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文献综述 REVIEW

非酒精性脂肪肝的发病机制及肠促胰素在治疗中的研究进展

郭晓宇, 刘 剑, 高 宇

背景资料
肠促胰素以葡萄糖依赖模式促胰岛素分泌, 已成为治疗2型糖尿病(type 2 diabetes mellitus, T2DM)的新型药物. 随着研究的不断深入, 胰高血糖素样肽-1(glucagon-like peptide-1, GLP-1)受体激动剂及二肽基肽酶-4抑制剂不仅局限于降糖的作用, 还可以显著改善肝内脂质代谢. 本文对GLP-1类似物治疗非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)进行深入的研究.

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Nonalcoholic fatty liver disease: Pathogenesis and incretin based therapies

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Abstract
Nonalcoholic fatty liver disease is considered a hepatic manifestation of metabolic syndrome (MS). The current treatment of non-alcoholic fatty liver disease (NAFLD) principally involves amelioration of MS components by lifestyle modification. Effective pharmacological agents for fatty liver treatment are lacking. Incretins are gut derived hormones secreted into the circulation in response to nutrient ingestion that can enhance glucose-stimulated insulin secretion, and represent a new class of drugs for treatment of type 2 diabetes, including glucagon-like peptide 1 analogues and dipeptidyl aminopeptidase 4 inhibitors. There are several experimental and clinical trials exploring the efficacy of incretin based therapies in NAFLD treatment, however, further studies are needed to assess the long-term effect of incretin based therapies on NAFLD.

Key Words: Nonalcoholic fatty liver disease; Insulin resistance; Glucagon-like peptide-1; Dipeptidyl peptidase-4; Metabolic syndrome

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摘要
非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)是代谢综合征重要组成部

分, 目前治疗方法主要以改善生活方式和调整饮食结构为主, 尚缺乏针对性药物. 肠促胰素是肠道内分泌细胞分泌的胃肠激素, 主要通过葡萄糖浓度依赖模式刺激胰岛素的分泌, 胰高血糖素样肽-1(glucagon-like peptide-1, GLP-1)类降糖药物是用于治疗2型糖尿病的新型药物, 其中包括GLP-1类似物和二肽基肽酶-4(dipeptidyl peptidase 4)抑制剂. 基础及临床研究表明, 肠促胰素可通过多种机制发挥对NAFLD的改善作用, 但肠促胰素对NAFLD治疗的长期安全性仍需要进一步研究.

关键词: 非酒精性脂肪性肝病; 胰岛素抵抗; 胰高血糖素样肽–1; 二肽基肽酶–4; 代谢综合征

核心提示: 胰岛素抵抗、糖耐量异常是非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)的病理生理基础. 肠促胰素包括胰高血糖素样肽-1(glucagon-like peptide-1, GLP-1)类似物和二肽基肽酶-4抑制剂, 目前实验和临床数据表明, GLP-1类似物可以改善肝脏功能, 脂肪含量及分布, 脂质代谢以及相关的信号转导途径. 因此, GLP-1类似物有望成为NAFLD潜在的治疗方法.

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0 引言

非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)是最常见的肝脏疾病, 其发病率逐渐增高[1]. 除酗酒、病毒性或自身免疫性肝病、α-1抗胰蛋白酶缺乏、药物干预(如糖皮质激素、雌激素)等致病因素外, 肝组织内脂肪蓄积亦是导致肝脏慢性疾病的重要原因[2]. 随着疾病进展, NAFLD可发展为更为严重的肝脏疾病, 如非酒精性脂肪性肝炎(nonalcoholic steatohepatitis, NASH), 甚至约有10%-15%NASH患者发展为肝硬化, 最后导致肝癌[3]. NAFLD与代谢综合征(metabolic syndrome, MS)关系密切, 特别是肥胖, 血脂升高, 胰岛素抵抗(insulin resistance, IR)和随之而来的糖耐量异常及2型糖尿病(type 2 diabetes mellitus, T2DM)[4]. 目前治疗NAFLD主要以改变生活方式、调整饮食结构、增强运动、减轻体质量和增强外周组织对胰岛素的敏感性为主[5,6]. 药物治疗NAFLD的临床和基础研究尚在探索中.

