胰高血糖素样肽-1 受体激动剂改善认知功能障碍的研究进展

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摘 要：认知功能障碍是一类以记忆衰退、执行功能下降为核心特征的神经退行性疾病。胰高血糖素样肽-1（GLP-1）受体激动剂可通过直接神经保护作用、抑制神经炎症和氧化应激、改善胰岛素抵抗、调节脑－肠轴改善认知功能障碍。利拉鲁肽、艾塞那肽在临床前研究、临床研究中展现出改善认知功能障碍的潜力。总结了 GLP-1 受体激动剂改善认知功能障碍的研究进展，为其在认知功能障碍防治中的转化应用提供参考。

关键词：胰高血糖素样肽-1 受体激动剂；认知功能障碍；神经保护；神经炎症；胰岛素抵抗；利拉鲁肽；艾塞那肽

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Research progress on improvement of cognitive impairment by glucagon-like peptide-1 receptor agonist

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Abstract: Cognitive dysfunction is a type of neurodegenerative disease characterized by memory decline and decreased executive function. Glucagon like peptide-1 (GLP-1) receptor agonists can improve cognitive impairment through direct neuroprotection, inhibition of neuroinflammation and oxidative stress, improvement of insulin resistance, and regulation of the brain gut axis. Liraglutide and exenatide have shown potential in improving cognitive impairment in preclinical and clinical studies. This article summarizes the research progress of GLP-1 receptor agonists in improving cognitive dysfunction, providing reference for their translational application in the prevention and treatment of cognitive dysfunction.

Key words: Glucagon like peptide-1 receptor agonists; cognitive dysfunction; neuroprotection; neuroinflammation; insulin resistance; liraglutide; exenatide

认知功能障碍是一类以记忆衰退、执行功能下降为核心特征的神经退行性疾病，以阿尔茨海默病、帕金森病最典型，2 型糖尿病、慢性脑灌注不足等是其重要危险因素[1]。其病理机制涉及神经炎症、氧化应激、突触可塑性受损和代谢紊乱[2]。随着全球人口老龄化加剧，其疾病负担日益沉重，而现有治疗手段的疗效有限，亟需开发新的疾病修饰疗法。近年来，胰高血糖素样肽-1（GLP-1）受体激动剂因其多方面的生理功能和潜在神经保护作用受到广泛关注。GLP-1 受体激动剂最初被开发用于血糖控制和肥胖治疗的药物，因其独特的代谢调节和神经保护双重作用，成为认知障碍治疗领域的研究热点。如 GLP-1 受体广泛分布于海马、丘脑、纹状体等调控认知功能的关键脑区，激活这些受体可促进突触可塑性，并增强记忆形成[3]。此外，GLP-1 受体激动剂还具有穿越血脑屏障的能力，使其能够直接作用于中枢神经系统，发挥神经保护、抗炎和抗氧化应激等多重作用[4]。GLP-1 受体激动剂可通过直接神经保护作用、抑制神经炎症和氧化应激、改善胰岛素抵抗、调节脑－肠轴改善认知功能

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障碍。本文总结了 GLP-1 受体激动剂改善认知功能障碍的研究进展，为其在认知功能障碍防治中的转化应用提供参考。

1　潜在机制

GLP-1 受体激动剂通过多途径、多靶点发挥神经保护作用，机制涉及代谢调节、神经保护、炎症抑制、脑－肠轴调控多个层面，形成协同保护网络。分子层面，这些作用通过环磷酸腺苷/蛋白激酶 A/环磷腺苷反应元件结合蛋白（cAMP/PKA/CREB）、丝裂原活化蛋白激酶（MAPK）信号通路和调控糖原合成酶激酶-3β（GSK-3β）关键分子实现。

