DOI:10.16781/j.0258-879x.2017.06.0780

·综 述·

胆汁酸与糖脂代谢疾病

何逸飞,王奇金*
第二军医大学长海医院内分泌科,上海 200433

[摘要] 胆汁酸(bile acid, BA)作为胆汁的成分之一,参与脂肪消化吸收和胆固醇代谢。近年研究发现,胆汁酸还是一种信号分子,不仅可以与法尼酯衍生物X受体(farnesoid X receptor, FXR)、G蛋白偶联胆汁酸受体(G protein coupled bile acid receptor 5,TGR5)等结合调节自身代谢,还在糖尿病、肥胖、非酒精性脂肪肝病及其他代谢性疾病中发挥重要作用,因此,阐明其作用机制将为诊治代谢性疾病提供理论依据。本文就胆汁酸在糖脂代谢疾病中的研究进展作一综述。

[关键词] 胆汁酸类和盐类;2型糖尿病;减重手术;非酒精性脂肪肝;法尼酯衍生物X受体;G蛋白偶联的胆汁酸受体
[中图分类号] R 58 [文献标志码] A [文章编号] 0258-879X(2017)06-0780-05

Bile acid in glucolipid metabolic diseases: an update

HE Yi-fei, WANG Qi-jin*
Department of Endocrinology, Changhai Hospital, Second Military Medical University, Shanghai 200433, China

[**Abstract**] Bile acids, as one of the constituents of bile, can promote the digestion and absorption of fat and cholesterol metabolism. Studies find that bile acid is a signal molecule that not only combines with nuclear hormone receptors such as farnesoid X receptor, and G protein coupled bile acid receptor 5, to regulate their own metabolism, but also plays an important role in diabetes, obesity, non-alcoholic fatty liver disease and other metabolic diseases. The research on its mechanism will provide a solid theoretical basis for the diagnosis and treatment of metabolic diseases. In this review, we summarized the research progress of bile acids in glucolipid metabolic diseases.

[**Key words**] bile acids and salts; type 2 diabetes mellitus; bariatric surgery; nonalcoholic fatty liver disease; farnesoid X receptor; G-protein coupled bile acid receptor

[Acad J Sec Mil Med Univ, 2017, 38(6): 780-784]

胆汁酸是胆汁的主要成分,在肝脏合成进入肠道,通过"肝肠循环"在机体内被反复利用,使其发挥最大效应,以满足人体对胆汁酸的需求。以往研究认为它的作用是促进脂质在肠道的吸收及参与胆固醇代谢,但近年来发现它可作为配体与法尼酯衍生物X受体(farnesoid X receptor, FXR)、G蛋白偶联胆汁酸受体(G protein coupled bile acid receptor 5, TGR5)等结合后介导一系列信号转导通路,从而在糖脂代谢疾病[1]、肠道菌群[2-3]、免疫系统[4]中发挥作用。本文就胆汁酸在糖尿病、肥胖、非酒精性脂肪肝病(nonalcoholic fatty liver disease, NAFLD)等糖脂代谢疾病中的研究进展作一综述。

1 胆汁酸的代谢及反馈调节

1.1 胆汁酸代谢 胆汁酸由胆固醇在肝脏中通过经典途径及替代途径转化而来[5],按结构可分为游离型和结合型胆汁酸,游离型胆汁酸包括胆酸、脱氧胆酸、鹅脱氧胆酸、石胆酸,结合型胆汁酸主要有甘氨胆酸、牛磺胆酸、甘氨鹅脱氧胆酸、牛磺鹅脱氧胆酸。按来源将胆汁酸分为两类,一类为初级胆汁酸,是指在肝内由胆固醇直接生成的胆汁酸,包括胆酸、鹅脱氧胆酸及与甘氨酸或牛磺酸的结合物;另一类为次级胆汁酸,即初级胆汁酸进入肠道由肠道菌群催化合成的胆汁酸,包括脱氧胆酸和石胆酸。肝脏产生的胆汁酸进入肠道后,95%会被肠道重吸收,其中结合型胆汁酸主要在回肠远端通过主动吸收被重吸收,游离型胆汁酸在小肠和结肠通过被动运输被重吸收,这些重吸收的胆汁酸随门静脉再次进入肝脏,肝脏再将游离型胆汁酸转化为结合型胆汁酸并与新合成的胆汁酸一起进入肠道,即"肝肠循环"。

