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文献综述 REVIEW

肠促胰素分泌分子机制的研究进展

刘 剑, 吴明昊, 高 宇

背景资料
肠促胰素相关药物与传统降糖药物相比具有较低的低血糖风险和减轻体质量的作用, 故目前促进内源性肠促胰素的释放已成为治疗2型糖尿病和肥胖的新策略. 营养物质对肠道内分泌细胞有促分泌作用, 本作者对营养素与肠促胰素分泌的关系进行深入的研究.

刘剑, 吴明昊, 承德医学院研究生学院 河北省承德市 067000
高宇, 承德医学院附属医院内分泌科 河北省承德市 067000
刘剑, 在读硕士, 主要从事内分泌学的研究.
作者贡献分布: 本文综述由刘剑与吴明昊完成; 高宇审校.
通讯作者: 高宇, 教授, 主任医师, 医学博士, 硕士生导师, 067000, 河北省承德市双桥区南营子大街36号, 承德医学院附属医院内分泌科. yugao815@163.com
电话: 0314-2279662
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Molecular mechanisms of incretin hormone secretion

Jian Liu, Ming-Hao Wu, Yu Gao

Jian Liu, Ming-Hao Wu, Graduate School of Chengde Medical College, Chengde 067000, Hebei Province, China
Yu Gao, Department of Endocrinology, Affiliated Hospital of Chengde Medical College, Chengde 067000, Hebei Province, China
Correspondence to: Yu Gao, Professor, Chief Physician, Department of Endocrinology, Affiliated Hospital of Chengde Medical College, 36 Nangyingzi Street, Shuangqiao District, Chengde 067000, Hebei Province, China. yugao815@163.com
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Abstract
Incretin is a kind of intestinal hormone secreted by the enteroendocrine cells in the intestinal epithelium. There has been plenty of research to explore the molecular mechanisms of incretin hormone secretion, including secretion-promoting factors such as glucose, lipid, protein and other nutrients in enteroendocrine cells. This review aims to discuss the signal pathways related to incretin hormone secretion.

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Key Words: Incretin; Molecular mechanisms; Type 2 diabetes mellitus; Nutrient signaling

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摘要
肠促胰素是由肠上皮内分泌细胞分泌的一类肠源性激素. 已有大量研究去探索肠促胰素分泌的分子机制, 包括葡萄糖、脂质、蛋白质等营养素对肠道内分泌细胞的促分泌作用. 本文将对影响肠促胰素分泌的相关感应信号通路研究进展作一综述.

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关键词: 肠促胰素; 分子机制; 2型糖尿病; 营养素信号

核心提示: 肠促胰素具有改善血糖稳态、减轻体质量等作用, 但其分泌机制尚不明确, 本文就影响肠促胰素分泌的相关感应信号通路进行总结, 旨在寻找促进内源性肠促胰素释放机制, 为治疗2型糖尿病和肥胖提供新策略.

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同行评议者
高凌, 副教授, 副主任医师, 武汉大学人民医院内分泌科

0 引言
肠道除了能消化吸收营养物质外, 还具有内分泌功能. 肠促胰素是由肠上皮内分泌细胞

分泌的一类肠源性激素, 主要包括胰高血糖素样肽-1(glucagon-like peptide-1, GLP-1)和葡萄糖依赖性促胰岛素激素(glucose-dependent insulinotropic polypeptide, GIP)两种激素. 他们能够调节摄食后机体的代谢反应, 比如在调控食欲[1]、影响体质量[2]、稳定血糖[2,3]、调节肠道动力[4]等方面发挥着重要作用. 目前促进内源性肠促胰素的释放已成为治疗2型糖尿病和肥胖的新策略[5]. 已有大量研究[6-8]去探索肠促胰素分泌的分子机制, 其中包括葡萄糖、脂质、蛋白质等营养素对肠道内分泌细胞的促分泌作用, 并有学者大胆推测营养素感应信号通路将是治疗糖尿病和肥胖的新靶点[9]. 本文将对影响肠促胰素分泌的相关感应信号通路研究进展作一综述.