1.1　直接神经保护作用

GLP-1 受体刺激具有神经保护和神经营养特性。海马体和下丘脑中的胰高血糖素样肽-1 受体（GLP-1R）信号传导可改善记忆功能[5]。GLP-1 受体激动剂艾塞那肽-4 可增强大鼠海马神经元对谷氨酸毒性的抵抗力，促进神经生长分化[6]。GLP-1R 缺陷小鼠存在学习、记忆、突触可塑性受损[7]。过度表达 GLP-1R 的神经母细胞瘤细胞系在氧化应激下存活率和增殖能力显著提升[8]。GLP-1 本身是一种生长因子，能促进神经突触生长、细胞修复和替代、增强细胞代谢，并减少细胞凋亡[9]。分子机制上，GLP-1R 激活后通过 cAMP/PKA/CREB 通路增强抗凋亡基因表达，同时激活磷脂酰肌醇 3 激酶/蛋白激酶 B（PI3K/Akt）通路抑制凋亡信号[10]。

1.2　抑制神经炎症和氧化应激

GLP-1R 在大脑神经元、小胶质细胞、星形胶质细胞中均表达，其激动剂可激活 GLP-1R 触发多重抗炎和抗凋亡信号通路，降低促炎细胞因子如肿瘤坏死因子-α（TNF-α）、白细胞介素（IL）-1β 的水平[11-12]。在细胞实验中，GLP-1 可通过抗凋亡、抗氧化机制促进神经元存活，增强 PKA 和 PI3K 通路活性；其代谢物 GLP-1（9-36）能减少 M1 型小胶质细胞数量，降低 IL-6、TNF-α 分泌[13]。

动物模型证实，GLP-1 可抵御 β 淀粉样蛋白诱导的神经毒性，减少胶质细胞活化和环氧化酶-2（COX-2）、TNF-α 表达，抑制核因子-κB/Toll 样受体 4（NF-κB/TLR4）、Akt/GSK-3β 炎症通路，改善认知功能[14-15]。司美格鲁肽可通过抑制星形胶质细胞和小胶质细胞活性减轻炎症和氧化应激[16]。GLP-1R 激活还可刺激 MAPK 通路促进细胞存活、增殖[17]。

1.3　改善胰岛素抵抗

中枢胰岛素抵抗可在无外周糖尿病的情况下独立发生[18]。肠促胰岛素是连接肠道与大脑的“信使”，能调节食欲和记忆。大脑出现“胰岛素抵抗”时，会导致神经元能量代谢障碍[19]。帕金森病患者黑质多巴胺能神经元中胰岛素受体表达降低，信号传导障碍[20]。胰岛素抵抗会损害血脑屏障通透性，激活小胶质细胞进入促炎状态，触发神经炎症级联反应[21]。神经炎症又进一步破坏血脑屏障，形成恶性循环[22]。同时慢性高血糖和胰岛素抵抗可刺激脑线粒体过度呼吸，增加活性氧生成，激活 NF-κB 通路，加剧神经炎症[22-23]。

在阿尔茨海默病中，胰岛素信号障碍可加剧小胶质细胞活化、认知缺陷、病理改变，促进 tau 蛋白过度磷酸化[23-24]。反之，β 淀粉样蛋白寡聚体可恶化脑部胰岛素抵抗，形成正反馈循环[25]。胰岛素抵抗、神经炎症、β 淀粉样蛋白沉积、tau 蛋白过度磷酸化之间的恶性循环加速神经退行性病变[26]。GLP-1 受体激动剂还可通过调节 GSK-3β 信号通路改善胰岛素信号障碍，并减轻糖基化终末产物对神经元的损伤[12]。

1.4　调节脑－肠轴

肠道氨基酸代谢肽、胃抑制多肽和胰腺肽的失调可导致炎症和神经退行性疾病[27]。肠道菌群通过调控细胞因子释放激活中枢小胶质细胞，促进神经元损伤[28-29]。慢性小胶质细胞活化是神经退行性疾病的标志，会释放神经毒性物质，加剧疾病进展[30]。肠道菌群还通过产生短链脂肪酸等代谢物影响血脑屏障通透性[31]，屏障受损会导致毒素和炎症因子进入大脑[32]。GLP-1R 在整个肠脑轴中广泛表达。司美格鲁肽可调控与认知功能和炎症相关的肠道菌群结构和组成[33]。因此，影响肠道菌群是 GLP-1 受体激动剂减轻认知功能障碍的潜在机制之一，在分子层面与调控 NF-κB 等炎症通路密切相关。