[收稿日期] 2016-11-15 [接受日期] 2017-02-22
[基金项目] 长海医院探索项目(CH125541900). Supported by Exploration Program of Changhai Hospital (CH125541900).
[作者简介] 何逸飞,硕士,住院医师. E-mail: 798775654@qq.com
*通信作者 (Corresponding author). Tel: 021-31161394, E-mail: wangqijin8668601@163.com

1.2 胆汁酸的自身反馈调节 胆汁酸通过负反馈调节自身合成,在进入小肠后,与小肠细胞核受体 FXR 结合可激活成纤维细胞生长因子 19(FGF19),该因子可以抑制胆固醇 7α-羟化酶(CYP7A1)基因的表达,而 *CYP7A1* 基因编码的胆固醇 7α-羟化酶为胆汁酸合成的限速酶[6]。除了 FGF19 信号转导途径,胆汁酸的合成也受另一 FXR—小分子异源二聚体伴侣(small heterodimer partner,SHP;非典型的孤儿核受体)信号通路的调节,FXR 诱导 SHP 的表达,而 SHP 介导 *CYP7A1* 基因的下调,从而反馈性抑制胆汁酸的合成[7]。

1.3 胆汁酸受体 虽然近年来才发现胆汁酸能够在信号通路中发挥作用,但对其受体的研究却已较详细[8]。涉及的受体有核受体 FXR、胞质 G-蛋白偶联受体 TGR5、维生素 D 受体(vitamin D receptor,VDR)、组成型雄烷受体(constitutive androstane receptor, CAR)、孕烷 X 受体(pregnane X receptor,PXR)等。FXR 不仅介导胆汁酸的反馈调节,还参与糖脂代谢[9],另外 FXR 可在冠状动脉、主动脉以及粥样硬化的动脉[10]中表达。同样在这些部位表达的还有 VDR[11]和 PXR[12],多种受体在多个器官的表达也提示胆汁酸在各器官及系统代谢中的复杂性。TGR5 是 G 蛋白偶联受体中视紫红质样(A 类)超家族成员之一,除了在小肠细胞表达,在甲状腺、棕色脂肪组织、骨骼肌、肝脏、胰腺均有表达[8],近期发现在胰岛 β 细胞中亦有表达[13],越来越多的证据显示 TGR5 在能量稳态、糖代谢[14]和免疫功能的调节[15]方面发挥作用。CAR 与胆汁酸结合后可提高胰岛素敏感性[16],并可改善脂质代谢[17]和甲状腺功能[18]。胆汁酸激活 PXR 后的作用机制虽然尚未明了,但是其对能量代谢的作用已被证实[19],此外 PXR 还参与了先天免疫系统的调节[12]。

2 胆汁酸与 2 型糖尿病

目前报道 2 型糖尿病人群总胆汁酸库与健康人群比较差异无统计学意义[20-21],但胆汁酸亚组脱氧胆酸较健康人升高,Brufau 等[20]研究发现,2 型糖尿病患者的总胆汁酸库大小并没改变,但脱氧胆酸的含量增加,鹅脱氧胆酸的含量减少。另一项研究也发现,2 型糖尿病总胆汁酸浓度与正常人相比差异无统计学意义;但血浆中脱氧胆酸浓度较对照组要显著增加,肥胖者体内胆酸水平较健康者升高,进行统计分析后发现脱氧胆酸和胆酸与胰岛素敏感性呈负相关,而与血糖、体质量指数等并无相关性,其机制可能为胰岛素抵抗时 FXR 及 TGR5 受抑制,作为受体最有效的自然配体胆酸和脱氧胆酸代偿性升高[21]。这些均说明胆汁酸的代谢调节与 2 型糖尿病关系密切。

