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GLP-1受体激动剂通过抑制食欲而减重的机制

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摘　要

目的：本文综述了GLP-1受体激动剂食欲抑制的机制，对食欲影响的评估方法。方法：首先，本文对GLP-1受体激动剂的发展作出了简述，对比了一般的食欲调节和GLP-1受体激动剂食欲调节的相同及不同机制。重点阐述了食欲量化评估部分，将各类评估方法的优缺点与GLP-1具体的作用机制相结合，并分析了关键的神经影像学证据。结果：本文发现以GLP-1受体为药物作用靶点的减重新药层出不穷，但食欲抑制的机制尚不明确；现有研究在食欲量化评估上存在方法学短板，缺乏将主观感受、客观摄入行为与神经影像数据的多维整合。结论：本文旨在为药物减重的研究人员及减重科的临床医生提供一些参考，特别是通过提出“中枢各脑区作用的整合与协同机制”假说，为未来研究方向及个体化用药策略提供启发。

关键词

肥胖，GLP-1受体激动剂，食欲抑制

Mechanism of GLP-1 Receptor Agonists in Weight Loss through Appetite Suppression

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Abstract

Objective: This article reviews the mechanisms by which GLP-1 receptor agonists suppress appetite and summarizes the methods for evaluating appetite. Methods: Firstly, this article provides a brief overview of the development of GLP-1 receptor agonists. It compares the similarities and differences

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between general appetite regulation mechanisms and those mediated by GLP-1 receptor agonists. Crucially, it elaborates on appetite quantification assessments, integrating the strengths and limitations of various evaluation methods with the specific mechanisms of GLP-1. Results: The review finds that while new weight-loss drugs targeting the GLP-1 receptor are emerging constantly, the appetite suppression mechanisms remain unclear. Furthermore, existing studies exhibit methodological shortcomings in appetite quantification, lacking a multidimensional integration of subjective sensations, objective intake behaviors, and neuroimaging data. Conclusion: This article aims to provide a reference for researchers in pharmacological weight loss and clinicians in weight management departments. Specifically, by proposing the hypothesis of an "integrative and synergistic mechanism across central brain regions", it offers insights for future research directions and strategies for individualized medication.

Keywords

Obesity, GLP-1 Receptor Agonists, Appetite Suppression

1. 引言

肥胖症作为当今世界的“新型疾病”，已逐渐成为我国的常见病，它引起的不仅仅是体型的变化，更是心、脑、内分泌等全身各系统的损伤。WHO 对于肥胖的定义是脂肪过多或异常堆积，并危害健康[1]；我国定义的肥胖是 BMI ≥ 28 kg/m^2，超重则是 BMI 在 24~27.9 kg/m^2 之间。作为一个全球范围内的流行疾病，肥胖的患病率正在逐年增加，已成为全球公共健康的重大挑战之一。我国 18 至 35 岁成年人的 BMI 由 1989 年的 21.3 kg/m^2 上升至 2018 年的 23.3 kg/m^2，超重率从 12.1%上升至 36.8% [2] [3]。肥胖的并发症包括高脂血症、高尿酸血症、糖尿病等，均严重危害健康甚至会引起死亡，这主要是由于胰岛素抵抗增加和慢性低级别炎症所致。本综述所指的肥胖皆为非病理性因素(排除激素等药物治疗所致肥胖、甲状腺功能减退症、库欣综合征等)引起的单纯性肥胖[3]。

目前对于肥胖治疗的主要方式有 3 种：生活方式干预(包括运动及饮食)、药物治疗及手术治疗[4]。生活方式干预为减重的基石，但单纯的生活方式干预困难且效果不明显；减重手术由于其严苛适应症、创伤性及昂贵费用暂未能得到推广。多年来，研究人员将目光投掷于药物减重：作用于大脑的 γ-氨基丁酸(Gamma-Aminobutyric Acid, GABA)受体激动剂(例如托吡酯)，5-羟色胺受体 2A (5-Hydroxytryptamine Receptor 2A, 5-HT2A)受体激动剂(例如氯卡色林)，多巴胺/去甲肾上腺素(Dopamine/Norepinephrine, D/N)受体激动剂、μ 阿片肽受体(Mu Opioid Peptide, MOP)受体激动剂(例如纳曲酮、安非他酮)；作用于胃肠道的脂肪酶抑制剂(例如奥利司他) [4]-[6]。由于它们在精神系统及胃肠道内有大小不一的副反应，药物减重一度成为大众望而却步的领域。此时，胰高血糖素样肽-1 (Glucagon-like peptide-1, GLP-1)受体激动剂的出现给药物减重带来了巨大的转机。随机对照试验(Randomized Controlled Trial, RCT)证明了其有效性[7]-[9]。GLP-1 受体激动剂通过促进饱腹、抑制食欲并改善代谢达到减重的目的[10] [11]。现在越来越多的 GLP-1 受体激动剂相关药物投入了临床使用，其减重的效果已得到了很好的证明，其减重的基本机制已在过去的研究中得到了部分的证实，本文主要总结并对 GLP-1 受体激动剂通过控制食欲而减重的机制进行综述，对 GLP-1 受体激动剂减重的基本机制稍加补充。

