

• 综 述 •

利拉鲁肽的临床应用及其作用机制的研究进展

李莹^{1,2}, 高杉¹, 张荣¹, 李柏岩^{1*}

1. 哈尔滨医科大学 药学院 药理教研室, 黑龙江省生物医学工程重点实验室-省部共建国家重点实验室培育基地, 心血管药物研究教育部重点实验室, 黑龙江 哈尔滨 150081
2. 天津市肿瘤医院空港医院 药学部, 天津 300308

摘 要: 胰高血糖素样肽-1 (GLP-1) 是小肠消化食物时 L 细胞分泌的一种促胰岛素激素, 可以促进胰岛素分泌, 从而维持葡萄糖稳态, 其受体广泛分布于胰岛、心脏、肺、皮肤等器官中。利拉鲁肽是一种长效的 GLP-1 类似物, 目前被广泛用于治疗 2 型糖尿病。近年来研究发现, 利拉鲁肽在肥胖症、神经系统疾病、心血管系统疾病中均发挥有益作用。对利拉鲁肽治疗糖尿病、肥胖症、神经系统疾病、心血管系统疾病和精神疾病等的临床研究及其作用机制进行综述, 旨在为拓展和开发利拉鲁肽类药物的临床应用提供新思路。

关键词: 利拉鲁肽; 糖尿病; 肥胖症; 临床应用; 作用机制

中图分类号: R977 文献标志码: A 文章编号: 1674-5515(2022)01-0197-06

DOI: 10.7501/j.issn.1674-5515.2022.01.035

Research progress on clinical application and its mechanism of liraglutide

LI Ying^{1,2}, GAO Shan¹, ZHANG Rong¹, LI Bai-yan¹

1. State-Province Key Laboratories of Biomedicine-Pharmaceutics of China, Key Laboratory of Cardiovascular Medicine Research, Ministry of Education, Department of Pharmacology, College of Pharmacy, Harbin Medical University, Harbin 150081, China
2. Department of Pharmacy, Tianjin Tumor Hospital Konggang Branch, Tianjin 300308, China

Abstract: Glucagon-like peptide-1 is an insulin-stimulating hormone secreted by L cells while the small intestine digests food. It can promote insulin secretion to maintain glucose homeostasis. The receptors are widely distributed in organs, such as pancreatic islets, heart, lungs, and skin. As a long-acting GLP-1 analogue, liraglutide has recently become the first-line treatment for type 2 diabetes mellitus. Recently, studies have found that liraglutide plays a beneficial role in obesity, neurodegenerative diseases, cardiovascular diseases, and so on. This review article summarizes its application and mechanism of liraglutide, and aims to provide novel ideas for the expansion and development of the clinical application of liraglutide.

Key words: liraglutide; diabetes; obesity; clinical application; mechanism

利拉鲁肽是一种人工合成的胰高血糖素样肽-1 (GLP-1) 类似物, 于 2009 年正式上市, 应用于 2 型糖尿病的治疗。利拉鲁肽通过基因重组技术在 GLP-1 的 26 位添加一个 16 碳棕榈酰脂肪酸, 并用精氨酸取代 GLP-1 上的赖氨酸第 34 位而形成的; 这些结构修饰增加聚集, 促进非共价蛋白的结合, 从而抑制二肽基肽酶-4 (DPP-4) 的降解^[1]。因此, 利

拉鲁肽的半衰期远大于 GLP-1, 可实现每天给药 1 次, 具有突出的临床优势。利拉鲁肽能够有效阻止胰岛 B 细胞功能衰退, 从而控制血糖长期稳定达标, 并减少消化道反应和低血糖等药物不良反应。近年来, 随着对利拉鲁肽的深入研究, 发现除治疗 2 型糖尿病外, 其在控制肥胖症患者体质量^[2]、心血管系统疾病^[3]和神经系统疾病^[4]中均发挥有益作用,

收稿日期: 2021-11-07

基金项目: 国家自然科学基金资助项目 (81573431, 81971326, 82070236)

