

胆汁酸核受体FXR在非酒精性脂肪性肝病中的作用

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背景资料

非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)已成为一个全球关注的健康问题,至今发病机制仍未阐明,尚无有效药物治疗手段。近年来研究显示胆汁酸(bile acid, BA)核受体法尼醇X受体(farnesoid X receptor, FXR)参与调控胰岛素抵抗(insulin resistance, IR)、脂质代谢异常等NAFLD的重要环节。提示FXR可能是NAFLD的治疗靶点。目前,FXR应用于NAFLD仍存有争议。

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Role of farnesoid X receptor in nonalcoholic fatty liver disease

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is characterized by the aberrant accumulation of triglycerides in hepatocytes in the absence of significant alcohol consumption, viral infection or other specific causes of liver disease. NAFLD has become a global health problem, but its pathogenesis remains poorly understood and no efficient pharmaceutical

treatments have yet been established. The farnesoid X receptor (FXR) is a member of nuclear receptors of intracellular ligand-activated transcription factors and plays an important role in metabolism of bile acids, lipid and glucose. In addition, it has been recently reported that FXR participates in regulating insulin resistance and lipid metabolic disorder, inhibiting the activation of hepatic stellate cells and penetration of inflammatory cells, and promoting the enterohepatic circulation and regeneration of liver cells to defer liver fibrosis, which is significant for NAFLD. Several FXR agonists have been identified and proved to be optimistic in preventing and treating NAFLD both experimentally and clinically, indicating that FXR may be a therapeutic target for NAFLD. The use of FXR in NAFLD remains controversial currently.

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Key Words: BAs; Nonalcoholic fatty liver disease; Farnesoid X receptor; FXR agonist

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摘要

非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)是以肝细胞脂肪变性和脂质沉积为特征,但无过量饮酒史、排外病毒感染和其他原因引起的肝脏疾病。NAFLD已成为一个全球关注的健康问题,其发病机

制仍未阐明, 尚无有效的药物治疗手段. 法尼醇X受体(farnesoid X receptor, FXR)是需配体激活的转录因子, 在胆汁酸、糖脂代谢中起着重要的调节作用. 近年来研究显示FXR参与调控胰岛素抵抗(insulin resistance, IR)、脂质代谢异常、抑制肝星状细胞活化及炎症细胞渗入、促进肝内循环及肝细胞再生、延缓肝纤维化进程等NAFLD的重要环节. 动物实验和临床研究也证实, FXR激动剂有延缓、治疗NAFLD的作用. 提示FXR可能是NAFLD的潜在治疗靶点. 目前, FXR应用于NAFLD仍存有争议.

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关键词: 胆汁酸; 非酒精性脂肪性肝病; FXR; FXR激动剂

核心提示: 非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)发病机制复杂, 尚无有效药物治疗手段. 法尼醇X受体(farnesoid X receptor, FXR)为多效性的胆汁酸核受体, 不仅调节糖脂代谢, 同时参与调控胰岛素抵抗、脂质代谢异常等NAFLD的重要环节. 近年来, 国内外实验和临床研究发现FXR具有抗NAFLD的作用, 提示FXR可能成为治疗NAFLD的作用靶点.

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0 引言

非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)是以肝细胞脂肪变性和脂质沉积为特征, 但无过量饮酒史的临床综合征, 与胰岛素抵抗(insulin resistance, IR)、氧化应激、代谢综合征密切相关, 疾病谱包括非酒精性单纯性脂肪肝、非酒精性脂肪性肝炎(nonalcoholic steatohepatitis, NASH)及其相关肝硬化和肝细胞癌. 普通成年人群患病率高达15%-30%^[1], 是我国临床上最常见的肝病, 其中约3%-15%^[2]的NASH患者发展为肝硬化, 是导致我国慢性肝脏损伤及死亡的常见原因之一^[1]. 目前全世界超过1千万人患有肝纤维化(liver fibrosis, LF), 随着NAFLD发病率的上升, 未来10-15年LF患者将增至目前的3倍^[3]. NAFLD发病机制复杂, 尚无有效药物治疗手

段, 对于进展为终末期肝病的患者, 肝移植是唯一有效的治疗方法^[4], 但受肝源和经济等限制. 因此, 早期防治是提高NAFLD患者生存率和生活质量的关键^[5].

