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文献综述 REVIEW

蛋白酶激活受体的研究进展

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■背景资料
蛋白酶激活受体属于与G蛋白相偶联、有七个跨膜单位的受体家族, 其四个成员广泛的分布于各脏器及组织中, 目前研究较多的是PAR-1和PAR-2对胃黏膜的作用, 尤其是PAR-2对胃黏膜的保护作用, 可能成为胃黏膜疾病治疗研究的新靶点.

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摘要
蛋白酶激活受体属于与G蛋白相偶联、有七个跨膜单位的受体家族, 有四个成员: PAR-1, PAR-2, PAR-3和PAR-4. PAR-1是凝血酶受体, PAR-2是胰岛素、肥大细胞纤维蛋白溶酶、凝血因子Ⅶa和Ⅹa和其他未知蛋白水解酶的受体. PAR-2可诱导唾液腺和胰腺的分泌. PAR-1和PAR-2都对胃黏膜有保护作用, 但机制不尽相同. 在肠黏膜, PAR-2有前炎性和抗炎性双重作用, 其和PAR-1, PAR-4均可调节胃肠道平滑肌. 蛋白酶激活受体, 尤其是PAR-1和PAR-2对调节胃肠道功能有非常重要的作用.

关键词: 蛋白酶激活受体; 黏膜; 血管收缩; 血管舒张

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0 引言
蛋白酶激活受体(protease/proteinase-activated receptors, PARs)属于与G蛋白相偶联、有七个跨膜单位的受体家族[1], 这个家族在血液循环、呼吸系统、神经系统和消化系统中都具有非常重要的作用, 其有四个成员: PAR-1, PAR-3和PAR-4是凝血酶受体[2-5], PAR-2是胰岛素、肥大细胞纤维蛋白溶酶、凝血因子Ⅶa和Ⅹa和其他未知蛋白水解酶的受体[1,6]. PAR-1, PAR-2, PAR-4可由外源性5-6个氨基酸合成肽激活各自的受体. 激活PARs后的大部分信号传导途径是由活化磷脂酶C通过$G_{q/11}$蛋白介导的[1,7]. PAR-1, PAR-3, PAR-4可以激活血小板. 人和豚鼠的血小板可以表达PAR-1和PAR-4, 小鼠和大鼠的血小板可以表达PAR-3和PAR-4. PAR-1在许多组织和细胞中均是重要的因子. PAR-1 在胃肠道内分布广泛[1,8-9], 其激动剂可增加胃黏膜血流量, 预防应激性溃疡的产生[10]. PAR-2不存在于血小板中, 其在哺乳动物中的组织和细胞中不均衡的分布, 并在体内外的炎症反应中起到间介作用. PAR-2有前炎性和抗炎的双重作用, 可引起的炎症反应机制包括多重级联、血管渗透性增加、细胞因子生成和黏附因子的表达, 进一步引起白细胞聚集. 此外, PAR-2可促使类前列腺素和NO生成, 增加炎症反应, 激活神经末梢PAR-2可释放降钙素基因相关肽和P物质. 因此, 进一步研究PAR-2, 可为治疗许多炎症提供靶向, 包括: 变应性皮炎、类风湿性关节炎、哮喘、胃肠道疾病和神经痛. PAR-3广泛的分布于心脏、小肠、骨髓、气道平滑肌、血管内皮和星形胶质细胞[7]. PAR-4主要分布于肺脏、胰腺、甲状腺、睾丸和小肠[7]. PAR-3和PAR-4作为其他PARs受体(尤其是PAR-1)的初级或辅助受体, 二者均分布于血小板[11], 并在血液凝集过程中起重要作用[12].