1 NAFLD的发病机制

NAFLD的发病机制主要与遗传易感性、糖脂毒性和胰岛素抵抗有关. 机体将过剩的能量以甘油三酯(triglyceride, TG)的形式贮存于白色脂肪组织中, 当白色脂肪过度蓄积时, 可导致脂肪细胞体积的增大以及数量的增多, 有研究表明脂肪细胞体积的增大与IR正相关[7]. 脂肪细胞体积增大后, 胰岛素对白色脂肪组织脂解作用减弱, 导致外周组织的IR与肝脏脂肪堆积. 由于脂解作用被抑制, 血浆中游离脂肪酸(free fatty acids, FFA)浓度增高, 破坏了肝脏内FFA平衡, 成为NAFLD TG的主要来源[8]. 除白色脂肪组织和骨骼肌外, 肝脏是胰岛素作用的主要部位. 在空腹状态下, 胰岛素可以抑制肝糖原的分解以维持机体血糖浓度的平衡. IR是MS、T2DM和NAFLD联系的中心环节[9], 当机体处于IR状态时, 胰岛素抑制肝糖原分解的能力受损, 导致了机体高血糖状态和高胰岛素血症. 胰岛素还可抑制肝脏极低密度脂蛋白(very low density lipoprotein, VLDL)的合成, 在IR状态下, 脂肪组织中脂肪动员增强, 大量FFA释放入血, VLDL合成的原料增多, 同时分解VLDL的脂质蛋白酶活性下降, 导致VLDL释放及合成增多[10]. 内质网是机体细胞代谢活动中重要的细胞器, 参与机体蛋白的加工与修饰. 高血糖状态、脂质蓄积及某些化学损伤均可导致内质网稳态的破坏, 内质网腔内蛋白质折叠出现错误或不折叠, 导致其失去正常的生理功能, 当未折叠或折叠错误的蛋白质在腔内积聚时则会引起内质网应激(endoplasmic reticulum stress, ERS)[11]. 若胰岛素作用的主要靶组织(肝脏、脂肪、肌肉等)发生持续、严重的ERS即可引起IR[12].

固醇调节原件结合蛋白1c(SREBP-1c)是肝内乙酰辅酶A羧化酶(acetyl-CoA carboxylases, ACCs)和脂肪酸合成酶(fatty acid synthetase, FAS)的转录的关键激活因子, 直接参与调控有关TG、脂肪酸合成基因的表

研发前沿

肠促胰素不仅可以维持体内血糖稳态, 还可以通过抑制食欲、减轻体质量, 减轻内质网应激, 增加组织对胰岛素的敏感性, 从而改善胰岛素抵抗(insulin resistance, IR), 减少肝细胞内脂质沉积, 有望成为脂肪肝有效安全的治疗药物.

相关报道 众多学者研究表明GLP-1类似物可以改善T2DM患者血脂谱, 甘油三酯、总胆固醇、极低密度脂蛋白水平降低, 高密度脂蛋白水平升高. 在减轻5%-10%的体质量时, 可减少肝内约40%-80%的脂肪蓄积.

达. 过多的饱和脂肪酸在肝细胞内集聚可触发肝细胞ERS, 激活未折叠蛋白反应(unfolded protein response, URP)和固醇调节级联反应, SREBP-1c及脂质从头合成相关酶基因如HMG CoA还原酶、乙酰CoA羧化酶mRNA表达水平均有不同程度的升高, 进而促进三酰甘油、胆固醇的合成与异常堆积, 最终导致肝细胞脂肪变[13]. 有研究[14]表明, SREBP-1c过表达的大鼠均表现出现IR、脂肪代谢障碍及肝脏脂肪变等病理变化. 长期严重的ERS可导致肝细胞IRE1/JNK途径、Caspase激活途径、CHOP/TRB3途径的激活, 导致肝细胞的凋亡及纤维化[15,16]. 有研究[17,18]指出, 肝脏内脂肪蓄积可能导致ERS, 进而造成肝脏的IR, 尤其是甘油二酯的蓄积对肝细胞有毒性作用, 导致肝脏IR和肝脂肪变性. 此外, 高糖或饱和脂肪酸棕榈酸诱导HepG2细胞发生ERS, PERK-eIF2α通路中SREBP-1c转录因子被激活, 增加了细胞内脂肪的蓄积[19]. 李小山等[20]高脂喂养大鼠12 wk后, 肝脏组织*FAS*、*ACCs*基因在mRNA和蛋白质水平上表达进显著增高. ERS对肝脏中载脂蛋白B受体100的合成与分泌具有调节作用, 可以通过减少VLDL形成来减少肝脂肪输出促进肝细胞中脂肪堆积加重[21].

