黏膜损伤, 而SOD同时灌注可以减轻胃黏膜损伤. 因此, OFR是急性胃黏膜损害的重要致病因子. 急性胃黏膜损害时OFR的来源因病因不同而异<sup>[38-40]</sup>: 缺血-再灌注损伤时主要来自黄嘌呤氧化酶; NSAIDs引起的胃黏膜损伤时OFR主要来源于白细胞; 酒精性胃黏膜损伤可能来自醛氧化酶. 另一方面, 是共价键结合性损伤. OFR作用于含巯基的氨基酸, 使蛋白质变性和酶失活; 作用于辅酶, 使辅酶活性下降; 作用于碳水化合物, 使表面受体改变. 特别值得注意的是, OFR能破坏上皮间质中的透明质酸和胶原纤维网, 促进黏膜损伤<sup>[41]</sup>.

流行病学调查提示, 自由基清除剂维生素C和维生素E的缺乏与胃癌发生有关, 补充维生素C可减少胃黏膜中DNA损害. 临床研究发现胃癌和萎缩性胃炎患者血浆与组织中脂质过氧化物明显高于对照组, 并且发现胃癌组织中自由基浓度明显比对照组高, 提示自由基可能参与胃癌的发生. 自由基清除剂对胃黏膜损伤的保护作用, 瑞巴派特(rebamipide)是一种新的黏膜保护药, 通过抗氧化作用对多种OFR产生损伤



的动物模型具有抗损伤保护作用; 促进胃黏膜内源性前列腺素(PG)的合成释放, 保护胃黏膜, 增加胃黏膜血流量, 从而对溃疡的发生和发展产生抑制作用, 减少溃疡的发生<sup>[42,43]</sup>.

### 3 幽门螺杆菌与胃黏膜保护

幽门螺杆菌(*helicobacter pylori*, *H pylori*)产生的毒素和有毒毒素作用的酶能破坏胃黏膜屏障;*H pylori*感染还能使机体产生炎症和免疫反应, 影响胃酸、胃肠激素的分泌, 引起胃上皮细胞的凋亡, 导致一系列疾病的形成<sup>[44-46]</sup>.

*H pylori*感染时胃上皮细胞可递呈抗原, 起着"非专业性"抗原递呈细胞(APC)的作用, 可介导免疫反应<sup>[47]</sup>. APC是指能捕捉、加工和处理抗原, 并将抗原递呈给抗原特异性淋巴细胞的一类免疫细胞.*H pylori*感染可刺激浆细胞产生局部和全身的*H pylori*特异性抗体, 参与体液免疫反应, 这种抗体多半为非分泌型IgA, 不能很好地与补体结合清除细菌, 却可造成宿主自身的损伤, 如自身抗体可造成胃上皮的损伤<sup>[48]</sup>.

*H pylori*感染时胃窦黏膜、胃液中的胃液生长抑素(SS)含量均下降, D细胞数目和SS的mRNA表达也减少; 根除*H pylori*后这些指标均恢复, 提示*H pylori*抑制SS的释放<sup>[49]</sup>. 研究表明: *H pylori*感染时胃液中TNF- $\alpha$ 和IL-8分泌增多, TNF- $\alpha$ 能剂量依赖地增加SS释放, 且此效应可被IL-8所增强<sup>[50]</sup>. SS对G细胞有抑制作用, SS减少时促胃液素分泌增多, 同时SS在人胃腔中有抑制*H pylori*增殖的作用<sup>[51]</sup>. 促胃液素刺激和SS抑制壁细胞释放胃酸, 共同保持胃酸分泌的平衡.