1 蛋白酶激活受体的分布
1.1 唾液腺 PAR-1和PAR-2的信使RNA广泛的分布于腮腺、舌下腺和下颌腺[10]. 向小鼠或大鼠腹腔内注入PAR-2激动剂——SLIGRL后, 其迅速分泌唾液, 而PAR-1的激动剂——TFLIR-amide则没有这种作用[7,10]. PAR-2激动剂和胰岛素——内源性PAR-2激动剂, 可以诱导离体大鼠腮腺[10]、舌下腺[12]分别分泌淀粉酶和黏蛋白. 由PAR-2启动的体内唾液和淀粉酶的分泌可被NO合酶阻滞一部分, 而不会被辣椒素阻断, 由此证明起作用的是内源性NO, 而不是感觉神经元[12]. 由PAR-2启动的唾液分泌信号传导机制还不十分清楚.

1.2 胃黏膜 PAR-1和PAR-2的mRAN广泛的分布于胃黏膜组织中[13]. PAR-1和PAR-2在胃黏膜中起到双重作用, 主要是保护作用[8-9]. 给予PAR-2激动剂后, 在结扎幽门的麻醉大鼠, 胃黏液分泌

增多[14]. 反复给予辣椒素、降钙素基因相关肽拮抗剂或NK_2受体拮抗剂, 可终止由PAR-2介导的黏液分泌. 因此表明, 黏液分泌的机制可能和辣椒素敏感性神经元、内源性CGRP、神经激肽A和NK_2拮抗剂有关. 分别给予大鼠外源性CGRP和神经激肽A, 可诱导胃黏膜通过CGRP和NK_2受体分泌黏液[14]. 给予PAR-2后, 不仅使黏液分泌增多, 也通过激活辣椒素敏感性感觉神经元, 在不同类型的大鼠胃黏膜损伤模型中起到胃黏膜保护作用. 由PAR-2产生的胃黏液分泌和黏膜的保护作用, 并不包括内源性类前列腺素的形成[14]. 当PAR-2激活感觉神经元后, 可释放CGRP和神经激肽A, 通过CGRP1和NK_2受体促进黏液分泌. 起到黏膜的细胞保护作用. PAR-1同样也有胃黏膜保护作用, 而其主要的保护机制和PAR-2介导的黏膜保护机制不同[14]. PAR-1激动剂产生的保护作用可被消炎痛(一种环丙烷加氧酶)阻断, 而不被辣椒素所阻断, 提示其作用机制和内源性类前列腺素有关, 和感觉神经元无关. PAR-2激动剂可使离体大鼠胃小动脉扩张, 全身给药后, 可使麻醉大鼠胃黏膜血流量增加[8-9,14], 也可促使NO、类前列腺素、EDHF发挥舒张血管作用, 其和PAR-2的舒张作用是互相促进的, 而PAR-1则没有这种促进关系. 连续给予PAR-1和PAR-2激动剂可使血管舒张作用部分或者全部消失. 这些作用包括PAR介导的收缩/舒张反应和钙离子信号途径, 并且和急性脱敏或快速免疫法有关. 诱发舒张作用的降低和消失并不能说明PAR-1和PAR-2具有收缩作用, 在对静止标本的实验中, 激动剂并没有显示出收缩作用[10]. PAR-2也有抑制胃酸分泌的作用, 其抑酸作用是由卡巴胆碱-2-脱氧-D-葡萄糖或五肽胃泌素诱导的, 和辣椒素敏感性神经元及内源性类前列腺素无关[13]. PAR-1激动剂也可以增加胃黏膜血流量并抑制胃酸分泌[15]. PAR-1激动剂的这些胃黏膜保护作用可能促进了内源性类前列腺素的产生[15], 其作用机制和PAR-2明显不同. 应用免疫组化方法分析PAR-2在胃的表达, 可发现胃黏膜主细胞被抗PAR-2抗体明显染色[16], 表明PAR-2可能调节胃蛋白酶分泌. 反复给予PAR-2激动剂, 可以逐步的增加胃蛋白酶在结扎幽门的麻醉大鼠中的分泌[16], 这是由于直接激活了主细胞中的PAR-2. 而PAR-1的免疫反应并不在主细胞上[17]. 而反复的给予PAR-1激动剂, 也可以轻微的使胃蛋白酶分泌增加[20]. PAR-1和PAR-2在胃黏膜中都起到多重的作用, 其主要作用为保护作用, 但二者机制截然不同.

