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述评 EDITORIAL

胰高血糖素样肽-1受体激动剂在代谢性疾病治疗中的应用前景

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Application prospects of glucagon-like peptide-1 receptor agonists in treatment of metabolic diseases

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Abstract

Metabolic syndrome [overweight, obesity, type 2 diabetes mellitus (T2DM), and lipid metabolism disorder] is directly related to cardiovascular diseases, non-alcoholic fatty liver disease (NAFLD), tumors, and other diseases, and its prevalence has been increasing sharply, bringing an increasingly heavy burden on society. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a novel class of glucose-dependent hypoglycemic drugs modified from glucagon-like peptide-1. Since their mechanism of action is different from that of traditional insulin and oral secretagogues, they overcome the adverse reactions associated with traditional oral medications and insulin, can improve the success rate of T2DM control, and has been widely used in the treatment of T2DM. Recent studies have found that, in addition to hypoglycemic effect, GLP-1RAs can improve metabolic diseases, such as diabetes-related complications, NAFLD, and cardiovascular diseases, and therefore have broad application prospects. This paper reviews the potential role of GLP-1RAs in these diseases.

Key words: Glucagon-like peptide-1 receptor agonists; Diabetes mellitus; Cardiovascular diseases; Nonalcoholic fatty liver disease; Metabolic dysfunction; Application prospect

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摘要

代谢综合征[超重、肥胖、2型糖尿病(type 2 diabetes mellitus, T2DM)、脂代谢紊乱]与心血管疾病、非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)、肿瘤等多种疾病直接相关, 年来患病率急剧上升, 给社会带来了日益沉重的负担. 胰高血糖素样肽-1受体激动剂(glucagon-like peptide-1 receptor agonists, GLP-1RAs)是对胰高血糖素样肽-1改造而来的一种新型葡萄糖依赖性降糖药物, 作用机制不同于传统胰岛素和口服促泌剂, 克服了口服降糖药及传统胰岛素的多种不良反应, 可提高T2DM的控制达标率, 已被广泛用于T2DM的治疗. 近年研究显示, GLP-1RAs除降糖作用外, 对糖尿病相关并发症、NAFLD、心血管疾病等代谢功能障碍性疾病均具有改善作用, 具有广泛的应用前景, 本文就GLP-1RAs在上述疾病中的潜在作用作一述评.

关键词: 胰高血糖素样肽-1受体激动剂; 糖尿病; 心血管疾病; 非酒精性脂肪性肝病; 代谢功能障碍性疾病; 应用前景

核心提要: 胰高血糖素样肽-1受体激动剂(glucagon-like peptide-1 receptor agonists, GLP-1RAs)一种新型葡萄糖依赖性降糖药物, 可通过促进胰岛素分泌, 胰岛β细胞的增殖、抑制其凋亡, 抑制胰高血糖素分泌等有效降低2型糖尿病(type 2 diabetes mellitus, T2DM)患者的血糖水平并维持血糖稳态, 已被广泛应用于糖尿病治疗. 近年研究发现, GLP-1RAs还具有抑制食欲、延缓胃排空、调节血脂代谢、改善心功能、减少肝脏脂肪沉积等多重生物学效应, 可显著改善合并T2DM的肥胖症及非糖尿病的单纯性肥胖. 以上作用为GLP-1RAs在代谢性疾病中的治疗提供了应用前景和方案选择.