作者简介: 李莹, 女, 硕士, 主要从事 H₂S 对血压神经调控的研究。E-mail: ly5300621ly@163.com

*通信作者: 李柏岩 E-mail: liby@ems.hrbmu.edu.cn

其药理作用和临床应用在不断扩展。因此本文对利拉鲁肽治疗糖尿病、肥胖症、神经系统疾病、心血管系统疾病和精神疾病的临床研究进行了总结,探讨了其作用机制,以期为利拉鲁肽的临床应用提供参考。

1 糖尿病

2 型糖尿病是一种慢性高血糖代偿性疾病,主要表现为胰岛素分泌减少、肝脏葡萄糖输出升高等。利拉鲁肽于 2009 年在欧洲和 2010 年在美国被批准用于成人 2 型糖尿病。其降血糖机制主要是通过刺激胰岛 B 细胞增殖,同时通过抑制凋亡来实现胰岛功能再生^[5]。有研究表明,利拉鲁肽可以抑制小鼠骨骼肌细胞 IRS-1 丝氨酸磷酸化来增强胰岛素诱导的葡萄糖转运蛋白 4 易位,从而降低胰岛素抵抗^[6]。临床发现,利拉鲁肽可作为代谢性手术术后复发 2 型糖尿病的辅助治疗,且其联合用药对 2 型糖尿病的治疗效果更优^[7]。

1 型糖尿病是 T 细胞介导胰岛细胞损伤的自身免疫性疾病,目前以注射胰岛素的治疗方法为主。有临床数据显示利拉鲁肽可作为 1 型糖尿病患者的补充治疗,可显著改善血糖,降低严重低血糖风险,增加脂质氧化和产热来减轻体质量,但增加了胃肠道不良反应^[8]。此外,利拉鲁肽也可以抑制 1 型糖尿病中胰高血糖素和脂解的形成^[9]。一项研究指出,利拉鲁肽在高糖条件下可通过 JAK-STAT 途径抑制人 T 型淋巴细胞产生 γ 干扰素,这一结果暗示利拉鲁肽在 1 型糖尿病免疫调节过程中同样发挥潜在的治疗作用^[10]。

2 肥胖症

肥胖症是一种由遗传、环境等多因素引起的脂肪过度蓄积而导致的体质量远超出正常的慢性代谢性疾病^[11]。目前大多数肥胖治疗指南包括在改变生活方式的同时辅以药物治疗的建议,而其中利拉鲁肽被美国食品药品监督管理局(FDA)批准作为减肥安全有效药物之一,其效果优于单独肥胖症的强化行为治疗^[12]。利拉鲁肽主要是通过控制食欲从而减少进食来控制肥胖,其机制主要包括激活大脑中的 GLP-1 受体,产生厌食作用^[13];同时调节肠道菌群,延迟胃排空来增加饱腹感^[14]。另外,它也可能通过可溶性鸟苷环化酶依赖途径诱导白色脂肪组织褐变、激活腺苷酸环化酶途径来降低体质量,改善肥胖症[小鼠 sc 400 $\mu\text{g}/(\text{kg}\cdot\text{d})$]^[15]。有临床数据分析表明,利拉鲁肽控制肥胖不依赖于降糖作用,

对于糖尿病和非糖尿病患者均有治疗作用^[16]。长效神经降压素与利拉鲁肽协同作用可通过黑色素依赖途径逆转肥胖,并具有更好的耐受性[小鼠 sc 7.5、11.3、30 $\mu\text{g}/(\text{kg}\cdot\text{d})$]^[17]。

3 神经系统疾病

3.1 阿尔茨海默病

阿尔茨海默病是一种认知功能减退,伴随神经原纤维缠结、淀粉样 β -蛋白沉积和 tau 蛋白过度磷酸化为特征的神经退行性疾病^[18]。阿尔茨海默病是 2 型糖尿病的危险因素之一,两者存在共同作用机制,部分抗 2 型糖尿病药物可以降低 2 型糖尿病患者患阿尔茨海默病的风险,其中 GLP-1 受体激动剂作用尤为显著^[19-20]。其作用机制可能是影响 γ -氨基丁酸能、谷氨酸能神经传递,部分缓解氧化、亚硝酸应激和炎症,减少海马 CA1 (氨角 1) 等区域的淀粉样斑块总数,延缓记忆功能减退,同时可以保护特定脑区胰岛素受体、突触,并减少 tau 样病变[小鼠 sc 200 $\mu\text{g}/(\text{kg}\cdot\text{d})$]^[18, 21-24]。Watson 等^[25]通过临床试验证明利拉鲁肽对阿尔茨海默病患者具有保护作用。2019 年开展的一项随机对照试验研究方案用于评价利拉鲁肽治疗 12 个月后对脑葡萄糖代谢率的变化^[26]。如果该试验成功,代表着利拉鲁肽可能是阿尔茨海默病治疗的一个突破性进展,对阿尔茨海默病的临床治疗产生积极影响。