2. GLP-1 受体激动剂的发展与现况

上世纪 80 年代，研究人员在对肠促胰岛素的研究中发现了 GLP-1 分子并最终在人类研究中将其鉴定为一种潜在的肠促胰岛素激素[12]-[14]。研究人员以静脉给药的方式给患者输注 GLP-1，当剂量被增大后，一些患者开始恶心，甚至出现了呕吐症状，GLP-1 对胃肠道的作用初见端倪[15]。2005 年初艾塞那肽作为糖尿病口服药物的辅助疗法在美国获得批准上市[16]。2014 年 12 月，商品名为善纤达(Saxenda)的利拉鲁肽成为第一款被美国食品药品监督管理局(Food and Drug Administration, FDA)批准用于减重的 GLP-1 受体激动剂[17]。此后经过不断的改良、研发，艾塞那肽、度拉糖肽及司美格鲁肽等药物也逐渐投入了减重药物市场[18] [19]。2023 年 6 月，诺和诺德进口原研的利拉鲁肽在国内被批准减重适应症，此后贝那鲁肽(国产)、司美格鲁肽(诺和诺德)、替尔泊肽(礼来)也先后在国内获批了减重适应症[6]。至此，GLP-1 受体激动剂在国内减重市场大放异彩。

2.1. GLP-1 受体激动剂临床应用及减重效果

GLP-1 受体激动剂目前在我国临床上最多用于 2 型糖尿病(Type 2 Diabetes Mellitus, T2DM)患者的降糖治疗，相关试验表明，使用利拉鲁肽 3.0mg 降糖的 HbA1c 降幅在 0.3%~0.6% [20]，使用司美格鲁肽 2.4 mg 降糖的降幅约在 0.45%~1.8% [7] [8]；从 2023 年开始，利拉鲁肽、司美格鲁肽等 GLP-1 受体激动剂逐渐在国内获批减重适应症，用于 BMI ≥ 28 kg/m^2 或≥24 kg/m^2 合并代谢综合征(高尿酸血症、高脂血症等并发症)人群[6]。使用日制剂利拉鲁肽 3.0 mg 减重 56 周的平均值 8 kg [20]；周制剂司美格鲁肽 1.7~2.4 mg 减重 12~64 周的平均值在 7~12 kg [9]，减重 1 年左右的平均值约 15 kg [8] [21]。除此之外，使用双通道激动剂替尔泊肽 5~15 mg 减重 20 周左右的平均值 12.8 kg [18]，减重 1 年左右的减重平均值甚至可达 17.2 kg [21]。

除了降糖及减重的作用，根据相关报道，GLP-1 受体激动剂还具有心脏保护作用[22] [23]、能够降低心血管事件[24]、改善脂肪肝[25] [26]、降压调脂[25]-[27]、改善睡眠呼吸暂停综合症[28]；另外有文献报道称其具有减少酒精药物成瘾的作用[29]，具有治疗阿尔兹海默症的潜力[30]-[32]。除此之外，使用 GLP-1 受体激动剂降糖时发生低血糖风险较低[33]；尽管它具有一过性胃肠道症状的不良反应[28] [30]，随着多靶点激动剂的研发，这种不良反应的发生率也在逐渐降低。