1 肠道内分泌细胞的生理作用

肠道内分泌细胞L细胞和K细胞贴附于肠道上皮, 并向肠腔伸出富含微绒毛的顶端. 分泌GIP的K细胞主要是位于十二指肠, 而分泌GLP-1的L细胞主要在远端回肠和结肠, 可能正因他们分布位置的不同, GLP-1与GIP的分泌呈不同时相[10]. 随着对肠道内分泌细胞研究的深入, 观察到肠源性激素种类远超出研究者之前的预想. 目前已证实肠道L细胞除了能够分泌GLP-1、GLP-2、胃泌酸调节素, 也可以生成酪酪肽(peotide YY, PYY), 还发现大多数K细胞和L细胞均能生成胆囊收缩素(cholecystokinin, CCK)[11]. 有学者认为肠促胰素的分泌是由于营养素如蛋白质、脂肪和葡萄糖能激活内分泌细胞相关感应信号通路, 其中K细胞能较早接触到摄食中的营养素, 故摄食后短时间内就有GIP的分泌, 而L细胞主要在肠道远端, 因此有学者提出GLP-1的分泌还受营养素消化吸收过程和肠道菌群的影响[12]. 体外研究[13]证实, L细胞分泌GLP-1的过程是一种电生理活动, 葡萄糖转运导致的电生理变化可诱导动作电位的产生和钙离子内流, 最终引起细胞内钙离子浓度增加, 促进激素的释放.

2 葡萄糖对肠促胰素的分泌的影响

葡萄糖感应信号通路的提出是因为在动物实验中发现葡萄糖对于肠促胰素的释放有较强的促进作用, 并且此作用可被根皮苷(葡萄糖吸收阻断剂)所抑制. 葡萄糖在肠上皮细胞的吸收和肾小管的重吸收主要依靠钠-葡萄糖协同转运蛋白(sodium-glucose transporter, SGLT)完成[14]. SGLT-1主要分布小肠内, 而SGLT-2几乎仅分布于肾近曲小管中, SGLT-2可将尿液中的葡萄糖逆浓度转运至肾小管上皮细胞, 而后通过上皮细胞基底膜上的葡萄糖转运体2(glucose transport-2, GLUT-2)顺浓度梯度进入血液中, 临床应用的SGLT-2抑制剂就是通过阻断此作用、增加尿糖的排除进而降低血糖[15,16]. 研究[17]发现在小肠上部, GLP-1和GIP的释放受位于肠刷状缘的SGLT1调节, SGLT1激活引起钠离子内流, 细胞膜去极化、钙离子电压门控通道开放, 引发细胞内钙离子聚集, 导致GLP-1和GIP激素释放. 在体外, SGLT1抑制剂可以阻止葡萄糖介导的GLP-1和GIP的分泌[18], 同样, 对*SGLT1*基因敲除小鼠喂糖之后发现葡萄糖介导GLP-1和GIP分泌功能遭到破坏[18,19]. 但出人意料的是, 对*SGLT1*基因表达减少的小鼠, 经喂糖之后, 血浆GLP-1水平却有所升高, Powell等[20]认为SGLT1表达减少使得小肠上部对葡萄糖的吸收作用减退, 这意味着含有大量L细胞的小肠末端的葡萄糖相对增多, 激活了该处的其他传导信号通路导致血浆GLP-1水平升高; 也有学者提出另一种假说, 增加远端糖负荷能够促进微生物发酵和短链脂肪酸的产生, 并利用其他信号通路刺激L细胞分泌GLP-1增加[21]. 有学者[7]发现, 胰岛β细胞的葡萄糖应答与ATP敏感型K离子通道(ATP-sensitive potassium channel, KATP)关闭有关, 其中L细胞和K细胞均高表达KATP. 磺脲类药物可以刺激原代培养的细胞分泌GLP-1和GIP, 不过这一现象对进食后的早相肠促胰素分泌不起作用, 因为使用KATP抑制剂并未发现肠促胰素浓度的改变[22]. 更让人疑惑的是, 实验发现缺乏KATP通道的小鼠经喂糖后, 血循环中的GIP水平是升高而非预想的下降, 葡萄糖刺激肠促胰素的分泌是否经KATP介导还需进一步验证.

