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文献综述 REVIEW

以游离脂肪酸为结合配体的GPCRs的研究进展

冯泽猛, 伍 力, 张珍珍, 傅德智, 周 栋, 唐志如, 印遇龙

■背景资料
G蛋白偶联受体超家族(GPCRs), 是目前尚未确定的最大基因家族之一, 拥有保守的7次跨膜螺旋结构域. 以游离脂肪酸为结合配体的该家族受体参与调节体内一系列的脂代谢过程, 如胰岛素分泌、脂肪细胞增殖等, 与糖尿病、肥胖等代谢疾病有重要关系.

冯泽猛, 伍力, 傅德智, 周栋, 唐志如, 印遇龙, 中国科学院亚热带农业生态研究所 亚热带农业生态过程重点实验室 湖南动物健康养殖中心 湖南省长沙市 410125
冯泽猛, 伍力, 傅德智, 周栋, 中国科学院研究生院 北京市 100039
张珍珍, 东莞泛亚太生物科技有限公司 广东省东莞市 523808
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通讯作者: 唐志如, 副研究员, 410125, 湖南省长沙市芙蓉区马坡岭, 中国科学院亚热带农业生态研究所, 亚热带农业生态过程重点实验室, 湖南动物健康养殖中心.
tangzhiru2326@yahoo.com.cn
电话: 0731-84619767
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Progress in the understanding of GPCRs for free fatty acids

Ze-Meng Feng, Li Wu, Zhen-Zhen Zhang, De-Zhi Fu, Dong Zhou, Zhi-Ru Tang, Yu-Long Yin

Ze-Meng Feng, Li Wu, De-Zhi Fu, Dong Zhou, Zhi-Ru Tang, Yu-Long Yin, Hunan Engineering and Research Center of Animal and Poultry Science, Key Laboratory for Agro-ecological Processes in Subtropical Region, Institute of Subtropical Agriculture, Chinese Academy of Sciences, Changsha 410125, Hunan Province, China
Ze-Meng Feng, Li Wu, De-Zhi Fu, Dong Zhou, Graduate School of the Chinese Academy of Sciences, Beijing 100039, China
Zhen-Zhen Zhang, AsiaPac (Dongguan) Bio-technology Co., Ltd., Dongguan 523808, Guangdong Province, China
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Correspondence to: Zhi-Ru Tang, Hunan Engineering and Research Center of Animal and Poultry Science, Key Laboratory for Agro-ecological Processes in Subtropical Region, Institute of Subtropical Agriculture, Chinese Academy of Sciences, Changsha 410125, Mapoling, Furong District, Hunan Province, China. tangzhiru2326@yahoo.com.cn
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Abstract
Dietary nutrients can be decomposed to generate free fatty acids (FFA) in the intestine. Although the majority of FFA are absorbed and oxidized to produce energy for the organism, FFA are also involved in the regulation of many physiological functions, such as maintenance of energy balance, metabolic homeostasis, synthesis and decomposition of lipids, immunity, and intestinal flora regulation, through binding to FFA receptors and activating related signaling pathways. Several FFA receptors have been identified, including GPR41 and GPR120, activated by long-chain fatty acids, GPR84, activated by medium-chain fatty acid, GPR41 and GPR43, activated by short-chain fatty acids. Elucidation of mechanisms of action of these FFA receptors will help understand the digestion and absorption of fatty acids in the intestine, energy balance and lipid metabolism, which has great significance in enhancing nutrition, regulating immunity, and developing drugs for lipid metabolism disorders.

Key Words: Free fatty acid; Fat metabolism; G protein-coupled receptors

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摘要
食物营养成分在肠道中可被分解产生游离脂肪酸. 游离脂肪酸除了被吸收氧化分解产生能量供机体利用外, 还能通过结合脂肪酸受体激活信号通路, 参与多种生理功能的调节, 如维持能量平衡、代谢稳态、调节脂质形成与分解、影响机体免疫、结识流动消化成分间接监测菌群数量等. 被确认的游离脂肪酸受体包括结合长链脂肪酸的G蛋白偶联受体(GPR)120, 结合中链脂肪酸的GPR84, 结合短链脂肪酸的GPR41及GPR43. 对这些脂肪酸受体的研究可进一步了解肠道脂肪酸的消化与吸收、机体能量平衡与脂质代谢, 对增强肠道营养、调节机体免疫和开发针对脂质代谢紊乱疾病的药物有着重要意义.