2.2. 多靶点激动剂

如今，以 GLP-1 受体为主要靶点，包括葡萄糖依赖性促胰岛素多肽(Glucose-dependent insulinotropic polypeptide, GIP)受体、胰高血糖素(Glucagon, Gcg)受体及瘦素(Leptin)受体在内的多个靶点，均已被纳入了新型的药物研发中[34] [35]。GLP-1/GIP 双受体激动剂替尔泊肽已在全球获批用于 T2DM 和长期体重管理。它通过刺激胰岛素、抑制胰高血糖素、延缓胃排空并作用于中枢降低食欲，实现“降糖 + 减重”双重获益[18]。相关实验发现，其减重效果可以达到惊人的 25% [18] [36]。除了替尔泊肽外，GIP/GLP/Gcg 三重激动剂也在研发当中[37]。更新的药物 GIP/GLP/Gcg/Leptin 融合分子，则是在三靶基础上再融合瘦素功能域或共价连接瘦素类似物，它补充了“中枢–外周”能量平衡轴，同时抑制食欲并增加能量消耗[38]。

目前有多种处于研发阶段的减重药物。诺和诺德研发的高剂量版皮下注射的司美格鲁肽现处于 III 期临床，其研究目标是争取体重 1%~2%的额外降幅；除此之外，礼来、辉瑞、诺和诺德等公司正在投入口服 GLP-1 制剂的研究。诺和诺德公司、西兰制药公司、日本 Scohia 公司等均投入了 GLP-1/GIP 双靶激动剂的研究；其他例如 GLP-1/Glucagon 双靶激动剂、GLP-1 与胰淀粉酶(Amylin)的双靶激动剂也在研发中。GLP-1 与肽 YY (Peptide YY, PYY)双靶或联合、Glucagon 单靶或组合、GIP 单靶、GLP-1/GIP 拮抗(反向

代谢)、Amylin 单靶等，这些多机制组合从不同角度试图再突破疗效或给药便利性[35]。礼来研发的 GLP-1/GIP/Glucagon 三靶激动剂 Retatrutide 12 mg 在 II 期临床试验阶段达到了 48 周平均减重 24.2%的效果，已刷新减重纪录[39]。口服小分子及肽混合药物为研发中的下一代减重药物，有望将减重药物从有创治疗变成口服治疗。

3. GLP-1 受体激动剂作用机制

GLP-1 受体激动剂减重的主要机制包括降低能量摄入、增强饱腹感、减少对高脂肪食物的渴望、减少体脂和增加瘦体重[40]。

3.1. 食欲调节的机制

目前普遍观点将食欲调节的机制分为稳态调节及非稳态调节两种。稳态调节即在热量摄入不足时，动物会主动寻找并摄取食物，以求能量稳态[41] [42]。其中，外周激素，包括胃肠激素 GLP-1、PYY、胆囊收缩素(Cholecystokinin, CCK)，脂肪因子及神经递质等，被认为是将“能量储备及营养素可用性”信息传递给特定中枢神经元的主要信使[43] [44]。这些内感受性激素可通过多种途径进入血脑屏障(Blood-Brain Barrier, BBB)后的中枢神经元，包括在室周器官(Circumventricular Organs, CVOs)内被动运输；通过作用于迷走传入神经，间接向延髓神经元传递能量状态信号[44]。而中枢神经元在直接或间接接收到“能量或营养赤字”的外周信号后，被激活并驱动稳态性摄食[45]。

非稳态调节则在能量摄入充足的情况下，食物的形态以及预示食物奖励的情境线索也能诱发食欲，从而促使进食[46]。目前，已发现并鉴定了多种调控这种“非稳态食欲”的神经群，位于丘脑、中脑等部位[47]：其中部分神经元能够在不受内在能量状态限制的前提下驱动对可口食物的摄食[48]；另一些群体则能在饱足状态下，因条件化感觉线索(色香味等)而促进进食[49]。这些食欲促使个体超越当前的生理需求过量摄食，在当今“致胖环境”中，食物富足而非短缺，这种非稳态食欲被视为肥胖症发生的重要病因[50]。

稳态调节与非稳态调节的通路在结构与功能上的广泛重叠，提示其存在显著交互：空腹时瘦素下降，刺鼠相关蛋白(Agouti-related Protein, AgRP)激活腹侧被盖区(Ventral Tegmental Area, VTA)多巴胺释放，放大对高脂食物的奖赏渴求；而餐后 GLP-1 分泌既抑制胃排空，又能够通过 GLP-1 受体在腹侧被盖区–伏隔核通路(Ventral Tegmental Area-Nucleus Accumbens pathway, VTA-NAc)降低多巴胺放电，削弱非稳态进食欲望。因此，这种稳态–非稳态交叉使能量需求与奖赏价值实时匹配，其失衡导致肥胖[51] [52]。