另一条葡萄糖感应信号通路是甜味感受器, 他由G蛋白偶联受体异二聚体T1R2和T1R3构成, 与G蛋白α-味蛋白连接, 作为葡萄糖和其他甜味剂的感应器[23,24]. 有实验应用免疫染色法证实α-味蛋白、T1R2和T1R3在肠道内分泌细胞表达. 支持这条通路存在的有利证据是在缺乏α-味蛋白的小鼠上, 发现葡萄糖诱导的GLP-1和GIP分泌作用减弱[25]. 但也有研究[26,27]

研发前沿

肠促胰素呈葡萄糖浓度依赖方式, 刺激胰岛素分泌, 维持体内血糖稳态, 在营养素与肠促胰素分泌的关系上, 葡萄糖、脂质、蛋白质的肠促胰素分泌的分子机制是研究的重点和热点, 非营养素感应信号通路与肠促胰素分泌的机制尚待进一步阐明.

相关报道

Nauck等学者发表多篇文章, 阐述了肠促胰素对于进餐后的胰岛素分泌作用和影响其分泌的药物、食物营养素等作用机制, 其中在糖尿病患者和糖耐量减低人群中, 食物致肠促胰素分泌减少或缺乏, 是血糖升高的原因之一.

创新盘点

本文通过对目前营养素与肠促胰素关系的大量文献研究, 总结了这方面的最新研究成果, 对营养素影响肠促胰素分泌的机制做了深入全面总结和分析.

表明他们可能不是作为L细胞的葡萄糖传感器, 因为在啮齿动物和人类身上, 人工甜味剂无法促进肠促胰素的分泌.

3 脂类对肠促胰素分泌的影响

机体存在许多不同机制作用于肠腔内脂质的感应[28]. 已证实在小肠内分泌细胞上有许多脂肪酸受体表达, 例如G蛋白受体(G-protein receptor, GPR), 其中包括GPR40、GPR41、GPR43、GPR120等. GPR40属于Gαq家族成员, 与长链脂肪酸结合后会刺激磷脂酶C(phospholipase C, PLC)生成甘油二酯和3磷酸肌醇(inositol triphosphate, IP3), 这将激活蛋白激酶C通路和细胞内钙离子浓度增加, 最终导致肠道激素的分泌[29]. GPR120在小鼠和人肠道内分泌细胞以及STC-1细胞系高表达, GPR120受体激活会促进小鼠和人的CCK、GLP-1的分泌, 但在去除*GPR120*基因的小鼠, 仅发现GLP-1的分泌有所改变而CCK的分泌无明显变化. 有学者认为GPR介导的CCK分泌过程相当复杂且多种GPR受体调控, 其中涉及受IP3调控的细胞膜上瞬时受体电位通路5(transient receptor potential channel type M5, TRPM5)和L型电压依赖型门控钙离子通道(voltage-gated calcium channel, VGCC), 多种GPR受体与脂质结合会激活上述通道的开放, 引起细胞膜进一步去极化和钙离子内流活动增加, 最终促进CCK的分泌[30]. 短链脂肪酸(short-chain fatty acid, SCFA)是膳食纤维在结肠由细菌发酵所产生, 实验表明纤维种类、肠道菌群、肠道内分泌细胞之间存在一定的联系[31]. GPR41和GPR43在肠道末端高度密集, 并与短链脂肪酸结合后会抑制腺苷酸环化酶AC并且降低cAMP[32]. 体外实验研究[33]发现, 缺乏GPR43的小鼠在SCFA刺激下, 循环中GLP-1水平升高不明显, 证实了脂肪酸受体在肠促胰素分泌过程中发挥作用. 此外, 大量动物实验证实高脂喂养的肥胖大鼠, 其肠道GPR40、GPR41、GPR120等脂肪酸受体的表达发生改变, 一些相关的肠促胰素(如GLP-1、GIP等)的水平也产生变化, 这也再次证明食物中脂质对肠促胰素的分泌有着重要影响.

4 蛋白质对肠促胰素分泌的影响

研究[7,8,34,35]发现GLUTag、STC-1、NCL-H716细胞系(目前研究肠道相关激素分泌最常使用的三种细胞模型)均可被蛋白分解产物刺激GLP-1的分泌, 实验证明某些氨基酸能够促进GLP-1的释放. 有学者认为*L*-谷氨酰胺可能利用Na^+介导氨基酸吸收过程中的产电效应, 使细胞膜去极化, 同时还能通过G蛋白偶联受体(G protein-coupled receptors, GPCR)提高细胞质cAMP浓度. 在健康、肥胖、糖尿病人群中, *L*-谷氨酰胺证实能够刺激GLP-1释放[36]. 目前一般认为蛋白质对肠促胰素的分泌所发挥的作用与葡萄糖、脂质相比还是相对较弱, 但是对于CCK而言, 蛋白质分解产物的刺激作用最强. 有实验发现蛋白质分解产物可刺激小肠黏膜中Ⅰ细胞分泌一种CCK释放肽, 他可介导CCK的释放, 但其中相关机制还未明确, 还需进一步实验研究.