2.1 胆汁酸-法尼酯衍生物 X 受体(BA-FXR)信号途径 BA-FXR 信号途径广泛参与糖代谢。首先胰腺 β 细胞中存在 FXR,胆汁酸与 FXR 的结合可刺激胰岛素释放;其次小肠某些细胞中也存在 FXR,与胆汁酸结合后可激活 FGF19 分泌入血液,如前述 FGF19 有类胰岛素样作用;另外 FGF19 能抑制 cAMP 反应元件结合蛋白(cyclic AMP response element binding protein, CREB)的磷酸化从而减少肝脏糖异生[22],此外 FGF19 可激活 Ras/ERK 途径,促使糖原合成酶激酶(glycogen synthase kinase,GSK)α、β 磷酸化,使糖原合成酶(glycogen synthase, GS)活性增强以增加肝脏糖原合成[23]。另有报道胆汁酸还可以通过 FXR-SHP 途径来抑制糖异生相关基因的表达[24]。

2.2 胆汁酸-G 蛋白偶联胆汁酸受体(BA-TGR5)信号途径 TGR 5 属于 G 蛋白偶联受体,目前发现其与内源性配体胆汁酸结合后可促进 cAMP 合成,激活蛋白激酶 A 途径的信号转导[25]。如前所述,TGR5 可在人体多个器官中表达,与代谢性疾病相关的有肠道、胰腺、骨骼肌组织等。TGR5 活化诱导肠内分泌细胞分泌胰高血糖素样肽 1(glucagon-like peptide 1, GLP-1)[26]。另外胆汁酸亦可直接刺激胰岛细胞中的 TGR5 受体促进胰岛素释放[27]。在骨骼肌组织中,TGR5 的活化可诱导 2 型脱碘酶基因(deiodinase type 2,D2)的表达,增加能量消耗[26]。

3 胆汁酸与 NAFLD

随着人们生活质量的提高,体检发现 NAFLD 的患病人数居高不下,目前有观点认为胆汁酸的代谢紊乱促进了 NAFLD 的发展[28]。多个临床试验对比 NAFLD 患者与正常人胆汁酸水平的变化,结论各不相同。一项以青少年为研究对象的试验发现,在早期 NAFLD 中胆汁酸较健康组相比是下降的,作者认为在 NAFLD 早期胰岛素会抑制胆汁酸合成的限速酶 CYP7A1 从而使胆汁酸水平下降,但并未找到胰岛素与胆汁酸之间的相关性,故又认为早期一级炎性反应促进胆汁酸谱短暂性抑制,后期随着纤维化的加重,肝脏组织扭曲压迫胆管,肝脏胆汁酸潴留并反流入血液,晚期胆汁酸浓度升高[29]。另一项研究认为在成年 NAFLD 患者中血浆胆汁酸

浓度较正常人高，因肝细胞出现炎性，肝细胞对胆汁酸的摄取减少，代谢功能降低，消除障碍，导致血清胆汁酸升高[30]。

目前认为胆汁酸在 NAFLD 中的作用与其受体 FXR、TGR5、VDR 有关。$FXR^{-/-}$ 的小鼠高脂喂养后，三酰甘油（triglyceride，TG）的水平与对照组相比明显升高，若给予 FXR 激动剂则 TG 较未给药组下降[31]，其机制被认为是 FXR 诱导过氧化物酶体增殖物激活受体，抑制丙酮酸脱氢酶并增加脂肪酸的氧化[32]，胆汁酸对胆固醇的调节也主要是通过 FXR，应用 FXR 激动剂处理肥胖模型小鼠及糖尿病模型小鼠可明显改善小鼠的高胆固醇血症[33]，FXR 不仅能调节脂类代谢，在控制炎性方面还能发挥重要作用，回盲肠切除术后 FXR 缺失的无菌小鼠与野生型小鼠相比，TG、胆固醇均增多，且 FXR 缺失小鼠表现为脂肪性肝炎[34]。将 FXR 的配体 WAY-362450 喂养 NAFLD 小鼠后，发现小鼠肝脏炎性指标及纤维化指标均好转[35]。人及啮齿类动物脂肪细胞中表达 TGR5，在动物实验中，构建 TGR5 缺陷的小鼠，给予高脂喂养后小鼠肝脏脂肪含量增加，但是对 TGR5 缺陷的小鼠再给予 TGR5 激动剂 INT-777 后发现肝脏脂肪变性的指标和血浆游离脂肪酸、乳酸脱氢酶、丙氨酸转氨酶和天冬氨酸转氨酶降低[36]。考来维仑是二代胆汁酸螯合剂，它可通过 TGR5 抑制糖代谢和减少胆固醇合成，从而减轻脂肪肝的形成[37]。此外 VDR 缺乏也可导致肝脏的脂肪细胞变性[38]。