3.2 脑缺血性疾病

脑缺血性疾病是由多种原因引起的脑部供血不足,进而引起相应神经系统症状的疾病。目前 FDA 批准治疗脑缺血的药物仅有组织型纤溶酶原激活剂。但近年来研究发现,利拉鲁肽可能对脑缺血所诱发的疾病具有积极影响,其中对于中风有显著治疗作用。Han 等^[27-28]通过实验发现,大鼠 ip 利拉鲁肽 25 nmol/(kg d)可减少大鼠大脑中动脉阻塞引起的缺血和限制性神经功能缺损,降低应激引起的血糖升高,同时大鼠 ip 100 $\mu\text{g}/(\text{kg}\cdot\text{d})$ 可以增加 Bcl-2 和 Bcl-xl 蛋白的表达而发挥抗凋亡作用,减轻缺血神经元的氧化损伤,从而减少缺血性中风的发生。此外,利拉鲁肽 ip 大鼠 100 $\mu\text{g}/(\text{kg}\cdot\text{d})$,可激活伴有糖尿病的大脑中动脉阻塞大鼠的 Nrf2/HO-1 信号通路,激活抗氧化酶,从而降低脑缺血神经功能损伤^[29]。而在临床上,从利拉鲁肽治疗 2 型糖尿病的临床数据统计分析得知,利拉鲁肽可以降低具有中风病史患者的发病风险^[30]。

动脉粥样硬化是导致脑缺血事件的主要风险

因素之一,其病理学基础是慢性内皮炎症^[31]。有报道称,利拉鲁肽可能减缓动脉粥样硬化疾病的发展,即利拉鲁肽可通过抑制 NF- κ B 磷酸化从而降低内皮素的表达。血管收缩因子的增加是导致内皮功能障碍和动脉粥样硬化的已知风险因素^[32]。此外,利拉鲁肽通过调节 RMRP/miR-128-1-5p/gadd45G 信号通路抑制炎症细胞因子和凋亡相关蛋白在冠状动脉粥样硬化过程中的表达^[33]。临床上报道称利拉鲁肽可减少高甘油三酯血症的关键调节因子 apoCIII,从而降低 2 型糖尿病患者餐后致动脉粥样硬化的风险^[34]。以上为利拉鲁肽对冠状动脉粥样硬化的治疗提供了新的思路和靶点。

4 心血管系统疾病

心血管疾病是糖尿病患者的主要并发症之一。随着对抗 2 型糖尿病药物安全性、有效性的检测,2016 年利拉鲁肽被发现可以降低 2 型糖尿病的非致命性心肌梗死的比率^[35],并于 2017 年被 FDA 批准用于降低 2 型糖尿病心血管风险。近年来,对于利拉鲁肽保护心脏的机制研究逐渐被广泛关注。研究发现,利拉鲁肽对于预防糖尿病大鼠心功能障碍和保护成纤维细胞等至关重要,其主要是通过激活 PPAR α 途径[大鼠 sc 200 μ g/(kg·d)]^[36]、AMPK-Sirt1 途径和 DAG-PKC-NAD(P)H 途径降低氧化应激和细胞凋亡来实现的[大鼠 sc 300 μ g/(kg·12 h)]^[37]。不仅如此,利拉鲁肽还可以促进伴有肥胖的糖尿病大鼠自噬能力,减轻糖尿病心肌损伤,其机制包括降低血清肌酸激酶(CK)和乳酸脱氢酶(LDH)水平,增加 AMPK 磷酸化和降低 mTOR 磷酸化等[大鼠 sc 200 μ g/(kg·d)]^[38]。这些研究均为临床降低 2 型糖尿病患者心血管疾病发生率提供病理基础和理论依据。

