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慢性胰腺炎疼痛机制研究进展

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[摘要] 慢性胰腺炎导致的顽固性胰腺疼痛往往很难利用现有临床疗法有效解决。人们对这种疼痛的机制尚不清楚,虽然导管和实质压力增加是引起胰腺炎疼痛的主要原因,但充足的证据表明神经病理性疼痛也是很重要的原因之一。此外,最近的研究证实脊髓以上和较高的大脑中枢在胰腺炎疼痛维持中起到重要作用。本文重点阐述了对慢性胰腺炎疼痛产生和维持起作用的外周及中枢发病机制。

[关键词] 慢性胰腺炎;疼痛;神经病理性疼痛

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Pain mechanism in chronic pancreatitis: an update

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[Abstract] Pancreatic pain caused by chronic pancreatitis is often difficult to cure by current therapy. Such pain mechanism still remains unclear. Although the increase of pressure on the duct and solid tissue is the main cause of pancreatitis pain, enough evidence has showed that the neuropathic pain is a very important reason. In addition, recent studies have confirmed that the center of spinal cord above and higher centers in the brain play important roles in the maintenance of pancreatitis pain. This review focuses on the peripheral and central pathogenesis in the development and maintenance of chronic pancreatitis pain.

[Key words] chronic pancreatitis; pain; neuropathic pain

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慢性胰腺炎是由各种原因引起的胰腺持续性的炎症疾病,表现为胰腺实质和导管结构的破坏而产生的反复顽固的内脏痛。大多数慢性胰腺炎患者疼痛为持续的深部轻度至无法忍受的上腹部疼痛,通常辐射到背部,饭后或酒后加剧,但位置和程度因人而异,差别很大^[1]。现有的疼痛治疗方法只对某些患者疗效确定,治疗结果在疾病的不同阶段各不相同;在少数患者中疼痛可自发消失,出现所谓的“烧毁”现象,然而这种现象的发生不可预知^[2]。慢性胰腺炎疼痛的发病机制尚不清楚,越来越多的研究表明胰腺炎疼痛是多因素的,如胰腺导管和实质组织压力增高、生物活性物质改变、胰腺神经分布改变等都可能与胰腺疼痛有关。

1 胰腺炎引起疼痛的外周机制

1.1 胰腺组织压力增加 目前普遍认为胰腺导管内压力持续升高是产生胰腺疼痛的主要原因。慢性胰腺炎患者中胰腺导管内压力可达 20~80 mmHg(正常值 7~15 mmHg, 1 mmHg=0.133 kPa)^[3]。然而, Morgan 等^[4]研究发现胰腺炎的严重程度和胰腺压力之间没有关联,且极轻度的慢性胰腺炎患者导管内的压力并不增加。

慢性胰腺炎患者通常胰腺实质压力升高可达 30 mmHg^[5],

文献报道慢性胰腺炎患者胰腺实质压力最高可达 662 mmHg^[6]。

慢性胰腺炎患者的反复炎症使胰腺神经受压,最终导致纤维组织形成,使发病机制变得更加复杂。增加胰腺导管和组织压力可进一步导致胰腺组织缺血,从而促使胰腺疼痛加剧(此类报道很罕见并且慢性胰腺炎患者极少伴有胰腺缺血)^[7]。

1.2 生物活性物质改变 胰腺是具有丰富神经支配的器官,胰腺炎症累及神经,使神经周围炎症细胞活化,嗜酸性粒细胞、CD4⁺ 和 CD8⁺ 淋巴细胞、巨噬细胞、肥大细胞等释放多种炎症因子,并产生神经营养因子,在胰腺炎疼痛中发挥作用^[8-10]。

1.2.1 神经生长因子(NGF) NGF 在神经元生长与分化中具有关键作用。研究表明 NGF 是维持炎症疼痛的重要疼痛介质^[11]。Winston 等^[12]采用三硝基苯磺酸(TNBS)诱导产生胰腺炎模型,观察到 NGF 水平上调并随着胰腺炎症消退而恢复至正常水平。Ceyhan 等^[13]对慢性胰腺炎患者的胰腺 NGF 表达研究发现,化生的导管上皮细胞中 NGF mRNA 表达增强,但 NGF 和疼痛之间没有任何关系,而酪氨酸激酶 A 受体和疼痛强度之间呈相关性。Della Seta 等^[14]和 Lewin 等^[15]的实验证实 NGF/TrkA 途径激活可影响慢性胰腺炎的疼痛产生; NGF 可产生持久剧烈的热痛觉过敏和机械触痛;在疼痛动物

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模型研究中,注射抗内源性 NGF 抗体或 TrkA 的免疫球蛋白 G(IgG)将降低痛觉过敏。

1.2.2 胶质细胞源性神经营养因子(GDNF) GDNF 家族中的神经营养因子,如青蒿琥酯可调节慢性胰腺炎的疼痛。Ceyhan 等^[16]的研究表明慢性胰腺炎患者中青蒿琥酯及其受体 GFR α 3 的过度表达与疼痛的频率和强度有关。

Zhu 等^[17]的研究表明脑源性神经营养因子(BDNF)在疼痛调制中起到关键作用。慢性胰腺炎患者的胰腺组织 BDNF 的水平与疼痛强度关系密切。

1.2.3 生长相关蛋白-43(GAP-43) GAP-43 与神经髓鞘的组成及修复密切相关,常被用于检测正常人体胰腺组织和慢性酒精性胰腺炎的神经支配。Di Sebastiano 等^[18]发现在慢性胰腺炎患者的大直径神经纤维中的 GAP-43 表达水平增加,且 GAP-43 与疼痛强度和免疫细胞的组织浸润均呈阳性相关。