表皮生长因子(EGF)和TGF $\alpha$ 通过同一受体(即EGFr)而起作用. 它们对胃肠道的作用有促进细胞增生、溃疡愈合、抑制胃酸分泌等.*H pylori*急性接触体外培养的胃黏膜细胞, 即引起细胞损伤, 并损及细胞的移行和增殖; EGF相关生长因子, 能保护胃黏膜免受损伤, 且使损伤的黏膜愈合.*H pylori*抑制EGF与其受体结合, 和抑制EGF刺激的胃细胞增殖, 是溃疡生成和难以愈合的机制<sup>[52,53]</sup>. 而最近Liu *et al* <sup>[54]</sup>报道在*H pylori*感染的慢性胃炎患者EGFr明显增高, *H pylori*感染可以促进胃黏膜细胞的增殖. Schiemann *et al* <sup>[55]</sup>报道根除*H pylori*后, 萎缩性胃炎胃黏膜中的TGF  $\alpha$ 的mRNA表达明显上调.*H pylori*感染时胃黏膜的C-myc基因蛋白和EGFr呈过表达, 可能为胃黏膜上皮过分增殖的分子基础<sup>[56]</sup>.

*H pylori*感染可导致胃上皮细胞的凋亡<sup>[57]</sup>. *H pylori*感染所致的细胞凋亡机制可能与以下因素有关<sup>[58]</sup>: (1) *H pylori*感染后产生的炎性细胞因子可增加Fas抗原的表达, Fas抗原是一种细胞表面的膜蛋白, 与Fas配体结合后可诱导细胞的凋亡; (2) *H pylori*感染时呼吸爆发产生的反应性氧代谢物(ROS)可导致DNA的单链裂解, 碱

基损伤. DNA损伤后可诱导产生P53蛋白, 造成细胞凋亡; (3) *H pylori*感染时中性粒细胞和巨噬细胞可表达一氧化氮(NO)合成酶, 产生反应性氮代谢产物(RNS). NO合成酶产生的NO与过氧化物反应可形成过氧亚硝酸盐(ONOO<sup>-</sup>). ONOO<sup>-</sup>可自行裂解形成羟基或单氧, 两者均能与DNA作用, 损伤DNA导致凋亡; (4) 炎性细胞因子如TGF  $\alpha$ 和IFN- $\gamma$ 除了可直接诱导细胞凋亡外, 还可促进上皮细胞表达主要组织相容复合物II(MHC-II)抗原, 通过TH1应答介导的损伤造成细胞凋亡. 胃上皮细胞的过度凋亡有利于糜烂和溃疡形成, 凋亡时程序错误或凋亡与增生不平衡则可导致肿瘤形成.

### 4 酒精与胃黏膜保护

急性酗酒所致的急性糜烂性胃炎是临床上常见的上消化道出血原因之一, 慢性酗酒可致酒精性肝炎、脂肪肝、肝硬化等酒精性肝病. 了解乙醇对胃黏膜损伤机制及其防护具有重要意义. 摄入乙醇后, 一方面, 乙醇可造成胃黏膜损伤, 组织学证据表明乙醇可使胃黏膜上皮层发生改变、破坏上皮顶端胞浆膜, 导致细胞脱落及胃多发糜烂、溃疡, 如累及血管则可引起出血; 另一方面, 胃可能参与乙醇的代谢, 与乙醇的"首过清除"有关, 表现为胃黏膜中存在多种乙醇脱氢酶同工酶, 但亦有不同观点<sup>[59-61]</sup>.

乙醇对胃黏膜的损伤包括急性及慢性两方面. 前者主要表现为急性糜烂性胃炎甚至溃疡, 内镜下表现为黏膜表面点状糜烂, 直径常为1-2 mm, 常不累及深层, 多伴有一定程度的出血(多为黏膜下瘀点), 活检时黏膜炎症常并不突出. 如累及黏膜肌层, 则形成溃疡. 如与NSAIDs(如布洛芬)协同作用, 则对胃黏膜的损伤更为显著. 后者表现为胃肠黏膜糜烂伴有上皮代偿性增生, 时间较长可出现肠上皮化生、上皮不典型增生, 甚至癌变, 这可能与氧化应激及脂质过氧化反应有关<sup>[62,63]</sup>. 此外, 慢性酗酒者*H pylori*感染所致的慢性胃炎发病率较高, 但治疗后黏膜常可完全恢复正常.