关键词: 游离脂肪酸; 脂肪代谢; G蛋白偶联受体

■同行评议者
李君文, 研究员, 军事医学科学院卫生学环境医学研究所

冯泽猛, 伍力, 张珍珍, 傅德智, 周栋, 唐志如, 印遇龙. 以游离脂肪酸为结合配体的GPCRs的研究进展. 世界华人消化杂志 2011; 19(8): 820-826
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图 1 GPR40家族与CD22基因串联排列示意图.

■研发前沿
阐明以FFA为配体的GPCRs在肠道脂肪酸吸收代谢和脂肪沉积过程中的作用机制, 开展肠道微生物对FFA与其受体GPCRs结合影响方面的研究, 已成为现代医学研究热点.

0 引言

游离脂肪酸(free fatty acid, FFA), 又称非酯化脂肪酸, 是脂肪酸中重要的一类, FFA除了作为机体结构原料以及能量来源维持能量平衡外, 还可影响胃肠消化系的各种功能, 如短链脂肪酸(short chain fatty acids, SCFAs)影响结肠的血流量、水和电解质的摄取[1], 通过释放5-羟色胺(5-hydroxytryptamine, 5-HT)促进结肠蠕动[2-5]和离子运输、影响肠道菌群[6]、清除肠道有害菌[7]和调节机体免疫[8-10], SCFAs作为信号分子参与细胞生长、分化、分泌和迁移等, 在机体营养调控和健康维持方面有着重要作用. 根据C链长度可将FFA分成SCFAs和中链及长链脂肪酸(long chain fatty acids, LCFAs). SCFAs主要是2C到5C的弱酸, 主要是小肠厌氧细菌对抗性淀粉和难消化纤维发酵过程中产生的[11-14]. SCFAs是哺乳类主要能量来源[15], 分别为反刍动物和非反刍动物提供70%和5%-10%的能量. LCFAs则是由膳食摄入的中性脂肪、胆固醇酯、磷脂通过肝转化而来. FFA主要是通过结合脂肪酸受体, 引发下游信号通路, 进而影响机体生理活动. 目前已确定的脂肪酸受体有G蛋白偶联受体40(G protein-coupled receptor 40, GPR40)家族包括GPR40(也称FFA1)、GPR41(也称FFA3)、GPR43(也称FFA2)以及其他家族的GPR84、GPR120. 这些脂肪酸受体属于G蛋白偶联受体超家族(G protein-coupled receptors, GPCRs), 是目前尚未确定的最大基因家族之一, 拥有保守的7次跨膜螺旋结构域[16,17]. 该家族受体序列具有相似性但各自拥有多种多样的配基, 如光子、离子以及包括有机胺、脂肪酸、多肽、蛋白质、类固醇在内的小分子. 参与调节体内一系列的脂代谢过程, 如胰岛素分泌、脂肪细胞增殖等, 与糖尿病、肥胖等代谢疾病的关系. GPCRs也是现代医学研究最多的治疗靶标之一, 据估计约有半数现代药物都是以这些受体为靶标, 全球年度交易额500亿美元, 此受体家族在生物医药研制中备受关注[18].

1 GPR40家族

GPR40家族, 包括GPR40、GPR41、GPR42和GPR43, 其中GPR40是中链脂肪酸和LCFAs的受体, GPR41和GPR43则是SCFAs的受体蛋白. 他们编码的基因串联排列于CD22基因的下游(图1)[19], 定位于19q13.1, 主要在胰岛β细胞、脂肪组织和消化系中表达.