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0 引言

胰高血糖素样肽-1 (glucagon-like peptide-1, GLP-1)是由小肠L细胞分泌的一种葡萄糖依赖性肠促胰素, 在受到食物刺激后被释放入血, 作用于胰岛β细胞促进胰岛素基因的转录、增加胰岛素的生物合成和分泌, 也可通过作用于生长抑素抑制胰岛α细胞产生胰高血糖素而发挥降糖作用[1]; GLP-1还能诱导胰岛β细胞的增殖、抑制其凋亡, 增加胰岛素的敏感性[2], 因此在调节糖代谢及维持血糖稳态方面发挥重要作用. 由于GLP-1半衰期较短, 在体内可被二肽基肽酶IV (dipeptidyl peptidase-IV, DPP-IV)快速降解[3], 因此对其结构进行修饰, 开发出具有同样药理活性和生物学作用、掩盖DPP-IV的结合位点、延长半衰期的新型制剂, 即胰高血糖素样肽-1受体激动剂(glucagon-like peptide-1 receptor agonists, GLP-1RAs). 根据作用时间可分为短效、长效和超长效制剂, 目前常用短效制剂有艾塞那肽、利司那肽, 长效制剂有利拉鲁肽、艾塞那肽周制剂、阿比鲁肽等, 度拉糖肽属于超长效制剂. 艾塞那肽作为GLP-1RAs的代表性药物, 于2005年被美国食品药物管理局(food and drug Administration, FDA)批准上市用作2型糖尿病(type 2 diabetes mellitus, T2DM)的治疗[4]. 美国临床内分泌医师协会联合美国内分泌学会的共识声明中将GLP-1受体激动剂列为糖尿病的一线治疗方案, 在《中国2型糖尿病防治指南(2017年版)》中被列为二联降糖治疗方案之一. 在治疗糖尿病过程中逐渐发现, 除调节血糖、避免传统胰岛素不良反应外, GLP-1RAs还具有抑制食欲、延缓胃排空、调节血脂代谢、改善心功能、减少肝脏脂肪沉积等多重附加生物学效应, 因此GLP-1RAs对代谢性疾病及非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)的潜在作用收到极大关注.

1 GLP-1RAs在糖尿病并发症中的应用

目前已有6种GLP-1RAs获批用于T2DM治疗. 经GLP-1RAs治疗后, 糖化血红蛋白的平均下降率与其他降糖药物效果相当, 而且低血糖发生率较低, 安全性高[5]. T2DM并发症的发生是导致预后不良的重要原因, 发生机制与遗传易感性、胰岛素抵抗(insulin resistance, IR)、高血糖、氧化应激等因素及相互作用有关. 慢性肾脏病是糖尿病(diabetic mellitus, DM)的主要并发症, 40%的T2DM患者受糖尿病肾病(diabetic kidney disease, DKD)的影响, DKD是需要肾脏替代疗法的终末期肾脏疾病的最常见原因[6,7]. 临床前研究证实近端小管细胞、肾小球和肾血管平滑肌细胞中存在GLP-1受体的表达, 并且GLP-1RAs可能通过改善肾小管的水钠处理能力、影响肾脏血流动力学和减少肾脏的氧化应激等机制发挥肾脏保护作用[8-10]. 然而, 目前尚无将肾脏预后作为主要终点的GLP-1RAs临床研究, 一项以肾脏结局作为研究终点的索马鲁肽安慰剂对照试验正在进行, 预计将在2024年结束[11]. 此外, Goncalves等[12]发现艾塞那肽能抑制活化的小胶质细胞产生炎症因子, 从而预防IR诱发的血-视网膜屏障分解和炎症; Hernandez等[13]证实

GLP-1RAs可防止视网膜神经变性, 并减少视网膜毛细血管中白蛋白渗漏, 减轻眼底微血管损害; 这些数据表明GLP-1RAs是治疗以血管通透性增加和神经炎症为特征的糖尿病性视网膜病变的潜在治疗选择. DM是外周神经病变的最常见的原因, 可并发糖尿病性周围神经病(diabetic peripheral neuropathy, DPN), 严格的血糖控制可有效减缓DPN的发展, 但不能完全预防DPN的发展[14]. 多项研究表明GLP-1RAs对某些神经元和神经细胞具有神经营养和神经保护特性, 在动物模型中对中风、帕金森病都有治疗效果[15,16]. Himeno等[17]证实GLP-1RAs可能直接通过小鼠的腰背根神经节神经元及其轴突改善小鼠糖尿病DPN的严重程度. 以上研究结果表明, GLP-1RAs可能通过减轻DM并发症从而改善其预后, 但具体作用机制尚未明确, 需要更多的基础和临床研究进一步证实和阐明.