2 肠促胰素的生理作用

肠促胰素由肠道细胞分泌, 目前发现的肠促胰素有肠道K细胞分泌的葡萄糖依赖性促胰岛素多肽和L细胞分泌的胰高血糖素糖肽-1(glucagon-like peptide-1, GLP-1). 研究[22]发现在胰岛细胞、肺、脑、肾、肝以及动物脂肪组织均存在GLP-1受体(GLP-1R). 随着对肠促胰素研究的不断深入, 研究发现GLP-1受体激动剂和二肽基肽酶-4(dipeptidyl peptidase-4, DPP-4)抑制剂不仅局限于降糖的作用, 而且还可显著改善肝内脂质代谢. GLP-1不仅具有葡萄糖依赖的促胰岛素分泌作用, 增加胰岛β细胞数量及保护其功能外, 还可以在胰腺外发挥诸多效应[23]. GLP-1受体激动剂可以通过抑制食欲、减轻体质量, 减轻ERS, 增加组织对胰岛素的敏感性, 从而改善IR[24]; 还可通过延缓胃排空, 抑制进食信号, 增强饱腹感, 抑制肠内对TG的吸收, 减少乳糜微粒形成, 从而间接减少脂类物质的吸收, 减少肝细胞内脂质沉积. 因此研究者认为, 作为新型降糖药物的肠促胰素有望成为有效、安全治疗脂肪肝的药物.

3 肠促胰素对NAFLD作用机制的临床与基础研究

GLP-1受体激动剂(如艾塞那肽、利拉鲁肽)是治疗T2DM的新型药物. 艾塞那肽是临床应用中被批准的第一个GLP-1受体激动剂, 一项为期52 wk的研究[25]表明, 艾塞那肽1次/wk治疗可以降低收缩压6 mmHg, 同时还可以改善T2DM患者高血脂水平. 研究[26]表明, T2DM患者经艾塞那肽治疗3年, 血脂成分的有所改善: TG水平下降12%(P = 0.0003), 总胆固醇(total cholesterol, TC)水平降低5%(P = 0.0007), VLDL水平降低6%(P<0.0001), 高密度脂蛋白(high density lipoprotein, HLDL)水平升高24%(P<0.0001). 在一项对肥胖T2DM患者应用艾塞那肽单药治疗长达24 wk试验, 无论是T2DM组还是非糖尿病对照组, 当减轻5%-10%的体质量时, 可减少肝内约40%-80%的脂肪蓄积[27]. 一项包含12个临床试验的荟萃分析表明, T2DM患者经20 wk利拉鲁肽治疗后, 肝脏谷丙转氨酶(alanine transaminase, ALT)水平下降[28]; 艾塞那肽治疗52 wk后, 肝脏ALT水平显著下降(P<0.0001)[29]. Sathyanarayana等[30]在研究吡格列酮与艾塞那肽配伍对T2DM患者肝脏脂肪的影响时发现, 虽然吡格列酮不能显著的减轻体质量, 但是当配伍艾塞那肽治疗后可显著减少肝脏脂肪的堆积, 降低血浆TG水平. DPP-4抑制剂维格列汀和西格列汀可以有效降低餐后TG、血清载脂蛋白B-48和FFA水平[31], 还可增加神经肽Y在人体腹部脂肪细胞的抗脂解作用, 从而减少肝脏对FFA的摄取.

GLP-1类似物艾塞那肽可明显改善ob/ob糖尿病小鼠IR状态, 显著减少肝脏内脂肪堆积, 降低ALT水平[32]. Svegliati-Baroni等[33]发现艾塞那肽治疗NASH大鼠, 可以增加PPARα及其下游靶基因酰基辅酶A氧化酶(*ACOX*)、肉碱棕榈酰转移酶1(*CPT1A*)的表达(ACOX是β过氧化作用中的限速酶, CPT1A是脂肪酸进入线粒体开始氧化作用的关键酶). Gupta等[34]证实GLP-1在人体肝细胞内表达; Lee等[35]发现在人肝癌细胞系中, GLP-1受体数量随着艾塞那肽应用剂量的增加而增加. 也有证据表明, GLP-1受体激动剂可以通过调节成纤维

细胞生长因子-21(fibroblast growth factor 21, FGF-21)信号通路改善肝细胞脂肪变性. 在啮齿类动物中, FGF21主要在肝脏内表达, 在机体的新陈代谢中起到重要作用, 可增强肝细胞内脂肪氧化, 减少TG含量及肝脏脂肪变性, 增加脂肪组织对胰岛素敏感性, 调节白色脂肪组织的脂解作用, 改善糖耐量异常[36], 肝细胞ERS时, FGF21可通过IRE-1α/XBP1和PERK/ATF4途径增加其表达量, 缓解ERS, 进而改善肝脏IR[37-39]. 这些改变可能与FGF-21提高了AMP激活的蛋白激酶的活性, 增强肝细胞脂肪酸氧化作用有关. Nongaki等[40]发现在易感肥胖及T2DM小鼠模型中, GLP-1类似物可通过上调肝脏PPARγ表达, 激活成FGF-21信号通路, 减轻肝脏脂质沉积, 提高外周组织对胰岛素的敏感性. DPP-4抑制剂可通过减少T2DM小鼠模型关键酶SREBP-1c、FAS及固醇酰辅酶A脱氢酶1的表达, 从而减少肝脏的脂质的从头合成, 促进肝脏脂肪酸代谢, 减少肝细胞内的脂质沉积[41].