1.2.4 P 物质 Michalski 等^[19]发现在 P 物质降解酶的水平保持不变的情况下,神经激肽受体(NK1、NK2)和 P 物质编码基因(PPT-A)的上调可能在慢性胰腺炎患者顽固性疼痛的产生中发挥作用。

1.2.5 瞬时受体电位通道香草酸亚型 1(TRPV1) TRPV1 即辣椒素受体,被证实各种疼痛状态下包括慢性胰腺炎模型中发挥重要作用。Xu 等^[20]对慢性胰腺炎疼痛大鼠的研究发现胰腺组织中 TRPV1 水平上升,但是没有发现患者的疼痛强度和 TRPV1 表达之间的关系。Van Esch 等^[21]研究表明,在荷兰的慢性胰腺炎患者中没有发现与 TRPV1 基因多态性的关联。

1.2.6 蛋白酶激活受体 2(PAR2) PAR2 是最新公认的能引起胰腺炎疼痛的物质。PAR2 在胰腺腺泡细胞和导管上皮表达,是胰腺外分泌功能主要调节因子(胰蛋白酶是公认的最强 PAR2 激活剂)。在胰腺炎模型中,蛋白酶抑制剂,如卡莫司他和奈莫司他可阻止腹部痛觉过敏^[22]。Takeda 等^[23]的研究证实奈莫司他可显著减少急性胰腺炎疼痛持续时间。Kawabata 等^[24]的研究表明,PAR2 基因敲除小鼠腹部疼痛过敏较野生型小鼠更为严重。

1.3 自主支配神经分布改变 慢性胰腺炎的“神经重建”已成为产生剧烈疼痛的机制之一。Ceyhan 等^[13]报道慢性胰腺炎患者与正常捐助胰腺组织相比胰腺交感神经支配下降,但胆碱能神经支配无统计学差异。研究还发现,神经巢蛋白表达增加,这表明慢性胰腺炎过程中神经元损伤后发生神经元再生。

1.4 胃肠激素改变 Slaff 等^[25]研究证实慢性胰腺炎疼痛可能是由于血液中胆囊收缩素(CCK)升高造成。事实上,口服 CCK 抑制剂,可以缓解部分慢性胰腺炎患者的痛苦。然而,并非所有慢性胰腺炎患者的 CCK 水平均升高,单独替代疗法并不可缓解所有患者的疼痛。尽管如此,胃肠激素仍然是慢性胰腺炎复杂疼痛机制中主要原因之一^[26]。

2 胰腺炎引起疼痛的中枢机制

慢性胰腺炎疼痛中枢机制包括大脑皮质功能区重建和脊髓传导途径两部分。大脑皮质功能区重建主要包括大脑皮质

活动区域增大、大脑皮质内脏感受区重组和脑干下行抑制传导^[27];脊髓传导途径主要包括“时间总和”效应^[28]、脊髓敏感性上升及中枢兴奋性增加、痛觉敏感^[29]和涉痛区域增大^[30]。

慢性胰腺炎疼痛通常辐射到背部,即“牵涉痛”,临床上将内脏患病时体表发生的感觉过敏区以及该区的骨骼肌反射性僵硬和血管运动、汗腺分泌的障碍等体征称为海德带(Head zones)。发生“牵涉痛”的体表部位与病变器官受同一节段脊神经支配,体表部位与病变器官的感觉神经进入同一脊髓节段,并在后根神经节内密切联系,Dimcevski 等^[30]研究发现慢性胰腺炎患者牵涉痛区域为 30.1 cm²(对照组为 7.7 cm²)。

Dimcevski 等^[27]利用诱发脑电位技术的研究发现与健康对照组相比电刺激慢性胰腺炎患者食管、胃和十二指肠可引起患者双侧脑岛、前扣带回和双侧躯体感觉区早期诱发电位缩短。此项研究表明接收和调节内脏痛的大脑中枢发生功能重组。

2009 年 Westlund 等^[31]研究持续性化学诱导大鼠胰腺炎模型时,发现脊髓上和较大大脑中枢磁共振成像(MRI)信号增强。这些整合内脏伤害性刺激区域包括延髓头端腹外侧、中缝背核、中脑导水管周围灰质、杏仁核、丘脑、扣带皮质和顶叶皮质等^[32],结果意味着以上功能区域与胰腺炎伤害性刺激信息处理相关。

Vera-Portocarrero 等^[32]对大鼠慢性胰腺炎模型的研究表明延髓头端腹外侧区域在维持内脏痛下行易化作用中发挥至关重要的作用,而不是在最初起作用。

通过对大脑的研究,发现慢性胰腺炎患者下行疼痛抑制调节功能受损,从而对疼痛刺激敏感性增高^[33]。Drewes 研究小组^[34]证实慢性胰腺炎患者大脑皮质厚度减少,而大脑皮质厚度改变通常是衡量疼痛系统功能障碍的一个重要指标。

3 小结

慢性胰腺炎疼痛对医务人员和患者来说仍然是一个挑战。尽管对慢性胰腺炎疼痛的研究已有了一些显著进展,但其发病机制仍然未被完全了解。胰腺炎复杂的病理机制使得疼痛治疗变得困难而效果有限。疼痛的产生因素很多,不同研究结果往往存在矛盾,需要进一步探索新治疗方法以帮助慢性胰腺炎患者解决疼痛。

4 利益冲突

所有作者声明本文不涉及任何利益冲突。

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