法尼醇X受体(farnesoid X receptor, FXR)是具有配体活性的核受体超家族成员^[6], 在肝脏、回肠、肾脏、肾上腺中高度表达^[7], 最早于1995年在小鼠肝脏cDNA文库中克隆发现, 因其转录活性可被生理浓度的法尼酯增强而命名. 1999年发现生理水平的胆汁酸(bile acid, BA)是FXR的内源性配体, 因此FXR又称为BA受体. 法尼醇是最初发现的FXR激动剂, 之后鹅脱氧胆酸、脱氧胆酸、石胆酸、GW4064、INT-747和WAY-362450也被证实为FXR重要的激动剂^[8]. FXR不仅是调节糖脂代谢的重要因子, 而且作为一种信号分子参与胰岛素信号转导、氧化应激、炎症、肝星状细胞(hepatic stellate cell, HSC)活化等重要过程^[9,10]. FXR基因敲除小鼠表现为高脂血症, 高糖血症, BA超负荷, 肝脏炎症及脂肪病变甚至LF^[11-14]. 此外, 发现NAFLD患者FXR表达下降, 可能与IR、肝脏脂肪病变有关^[15], 且使用FXR激动剂可改善, 提示FXR可能是NAFLD的潜在治疗靶点.

1 FXR调控BA代谢

BA是胆固醇在胆固醇7 α -羟化酶(cholesterol-7 α -hydroxylase, CYP7A1)的作用下合成的终产物, 经胆管进入胆囊储存, 进餐后分泌至小肠, 约95%的BA经回肠末端被重吸收, 仅5%经粪便排出体外. 当体内BA超负荷时对肝细胞毒性增加, 可能引起肝细胞氧化应激、炎症、坏死、LF甚至肝硬化. 近期一项研究^[16]也提出BA的合成以及血清中BA浓度与NAFLD的病情严重程度相关. BA不仅有助于脂类和维生素的吸收与转运、抑制胆固醇析出形成结石, 而且作为一种信号分子激活核受体FXR调节糖脂代谢、肝内循环、发挥抗炎、抗纤维化^[17]、促进肝细胞再生^[18]、调控肿瘤形成等重要作用^[19]. FXR具有典型的核受体结构, 羧基末端具有配体结合域(ligand binding domain, LBD)和配体依赖性转录激活功能区, 氨基末端具有高度保守的DNA结合区(DNA binding domain, DBD)和配体非依赖性转录激活功能区. 当体内BA超负荷时, BA与FXR的LBD结合增加并诱导FXR变构, 进而与视黄醇衍生物受体结合形成异源二聚体, 借助其

■ 研究前沿

目前FXR抗NAFLD研究热点、重点是FXR激动剂抗NAFLD的作用机制, 以及何种FXR对NAFLD是有效地, 如何阻断FXR激动带来的不良反应, 单一用药还是联合其他药物效果好, 且FXR抗NAFLD的证据大多来源于临床前期研究, 需要更多的临床证据支持.

■ 相关报道

Mudaliar等在NAFLD患者中开展INT-747的Ⅱ期临床实验,证实25、50 mg INT-747用于患者是安全的,且能增加胰岛素敏感性、降低炎症及纤维化相关指标,并提出FXR激动后带来的安全问题,FXR抗NAFLD的证据仍需开展长期及更全面的临床研究。

DBD结合至FXR目的基因上游的启动子的反向重复序列^[20,21],主要通过调节以下靶基因的表达,来实现BA的反馈调节:(1)小异二聚体伴侣(small heterodimer partner, SHP),FXR激活后诱导SHP的表达,进而SHP促进与肝脏核受体-4(hepatic nuclear factor-4, HNF-4)、肝受体同源物-1(liver receptor homolog-1, LRH-1)结合的共活化物的分离使其失活,从而降低HNF-4、LRH-1对CYP7A1的转录活化作用,最终抑制BA的生成;(2)FXR可刺激多重耐药相关蛋白2(multidrug resistance-associated protein 2, MRP2)、MRP3、胆酸盐输出泵、组织相容性转运体(organic solute transporter α - β , OST α -OST β)的表达,使BA输出增多;上调回肠BA结合蛋白,增加肠腔对BA的重吸收;同时下调钠离子依赖性牛磺胆酸钠协同转运蛋白的表达,减少胆汁在肝的重吸收,从而调控体内BA稳态^[22];(3)FXR诱导人肠道成纤维生长因子-19(fibroblast growth factor-19, FGF-19)的表达或在小鼠诱导FGF-15的产生^[23],与相应的成纤维细胞生长因子受体-4(fibroblast growth factor receptor 4, FGFR-4)结合,通过JNK(c-Jun N-terminal kinase)信号途径下调CYP7A1的表达而抑制BA的合成。FXR通过以上途径反馈调节BA的生成,加速BA的生物转化与排泄,避免肝细胞内BA超负荷和过多堆积所引起的组织损伤。此外,体内BA升高时FXR被BA激活,诱导调控细胞周期的转录因子Foxmlb(forkhead box M1b)的表达,提高肝细胞DNA复制,从而促进肝脏的再生,抵抗BA超负荷的潜在毒性^[24]。由此可见,FXR在BA代谢、维持BA的内稳态和保护肝功能免受BA毒性损害的核心作用。