1.3 胃肠道平滑肌 PARs在调节胃肠道平滑肌蠕动方面具有重要的作用. 在大鼠离体的食道黏膜肌层, 凝血酶的两个受体, PAR-1和PAR-4, 起到相反的作用, 分别产生收缩和舒张作用[18]. 激活PAR-2和PAR-1后, 对静止的胃的纵向的平滑肌产生收缩作用[19-20], 对碳酰胆碱处理过的标本产生舒张作用[21]. 激活PAR-1后产生双重的效应, 在离体的大鼠十二指肠平滑肌表现为收缩之后舒张, PAR-2激活后产生缓慢的舒张反应[22-23]. 由PAR-1和PAR-2在不同的胃肠道平滑肌组织中产生的舒张作用是由活化的蜂毒明肽敏感的钾离子通道介导的[24]. PAR-1和PAR-2激动剂和抑氨肽酶素的联合腹腔注射, 可促进小鼠胃肠道蠕动[25]. PAR-1和PAR-2激动剂是由L型钙离子通道介导的, 并可被蜂毒明肽敏感的钾离子通道稀释. PARs, 尤其是PAR-1和PAR-2, 在调节胃肠道蠕动方面具有复杂的机制. PARs在调节胃肠道平滑肌运动性方面的生理学和病理生理学的意义还有待进一步研究.

1.4 肠黏膜 PAR-1和PAR-2都可以调节肠道离子转运[26-29]. PAR-1和PAR-2产生的离子转运调节是由激活的环丙烷-加氧酶和随后分泌增加的前列腺素E_2介导的[27-28]. PAR-2在结肠炎症发展过程中起到双重作用. Fiorucci *et al*[30]证实: 反复的皮下给予PAR-2激动剂——SLIGRL-amide, 可以阻止Th1细胞介导的实验性大肠炎的发展, 并可使其痊愈. PAR-2激动剂的这种保护作用, 同其胃黏膜保护作用相同, 也是通过激活的辣椒素敏感性神经元介导的[14]. 而不同的是, 结肠内给予PAR-2激动剂, 可引起结肠炎症的迅速发展, 辣椒素敏感性神经元、NO和细胞渗透性改变参与了此机制[31-32]. 因此, PAR-2在结肠炎症中的作用是复杂的, 在临床上应用PAR-2激动剂或拮抗剂治疗炎性肠疾病还有待进一步研究.

1.5 胰腺 在PAR家族中, 只有PAR-2参与了胰腺的外分泌机制. PAR-2激动剂, 可使麻醉大鼠胰液分泌短暂减少, 随后胰液分泌持续升高[33]. PAR-2造成胰液分泌的复杂机制目前还不十分清楚. 无论是在离体大鼠的胰腺[33]还是在意识清醒的大鼠的胰腺内[34], PAR-2激动剂均可以促进淀粉酶的分泌. PAR-2在促进小鼠胰腺分泌淀粉酶的同时, 也促进NO的产生[34]. 在狗胰管的上皮细胞, PAR-2激动剂可迅速开放并迅速关闭离

子通道[35]. 由PAR-2产生的体外快速离子通道激活, 可能与PAR-2在体内诱导的胰液瞬间分泌升高有关. 有报道称PAR-2能被胰蛋白酶激活, 来影响组织功能, 胰蛋白酶是PAR-2的内源激活剂[36].

2 展望

PAR家族, 尤其是PAR-1和PAR-2, 在胃肠道系统广泛的分布. PAR-1和PAR-2激动剂或拮抗剂可能在治疗各种胃肠道营养性疾病中具有意义. 据报道, 已有PAR-1的拮抗剂[37-38], 而还没有PAR-2拮抗剂, 可能是由于很难建立高度特异、有效的PAR-2受体结合测定方法. 目前, PAR-1和PAR-2被认为是重要的药物治疗靶向. PAR-2和肿瘤的关系也日益值得关注.

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