乙醇对胃黏膜的损伤是个复杂的、多方面的过程. 总的来说, 与胃黏膜的侵袭因素和防卫因素之间的不平衡有关. 前者包括胃酸、胃蛋白酶及黏膜刺激物等; 后者包括胃黏液层、黏膜血流、HCO<sub>3</sub><sup>-</sup>、PG、表皮生长因子、上皮细胞更新等. 侵袭因素相对增强表现为: 促进胃酸、胃蛋白酶分泌: 试验表明, 乙醇能增加壁细胞膜上H<sup>+</sup>-K<sup>+</sup>-ATP酶表达, 从而促进胃酸分泌, 并可促进胃蛋白酶的分泌<sup>[64]</sup>; 慢性乙醇中毒也存在酸高分泌现象<sup>[65]</sup>, 但也有不同观点<sup>[66]</sup>. 对胃肠道黏膜的刺激: 乙醇能影响胃肠道黏膜中乙醇脱氢酶、过氧化氢酶、微粒体乙醇氧化系统、乙醛脱氢酶等表达, 使得乙醛产生量多于被氧化量, 有潜在致癌活性<sup>[67-69]</sup>; 产生过多的

OFR对胃黏膜造成损伤. 乙醇可引起胃黏膜血管内皮损伤, 导致微循环障碍和缺血, 从而使OFR产生增多, 乙醇代谢亦可产生OFR. OFR可引起细胞膜中不饱和脂肪酸氧化导致膜顺应性下降, 并可氧化蛋白质中巯基以及造成DNA断裂. 应用巯基化合物清除OFR有助于黏膜修复<sup>[70,71]</sup>.

## 5 NSAIDs与胃黏膜保护

自1898年阿司匹林上市以来的一个多世纪里, NSAIDs已增至百余种, 成为全球最畅销的药品, 被广泛应用于治疗各种风湿性疾病及心脑血管疾病. 但NSAIDs的广泛应用引起了一系列并发症, 其中最重要的是NSAIDs相关性胃肠病, 轻者黏膜充血、水肿、糜烂及一过性浅表溃疡形成, 重者造成大面积溃疡合并消化道出血、穿孔甚至危及生命. 由于NSAIDs的镇痛作用, 使用NSAIDs的患者发生胃肠病时多数是无症状的, 当相应症状出现时, 往往病情已较严重. 这正是NSAIDs相关性胃肠病可导致高死亡率的原因. 据统计, 在美国每年有超过10万的患者因为服用NSAIDs导致胃肠道并发症而住院治疗, 死亡人数达1.65万<sup>[72]</sup>. 因此, 阐明NSAIDs相关性胃肠病的发病机制, 制定系统性防治措施是目前胃肠黏膜保护领域的一个重要课题.

NSAIDs相关性胃病病变主要位于胃窦、幽门、胃体部, 临床表现多样, 可毫无症状, 或表现为消化不良、腹胀、腹痛、溃疡、出血、穿孔等. 有时也表现为胃食管反流<sup>[73]</sup>. Roberts *et al* <sup>[74]</sup>对1991年至2002年之间PubMed收录的多篇关于NSAIDs的文章进行统计分析, 总结NSAIDs相关性胃肠病的危险因素如下: 与长期低剂量阿司匹林联用, 高龄, 既往有胃肠道溃疡、出血或穿孔史, 性别(男性高于女性), 与皮质激素联用, 与抗凝剂联用, 用药剂量大、用药时间长等. 其中, 合并多种危险因素者其胃肠病发生率明显高于仅有一种危险因素者.

细胞膜中的花生四烯酸在磷脂酶A2的作用下释放出来, 通过两条途径代谢: 一是在环氧化酶(COX)的作用下转化为PG和血栓素A2(TXA2); 二是在脂氧化酶(LOX)作用下产生白三烯(LT)<sup>[75]</sup>. PGs可增加黏液和HCO<sub>3</sub><sup>-</sup>分泌、促进上皮修复和细胞更新、增加胃黏膜血流、抑制胃酸分泌, 具有胃黏膜保护作用及适应性细胞保护作用. NSAIDs通过抑制COX从而抑制花生四烯酸生成PGs, 减少PGs对胃黏膜的保护作用, 最终导致胃黏膜损伤<sup>[76]</sup>. 同时, COX的抑制也使血栓素A2的合成减少, 从而抑制血小板凝集, 易诱发损伤的胃黏膜出血. 有研究发现, 口服NSAIDs后数小时至几天, 即可致胃黏膜瘀点、糜烂, 并进一步发展成急性溃疡, 停药后几天由于药物对血小板聚集及PGs合成的抑制作用