2　临床前研究

目前，阿尔茨海默病、帕金森病的治疗主要针对症状而非病因。全基因组关联研究提示，炎症通路激活是这些慢性疾病的风险驱动因素[34]。大量针对中风、帕金森病、阿尔茨海默病、创伤性脑损伤的动物模型研究证实了胰岛素受体激动剂的治疗可行性[35-38]。激活脑内 GLP-1R 可调节神经炎症、氧化应激、凋亡和线粒体功能障碍，促进细胞存活，并改善神经元功能[39]。

2.1　艾塞那肽制剂

艾塞那肽及其缓释制剂是研究较多的药物。在

细胞和转基因动物研究中，艾塞那肽-4（100 μg/kg，2 次/d，sc 疗程 16 周）可提高人类神经母细胞瘤细胞存活率，减轻 β 淀粉样蛋白诱导的氧化应激和神经炎症，并通过抑制小胶质细胞活化来改善神经元存活[40-41]。长效缓释制剂 PT320（双周 ip，从 5 周龄起持续给药至 24 周）在渐进性帕金森病小鼠模型中展现出显著疗效：可改善动物的自发运动和主动性行为，保护纹状体和伏隔核的多巴胺（DA）释放和再摄取功能，并减轻左旋多巴诱发的异常不自主运动[42-43]。在阿尔茨海默病相关模型中，艾塞那肽（100 μg/kg，2 次/d，ip 疗程 8 周）还能逆转高脂饮食诱导的脑源性神经营养因子信号障碍，降低炎症相关蛋白水平[44]。

2.2 利拉鲁肽

GLP-1 受体激动剂利拉鲁肽（0.2 μg/kg，2 次/d，sc 疗程 4 周）同样表现出神经保护作用。研究显示，在链脲佐菌素诱导的胰岛素抵抗和 5xFAD 小鼠模型中，利拉鲁肽可逆转神经炎症标志物，并减少 β 淀粉样蛋白斑块沉积[45]；在冈田酸诱导的阿尔茨海默病大鼠模型中，它还能改善记忆和认知功能，降低神经元凋亡[46]。

3 临床研究

流行病学研究表明，2 型糖尿病患者使用 GLP-1 受体激动剂可降低帕金森病风险[18]，且 GLP-1 受体激动剂使用者中风风险更低[47]，提示这类药物具有中枢神经系统疾病修饰潜力。目前利拉鲁肽、艾塞那肽的临床试验结果比较充分。

3.1 利拉鲁肽

在利拉鲁肽研究中，针对阿尔茨海默病的II期临床试验显示，sc 利拉鲁肽 1.8 mg/d 可提升患者血脑屏障葡萄糖转运能力和脑部代谢率，12 周治疗能改善脑部连接性，但对认知功能无显著影响[48]；同样剂量在为期 12 个月的 ELAD IIb 期试验中，主要终点（皮质葡萄糖代谢率变化）未达显著差异，但次要指标（ADAS-Exec 执行功能领域）优于安慰剂组[49]。针对帕金森病的 52 周II期试验表明，利拉鲁肽安全耐受，可改善非运动症状、活动能力和生活质量[50]。在非糖尿病人群中，疗程 26 周，利拉鲁肽可避免阿尔茨海默病患者脑葡萄糖代谢下降、恢复海马体连接性，但未改善认知功能测试评分[51]。