2 GLP-1RAs对NAFLD的作用

NAFLD的患病率在全球范围内呈上升趋势, 已成为世界许多地区慢性肝病的主要病因, 也是美国肝脏移植的第二大适应证, 并可能在未来20年内成为肝移植的主要适应证[18], 它的发生与多种机制相互及平行作用有关[19]. 迄今NAFLD治疗指南中仍然缺乏确切的标准化药物治疗方案[20]. 近年研究发现GLP-1RAs可以通过: (1)改善IR; (2)调节脂质代谢; (3)抑制肝脏炎症; (4)改善肠道菌群失调等机制减轻肝脏脂肪积聚, 从而延缓NAFLD的发生与进展, 这为其进入临床试验和未来在NAFLD治疗中的应用奠定了基础.

2.1 GLP-1RAs与IR IR是NAFLD发生的关键病理机制[21], 胰岛素信号通路是调节脂质代谢的重要途径. Gupta等[22]发现GLP-1RAs可激活肝细胞中胰岛素信号通路的胰岛素受体底物-2来减少甘油三酯积聚; Baumeier等[23]发现肝脏中DPP-IV表达增多会促进IR和NAFLD的发生, 表明了GLP-1的胰岛素增敏作用. 白色脂肪组织存在IR时, 血清游离脂肪酸浓度增高, 肝脏脂质合成相应增加, 导致肝脏脂质积聚; Sancho等[24]的研究表明艾塞那肽可通过增强人脂肪细胞中由PI3K和MAPK介导的葡萄糖摄取来改善其IR. 以上研究结果证明, GLP-1RAs可通过直接增强肝细胞和脂肪组织胰岛素敏感性改善肝细胞脂质代谢和减轻脂质积聚.

2.2 GLP-1RAs与脂质代谢 肝脏是人体内脂质代谢的主要器官, NAFLD患者的肝脏IR导致脂质从头合成(de novo lipogenesis, DNL)途径[25]产生的脂质增多, 这成为NAFLD脂肪沉积的重要来源. 近来研究发现GLP-1RAs可以通过减少DNL途径来源的脂质来改善脂肪积聚, Armstrong等[26]证实利拉鲁肽可显著降低NASH患者的DNL水平; Samson等[27]发现GLP-1RAs可下调肝脏DNL的基因表达水平来抑制肝脏DNL的过程. 由于NAFLD患者肝脏脂肪产生量远远超过肝脏的处理能力, 因此有学者试图证实GLP-1RAs对肝脏脂肪酸β氧化的影响, Yoo等[28]在体内和体外实验中均证实艾塞那肽可通过恢复调控β氧化基因的表达来降低肝脏脂肪堆积; Svegliati-Baroni等[29]发现GLP-1RAs可以提高PKA的活性, 并促进Akt和AMPK的磷酸化, 从而促进脂肪酸的β氧化. 总之, GLP-1RAs有可能通过减少肝脏脂肪合成、增加脂肪酸的β氧化而改善NAFLD.

2.3 GLP-1RAs与肝脏炎症 慢性、持续、低度炎症是NAFLD的重要病理机制之一, 因此抑制肝脏炎症反应可作为治疗NAFLD 的一个重要靶点, 近年研究发现了GLP-1RAs对肝脏炎症的积极作用. Gao等[30]应用利拉鲁肽处理高脂高醇饮食诱导的NAFLD大鼠4 wk后评估其对炎症反应的影响, 发现超氧化物歧化酶、丙二醛、肿瘤坏死因子-α (tumor necrosis factor alpha, TNF-α)等氧化应激和炎性指标均有明显改善; Chen等[31]也证实艾塞那肽治疗后可以显著降低TNF-α和白介素-6 (interleukin-6, IL-6)的mRNA水平; 有趣的是, 利拉鲁肽干预4 wk后可以显著降低非肥胖型豚鼠肝脏的炎症反应和气球样变[32], 这为非肥胖型NAFLD患者的治疗提供了新的思路和方案. 以上研究提示, GLP-1RAs可作为抑制肝脏炎症反应的靶向药物改善NAFLD的进展, 但具体机制仍需进一步研究以证实.