1.1 GPR40 GPR40是中链脂肪酸和LCFAs的受体, 基因定位于CD22下游约4 kb处. 在两者阅读框之间有3个对DNA酶超敏感的高度保守的区域HR1-HR3[11]. 其中HR3包含GPR40的核心启动子, 而HR2是一个强的转录增强子. HR2的8-9亚区可与β细胞特异性表达的蛋白bHLH(basic helix-loop-helix)BETA2[12,13]结合, 而HR2的3-5亚区域可与β细胞同源转录因子PDX1结合, 使GPR40有选择地在β细胞表达而发挥重要作用, 参与调控葡萄糖感受基因及胰岛素基因表达, 促进胰岛素分泌, 从而维持机体葡萄糖稳定. 具体过程是, 当GPR40通过耦合G蛋白中的Gi/o家族开始启动信号传导, 激活磷脂酶C(phospholipase C, PLC), 把磷酸肌醇4, 5-磷酸分解(phosphatidylinositol-4, 5-bis-phosphate, PIP-2), 生成了1, 4, 5-三磷酸肌醇(inositol 1, 4, 5 triphosphate, IP3), 刺激内质网钙离子释放; 同时GPR40通过提高胞内环磷酸腺苷(cyclic adenosine monophosphate, cAMP)浓度, 延迟整流性K^+通道失活, 延长细胞去极化使Ca^{2+}涌入细胞, 最终造成细胞内Ca^{2+}浓度迅速增加, 触发胰岛素颗粒释放[14,15,19-21]. 即使在胰岛素拮抗状态下, 急性的GPR40激活或者过表达都可以增强葡萄糖诱导的胰岛素分泌, 促进葡萄糖耐受[22,23]. 因此筛选开发GPR40拮抗剂, 可能成为将来寻找糖尿病疗法的一个十分有潜力的途径. 研究发现了GPR40的多种高效激活剂[24-30], 高效拮抗剂[31,32], 对进一步研究GPR40功能和发现、设计糖尿病治疗药物先导物有重要的意义.

此外, GPR40在大脑多个部位表达[33], 如大脑皮质、海马、杏仁核、下丘脑、小脑、黑质、脑桥、延髓、脊髓和垂体. GPR40还分布在成人脑产生新神经元的前脑的脑室下区(subventricular zone, SVZ)和海马齿状回(dentate gyrus, DG), 显示GPR40可能参与神经形成[34].

1.2 GPR41 GPR41主要在白色脂肪组织表达, 在骨骼、内脏器官、脑等不同组织的表达量也很高, 另外还可在各种分化的细胞系中检测到

■相关报道
Lee等通过高通量药物筛选鉴定出苯乙酰胺1和2是GPR43有效的合成配基.

GPR41, 如浆细胞、树突状细胞、淋巴细胞和外周血单个核细胞以及动脉和小动脉内皮细胞等[35]. GPR41是通过耦合G蛋白中的Gi/o家族开始启动信号传导的. 丙酸是GPR41其最有力和有效的配体, 丁酸和戊酸都能有效激活GPR41, 醋酸则显示较低的效力[36].

最近几年, 由于GPR41被发现在监控能源储存和循环方面发挥作用, 得到了研究者们的较大关注. GPR41可能和肥胖有关, 虽然他并不直接调控脂肪降解[37], 但可诱导脂肪细胞中瘦素的合成[36]. GPR41能促进酪酪肽(peptide tyrosine tyrosine, PYY)表达, 抑制胃肠运动, 增加肠道转运效率, 以及降低饮食中能源SCFAs的摄取. 在胰岛细胞和db/db糖尿病小鼠中GPR41表达量增加[38]. GPR41还可以通过影响肠道菌群调控机体的能量平衡, 是肠道菌群和宿主相互关系的重要调解者之一[39]. SCFAs对结肠功能的生理作用可能归功于结肠上皮细胞GPR41的激活[37]. GPR41可调节乳腺细胞内SCFAs诱导的信号通路[40]. 研究人员已确定GPR41为缺氧诱导细胞凋亡受体, 可通过P53/Bax通路诱导缺血/再灌注模型细胞凋亡[41].