除此之外,对于非糖尿病患者,利拉鲁肽也可发挥保护心功能的作用。研究发现,利拉鲁肽可改善心肌肥大、细胞凋亡、间质心肌纤维化以及炎症和氧化应激[大鼠 sc 300 μ g/(kg·12 h)]^[39-40]。2019 年, Nakamura 等^[41]利用犬房颤模型来探究利拉鲁肽对心房的影响。其研究结果发现,利拉鲁肽可抑制房颤,降低改善房室间传导速度等电生理改变[犬 sc 150 μ g/(kg·d)]。此外,2020 年的一项短期临床实验证明,利拉鲁肽可增加窦性心律慢性衰竭患者的心率,但与不良事件无关^[42]。由此可见,虽然利拉鲁肽可能是治疗心力衰竭患者的一种辅助疗法,但其安全性和有效性有待长期临床试验进一步的研究。

此外, Hulst 等^[43]发现,心脏手术患者术前短期服用利拉鲁肽后能更好地维持正常的心功能,而这项研究同样需要进一步评估 GLP-1 受体激动剂对心脏手术患者的潜在益处。目前,本研究课题组正在对利拉鲁肽对影响肌肥厚的作用展开研究,初步研究结果表明利拉鲁肽可能通过调节微小 RNA-27 的表达负性调控心肌肥厚病理生理过程。该研究将为利拉鲁肽治疗病理性心肌肥大肥厚性疾病提供新的理论基础和潜在的治疗靶点。

5 精神疾病

情绪障碍包括严重抑郁障碍和双相情感障碍,是世界范围内导致残疾和死亡的主要原因,其核心领域是认知^[44]。目前临床上有效治疗情绪障碍的方法有限,而患有严重精神疾病与心血管疾病、肥胖或代谢综合征有关^[45]。利拉鲁肽作为抗肥胖和抗糖尿病药物在进行的 II、III 期随机、双盲试验证明对精神健康是安全的^[46]。利拉鲁肽对于情绪障碍的非糖尿病患者具有良好的安全性和耐受性,且可改善认知功能^[47]。有趣的是,这种认知能力的提高与脑容量的变化有关密切相关,包括尾状体、壳核、额叶中皮层皮质、额叶上皮质皮层和眶额侧皮质皮层的体积的增加有关^[48]。不仅如此,利拉鲁肽联合氯氮平或奥氮平治疗超重或肥胖以及患有精神分裂症谱系障碍的糖尿病前期患者 16 周后,可显著减少糖酵解代谢紊乱和体质量的增加^[49]。这些结果表明,利拉鲁肽可能是一种潜在的治疗情绪障碍的新策略,不仅可以控制患者的体质量和代谢功能障碍,而且可以控制共存的认知障碍,但对精神疾病治疗的机制还有待进一步研究。

6 其他

利拉鲁肽对于早期糖尿病视网膜病变[小鼠角膜局部给药 400 μ g/(kg·d)]和多囊卵巢综合征也有治疗作用^[50-51]。近年来临床研究发现,利拉鲁肽可以降低非酒精性脂肪性肝炎的致病因素胰岛素抵抗和脂毒性,且可减少部分代谢障碍^[52]。研究发现,利拉鲁肽可减轻 H9N2 流感病毒诱导的小鼠急性肺损伤,抑制自然杀伤细胞介导的肝癌抗肿瘤反应[sc 小鼠 300 μ g/(kg·d)]^[53-54],但临床用于肺疾病的治疗至今尚未可知。有趣的是一项临床评估发现,利拉鲁肽对于肾脏也具有一定的保护作用,可以通过间接和直接途径降低糖尿病肾病的发病率^[55]。研究发现,利拉鲁肽可以通过激活 ERK5 信号通路来促进成骨细胞分化和增殖,从而达到骨保护的作用^[56],

