·综 述·

糖尿病肾病治疗潜在靶点胰高血糖素样肽 -1 受体

徐媛颖[1]，蔡兴华[2]，张会会[3]，孔稳稳[2]，沙雯君[1]，雷 涛[1*]

（1. 上海中医药大学附属普陀医院内分泌科，上海 200062；
2. 安徽医科大学上海普陀中心临床医学院，上海 200062；3. 成都中医药大学临床医学院，四川成都 610075）

摘要：糖尿病肾病（diabetic nephropathy，DN）致病机制复杂，涉及代谢、血流动力学及炎症等方面。目前，DN 主要治疗药物为肾素 - 血管紧张素系统抑制剂，但非所有患者都可获得满意疗效。胰高血糖素样肽 -1 受体（glucagon-like peptide-1 receptor，GLP-1R）作为一种治疗 DN 的潜在靶点，其在调节血糖稳态和心血管保护方面益处较大，对降低 DN 相关肾脏不良结局发生风险具有潜在作用。现概述 GLP-1R 作为治疗 DN 靶点在缓解疾病进展方面的作用机制，探讨相关制剂在临床应用中的疗效。

关键词：糖尿病肾病；胰高血糖素样肽 -1 受体；2 型糖尿病

中图分类号：R587.1；R692.9　　**文献标志码：**A　　**文章编号：**1672-9188（2023）09-0899-05

DOI：10.13683/j.wph.2023.09.002

A potential target for the treatment of diabetic nephropathy: glucagon-like peptide-1 receptor

XU Yuanying[1], CAI Xinghua[2], ZHANG Huihui[3], KONG Wenwen[2], SHA Wenjun[1], LEI Tao[1*]

（*1. Department of Endocrinology, Putuo Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 200062, China;*
2. School of Clinical Medicine, Shanghai Putuo Center Affiliated to Anhui Medical University, Shanghai 200062, China;
3. School of Clinical Medicine, Chengdu University of Traditional Chinese Medicine, Chengdu 610075, Sichuan Province, China）

Abstract: The pathogenesis of diabetic nephropathy（DN） is complex, involving metabolism, hemodynamics and inflammation. At present, the main treatment drugs for DN are renin-angiotensin system inhibitors, but not all patients can obtain satisfactory results. Glucagon-like peptide-1 receptor（GLP-1R）, as a potential target for the treatment of DN, has great benefits in regulating blood glucose homeostasis and cardiovascular protection, and has a potential role in reducing the risk of renal adverse outcomes related to DN. This article reviewed the mechanism of GLP-1R as a therapeutic target for DN in alleviating disease progression, and discusses the efficacy of related preparations in clinical application.

Key words: diabetic nephropathy; glucagon-like peptide-1 receptor; type 2 diabetes mellitus

糖尿病（diabetes mellitus，DM）患病率逐年升高，其中 2 型 DM（type 2 diabetes mellitus，T2DM）约占 DM 总数的 90% ～ 95%[1—2]，而 DM 肾病（diabetic nephropathy，DN）是 DM 的主要微血管病变之一。DN 患者临床表现为蛋白尿及肾小球滤过率（glomerular filtration rate，GFR）降低[3]。DN 发病机制复杂，涉及代谢、血流动力学因素及炎症等多方面[4]。超 30% 的 DM 患者最终发展为 DN，其中约 50% 进展为终末期肾病（end-stage renal disease）[5]。

肾素 - 血管紧张素系统（renin-angiotensin system，RAS）抑制剂对于 DN 疗效卓越，在临床上得到广泛应用，包括血管紧张素转化酶抑制剂

收稿日期：2023-04-28

作者简介：徐媛颖，主治医师，博士研究生，研究方向：糖尿病并发症。

通信作者：雷涛，主任医师，教授，博士研究生导师，研究方向：糖尿病并发症。

基金项目：上海市医学重点专科（ZK2019B16）；上海市卫生健康委员会科研课题（20204Y0154）；上海市卫健委课题（202240309）；上海市普陀区临床特色专科（2020tszk01）；上海市普陀区卫生健康系统科技创新项目（ptkwws202003）

（angiotensin converting enzyme inhibitor，ACEI）及血管紧张素Ⅱ受体阻滞剂（angiotensin Ⅱ receptor blocker，ARB）。ACEI、ARB具有一定肾脏保护作用，但仍存在潜在并发症发生风险[6—7]。