2 FXR调控脂质代谢

2.1 FXR与胆固醇代谢 在肝细胞中,胆固醇代谢包括胆固醇从头合成,以低密度脂蛋白(low density lipoprotein, LDL)和乳糜微粒(chylomicron, CM)的形式摄取,以极低密度脂蛋白(very low density lipoprotein, VLDL)分泌至血清中,此过程依赖胆汁的分泌及BA的合成。研究表明肝脏中胆固醇的沉积在NAFLD的进展中起着关键的作用。FXR通过调控胆固醇及脂蛋白代谢相关基因,如VLDL受体(very low density lipoprotein receptor, VLDLR),前蛋

白转化酶枯草溶菌素-9(proprotein convertase subtilisin kexin type 9, PCSK9),肝脏清道夫受体(scavenger receptor group B type 1, SRB1),从而调节胆固醇代谢。FXR基因敲除小鼠的血清总胆固醇、高密度脂蛋白胆固醇(high density lipoprotein cholesterol, HDL-C)升高^[25]。相反的,给予FXR激动剂,SRB1的表达增加,PCSK9活性降低,使胆固醇酯清除率增加而降低血清HDL-C水平^[26,27]。NAFLD患者的FXR表达下降,诱导VLDLR、集群分化蛋白-36(cluster differentiation protein-36, CD-36)的表达,抑制SRB1的表达^[28],通过抑制胆固醇的摄取及合成,增加胆固醇的分泌,维持胆固醇代谢稳态。由此可见,FXR在胆固醇代谢中的重要作用。磷脂转运蛋白(phosphor lipid transfer protein, PLTP)主要存在于肝脏和小肠,具有促进肝脏可溶性物质交换和运输的作用,FXR激活后可活化PLTP,介导磷脂和胆固醇从富含TG的脂蛋白向高密度脂蛋白(high density lipoprotein, HDL)转运,维持血浆HDL的水平。此外,FXR激动后抑制胆固醇生成BA,增加了肝脏的结合反应能力和胆管分泌,从而减少肝脏中有毒物质的积累而导致的组织损伤^[29],有效延缓LF及坏死进程,为治疗肝脏胆固醇性疾病如原发性胆汁性肝硬化(primary biliary cirrhosis, PBC)、LF等疾病提供了新思路。

2.2 FXR调节TG代谢 FXR对血浆和肝脏TG的调节主要通过两个途径:一是抑制肝脏合成新的脂肪。FXR通过诱导SHP的表达,下调肝脏X受体(liver X receptor, LXR)、固醇调节元件结合蛋白-1C(sterol regulatory element-binding protein-1C, SREBP-1C)和脂肪酸合成酶(fatty acid synthetase, FAS)的表达^[15],活化脂蛋白脂酶(lipoprotein lipase, LPL),抑制TG的合成和脂肪细胞释放肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α),并促进TG的分解和脂肪酸(fatty acids, FA)的氧化^[30,31],最终减少脂肪的生物合成^[32,33]和肝脏中TG的堆积,调节脂质代谢稳态;另一个途径是降解血浆中的TG,主要通过调控与其代谢密切相关的酶类以及一些重要脂蛋白和相应受体的表达来发挥作用。如FXR可诱导多配体聚糖(syndecan-1, SDC1)的转录,通过LPL、载脂蛋白E(apolipoprotein E, ApoE)等与脂蛋白相连,在肝脏清除脂蛋白残粒中发挥作用,最终降低血浆TG^[34]。LPL是清