1.3 GPR43 GPR43与GPR41一样同为SCFAs的受体, 作用于脂质的积累和消除, 但在信号传导方式, 配基选择和组织定位等方面与GPR41表现出有趣的差异. 丙酸也是GPR43最强的激活剂. 乙酸对GPR43更有选择性, 而丁酸和异丁酸对GPR41更有活性. 戊酸和丙酸以相同的效力激活GPR41, 但戊酸对GPR43的激活能力较弱, 这些区别可用区分GPR41和GPR43. GPR43主要是和Gq蛋白偶联[14], 也有证据表明可能与Gi/Gq通路偶联. 两者的激活都会使得细胞内Ca^{2+}浓度升高, 细胞外调节蛋白激酶(extracellular regulated protein kinases1/2, ERK1/2)活化和cAMP浓度的降低. GPR43和GPR41在表达方式有相当大的重叠, 均发挥着脂质积累和清除的作用, 但两种受体相互之间可能存在相互干扰. GPR43在免疫细胞中有最高的表达量, 在免疫和造血过程中起作用. 在脂肪组织也有较高的表达[42]. 用C2或C3处理细胞, GPR43 mRNA表达增加, 用GPR43的siRNA处理时细胞脂质积累减少. C2和C3呈剂量依赖性减少异丙肾上腺素诱发的脂肪降解. 喂食高脂肪饲料与那些喂食正常饲料相比, 老鼠脂肪组织中的GPR43 mRNA水平上调, 在DB/DB糖尿病和OB/OB肥胖小鼠胰岛过量表达[37]. Lee等[43]通过高通量药物筛选鉴定出苯乙酰胺1和2是GPR43有效的合成配基. 两种配基都对GPR43具有特异选择性, 苯乙酰胺1和2通过Gαi通路在脂肪细胞中抑制脂肪降解. GPR43还可以监控肠道膳食纤维代谢, 调节食欲[44], 调节SCFAs对瘦素分泌的调节作用[45], 参与机体能量与体质量调节. 同时还是肠道炎症状态下招募嗜中性细胞必需蛋白[46], 可作为调节机体代谢紊乱药物靶标[47]. 总之, 在糖脂代谢中的调节作用表明GPR43具有成为新的治疗肥胖、糖尿病和葡萄糖不耐症等的药物靶点潜力.

GPR43与PYY[48]一起共同定位于黏膜上皮细胞和肥大细胞, 以及载有5-HT的结肠远端肥大细胞, 通过5-HT与PYY控制胃肠道运动和分泌. GPR43在其他免疫细胞也存在大量表达, 包括粒细胞、单核细胞、嗜酸性粒细胞和B淋巴细胞等. 自SCFAs被证明有免疫效应, 这一受体(和/或GPR41)很可能在钝化各种职能白细胞识别, 招募和移动方面会发挥作用, 参与以过多或无效中性粒细胞募集和激活为特征的各种疾病的发生, 如肠道炎症疾病或酗酒相关免疫抑制症. 因此, GPR43可能为我们提供了能够对这些疾病进行免疫调节的靶标.

1.4 GPR42 GPR42与GPR41定位于相同染色体并相互邻近. 两者有着同样的长度和98%的氨基酸相似性, 只有7个位点的核苷酸不同(6个氨基酸差异), 但GPR42却不能被SCFAs所激活. GPR42可能是GPR41基因复制失误的结果. 其他物种GPR42/GPR41是一直系同源基因, 并且这些直系同源基因和人GPR41相似; 另外, 大鼠的直系同源基因和人GPR41一样对羧酸有相似活性, 说明GPR42可能是GPR41的非功能基因重复. 以前GPR42被推定为一假基因, 不过最近发现他应是功能基因, 应进行进一步的研究[49]. GPR42对羧酸的刺激没反应, 这种反应的缺失可能很大程度上与174位的氨基酸有关, 人GPR41和哺乳动物直系同源基因是精氨酸, GPR42是色氨酸. 通过突变改变此位置氨基酸可使GPR41失去功能, GPR42恢复部分功能. 不经处理的GPR42对SCFAs没有反应; 然而, 特别残基的突变可赋予GPR42被SCFAs诱导的能力. GPR41和GPR42很少的氨基酸差别显示GPR42很可能是GPCRs中由未知激活配基的功能受体. 利用荧光定量RT-PCR在正常的人类组织中检测不到GPR42[37]. 通过GPR40家族比对可知在跨膜区结构域有3个保守位点, 其中1个可通过离子键与脂肪酸作用. 人GPR41的174位精氨酸残基有重要的作用, 但