胰高血糖素样肽-1受体（glucagon-like peptide-1 receptor，GLP-1R）是治疗T2DM的关键靶点，GLP-1R激动剂（glucagon-like peptide-1 receptor agonist，GLP-1RA）和二肽基肽酶（dipeptidyl peptidase，DPP）-4抑制剂是基于GLP-1R开发的药物，二者安全性及心血管保护作用均较佳[8]，且可能具有一定肾脏保护作用[9—10]。

1 GLP-1R的结构与功能

GLP-1属于肠促胰岛素，分泌后与GLP-1R结合，使得环磷酸腺苷（cyclic adenosine monophosphate，cAMP）和葡萄糖依赖性胰岛素分泌增加，从而发挥血糖调节作用[11—12]。GLP-1R是一种G蛋白偶联受体（G-protein coupled receptor，GPCR），是细胞外刺激及细胞内反应的起源[13]，GPCR信号传导可能在增强胰岛细胞复制及增殖方面发挥作用[14]。

GLP-1R是目前治疗T2DM探索最深入的药物靶标，广泛分布于胰岛、胃、小肠、心脏、肾脏、肺及大脑等器官中[15—16]，在多个生理过程中发挥广泛作用。Li等[17]发现，GLP-1R通过激活cAMP/蛋白激酶（protein kinase，PK）A途径，辅助抑制子宫内膜癌（endometrial carcinoma）。靶向GLP-1R可抑制腺苷酸活化蛋白激酶（adenosine 5'-monophosphate-activated protein kinase，AMPK）信号激活、骨原细胞的分化和自噬[18]，具有一定肾脏保护作用，还可治疗代谢性肝病（metabolic liver disease）[19]。

2 基于GLP-1R治疗DN的作用机制

2.1 平衡活性氧（reactive oxygen species，ROS）与抗氧化防御

肾脏损伤机制涉及氧化应激、晚期糖基化终末产物（advanced glycation end product，AGE）和PKC的活化[20]。Wang等[21]观察到，激活GLP-1信号靶点可降低细胞ROS水平。GLP-1R通过调节高血糖大鼠系膜细胞中AGE受体，发挥抗炎作用[22]。GLP-1激活受体通过钙离子依赖性活化胰岛素分泌细胞中的磷脂酶C以激活PKC[23]。故而，GLP-1R靶向治疗可平衡ROS与抗氧化防御的关系，减弱AGE和PKC活化。

2.2 改善缺氧状态

DN患者的肾小球和血管病变可引起肾髓质缺氧和肾小管功能障碍，而缺氧诱导因子（hypoxia-inducible factor，HIF）增加可改善缺氧状态。研究表明，延长GLP-1R信号传导可促进HIF活性，改善缺氧状态[24—25]。

2.3 激活先天免疫性应答

先天性免疫系统免疫细胞的激活在炎症发生过程中发挥着关键作用[26]。GLP-1R激活具有抗炎特性，且对免疫系统起调节作用[27]。GLP-1R的激活可促进环磷酸腺苷水平升高，从而激活和调节调节性T细胞（regulatory T cell，Treg）的功能，并促进外周T细胞增殖[28]。Treg具有免疫抑制作用，主要通过分泌抗炎细胞因子参与各种免疫性疾病进展，抑制免疫细胞活性，从而控制炎症[29]。另外，激活GLP-1R可抑制促炎性细胞因子产生及肿瘤坏死因子-α释放[30]。

2.4 影响表观遗传调控

DN病理生理学遗传与表观遗传机制关系密切。研究显示，在早期DN模型小鼠中可检测到肾脏细胞DNA甲基化，在晚期DN模型小鼠中可表现为肾脏细胞DNA甲基化受损[31]。Scisciola等[32]通过体外试验证明，激活GLP-1R可防止高葡萄糖诱导的肾脏细胞DNA甲基化及基因表达变化。

2.5 调节足细胞自噬

在DN的发展过程中，可出现足细胞大量受损及凋亡，亦是导致DN的主要因素[33—34]。高葡萄糖可通过激活小鼠足细胞中两面神激酶/信号转导及转录激活蛋白途径抑制自噬，从而抑制受损蛋白质清除和抗细胞凋亡功能，最终加剧足细胞损伤和DN进展[35]。另外，GLP-1可降低肥胖小鼠自噬水平、恢复胰岛素敏感性，改善肾损伤[36]。