针对无糖尿病的重度抑郁症或双相情感障碍患者（执行功能受损），4 周利拉鲁肽治疗显著改善了连线测验-B 评分和多项认知任务综合 Z 评分，但因开放标签设计且无对照，结果需谨慎解读[52]。在无痴呆的 2 型糖尿病/糖尿病前期肥胖患者中，16 周利拉鲁肽治疗可改善延迟记忆、注意力、执行功能等认知亚领域，与左侧海马体激活直接相关[53]；另有研究证实 12 周利拉鲁肽治疗后，所有认知测试表现均改善[54]；认知正常或轻度认知障碍患者接受利拉鲁肽治疗 3 个月，MoCA 评分提高[55]。在 1 项平均 77 岁、无痴呆的老年糖尿病患者中，利拉鲁肽与其他降糖药相比认知改善不明显但趋于稳定，或与病程长、样本量小有关[56]。

3.2 艾塞那肽

艾塞那肽同样是阿尔茨海默病和帕金森病临床试验的常用治疗药物。在阿尔茨海默病领域，1 项为期 18 个月的双盲随机安慰剂对照II期试验中，艾塞那肽（10 μg/次，2 次/d，sc）治疗后患者外泌体中 $A\beta_{42}$ 浓度显著降低，但认知功能、脑结构、生物标志物等关键指标与安慰剂无显著差异；该研究因赞助方撤回药物提前终止，仅 18 人完成，样本量不足[57]。在帕金森病领域，1 项为期 12 个月的II期单盲试验中，艾塞那肽（sc，2 次/d）可显著改善 MDS-UPDRS 第 3 部分评分[58]，效果在停药后超 12 个月仍持续[59]；后续更大规模的双盲安慰剂对照试验采用每周一次注射用艾塞那肽微球，同样使停药期运动评分显著改善，其机制与脑内胰岛素、Akt、哺乳动物雷帕霉素靶蛋白（mTOR）信号通路相关[60-61]；事后分析还发现，12 周治疗可改善情绪、降低抑郁指标，效果持续至治疗后 48 周[62]。

3.3 其他

其他 GLP-1 受体激动剂同样显示神经保护潜力。REWIND 试验中，50 岁以上伴心血管危险因素的 2 型糖尿病患者接受每周 1.5 mg 度拉鲁肽、最长随访 8 年，严重认知功能障碍风险降低 14%[63]。整合分析显示，接受利拉鲁肽、皮下/口服司美格鲁肽治疗的患者痴呆症风险较安慰剂组显著降低[64]。系统评价表明，短效 GLP-1 受体激动剂可显著改善帕金森病运动症状[65]。流行病学数据进一步支持：在 2 型糖尿病患者中，GLP-1 受体激动剂和钠－葡萄糖协同转运蛋白 2 抑制剂均可显著降低阿尔茨海默病风险，两者无显著差异[66]；使用 GLP-1 受体激动剂的人群患阿尔茨海默病及相关痴呆症风险比使用其他降糖药者低 26%，该保护作用与糖化血红蛋白和身体质量指数无关[67]。此外，1 项丹麦病例对照研究显示，多种降糖药与痴呆风险降低相关，以

GLP-1 类似物、钠－葡萄糖协同转运蛋白 2 抑制剂效应最显著，但因仅以“曾使用”为标准且未考虑潜伏期，结果需谨慎解读[68]。

4　结语

GLP-1 受体激动剂通过代谢调控、神经保护、炎症抑制、肠脑轴调控等多重机制在糖尿病相关认知障碍、阿尔茨海默病等疾病中展现出显著的认知保护潜力，为认知功能障碍的防治提供了全新的代谢干预策略。现有临床证据支持其在改善认知功能、延缓疾病进展中的积极作用，但仍需通过更大规模的临床研究明确适用人群、最佳剂量和治疗时机。随着机制研究的深入和转化应用的推进，GLP-1 受体激动剂有望从单纯的降糖药物拓展为维护大脑健康、抵御认知衰退的重要武器，为无数患者和家庭带来新的曙光。

利益冲突　所有作者均声明不存在利益冲突

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