3.2. GLP-1 受体激动剂调节食欲的机制

目前对于 GLP-1 受体激动剂的试验表明，GLP-1 受体激动剂可以通过降低能量摄入[53]、增强饱腹感[54]、减少对高脂肪食物的渴望、减少体脂和增加瘦体重而减重[55]。

GLP-1 受体激动剂在外周通过激活胃窦及幽门部位的 GLP-1 受体，引发迷走–交感的协同作用[56]，进一步抑制胃排空，此时胃膨胀信号经迷走神经上传至脑干部位的饱食中心，形成了早期饱腹感[57]。除此之外，延迟胃排空也能延长营养素暴露的时间，增强肠道远端 L 细胞 GLP-1 分泌，形成正反馈反应，进一步地加强饱腹感。

GLP-1 受体激动剂在中枢的作用于迷走神经–脑干通路、下丘脑稳态核团及中脑边缘奖赏系统 3 个部位[58] [59]。然而，现有研究对于 GLP-1 作用的具体机制上仍存在显著的矛盾与局限性。首先，GLP-1 进入中枢的途径仍存在争议。2.1 章节所述，传统观点认为外周 GLP-1 难以通过 BBB，而是通过迷走神经传入间接发挥作用。然而，近年来的示踪研究发现，CVOs 处存在 GLP-1 受体，部分 GLP-1 类似物可

能通过特定转运体直接进入脑实质[60]。这种两种作用模式的不同提示我们需要重新审视外周给药后中枢效应的状态。其次，在下丘脑稳态调节方面，GLP-1 能激动抑食神经元前阿黑皮素原/可卡因和苯丙胺调节转录物(Pro-opiomelanocortin/Cocaine and Amphetamine-Regulated Transcript, POMC/CART)去极化、抑制促使神经元 AgRP/神经肽 Y (Neuropeptide Y, NPY)活动[60] [61]，但对于其起效速度和持续时间的报道不同研究结论不同。部分急性注射实验显示效应在分钟级别出现[59]，而长期给药研究则观察到受体脱敏现象[24]。这暗示了稳态调节可能存在快速与慢速的双重调控机制。最后，在奖赏系统调节上，虽然多数研究支持 GLP-1 能减弱对食物线索的“想要”而非“喜欢”[62]-[64]，但也有少数临床观察发现患者对美食的主观愉悦感下降。这种动物实验与人类主观报告之间的不一致，可能源于物种差异或评估工具的敏感度不足。

综上所述，当前机制研究多呈“孤岛状”，缺乏将外周信号传入、下丘脑稳态整合与边缘系统奖赏调控串联起来的系统性假说。

3.3. 中枢各脑区作用的整合与协同机制

延髓孤束核(Nucleus Tractus Solitarius, NTS)作为“第一站”，不仅接收来自迷走神经的外周饱腹信号(如胃扩张)，还整合来自血液循环的 GLP-1 浓度信息。NTS 随后通过两条路径向上投射：一是通过负反馈回路直接抑制胃排空；二是投射至下丘脑弓状核(Arcuate Nucleus, ARC)。ARC 接收 NTS 信号后，通过 POMC/CART 与 AgRP/NPY 神经元的拮抗作用，设定基础的能量摄入阈值。然而，单纯的稳态信号不足以解释 GLP-1 对高脂食物渴求的特异性抑制。因此，我们假设存在这样一条路径：GLP-1 信号直接作用于 VTA。VTA 在接收到 GLP-1 信号后下调多巴胺神经元对食物线索的反应性，而这一过程可能受到下丘脑状态的调节：当机体处于饥饿状态时，AgRP 神经元的激活可能会部分抵消 GLP-1 对 VTA 的抑制作用，解释了为何极度饥饿时药物效果可能打折；而在能量充足时，GLP-1 对 VTA 的抑制作用被放大，从而高效阻断非稳态进食。