2.4 GLP-1RAs与肠道微生态 近年研究发现胃肠道菌群失调参与NAFLD的发病. 肠道微生态失调除了破坏肠黏膜屏障外, 主要通过“肠-肝轴”使细菌及其毒性产物进入肝脏, 经Toll样受体和核苷酸结合寡聚化结构域样受体通路激活肝脏免疫系统, 诱发炎症反应从而导致NAFLD的发生[33]. 那么GLP-1RAs能否通过调节肠道菌群来改善NAFLD呢? Moreira等[1]发现利拉鲁肽可以使肠道菌群总体构成发生改变, 一些与体重相关的菌群组分也会发生变化, 其中*Akkermansia muciniphila*的丰度可提升346%, 而*Proteobacteria*的丰度下降9%, 这些肠道菌群丰度的改变与NAFLD的改善密切相关. 胆汁酸对于维持肠道内环境稳态具有重要作用, 法尼醇X受体(farnesoid X receptor, FXR)以及G蛋白偶联胆汁酸受体(G Protein-Coupled Bile Acid Receptor 1, GPBAR1/TGR5)与菌群相关性NAFLD的发病有关联, FXR的激活诱导TGR5刺激GLP-1的分泌, 可以改善胰岛素敏感性和肝脏代谢[34,35]. 研究还发现GLP-1分泌与肠道菌群有关: 细菌代谢物吲哚等可调节GLP-1的产生[36]; 硫化氢可促进GLP-1分泌, 硫酸盐也可促进GLP-1的释放及其下游代谢作用[37]; 这些研究结果为GLP-1RAs通过肠道微生态

系统改善NAFLD进展提供了新的研究思路.

2.5 NAFLD相关的GLP-1RAs临床试验 截止目前, 关于GLP-1RAs对NAFLD患肝脏功能影响的临床试验研究已完成3项. 一项纳入8例T2DM并经肝组织活检证实为NAFLD患者的前瞻性研究中(其中1例患者因持续恶心和腹痛, 在第20周停用艾塞那肽), 艾塞那肽(5-10 μg)皮下注射治疗28 wk后再次肝活检, 评估患者肝脏组织学改变, 发现5例患者均出现了肝脏NAS评分下降, 同时平均谷氨酸氨基转移酶(alanine transaminase, ALT)从69 IU/L下降到45 IU/L ($P = 0.036$)[38]; 而在一项研究利拉鲁肽对T2DM患者患者肝脏脂肪变性、蛋白尿改善状况的临床试验中, 利拉鲁肽可以降低内脏脂肪含量, 同时减少肝脏脂肪堆积、蛋白尿[39]. 从已发布的临床试验结果来看, GLP-1RAs对于NAFLD肝功能具有一定的改善作用, 但已完成的临床试验样本容量较少, 仍需多个大样本临床试验进一步证明GLP-1RAs的肝脏保护作用.

3 GLP-1RAs在其他代谢性疾病中的应用前景

GLP-1RAs通过结合GLP-1受体发挥生物学作用, 而GLP-1受体已被证实广泛分布在胰腺、胃、心脏、肠、脑等器官组织中, 因此GLP-1RAs在多种疾病中具有应用前景.