另外, 利拉鲁肽通过减少骨吸收和促进骨形成来改善骨密度, 进而改善骨微结构和骨强度, 并逆转糖皮质激素性骨质疏松[大鼠 sc 200 $\mu\text{g}/(\text{kg}\cdot\text{d})$]^[57]。但一项临床随机试验发现利拉鲁肽对于 2 型糖尿病患者骨吸收无明显作用, 值得进一步探究^[58]。

7 结语

利拉鲁肽作为与人 GLP-1 有 97% 的同源性的 GLP-1 类似物, 已被批准用于糖尿病、肥胖症的临床治疗, 而临床上不再局限于单独给药, 与其他降糖药甚至中药的联合用药成为热点, 且能够发挥更好的疗效。不仅如此, 利拉鲁肽对于糖尿病并发症的治疗被广泛关注, 并且它对非糖尿病性神经调节、精神疾病、心血管保护等也有不同程度的辅助治疗作用, 但其机制研究尚不完善, 仍需不断深入探索。另外, GLP-1 受体还广泛存在于肠、皮肤(毛囊)、胃等器官中, 利拉鲁肽作为 GLP-1 受体激动剂是否对于上述部位的病理生理过程具有潜在治疗作用还有待临床发现和进一步的实验探究。

利益冲突 所有作者均声明不存在利益冲突

参考文献

- [1] Russell-jones D. Molecular, pharmacological and clinical aspects of liraglutide, a once-daily human GLP-1 analogue [J]. *Mol Cell Endocrinol*, 2009, 297(1-2): 137-140.
- [2] Sheahan K H, Wahlberg E A, Gilbert M P. An overview of GLP-1 agonists and recent cardiovascular outcomes trials [J]. *Postgrad Med J*, 2020, 96(1133): 156-161.
- [3] Zhao T, Chen H, Cheng C, *et al.* Liraglutide protects high-glucose-stimulated fibroblasts by activating the CD36-JNK-AP1 pathway to downregulate P4HA1 [J]. *Biomed Pharmacother*, 2019, 118: 109224.
- [4] Wicinski M, Socha M, Malinowski B, *et al.* Liraglutide and its neuroprotective properties-Focus on possible biochemical mechanisms in Alzheimer's disease and cerebral ischemic events [J]. *Int J Mol Sci*, 2019, 20(5): 1050.
- [5] Kapodistria K, Tsilibary E P, Kotsopoulou E, *et al.* Liraglutide, a human glucagon-like peptide-1 analogue, stimulates AKT-dependent survival signalling and inhibits pancreatic beta-cell apoptosis [J]. *J Cell Mol Med*, 2018, 22(6): 2970-2980.
- [6] Li Z, Zhu Y, Li C, *et al.* Liraglutide ameliorates palmitate-induced insulin resistance through inhibiting the IRS-1 serine phosphorylation in mouse skeletal muscle cells [J]. *J Endocrinol Invest*, 2018, 41(9): 1097-1102.
- [7] Miras A D, Pérez-Pevida B, Aldhwayan M, *et al.* Adjunctive liraglutide treatment in patients with persistent or recurrent type 2 diabetes after metabolic surgery (GRAVITAS): A randomised, double-blind, placebo-controlled trial [J]. *Lancet Diabetes Endocrinol*, 2019, 7(7): 549-559.
- [8] Dimitrios P, Michael D, Vasilios K, *et al.* Liraglutide as adjunct to insulin treatment in patients with type 1 diabetes: A systematic review and meta-analysis [J]. *Curr Diabetes Rev*, 2020, 16(4): 313-326.
- [9] Garg M, Ghanim H, Kuhadiya N D, *et al.* Liraglutide acutely suppresses glucagon, lipolysis and ketogenesis in type 1 diabetes [J]. *Diabetes Obes Metab*, 2017, 19(9): 1306-1311.
- [10] Zhao Y, Xie Y, Li W. Liraglutide exerts potential anti-inflammatory effect in type 1 diabetes by inhibiting IFN-gamma production via suppressing JAK-STAT pathway [J]. *Endocr Metab Immune Disord Drug Targets*, 2019, 19(5): 656-664.
- [11] Rohde K, Keller M, La Cour Poulsen L, *et al.* Genetics and epigenetics in obesity [J]. *Metabolism*, 2019, 92: 37-50.
- [12] Wadden T A, Walsh O A, Berkowitz R I, *et al.* Intensive behavioral therapy for obesity combined with liraglutide 3.0 mg: A randomized controlled trial [J]. *Obesity* (Silver Spring), 2019, 27(1): 75-86.
- [13] Arden C. A role for Glucagon-Like Peptide-1 in the regulation of beta-cell autophagy [J]. *Peptides*, 2018, 100: 85-93.
- [14] Halawi H, Khemani D, Eckert D, *et al.* Effects of liraglutide on weight, satiation, and gastric functions in obesity: A randomised, placebo-controlled pilot trial [J]. *Lancet Gastroenterol Hepatol*, 2017, 2(12): 890-899.
- [15] Zhu E, Yang Y, Zhang J, *et al.* Liraglutide suppresses obesity and induces brown fat-like phenotype via soluble guanylyl cyclase mediated pathway *in vivo* and *in vitro* [J]. *Oncotarget*, 2016, 7(49): 81077-81089.
- [16] Zhang P, Liu Y, Ren Y, *et al.* The efficacy and safety of liraglutide in the obese, non-diabetic individuals: A systematic review and meta-analysis [J]. *Afr Health Sci*, 2019, 19(3): 2591-2599.
- [17] Ratner C, He Z, Grunddal K V, *et al.* Long-acting neurotensin synergizes with liraglutide to reverse obesity through a melanocortin-dependent pathway [J]. *Diabetes*, 2019, 68(6): 1329-1340.
- [18] Duarte A I, Ahmed J, Cha D S, *et al.* Liraglutide protects against brain amyloid-beta1-42 accumulation in female mice with early Alzheimer's disease-like pathology by partially rescuing oxidative/nitrosative stress and inflammation [J]. *Int J Mol Sci*, 2020, 21(5): 1746.