基于上述分散的证据，我们推测 GLP-1 受体激动剂的食欲抑制作用并非单一脑区的独立活动，而是依赖于“脑干–下丘脑–边缘系统”的协同作用。

4. 食欲量化

4.1. 食欲量表

0~100 mm 视觉模拟量表(Visual Analog Scale, VAS)及其衍生问卷(Control of Eating Questionnaire, CoEQ)因成本低而被广泛采用。GLP-1 的独特之处在于其可能选择性抑制非稳态欲望而非基础需要[65]。因此，未来的研究设计不应仅满足于总分变化，而应利用 CoEQ 的子维度(如“对甜食的渴望”、“无法控制的进食冲动”)进行细分分析。

4.2. 实验室摄食试餐法[66]

通用饮食监测器(Universal Eating Monitor, UEM)能提供精确的千卡摄入数据，被视为“金标准”。但标准化的用餐环境剥离了“食物线索”的作用。一项利用 UEM 的研究若未发现摄入量显著减少，并不能直接否定 GLP-1 的疗效，受试者在实验室环境下可能本身就处于“稳态进食”模式，因此若一项利用 UEM 的研究若未发现摄入量显著减少，并不能直接否定 GLP-1 的疗效。引入“线索暴露”环节能够弥补这一缺憾，从而测试 GLP-1 对非稳态食欲的阻断能力。

4.3. 移动生态瞬时评估[67] (Ecological Momentary Assessment, EMA)

EMA 结合智能手机与可穿戴设备，能捕捉自然状态下的食欲波动。对于半衰期较长、每日给药频率

不同的 GLP-1 制剂，EMA 是揭示药效动力学与食欲抑制时间窗匹配度的最佳工具。然而，其数据缺失率高及主观感受导致结论有偏差。将 EMA 与客观传感器，如连续血糖监测[68] (Continuous Glucose Monitoring, CGM)联用则有弥补作用：当 CGM 显示血糖平稳但受试者报告强烈食欲时，可精准定位为非稳态食欲发作，进而分析此时段 GLP-1 的血药浓度是否足以覆盖该波动。

4.4. 生物传感器与神经影像

功能磁共振成像(Functional Magnetic Resonance Imaging, fMRI)是解析 GLP-1 中枢机制的工具之一。现有的 fMRI 研究限于“某脑区激活减弱”而缺乏深度机制关联。van Bloemendaal 等人[69]利用 fMRI 发现，急性 GLP-1 输注显著降低了受试者在观看高热量食物图片时 NAc 和杏仁核(Amygdala)的激活水平。然而该研究也暴露了 fMRI 扫描时间短，无法反映长期用药后变化的局限性；且样本量小，难以排除个体差异。另一项由 Secher 等人[60]结合 PET-fMRI 的研究则得出利拉鲁肽特异性结合下丘脑和脑干的受体，结合率与食欲评分下降呈正相关。但其局限性在于，PET 的空间分辨率有限，难以区分具体的神经核团亚群。

因此，理想的食欲评估与 GLP-1 受体激动剂联系的研究应该结合主观感受、生理指标及脑成像，而不是单一使用。

5. 展望

如今，药物减重的研发稳步推进，本综述通过阐述 GLP-1 受体激动剂促进减重的机制之一——抑制食欲，更加支持了本文观点。特别是本文提出的中枢各脑区联合作用，强调了打破脑区孤立研究的重要性。临床上，越来越多的药物正在研发当中，认识到 GLP-1 受体激动剂抑制食欲的机制能够为研发人员指明方向，促使其找到更多更合适的靶点。基于前文对食欲量化方法的批判性分析，我们建议未来的临床试验应摒弃单一的食欲评分，转而采用主观感受与客观指标结合来评估疗效。除此之外，了解 GLP-1 受体激动剂如何通过抑制食欲而减重可以指导患者用药，通过食欲评分的方法预测用药后患者的效果(例：当评分低于某个数值，证明患者本身食欲便偏低，此时使用 GLP-1 受体激动剂可能并不能够充分抑制食欲；或是尽管能够抑制食欲，但因摄入量过低而带来副作用的风险会升高)。这也给研究人员带来新的方向：通过测定基线 GLP-1 的值或是间接测定体内 GLP-1 受体的值预测 GLP-1 受体激动剂的疗效。这有助于指导患者选择合适的剂量、联合用药方案从而实现个体化用药方案定制。同时，推动各种新药的研发，既能够补充调节食欲的机制，也能够提供更多的药物帮助临床医生择药，从而突破减重平台。

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