5 非营养素感应信号通路和抑制性通路

除了受营养素影响外, 肠促胰素的分泌还受肠腔其他成分的调控. 目前研究[37]已证实, 肠道菌群可以调节肠道内分泌细胞分泌肠道激素, 如PYY、GLP-1等.

肠内的孕酮通过激活细胞膜受体刺激肠促胰素的分泌[38]. 胆汁酸也参与代谢信号传导中, 在离体的小鼠结肠, 腔内输注胆汁酸可增加GLP-1的水平, 随后试验证明在L细胞, 胆汁酸可能通过与胆汁酸受体结合进而刺激GLP-1的分泌, 尤其进食后机体生成CCK增加, 这会导致更多的胆汁酸传递至富含L细胞的远端回肠处, 刺激GLP-1的分泌[39]. 最近研究[40]证实, 胆汁酸对人类葡萄糖稳态和血浆GLP-1水平有积极影响. 有趣的是, 接受减肥手术的患者, 术后血浆胆汁酸水平有所提高[41], 胆汁酸刺激GLP-1分泌可能有助于调控机体术后的代谢状态. 除了有增强肠促胰素分泌的途径, 肠内分泌细胞也表达相关因子抑制肠道激素的分泌. 例如, K细胞和L细胞表达与Gi蛋白耦联的生长抑素受体, 生长抑素会减少GLP-1和GIP的释放. 在肠内分泌细胞, 生长抑素会抑制由腺苷酸环化酶激活剂刺激的cAMP水平的变化, 进而抑制蛋白激酶A途径, 减少肠促胰素的释放[42]. 同样与Gi受体结合的大麻素Cnr1也与调节肠促胰素的激素分泌有关. Cnr1在K细胞中的表达高于在L细胞的表达, 并且首先抑制GIP的分泌而不是GLP-1[43].

6 结论

基于肠促胰素对葡萄糖稳态的重要性, 激活肠促胰素释放已然成为2型糖尿病和肥胖症治疗的新途径[5,44,45]. 一些肠内分泌细胞的靶点包括GPR40、GPR41、GPR43、GPR119、GPR120目前仍在研究中, GPR119受体激动剂在动物模型中作用显著, 但在人类降低血糖、肠促胰素作用有限, 其原因仍有待于进一步研究[46,47]. 令人惊讶的是, 最近研究[48]发现SGLT1抑制剂可以导致2型糖尿病动物和人的GLP-1和PYY水平升高. 通过给予肠道菌群药物提高含有丰富L细胞的远端肠道的短链脂肪酸的含量, 模拟SGLT1敲除效应, 结果发现餐后GLP-1和PYY水平明显升高[49]. 某些形式的减肥手术(其实与增加肠道远端营养物的机制相近)可以明显影响食欲和2型糖尿病的预后[50], 通过药物干预替代外科减肥手术将会是极具意义的治疗方式的突破.

应用要点

通过本文对营养素和非营养素与肠促胰素分泌机制的探讨, 为积极采取合理的饮食措施, 激活肠促胰素释放, 改善2型糖尿病和肥胖患者的血糖和体质量提供一个理论依据.

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名词解释

肠促胰素: 由肠上皮细胞分泌的一类激素, 主要包括胰高血糖素样肽-1和葡萄糖依赖性促胰岛素激素两种激素, 可通过刺激胰岛β细胞分泌胰岛素来降低血糖, 研发促进肠促胰素释放药物已成为治疗2型糖尿病和肥胖的新策略.

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编辑: 郭鹏 电编: 闫晋利

同行评价

本综述选题新颖, 通过对近年促进肠促胰素的分泌的多种机制作了一个较为详细全面的总结, 对于临床治疗方面的意义, 具有启示性和重要价值.