除血浆脂蛋白中所含TG的限速酶, 其活性受到脂蛋白的调控。载脂蛋白C-III(apolipoprotein C-III, ApoC-III)抑制该酶活性, 载脂蛋白C-II (apolipoprotein C-II, ApoC-II)和载脂蛋白A-V (apolipoprotein A-V, ApoA-V)增强酶活性^[35]。FXR激动后抑制ApoC-III的表达, 上调肝细胞ApoC-II、VLDLR的表达, 增加外周组织对胆固醇的吸收利用, 增强ApoA-V启动子的活性, 从而促进LPL介导的TG分解, 增加CM的清除率, 改善肝脏TG的堆积, 同时抑制游离脂肪酸(free fatty acid, FFA)的生成和肝细胞VLDL的分泌^[36], 改善脂质代谢异常。高脂饮食诱导的NASH小鼠模型, FXR基因敲除小鼠较野生型, 表现为更严重的肝脏脂肪变性、肝细胞气球样变、肝小叶炎症及胆红素堆积, 谷丙转氨酶(alanine aminotransferase, ALT)、BA水平增加, 给予FXR激动剂后改善。此外, 近年来发现NAFLD患者的FXR表达下降, 使SREBP-1C抑制TG的合成作用减弱, 加重肝脏脂质沉积, 由此可见FXR在脂质代谢中的重要作用。胆酸和GW4064是率先被证实具备调节TG合成能力的FXR激动剂。将GW4064用于SHP基因敲除小鼠, 发现GW4064可活化FXR并诱导SHP的表达, 下调SREBP-1C的表达和降低FAS的活性, 从而抑制TG的生物合成。魏钰等^[37]发现FXR在NAFLD患者中表达受抑, 其受体激动剂GW4064可明显减少脂肪病变的肝细胞中脂滴和TG含量, 显著改善肝细胞脂肪病变。此外, 发现FXR激动剂WAY-362450可显著改善果糖诱导的肝脏脂肪病变, 提示FXR在预防肝脏TG堆积方面具有多效性^[38]。

2.3 FXR与糖代谢 作为多效性的BA受体, FXR不仅参与BA、脂质代谢, 同时也参与调控糖原代谢稳态^[39]。研究^[32]已证实BA和FXR在糖代谢中的重要作用, 但具体的机制尚未阐明。FXR可活化FXR上的效应元件即葡萄糖载体-4(glucose transporter 4, GLUT-4)启动子, 诱导GLUT-4的表达^[40], 促进外周组织摄取利用葡萄糖, 抑制糖异生, 同时下调丙酮酸激酶的表达从而抑制糖酵解^[41], 促进糖原储存, 调控糖原合成与分解^[5]; 增加脂肪细胞以及外周组织对脂肪的摄取及利用, 抑制脂肪的从头合成, 降低血清TG、胆固醇水平; 增加外周组织对胰岛素的敏感性^[13], 诱导胰岛细胞分泌胰岛素, 最终改善IR, 调控糖原稳态。FXR基因敲除

小鼠由于缺失FXR, 对糖异生的抑制作用和外周组织对糖原的处理能力减弱而表现为糖耐量^[13,33,42]和胰岛素敏感性降低, 从而扰乱糖原稳态。有学者^[30]认为FXR激动后抑制磷酸烯醇式丙酮酸羧基酶和葡萄糖-6-磷酸酶的表达, 抑制糖异生, 诱导脂肪细胞的胰岛素信号转导和增加胰岛素刺激下的糖原摄取, 从而增加外周组织对血糖的利用, 降低血糖水平。由此可见, FXR用于治疗存在高糖血症及高脂血症的NAFLD患者可能是有效的。