- [19] Akimoto H, Negishi A, Oshima, S, *et al.* Antidiabetic drugs for the risk of Alzheimer disease in patients with type 2 DM using FAERS [J]. *Am J Alzheimers Dis Other Dement*, 2020, 35: 1533317519899546.
- [20] Karki R, Kodamullil A T, Hofmann-Apitius M. Comorbidity analysis between Alzheimer's disease and type 2 diabetes mellitus (T2DM) based on shared pathways and the role of T2DM drugs [J]. *J Alzheimers Dis*, 2017, 60(2): 721- 731.
- [21] Babateen O, Korol S V, Jin Z, *et al.* Liraglutide modulates GABAergic signaling in rat hippocampal CA3 pyramidal neurons predominantly by presynaptic mechanism [J]. *BMC Pharmacol Toxicol*, 2017, 18(1): 83.
- [22] Batista A F, Forny-Germano L, Clarke J R, *et al.* The diabetes drug liraglutide reverses cognitive impairment in mice and attenuates insulin receptor and synaptic pathology in a non-human primate model of Alzheimer's disease [J]. *J Pathol*, 2018, 245(1): 85-100.
- [23] Gupta G, Dahiya R, Dua K, *et al.* Anticonvulsant effect of liraglutide, GLP-1 agonist by averting a change in GABA and brain glutathione level on picrotoxin-induced seizures [J]. *EXCLI J*, 2017, 16: 752-754.
- [24] Holubova M, Hrubá L, Popelova A, *et al.* Liraglutide and a lipidized analog of prolactin-releasing peptide show neuroprotective effects in a mouse model of beta-amyloid pathology [J]. *Neuropharmacology*, 2019, 144: 377-387.
- [25] Watson K T, Woolie T E, Tong G, *et al.* Neural correlates of liraglutide effects in persons at risk for Alzheimer's disease [J]. *Behav Brain Res*, 2019, 356: 271-278.
- [26] Femminella G D, Frangou E, Love S B, *et al.* Evaluating the effects of the novel GLP-1 analogue liraglutide in Alzheimer's disease: study protocol for a randomised controlled trial (ELAD study) [J]. *Trials*, 2019, 20(1): 191.
- [27] Han L, Holscher C, Xue G F, *et al.* A novel dual-glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide receptor agonist is neuroprotective in transient focal cerebral ischemia in the rat [J]. *Neuroreport*, 2016, 27(1): 23-32.
- [28] Zhu H, Zhang Y, Shi Z, *et al.* The neuroprotection of liraglutide against ischaemia-induced apoptosis through the activation of the PI3K/AKT and MAPK pathways [J]. *Sci Rep*, 2016, 6: 26859.
- [29] Deng C, Cao J, Han J, *et al.* Liraglutide activates the Nrf2/HO-1 antioxidant pathway and protects brain nerve cells against cerebral ischemia in diabetic rats [J]. *Comput Intell Neurosci*, 2018, 2018: 3094504.