仍然存在, 故仍可继续导致消化道出血<sup>[77]</sup>. 在哺乳动物体内, COX有两种形式. COX-1为基础性酶, 正常存在于多数器官, 产生维持正常生理功能所需要的PGs和血栓素A2, 以保持胃黏膜的完整性; COX-2为诱导性酶, 在组织损伤过程中可诱导产生炎性PGs, 从而引起炎症、疼痛和发热<sup>[78]</sup>. COX-2在大多数器官不能检出, 但在炎症部位的炎症细胞中高浓度存在, 其PGs产物介导炎症发生. 传统的NSAIDs同时抑制两种COX, 因而在发挥其抗炎作用的同时, 也干扰了生理性PGs及血栓素A2的合成而产生胃肠损害作用.

目前认为*H pylori*和NSAIDs是消化性溃疡发生的两个重要独立危险因素, 两者相互作用. 单纯根除*H pylori*本身虽然不足以预防NSAIDs溃疡, 但较多意见倾向于根除*H pylori*对减少NSAIDs溃疡的发生有一定帮助. 到目前为止, 关于NSAIDs和*H pylori*相互作用的基础、临床和流行病学研究很多, 但来自各家的报道并不一致, 甚至结果相互矛盾. 这可能与不同的地理环境、不同*H pylori*亚型、疾病的不同阶段、有无消化性溃疡病史等因素有关. 对长期服用NSAIDs的患者, *H pylori*的感染是加重还是保护胃黏膜损害的发生, 以及如何治疗和预防消化性溃疡等问题仍未达成共识<sup>[79-83]</sup>. 然而, 近年有许多研究显示, 在*H pylori*感染者中, NSAIDs仍可引起黏膜PGs合成显著减少, 提示在NSAIDs存在时, *H pylori*引起PGs合成增加的作用并无明显意义. 因此, 从理论上推导, 由于*H pylori*与NSAIDs对黏膜的损害在许多方面有一致性, 两者对胃肠黏膜的损害作用会有相加效果<sup>[84,85]</sup>.

总之, 到目前为止, 关于NSAIDs和*H pylori*相互作用及其关系的认识还未形成共识, 进一步明确两者之间的关系, 需要进行更多设计严谨的大规模前瞻性临床研究.

## 6 上皮屏障与胃黏膜保护

处于高酸环境的胃黏膜上皮层有其自身特性. 胃上皮层在调节黏膜对食入抗原的反应过程中有一定意义. 给过敏体质动物食入抗原可刺激胃酸分泌、胃排空延缓. 胃上皮是紧密连接上皮, 可限制抗原进入黏膜固有层及体循环, 但白蛋白大小的分子(80 ku)可以以免疫特性完整的分子形式通过大鼠胃上皮, 提示胃内存在"抗原递呈"('antigen sampling')形式, 允许免疫系统探及胃腔内潜在有害的物质, 然后限制这些抗原性物质排空入肠腔.

整复(restitution)或重建(reconstitution)是指胃小凹健康细胞快速迁移以覆盖裸露基底膜的上皮修复过程. 离体研究发现该过程需数小时. 在体情况下需15-60 min. 离体情况下整复需要基底膜提供HCO<sub>3</sub><sup>-</sup>, 在



体情况下需要正常的黏膜血供. 上皮细胞黏附的基底膜对酸的损伤特别敏感. 在上皮受损、腔内pH较低情况下, 细胞碎片、黏液、血浆(纤维素、白蛋白等蛋白)组成的覆盖于损伤部位的"mucoïd cap"保护基底膜作为整复上皮迁移的支撑.