4　胆汁酸与减重手术

目前减重手术主要有 3 种：(1)限制性手术，即缩少胃的容积、减少食物摄入，这种术式包括腹腔镜袖状胃切除术、胃束带手术等；(2)吸收不良术，这种术式改变了胆肠循环，食物绕过部分胃、十二指肠、近段空肠，较早到达回肠被重吸收；(3)合并手术，是上述两种手术的结合，常见的有 Roux-en-Y 胃转流术。这些手术各有特点和适用人群，已有大量的临床数据说明对于肥胖合并代谢紊乱的人群施行减重手术不仅能显著减轻体质量，还能明显改善糖脂代谢[41]。而胆汁酸在减重术后明显升高，故推测胆汁酸在术后人体糖脂代谢的改善过程中也发挥作用，Patti 等[39]将行减重手术和未行减重手术的超重人群胆汁酸进行对比后发现，减重手术后患者的胆汁酸水平较术前和未行减重手术的患者明显升高，并指出胆汁酸可改善胰岛素抵抗及脂类代谢。

基础及临床研究发现胆汁酸可能通过 FXR 信号通路、TGR5 信号通路及与肠道菌群相互影响在减重手术中发挥作用。FXR 作为胆汁酸的受体，主要在肝脏及肠道表达，Ryan 等[41]将肥胖小鼠体内的 *FXR* 基因敲除后，对该群小鼠及野生型的肥胖小鼠均行相同的减重术式，术后 $FXR^{-/-}$ 小鼠体质量减轻程度及血糖下降幅度均较野生型小鼠减弱，说明 FXR 介导的信号通路在减重手术中具有重要作用。Nakatani 等[42]收集行腹腔镜胃旁路术后人群的胆汁酸及糖脂代谢指标，发现术后胆汁酸升高的水平与血清肠抑胃肽呈正相关，同时 GLP-1 也升高，因 TGR5 可促进 GLP-1 的表达和释放，提示减重术后胆汁酸的升高可能与 TGR5、GLP-1 有关。Belgaumkar 等[43]发现腹腔镜袖状胃切除术后 6 个月患者总体的胆汁酸水平未见明显改变，但是甘氨熊去氧胆酸及 FGF-19 水平较术前升高，而甘氨胆酸、牛磺胆酸、脱氧胆酸水平较术前下降，作者认为腹腔镜袖状胃切除术后患者脂肪肝的改善有 FXR—FGF-19 机制的参与。另有研究报道行减重术后肠道菌群发生变化，在 Roux-en-Y 术后 1 周就可以观察到肠道菌群的变化，肠杆菌和疣微菌数量明显升高，而拟杆菌数量无明显改变[44]，肠道菌群不仅可使初级胆汁酸转化为次级胆汁酸，还可以调节肝脏的胆汁酸代谢。

5　小　结

胆汁酸作为一个重要的信号因子，主要通过 FXR 及 TGR5 信号通路在糖尿病、NAFLD 及减重手术中发挥作用，同时胆汁酸与肠道菌群相互影响，调节糖脂及能量代谢。通过研究胆汁酸及其介导的信号通路机制，将为今后开发糖尿病、肥胖症、NAFLD 等糖脂代谢疾病药物提供理论基础。

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[本文编辑] 孙　岩