- [30] Verma S, Poulter N R, Bhatt D L, *et al.* Effects of liraglutide on cardiovascular outcomes in patients with type 2 diabetes mellitus with or without history of myocardial infarction or stroke [J]. *Circulation*, 2018, 138(25): 2884-2894.
- [31] Gimbrone M A Jr, Garcia-Cardena G. Endothelial cell dysfunction and the pathobiology of atherosclerosis [J]. *Circ Res*, 2016, 118(4): 620-636.
- [32] Wicinski M, Szadujkis-Szadurska K, Weclewicz M M, *et al.* The role of Rho-kinase and calcium ions in constriction triggered by ET-1[J]. *Microvasc Res*, 2018, 119: 84-90.
- [33] An J H, Chen Z Y, Ma Q L, *et al.* Liraglutide improves atherosclerosis by regulating long non-coding RNA RMRP/miR-128-1-5P/Gadd45g axis [J]. *Eur Rev Med Pharmacol Sci*, 2020, 24(5): 2725-2737.
- [34] Matikainen N, Soderlund S, Bjornson E, *et al.* Liraglutide treatment improves postprandial lipid metabolism and cardiometabolic risk factors in humans with adequately controlled type 2 diabetes: A single-centre randomized controlled study [J]. *Diabetes Obes Metab*, 2019, 21(1): 84-94.
- [35] Marso S P, Daniels G H, Brown-Frandsen K, *et al.* Liraglutide and cardiovascular outcomes in type 2 diabetes [J]. *N Engl J Med*, 2016, 375(4): 311-322.
- [36] Zhang Q, Xiao X, Zheng J, *et al.* Liraglutide protects cardiac function in diabetic rats through the PPARalpha pathway [J]. *Biosci Rep*, 2021, 150: 104645.
- [37] Inoue T, Inoguchi T, Sonoda N, *et al.* GLP-1 analog liraglutide protects against cardiac steatosis, oxidative stress and apoptosis in streptozotocin-induced diabetic rats [J]. *Atherosclerosis*, 2015, 240(1): 250-259.
- [38] Zhang Y, Ling Y, Yang L, *et al.* Liraglutide relieves myocardial damage by promoting autophagy via AMPK-mTOR signaling pathway in Zucker diabetic fatty rat [J]. *Mol Cell Endocrinol*, 2017, 448: 98-107.
- [39] Bai X J, Hao J T, Zheng R H, *et al.* Glucagon-like peptide-1 analog liraglutide attenuates pressure-overload induced cardiac hypertrophy and apoptosis through activating ATP sensitive potassium channels [J]. *Cardiovasc Drugs Ther*, 2021, 35(1): 87-101.
- [40] Gaspari T, Brdar M, Lee H W, *et al.* Molecular and cellular mechanisms of glucagon-like peptide-1 receptor agonist-mediated attenuation of cardiac fibrosis [J]. *Diab Vasc Dis Res*, 2016, 13(1): 56-68.
- [41] Nakamura H, Niwano S, Niwano H, *et al.* Liraglutide suppresses atrial electrophysiological changes [J]. *Heart Vessels*, 2019, 34(8): 1389- 1393.
- [42] Tougaard R S, Jorsal A, Tarnow L, *et al.* Heart rate increases in liraglutide treated chronic heart failure patients: association with clinical parameters and adverse events [J]. *Scand Cardiovasc J*, 2020, 54(5): 294-299.