尚不明确趋化因子(chemotactic factors)是否参与该过程. 有证据提示某些生长因子可能参与该过程<sup>[86-92]</sup>. 如碱性成纤维生长因子(bFGF)影响整复过程. 腔内应用硫酸铝以结合bFGF, 防止其被酸降解, 使上皮细胞在pH低于3的情况下仍可整复, 而无硫酸铝时, 不会发生整复. 腔内应用bFGF也可在低pH时整复. TGF  $\alpha$ 在肠道具有调节上皮整复作用. 培养的小肠上皮细胞加TGF  $\alpha$ 可加速迁移.

胃黏膜血流量(GMBF)在胃黏膜保护机制中处于非常基础的地位, PGs及NO等因子可通过改善GMBF而发挥胃黏膜保护作用<sup>[93-95]</sup>. 胃表面上皮层下致密毛细血管网给上皮提供营养物质、氧, 清除和稀释从胃腔逆流入黏膜内的毒性物质( $H^+$ ). 当上皮层损伤时, 微循环为损伤部位修复创造必需的微环境(包括维持黏液帽内pH). 通常凡能刺激胃分泌的因素也能升高GMBF, 反之凡能抑制胃分泌的因素也能降低GMBF, 即胃分泌与GMBF相耦合. 这有利于胃黏膜发挥生理功能, 也有利于胃黏膜自身保护. 黏膜血管结构特别适合 $HCO_3^-$ 运输至上皮细胞, 当壁细胞每分泌1 mol  $H^+$ 入胃腺腔内时, 就有1 mol  $HCO_3^-$ 通过其基底侧分泌入有窗孔的毛细血管内, 并被运输至黏膜表面, 弥散入上皮细胞, 通过与 $Cl^-$ 交换, 主动排出 $HCO_3^-$ , 进入胃黏液层. 酸活跃分泌过程中胃碱运输至黏膜表面上皮增多, 即形成碱潮. 很多内源性物质调节黏膜血流, 其中最重要的是CGRP、PG、NO. 当黏膜暴露于刺激剂或酸逆流发生时, GMBF明显而快速地升高, 其意义在于清除或稀释逆流的损伤因子. 国外有文献认为胃黏膜pH/GMBF比值是评价胃黏膜损伤的敏感指标. 但也有在某些干预情况下二者出现分离现象. CGRP和NO在调节腔内刺激引起黏膜充血效应中起重要作用.

当黏膜防御机制都被破坏后, 便发生溃疡, 侵及整个黏膜层和黏膜肌层, 这时便通过最后防线进行修复. 愈合过程首先发生于溃疡周边, 渐渐向溃疡中心进行. 肉芽组织为新分化的上皮细胞迁移和形成黏膜结构提供支撑, 肉芽组织内新生血管形成为重建胃腺提供条件.

溃疡修复过程有多种生长因子和细胞因子参与, 但其具体作用有待阐明<sup>[96,97]</sup>. EGF由唾液腺产生, 对胃黏膜有多种作用, 增强其抗损伤能力. 但发生溃疡时, 溃疡边缘新形成的细胞系可表达EGF. 在大鼠实验性溃疡模型修复过程中EGFR明显上调. 其他生长因子如bFGF、TGF  $\alpha$ 等也参与修复过程, 但其作用尚未阐明.

## 7 PG、NO与胃黏膜保护

很多化学介质参与协调黏膜对损伤刺激的保护性反应, 大量证据表明PG、NO是最基本的重要介质, 影响黏膜防御的每一种成分: 抑制酸分泌、促进黏液和胃碱分泌、升高GMBF、促进溃疡愈合. 多种药物或理化因素通过调节PGs及NO的合成而影响胃黏膜损伤的修复<sup>[98-126]</sup>. PG、NO对肥大细胞激活和白细胞黏附血管内皮有抑制作用, 可能为张力性免疫调制剂. 抑制PG、NO的合成将增加黏膜对损伤的敏感性<sup>[127,128]</sup>.