Gupta等[42]研究发现GLP-1可显著减少细胞坏死, 可能是由于GLP-1可以抑制脂肪沉积, 减少细胞凋亡, 减轻肝脏ERS[43], 从而保护性肝细胞. 利拉鲁肽可以减少高脂喂养小鼠肝内脂肪变性及改善ERS, 增加脂肪细胞的自噬[44]. Exendin-4可以增加沉默调节蛋白1抑制ERS, 减少肝细胞内脂质沉积[45]. 有研究[46]表明, 利拉鲁肽可以抑制高脂喂养大鼠内质网跨膜蛋白IRE1、ATF6和PERK的激活, 减少CHOP表达后一系列级联反应, 改善了肝脏的ERS, 延缓脂肪肝进程.

4 肠促胰素临床应用的安全性

虽然目前GLP-1受体激动剂已作为T2DM的常规治疗, 然而患有轻度慢性胰腺炎大鼠应用艾塞那肽治疗后增加了其患胰腺癌的风险, 仍有专家担心GLP-1类药物有导致胰腺炎、胰腺癌和甲状腺癌的风险. 然而, 最新一项长达2年的实验研究中发现, 当应用利拉鲁肽剂量为FDA批准的最大应用剂量血药浓度60倍时, 小鼠、大鼠及猴子模型并不能确定利拉鲁肽与罹患胰腺炎风险之间存在因果关系[47]. 在一项动物实验中, GLP-1治疗可以导致甲状腺C细胞增生, 然而其对人体甲状腺是否有不良影响尚未研究清楚[48].

虽然调节天然GLP-1生物活性的DPP-4酶抑制剂有很多, 但仅有一小部分(如西他列汀、维格列汀、沙格列汀、利拉利汀、阿格列汀)可供临床使用[49]. 有数据表明维格列汀与噻唑烷二酮配联合应用不仅对TG和HDL有改善作用, 还可以降低收缩压和舒张压[50]. 西格列汀经肾脏代谢, 不适用于中至重度肾脏损害或终末期肾病的患者[51]; 严重肝功能不全时严禁应用, 但轻中度肝功能不全时可以调整用药剂量[52]. 西格列汀批准上市后, 一系列的过敏反应报告随之而来, 如血管性水肿、剥脱性皮肤病和肝脏酶学指标升高, 因此其用药安全新还需要进一步持续监测[49].

5 结论

NAFLD的发病率不断上升, 带来了一系列健康问题, 包括糖尿病、肥胖、高血压、血脂异常[53]. GLP-1是一类治疗T2DM的新型药物, 可以依赖葡萄糖浓度刺激的胰岛素分泌, 抑制胰高血糖素的分泌, 延缓胃排空, 减少食欲和食物摄入量, 减轻体质量[54]. 此外, 众多的研究表明GLP-1可改善脂质代谢, 促进脂肪的重新分布, 减轻胰岛素抵抗, 减少肝内脂肪沉积. 然而, 到目前为止仅有对T2DM合并NAFLD/NASH患者应用GLP-1类似物或DPP-4抑制剂的研究, 因此, 还需要进行更多的基础和临床试验来验证基于肠促胰素治疗NAFLD的长期疗效和安全性.

创新盘点

本文通过对基于肠促胰素治疗NAFLD大量文献研究, 总结了这方面的最新研究成果, 对NAFLD的发病机制和应用肠促胰素治疗的研究进展做了深入全面总结和分析.

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应用要点

本文对NAFLD发病机制和基于肠促胰素治疗方案进行研究, 为改善T2DM和NAFLD患者血糖和血脂提供一个理论依据.

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名词解释

肠促胰素：是由肠上皮L细胞分泌的一类激素，主要包括GLP-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细胞分泌胰岛素降低血糖，还可以在胰腺外发挥诸多效应，研发促进肠促胰素释放药物有望成为NAFLD治疗的新策略.

同行评价

胰岛素抵抗, 糖耐量异常是非酒精性脂肪肝的病理生理改变. 本文从肠促胰素角度探讨了其在非酒精性脂肪肝发病与治疗中的作用, 对深化发病机制的认识, 探索新的临床治疗手段具一定意义.

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