2.6 改善线粒体功能障碍

DN 的持续高糖状态可直接损害肾小管，导致线粒体功能障碍。ROS 过量产生、凋亡途径激活及线粒体自噬缺陷相互关联，在 DN 进展中起关键作用。虽然肾小管细胞线粒体含量最高，但足细胞、系膜细胞及肾小球内皮细胞都可能受到 DM 诱导的线粒体损伤的影响[37—38]。Morales 等[39]研究表明，GLP-1 可通过增强内质网 - 线粒体耦合促进血管平滑肌细胞的线粒体代谢。另外，GLP-1RA 可通过沉默调节蛋白 1/AMPK/ 过氧化物酶体增殖受体 γ 辅激活因子 α 途径，部分恢复肥胖大鼠肾脏细胞的线粒体功能[40]。

3 GLP-1R 靶向治疗 DM 的肾脏保护作用

基于 GLP-1 的药物包括 GLP-1RA 及 DPP-4 抑制剂两类，均可增加循环中 GLP-1 水平，改善机体高血糖状态，在 DM 领域得到广泛应用。

3.1 GLP-1RA

GLP-1RA 肾脏保护作用较佳。Gerstein 等[41]评估了度拉糖肽 (dulaglutide) 对肾脏结局的长期影响，结果提示，度拉糖肽或能成为慢性肾脏病 (chronic kidney disease，CKD) 的替代疗法。艾塞那肽 (exenatide) 与达格列净 (dagliflozin) 联用对改善肾功能起到协同作用[42]。利拉鲁肽 (liraglutide) 对 T2DM 患者安全性较佳[43]。使用索马鲁肽 (somaglutide) 的 T2DM 患者新发或肾病恶化发生率较低，提示其肾脏保护作用显著[44—45]。

目前，新一类双葡萄糖依赖性促胰岛素多肽 (glucose-dependent insulinotropic polypeptide，GIP) 和 GLP-1 降糖药亦是热点，其中替西帕肽 (tesipatide) 为代表性药物。研究显示，合并高心血管风险的 T2DM 患者，使用替西帕肽治疗平均 85 周后，GFR 水平下降速度优于应用甘精胰岛素者，同时尿白蛋白与肌酐比值水平亦降低[46]，且肾功能受损者无需调整剂量，具有良好的肾脏安全性[47]。

3.2 DPP-4 抑制剂

DPP-4 在多数细胞表面表达，可使天然 GLP-1 失活，通过抑制 GLP-1 活性增强肠促胰岛素分泌。DPP-4 抑制剂属于低分子量口服药物，能快速、特异性抑制 DPP-4 活性，故 DPP-4 抑制剂在临床中得到广泛应用，主要制剂包括利格列汀 (linagliptin)、吉格列汀 (gigagliptin)、沙格列汀 (shagliptin)、西格列汀 (sigliptin) 及替格列汀 (teagliptin) 等。

Trakarnvanich 等[48]发现，吉格列汀可显著改善 DN 患者肾小管损伤生物标志物表达。研究显示，利格列汀可延缓蛋白尿进展，同时不增加低血糖发生风险[49]。Mohsen 等[50]发现，沙格列汀能明显改善伴蛋白尿 T2DM 患者的肾损伤标志物水平，而其降尿蛋白作用可能与改善肾小管损伤有关。替格列汀可改善 DN 患者内皮功能和肾脏、血管氧化应激状态[51]。DPP-4 抑制剂肾脏保护作用除与改善肾小管损伤有关，也可能与改善 T2DM 和 CKD 患者内皮功能障碍、减少肾脏血管氧化应激有关。

4 小结与展望

GLP-1R 靶向治疗 DN 显示出降尿蛋白及延缓 GFR 水平下降的潜力，故成为减少 DN 相关肾脏不良结局的潜在治疗靶点。既往研究主要集中于 GLP-1R 相关制剂的血糖调节和心血管获益，对于 GLP-1R 信号传导机制还需进一步探索，帮助优化相关疗效，并以期为患者提供更多、更好的治疗方案。

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（编辑：虞 瑛）