在整个家族中不保守, 在GPR42中由色氨酸取代. 这个位置的突变可使GPR41功能丧失或部分限制GPR42功能, 表明这一氨基酸的差异是GPR42缺乏SCFA反应的主要的原因.

2 GPR120

GPR120是最近发现的一个GPR, 属于进化保守的视紫红质类GPCR中比较特殊的一类, 其跨膜TM7中存在着视紫红质类受体典型的NSxxNPxxY结构, 而其胞内的TM3区域中则以ERM代替特征性DRY结构, 可能只存在于高等脊椎动物中[50]. Fredriksson等发现人类GPR120编码区是由3个外显子组成编码377个氨基酸的碱基序列, 其编码基因定位于10号染色体短臂(10q23.33). 大鼠GPR120的mRNA开放阅读框编码361个氨基酸, 大鼠GPR120不能被低于14C的FFA激活. GPR120 mRNA存在于小鼠所有受检组织, 尤其在脑垂体、肺、小肠和结肠及4种不同脂肪组织中表达量最高. GPR120在各类脂肪组织中的高表达, 而GPR40在这些脂肪组织中未见表达, GPR120调控脂肪形成的过程包括脂肪细胞的发育和分化[51]. GPR120还在味觉细胞中表达, 可能有直接感知外源脂肪酸包括食物中的脂肪成分的功能[52]. GPR120是C14-18的饱和LCFAs及C16-22的不饱和LCFAs[53]的受体. 部分LCFAs对GPR120活性的强弱顺序为: cis-5, 8, 11, 14, 17-二十碳五烯酸>亚油酸>棕榈酸>α-亚麻酸[28,54]. MEDICA16(化学式$C_{20}H_{38}O_4$)也是GPR120的合成化学激动剂[55].

GPR120的激活[56]参与调节一系列代谢过程, 如激素分泌、细胞增殖和脂质生成等, 在脂质代谢平衡中起重要作用. 上调GPR120表达是成熟脂肪组织中脂肪形成的不可缺少的调节. 在高脂肪饲喂小鼠的脂肪组织中表达量升高. 长链FFA可通过GPR120偶联Ca^{2+}信号通路可介导胆囊收缩素(cholecystokinin, CCK)分泌[56], 调节一系列肠道反应, 包括刺激胰液分泌、胆囊排空, 并抑制胃自主运动[50,54,57,58], 有助于脂肪消化. GPR120的信号转导通路途径如下: (1)在STC1细胞LCFAs与GPR120结合下游激活PLC, 分解PIP2生成IP3及二酰甘油(diacylglycerol, DAG), IP3引发胞内钙信号, 从而调控胰高血糖素样肽1(glucagon-like peptide 1, GLP-1)的释放, GLP-1作用于胰岛细胞引起胰岛素的释放: 另外在STC-1及表达了GPR120的HEK-293细胞上, 也通过PLC-丝裂原激活的蛋白激酶(mitogen-activated protein kinases, MAPK)途径调节细胞生长及功能, 同时调控FFAs引发的抑制细胞凋亡作用; (2)GPR120启动的磷脂酰肌醇-3-激酶-丙氨酸氨基转移酶(phosphatidylinositol-3-kinase alanine aminotransferase, PI3K-Akt)信号传导途径能诱导细胞增殖, 抑制细胞凋亡[59]. 这两条信号转导通路也存在一定交互作用, 但精确分子机制仍需进一步研究确证.