- [43] Hulst A H, Visscher M J, Cherpanath T G V, *et al.* Effects of liraglutide on myocardial function after cardiac surgery: A secondary analysis of the randomised controlled GLOBE trial [J]. *J Clin Med*, 2020, 9(3): 673.
- [44] Mansur R B, Lee Y, Subramaniapillai M, *et al.* Cognitive dysfunction and metabolic comorbidities in mood disorders: A repurposing opportunity for glucagon-like peptide 1 receptor agonists? [J]. *Neuropharmacology*, 2018, 136(Pt B): 335-342.
- [45] Cuomo A, Bolognesi S, Goracci A, *et al.* Feasibility, adherence and efficacy of liraglutide treatment in a sample of individuals with mood disorders and obesity [J]. *Front Psychiatry*, 2018, 9: 784.
- [46] O'neil P M, Aroda V R, Astrup A, *et al.* Neuropsychiatric safety with liraglutide 3.0 mg for weight management: Results from randomized controlled phase 2 and 3a trials [J]. *Diabetes Obes Metab*, 2017, 19(11): 1529-1536.
- [47] Mansur R B, Ahmed J, Cha D S, *et al.* Liraglutide promotes improvements in objective measures of cognitive dysfunction in individuals with mood disorders: A pilot, open-label study [J]. *J Affect Disord*, 2017, 207: 114-120.
- [48] Mansur R B, Zugman A, Ahmed J, *et al.* Treatment with a GLP-1R agonist over four weeks promotes weight loss-moderated changes in frontal-striatal brain structures in individuals with mood disorders [J]. *Eur Neuropsychopharmacol*, 2017, 27(11): 1153-1162.
- [49] Larsen J R, Vedtofte L, Jakobsen M S L, *et al.* Effect of liraglutide treatment on prediabetes and overweight or obesity in clozapine- or olanzapine-treated patients with schizophrenia spectrum disorder: A randomized clinical trial [J]. *JAMA Psychiatry*, 2017, 74(7): 719-728.
- [50] Papaetis G S, Filippou P K, Constantinidou K G, *et al.* Liraglutide: New perspectives for the treatment of polycystic ovary syndrome [J]. *Clin Drug Investig*, 2020, 40(8): 695-713.
- [51] Shu X, Zhang Y, Li M, *et al.* Topical ocular administration of the GLP-1 receptor agonist liraglutide arrests hyperphosphorylated tau- triggered diabetic retinal neurodegeneration via activation of GLP-1R/Akt/GSK3beta signaling [J]. *Neuropharmacology*, 2019, 153: 1-12.
- [52] Armstrong M J, Hull D, Guo K, *et al.* Glucagon-like peptide 1 decreases lipotoxicity in non-alcoholic steatohepatitis [J]. *J Hepatol*, 2016, 64(2): 399-408.
- [53] Bai Y, Ling P, Li J, *et al.* The active GLP-1 analogue liraglutide alleviates H9N2 influenza virus-induced acute lung injury in mice [J]. *Microb Pathog*, 2020, 150: 104645.
- [54] Lu X, Xu C, Dong J, *et al.* Liraglutide activates nature killer cell-mediated antitumor responses by inhibiting IL-6/STAT3 signaling in hepatocellular carcinoma [J]. *Transl Oncol*, 2021, 14(1): 100872.
- [55] Cherney D Z, Tuttle K R. Liraglutide for the treatment of type 2 diabetes and safety in diabetic kidney disease: liraglutide and diabetic kidney disease [J]. *Clin J Am Soc Nephrol*, 2020, 15(4): 444-446.
- [56] Sun Y, Liang Y, Li Z, *et al.* Liraglutide promotes osteoblastic differentiation in MC3T3-E1 cells by ERK5 pathway [J]. *Int J Endocrinol*, 2020, 2020: 8821077.
- [57] Yang L, Yang J, Pan T, *et al.* Liraglutide increases bone formation and inhibits bone resorption in rats with glucocorticoid- induced osteoporosis [J]. *J Endocrinol Invest*, 2019, 42(9): 1125-1131.
- [58] Hygum K, Harslof T, Jorgensen N R, *et al.* Bone resorption is unchanged by liraglutide in type 2 diabetes patients: A randomised controlled trial [J]. *Bone*, 2020, 132: 115197.

[责任编辑 解学星]