3.1 GLP-1RAs的心血管保护作用 心血管疾病(cardiovascular disease, CVD)的发生与代谢综合征风险因素的增加密切相关, 多项前瞻性研究和荟萃分析表明高血糖和高胰岛素血症能使心脏病和中风发生的风险增加[40,41]. GLP-1RAs在心血管保护方面又能扮演什么样的角色呢? 证据表明, GLP-1对健康人群和有心血管病理改变人群的心血管系统均具有特定的生物学作用[42,43]. 血压升高是发生CVD的既定危险因素, 在啮齿类动物中, GLP-1RAs慢性给药具有降低血压和预防高血压的作用[44,45], 但在临床短期试验中急性注射GLP-1RAs对血压和心率没有影响, 甚至两者都可能升高[43]. 多项长期临床试验得到了相似的结论, Zinman等人随访了利拉鲁肽与二甲双胍联合治疗26 wk的T2DM患者, 发现与安慰剂(1.1 mmHg)相比, 治疗组患者收缩压降低了6 mmHg[46]; 一项为期26 wk的利拉鲁肽试验的综合荟萃分析显示, 运用利拉鲁肽仅2 wk后便出现血压降低, 而体重减轻效果直到第8周才出现[47]. 过去4年, 共有GLP-1RAs相关的七项心血管预后试验, 其中一项针对有心血管疾病高危因素的糖尿病患者3期上市前试验发现, 与安慰剂相比, 索马鲁肽可以显著降低主要心脏不良事件(major adverse cardiovascular events, MACE)和非致命性中风的风险[48]. 利西拉肽可减少小鼠斑块炎性细胞浸润, 增加纤维化斑块所占的比例, 减少中心斑块的坏死面积, 从而稳定粥样斑块[49], 因此GLP-1RAs还具有抗动脉粥样硬化作用. 在一项纳入9463名参与者(71%有冠心病病史, 25%有外周动脉疾病, 25%有脑血管病, 20%有心衰史)的临床试验中, 每周一次皮下注射阿比鲁肽或安慰剂, 阿比鲁肽组致命或非致命心肌梗死发生率与安慰剂相比有显著统计学差异($P = 0.003$)[50]. 由上可见, GLP-1RAs在心血管保护方面具有重要应用价值, 其作用机制可能涉及多个信号通路共同参与, 仍有待大量研究进一步证实.

3.2 GLP-1RAs在肥胖症治疗中的作用 肥胖与糖尿病、心血管疾病以及一些癌症的发生关系密切, 对公众健康已经构成了严重的威胁. 2016年, 世界卫生组织估计全球有超过19亿18岁以上的成年人超重, 其中6.5亿属于肥胖人群[51]. 以饮食和运动为基础的生活方式的干预通常只能提供有限而短暂的减肥效果, 而减肥手术虽然在降低体重和提高葡萄糖耐受性方面效果显著, 因风险较高且价格高昂, 因此不能成为肥胖症治疗的首选方式[52]. 现有肥胖症治疗药物虽然有一定的减肥作用, 但胃肠道和心血管不良反应明显, 难堪大任. 近年来有关GLP-1RAs在控制体重方面的研究取得了较大进展, Krieger等[53]敲除大鼠传入迷走神经中的GLP-1受体后发现, 大鼠的摄食量增加, 胃的排空速度加快; GLP-1RAs还可通过作用于下丘脑上的GLP-1受体来抑制食欲, 减少能量摄入, 延缓胃排空, 从而减轻体重[54,55]. 大量临床试验也为GLP-1RAs的减肥作用提供了证据, 研究发现T2DM患者皮下注射利拉鲁肽1.8 mg/d, 在26 wk体重减轻可达3.6% (3.3 kg), 到56 wk体重减轻高达4.7% (5.0 kg)[56-58]; 在一项不伴有糖尿病的超重或肥胖患者的临床试验中, 每日皮下注射利拉鲁肽3.0 mg, 在第56周时平均体重减轻8.0%±6.7% (8.4 kg±7.3 kg), 而安慰剂组患者平均减轻2.6%±5.7% (2.8 kg±6.5 kg)[59]. FDA已于2014年批准利拉鲁肽用于BMI≥27 kg/m^{2}且至少存在一种肥胖相关并发症的超重或肥胖患者, 或者BMI≥30 kg/m^{2}的肥胖患者的慢性体重管理. 目前还有多种GLP-1RAs正在进行临床前或临床试验, 如果可用于超重和肥胖将会显著降低肥胖相关代谢性紊乱发生率, 以及由此而产生的巨大医疗负担.