NO由NOS催化生成. NOS有三种亚型: NOS I (nNOS)、NOS II (iNOS)及NOS III (eNOS), 其中NOS I及NOS III为 $Ca^{2+}$ -CaM依赖型. 许多文献采用不同方法证实正常胃黏膜均有3种NOS表达, 以eNOS表达高于iNOS, 其中nNOS主要在胃黏液上皮细胞表达, eNOS主要在胃腺底部、固有层组织细胞及血管内皮表达. 三种NOS均位于胞浆, 催化生成的NO作用不同. NO对效应细胞作用机制为以其高脂溶性通过细胞膜激活GC, 升高cGMP浓度, 发挥效应. 此外还可促进ADP核糖化, 促进ADP-核糖基与受体分子结合, 可引起3-磷酸甘油醛脱氢酶核糖基化, 封闭糖酵解过程而阻断ATP产生. 外源性NO可预防或减轻缺血-再灌注、乙醇、盐酸、PAF、内毒素、ET及应激等引起的急性胃黏膜损伤, 抑制内源性NO合成则加重上述因素引起的损伤, 拮抗NO合成抑制剂则可逆转其加重胃黏膜损伤效应. 内源性NO参与介导硫酸铝等药物的胃黏膜保护作用. 具有释放NO作用的新型NSAIDs无严重的胃黏膜毒性. NO胃黏膜保护机制与升高GMBF、抑制胃酸分泌、促进黏液分泌等因素有关. NO调节基础状态及 $H^+$ 、五肽胃泌素、CCK刺激状态下胃微血管张力, 扩张微血管, 升高GMBF. NO不影响基础状态下胃酸分泌, 但可抑制五肽胃泌素促肠嗜铬样细胞(ECL)释放组胺的效应, 并抑制组胺的促胃酸分泌效应. NO对 $HCO_3^-$ 分泌的影响报告不一.

人体胃黏膜PGs主要为PGA、PGE、PGF及PGI类, 以PGE和PGI<sub>2</sub>含量最高, 主要生理作用为抑制胃酸分泌和保护胃黏膜. PG参与介导直接和适应性细胞保护作用, 后者与其通过EP<sub>2</sub>/EP<sub>3</sub>受体作用促进黏液、 $HCO_3^-$ 分泌及维持黏膜血流等因素有关. 至少有两种COX参与PG合成. 胃内主要表达结构性COX-1, COX-2仅在暴露于某些细胞因子、有丝分裂原、内毒素和炎症部位诱导表达. 胃内炎症部位COX-2表达程度和其产生的PG对胃黏膜防御有何作用尚未阐明.

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● 消息 ●

## 我国科技论文总数连续三年世界第五

**本刊讯** 2004年度中国科技论文统计结果于2005-12-06在北京揭晓,与上一年度相比,我国科技论文SCI论文数增长15.2%,论文被引用篇数和次数分别增长4.4%和4.3%。更可喜的是,在过去十年间,我国论文被引用数已排在世界第14位,与上一年同一数据相比,位次提高了4位,

据介绍,2004年度《科学引文索引》(SCI)、《工程索引》(EI)和《科学技术会议录索引》(ISTP)共收录我国作者的论文111 356篇,比上年增加93 352篇,增长率为19.3%。我国科技论文占世界论文总数的6.3%,较上年增加1.2%,连续3年保持在世界第5位,前4位国家是美国、日本、英国和德国。根据生物医学专家的建议,今年在统计中新增加了美国《医学索引》(MEDLINE)检索系统,该系统是当今较权威的生物医学文献检索系统,我国大陆75种期刊被收录其中。

2004年度我国国内论文最多的学科仍是临床医学,基础医学名列第六。国内被引用次数最多的学科也是临床医学,基础医学名列第五。国际被引用论文篇数,基础医学与临床医学名列第八和第九。由于综合大学并校,高校论文产出前20位排名榜中已不见了医学院校,但在MEDLINE收录的高等院校排名中,仍可看到医学科技论文对综合大学论文排名的贡献。2004年排在SCI收录论文数第一的医疗机构是北京大学第一医院,解放军总医院在国内论文被引用次数、国内论文数和国际国内论文总数三个统计项目中,均名列医疗机构第一。

在同时公布的第四届中国百种杰出学术期刊中,22种医药卫生类期刊榜上有名。[摘自《健康报(记者张荔子)》]