3 FXR对NAFLD的作用机制

3.1 FXR改善IR IR是NAFLD发生及发展的重要环节, 因胰岛素易感底物-2(insulin-responsive substrate-2, IRS-2)异常的丝/苏氨酸磷酸化作用(生理性酪氨酸磷酸化消失)导致。由于IR, 外周组织摄取及利用葡萄糖障碍, 加之胰岛素对糖异生抑制作用减弱, 肝糖原过度合成, 导致高糖血症; 其次胰岛素对脂肪分解的抑制作用减弱^[43,44], 血清中FFA增加, 增加了糖原依赖的脂肪合成, 加重肝脏脂肪的沉积。FXR参与胰岛素的信号传导, 当胰岛素信号通路受抑可能导致BA激动FXR的能力减弱, 增加罹患NAFLD的风险^[45]。FXR基因敲除小鼠表现为IR, 使用FXR激动剂后肝脏和外周组织中的IRS-2酪氨酸磷酸化水平增加, 胰岛素的敏感性增加, 表现为血糖下降^[27,46]。过氧化物酶体增生激活受体(peroxisome proliferator-activated receptor, PPAR)激动剂噻唑烷酮类是临床上改善IR的常用药物。临床研究发现罗格列酮可增加胰岛素敏感性, 显著改善NASH患者的肝细胞损伤, 肝小叶炎症、肝脏脂肪病变及LF^[47,48]。尽管这些有利的作用, 由于使用后患者体质量增加的发生率高达10%, 噻唑烷酮类仍不能作为NASH患者的常规治疗药物。Cipriani等^[7]通过对比10 mg/kg的INT-747与同等剂量的罗格列酮治疗肥胖小鼠的疗效差异, 发现INT-747实验组小鼠的血糖、TG、FFA、HDL下降, 改善了肝脏、肌肉的脂肪沉积, 增加IRS-2的酪氨酸磷酸化作用, 使胰岛素敏感性增加, 体质量无显著变化。罗格列酮对照组TG、血糖、FFA下降、除LDL、HDL外的胆固醇脂蛋白水平下降, 体质量指数增加了20%且未改善脂质代谢障碍, 证实FXR能改善IR, 缓解肝脏脂肪病变。因此FXR治疗NASH可能

■创新盘点

本文较为全面地综述了“BA核受体FXR在NAFLD中的作用”, 内容比较全面, 观点明确, 较为真实、科学地反映了BA核受体FXR在NAFLD中的作用与研究进展, 可指导后续的动物实验和临床研究。

应用要点

目前, FXR激动剂应用于NAFLD还存有争议, 本文就FXR抗NAFLD作用机制和FXR激动剂应用于NAFLD的相关研究作综述, 指导后续的动物实验和临床研究, 为FXR抗NAFLD提供更多的临床证据, 寻找药物治疗NAFLD的新靶点。

具有实效性, FXR激动后抑制SREBP-1C和FAS的表达, 增加肝细胞及脂肪细胞PPAR的表达, 减少脂肪的合成, 改善IR, 增加糖原的合成, 中和由于IR受损的糖原分解作用, 与噻唑烷酮类相比, FXR改善IR、脂质代谢障碍, 且不引起体质量的增加。

3.2 FXR激动剂应用于NAFLD Yang等^[15]通过对比NAFLD患者和健康人群的FXR、LXR、SHP及SREBP-1C的表达, 发现FXR通过诱导SHP的表达, 进而活化LPL和PPAR, 促进TG分解和FA的氧化, 并下调LXR、SREBP-1C以及FFA的表达^[49], 最终减少脂肪的生物合成并增加其转运, 以此调控BA、脂质代谢稳态。Zhang等^[50]研究发现, GW4064增加了胆固醇的逆向转运, 抑制肠道对胆固醇的吸收, 降低血清HDL水平。此外, Ma等^[30]将GW4064用于高脂饮食诱导的脂肪变C57BL/6小鼠, 发现GW4064上调CD36的表达, 抑制TG的合成及FFA的产生, 增加胆固醇的转运, 显著改善小鼠肝脏脂肪变, 并抑制磷酸烯醇式丙酮酸羧基酶和葡萄糖-6-磷酸酶的转录, 改善高胰岛素血症、高血糖症。INT-767, FXR和TGR5的共激动剂, 诱导小肠内分泌细胞分泌胰高血糖素样肽, 增加脂肪细胞对脂质的摄取和肝糖原合成^[13], 减少肝脏VLDL的产生, 促进外周组织对胆固醇的摄取, 从而降低TG和胆固醇水平, 该效应在糖尿病小鼠模型中得到证实^[51]。Hubbert等^[52]给予NAFLD患者口服25、50 mg INT-747 6 wk, 发现INT-747能明显改善IR、肝脏炎症及纤维化指标, 目前该药用于治疗2型糖尿病、NAFLD已进入II期临床试验。Px-102, 非类固醇类FXR激动剂, 目前已通过I期临床试验。INT-747或Obeticholic acid, 是近年研制的一种抗NAFLD的新药, 鹅脱氧胆酸的半合成衍生物, 可激动FXR发挥抗胆汁淤积和保护肝脏的作用。此外, 两项II期临床试验评价了INT-747治疗PBC的效果: (1)165例PBC患者给予随机口服15、25、50 mg不同剂量的INT-747 12 wk, 与安慰剂对照组相比实验组碱性磷酸酶(alkaline phosphatase, AP)、ALT、 γ 谷氨酰胺转移酶(gamma glutamyl transferase, GGT)明显下降, 50 mg治疗组约33.3%的患者出现了严重的消化系不良反应, 提示50 mg不能作为治疗胆汁淤积性肝病的起始治疗剂量。165例患者中超过50%出现瘙