GLP-1是一种有力促胰岛素激素, 由专门的肠内分泌细胞(L细胞系)分泌, 用来消化脂肪[60]. GPR120的激活促进GLP-1的分泌[53], 参与调解不饱和脂肪酸对细胞凋亡的抑制作用[59]. 向大鼠饲料添加α-亚麻酸可提高血浆GLP-1水平, 长期添加α-亚麻酸导致胰岛β细胞增殖, 增加胰岛素分泌, 原因可能是GLP-1分泌的增强[61].

GPR120除影响激素分泌外还引起其他细胞作用[62], 包括脂肪酸细胞外信号调节激酶(extracellular signal-regulated kinase, ERK)和PI3K-Akt的通路[59], C16和C18脂肪酸的抑制破骨作用[63], 影响脂肪形成相关因子如过氧化物酶体增殖物激活受体(peroxisome proliferator-activated receptors, PPAR)-γ2[64]和aP2的表达. GPR40直接而GPR120间接促进胰岛素的分泌[53,65], 在LCFAs的作用下调解促进CCK的释放[56]. 并和GPR40一起调节机体脂肪酸的偏好性[66].

3 GPR84

GPR84是Wittenberger等利用序列表达标签(expressed sequence tag, EST)数据挖掘技术发现的属于GPCRs的新基因, 定位于12q13.13, 是9-14C的中链脂肪酸受体, 直接联系脂肪酸代谢和机体免疫反应[67], 被证明和GPR120相关[68]. 人GPR84是由单独阅读框编码, 共396个氨基酸组成[69]. GPR84特异在白细胞表达, 并能被脂多糖在单核细胞和巨噬细胞中诱导. GPR84并不是T淋巴细胞和B淋巴细胞分化的必须参与者, 但GPR84的缺失能选择性影响IL-4的产生[70]. GPR84也是视网膜以及其他眼组织正常生长发育所必须[71].

4 结论

FFA作为重要的营养物质, 在机体肠道营养、肠道微生物区系稳态、能量平衡维持、生理功能调节中起着重要的作用. GPCRs是一类具有重要的机体调节功能的通道蛋白[72], 具有成为药物作用靶点的潜力, 也是目前半数研发药物的重

■同行评价

本文对进一步研究GPCRs与脂肪酸代谢、吸收, 代谢疾病(糖尿病、肥胖)及神经、免疫学相关研究, 尤其是基于以GPCRs为靶点的药物研究提供理论依据, 具有重要的参考价值.

要靶标[73]. 以FFA为配体的GPCRs在肠道FFA的吸收、感知[74]、代谢调控、信号转导和能量平衡方面起关键作用. 阐明以FFA为配体的GPCRs在肠道脂肪酸吸收代谢和脂肪沉积过程中的作用机制, 开展肠道微生物对FFA与其受体GPCRs结合影响方面的研究, 已成为现代医学研究热点. 研究结果将有助于指导人类健康饮食及促进肠道营养的研究. 随着以FFA为配体的GPCRs研究越来越深入, 对其基因定位, 组织分布, 相关配基, 信号转导和生理功能的研究已趋于明晰, 为从分子水平研究FFA的营养调控作用机制和发现治疗糖尿病、肥胖等代谢性疾病药物奠定了基础.

作为机体主要能量来源, FFA已经研究很多, 但作为信号分子参与机体生理功能调节还有很大的研究空间, 目前仍有许多问题尚不清楚. 首先, 生理或病理情况下以FFA为配体的GPCRs的作用还未阐明, 对其基因敲除、RNA干扰等研究将填补这一空白. 详细了解蛋白水平上进行这几种GPCRs的分布和调节也将有助于阐明其在生理或病理组织中的作用. 通过计算机虚拟筛选、组合化学、基因芯片高通量筛选这几种GPCRs家族受体分子激动剂/拮抗剂用于药物发现是今后很有潜力的研究方向.

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