3.3 GLP-1RAs在骨代谢中的作用 骨质疏松是一种全身代谢性骨骼疾病, 治疗措施主要是调节骨吸收和骨形成平衡, 但是目前促进骨形成的药物只有甲状旁腺激素类似物[60]. 近年研究发现GLP-1RAs可以促进骨形成, 抑制骨吸收, 改善骨小梁体积、厚度和数量, 增加骨密度, 减少小梁间距, 因而在骨代谢中能发挥重要作用. Sun等[61]研究发现卵巢切除的非糖尿病Wistar雌鼠使用艾塞那肽后骨密度增加; 对该模型应用利拉鲁肽同样能增加股骨和腰椎骨的密度[62]. 除了增加骨密度外, Meng等[63]发现

艾塞那肽可以促进大鼠的骨形成, 增加骨量和骨质量. 有趣的是, 研究发现T2DM小鼠模型NSY骨密度与血糖水平呈负相关[64], 利拉鲁肽可通过下调脂肪细胞特异性转录因子过氧化物酶体增殖物激活受体-γ (peroxisome proliferator-activated receptor-γ, PPAR-γ)、上调Runt相关转录因子2 (runt related transcription factor 2, RUNTX2)的表达促进成骨细胞形成, 并减少大鼠和人骨髓干细胞的脂肪细胞分化[62], 提示GLP-1RAs可能通过改善血糖、血脂等来改善骨质疏松. 此外, GLP-1RAs具有增强血管功能的潜力, 研究发现10 μg/kg艾塞那肽可通过增加db/db小鼠的骨骼血流, 从而有助于糖尿病骨骼的骨血管形成, 这表明在糖尿病小鼠中艾塞那肽治疗诱导的骨形成增加可能部分归因于骨骼灌注的增加[65]. 然而虽有相关研究正在开展, 但是GLP-1RAs在骨代谢中的作用机制和临床试验研究依然相当欠缺, 仍需大量研究深入探讨, 总的来说, GLP-1RAs在骨代谢中的作用值得期待.

4 结论

大量研究证实了GLP-1RAs在DM并发症以及NAFLD等其他疾病中的潜在作用[66], 提示GLP-1RAs在代谢障碍性疾病中具有前景和潜力. 因长期使用基础胰岛素, 会导致体重增加, 进而引起IR及低血糖风险等诸多不良反应, 2014-09-18, Xultophy作为第一个上市的基础胰岛素德谷胰岛素和GLP-1RAs利拉鲁肽的复方制剂获得欧洲药品管理局(European Medicines Agency, EMA)批准; 另一个用于治疗肥胖症的利拉鲁肽与德谷胰岛素(超长效胰岛素, 48 h一次)复方制剂Ideglira (NN9068) 已完成III期临床研究. 此外, 处于三期临床试验的还有甘精胰岛素和利西拉来复方制剂、索马鲁肽、Taspoglutide、ITCA 650、LAEx4等. 然而, 有研究报道GLP-1RAs类药物可增加胰腺炎、胰腺癌风险, 2011年一项评估上市研究发现, 与其他降糖药物相比, 每天两次服用艾塞那肽的患者胰腺炎和胰腺癌的发病率显著增加[67]. FDA和EMA广泛评估了关于胰腺炎和胰腺癌风险的临床前和临床研究, 认为不能完全排除GLP-1RAs和胰腺癌之间的因果联系[68]. 2016年一项回顾性队列研究发现, GLP-1RAs治疗显著增加了胆囊相关不良反应(胆石症、胆囊炎和胆管炎)的风险[69]. 因此对GLP-1RAs的安全性及远期疗效仍需要进行充分论证, 但总的来说, GLP-1RAs类药物因其半衰期长、作用靶点多等优势为期在代谢性疾病及其相关并发症中的治疗提供了广阔的应用前景.

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