痒症, 瘙痒既是PBC的常见症状, 也是不容忽视的不良反应之一^[53]; (2)Kowdley^[54]给予PBC患者口服INT-747 10、50 mg 12 wk, 发现可显著改善肝酶、AP、PBC相关炎症及免疫标记物(C反应蛋白、TNF- α 、免疫球蛋白M)水平, 治疗组较安慰剂组更易出现瘙痒, 且发生率随INT-747剂量增加, 未见消化系不良反应。由此可见, INT-747可减轻肝脏损伤, 改善肝脏炎症及组织学改变, 延缓PBC进程并改善其预后, 基于II期临床试验的成果, III期临床试验已启动, INT-747的临床治疗效果及不良反应等仍待进一步研究。

4 FXR应用于NAFLD的争议

FXR激动后也同样带来一定的不良反应。旁氧代酶-1(paraoxonase-1, PON1)由肝脏分泌并与HDL形成复合物而被转运, FXR诱导FGF15/19的分泌, 抑制肝脏PON1、CYPTA1的表达^[55,56]及载脂蛋白A-I (apolipoprotein A-I, ApoA-I)的合成, ApoA-I是HDL的组成蛋白, 从而降低HDL-C。与野生型小鼠相比, FXR基因敲除小鼠的血清HDL-C、非HDL-C和TG升高^[57,58]。有学者则认为FXR基因敲除小鼠, 因丧失FXR活性, 使SRB1介导的选择性清除HDL-C的作用减弱, 血清LDL下降, 而HDL升高^[59]。此外, FXR可诱导VLDLR的表达, 增加LPL介导的TG的分解、VLDL及CM的清除, 上调SHP的表达, 活化的SHP与LRH-1结合并使之失活, 从而降低LRH-1对CYP7A1转录活化作用, 抑制BA的生物合成, 改善肝脏TG的沉积, 但是一定程度上升高血清LDL, 加重肝脏脂质代谢障碍, 且HDL水平降低增加了罹患动脉粥样硬化的风险。在饮食诱导的肥胖小鼠模型中, 发现FXR的缺失可抵御体质量的增加^[60], 改善高血糖症, 修复糖耐量受损, 可能与增加了能量消耗有关^[11]。Watanabe等^[61]也提出GW4064导致BA合成减少, 降低能量消耗, 导致IR及体质量增加。因此, FXR激动剂的有效性和安全性仍待进一步的研究。

5 结论

目前, 大量证据表明FXR可改善IR、脂质代谢障碍, 抑制LF、肝癌进展的炎症反应及纤维化过程, FXR可被特定激动剂激活, 可能成为药物治疗NAFLD的作用靶点。值得注意的是

如何阻断FXR激动后升高LDL, 降低HDL的不良反应, 还有何种FXR激动剂对NAFLD是有效地, 单一用药还是联合其他药物效果好, 且FXR抗NAFLD的证据大多来源于临床前期研究, 需要更多的临床证据支持. 我们期待学者做出更有说服力的研究, 解决尚存的问题, 为NAFLD的治疗提供新思路.

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■名词解释

法尼醇X受体(FXR): 是具有配体活性的核受体超家族成员, 在肝脏、回肠、肾脏、肾上腺中高度表达, 生理水平的BA是FXR的内源性配体, 因此FXR又称为BA受体. 鹅脱氧胆酸、脱氧胆酸、石胆酸、GW4064、INT-747和WAY-362450为FXR重要的激动剂.

同行评价

本文综述了BA核受体FXR调控BA、糖原、脂质代谢的作用机制以及FXR激动剂应用于NAFLD的相关研究, 较为真实、科学地反映了FXR在NAFLD中的作用, 具有一定的学术价值。

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