Advances in Clinical Medicine 临床医学进展, 2023, 13(2), 2811-2816
Published Online February 2023 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2023.132396

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胰高血糖素样肽1 (GLP-1)在肥胖外科治疗中的作用研究进展

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收稿日期：2023年1月21日；录用日期：2023年2月17日；发布日期：2023年2月24日

摘　要

肥胖，传统上被定义为导致健康受损的身体脂肪过量，在临床实践中通常通过体重指数(身体质量指数)来评估，该指数被表示为以千克为单位的体重除以以平方米为单位的身高(kg/m²)的比率。尽管有大量的研究致力于理解肥胖和能量平衡的生物学，显而易见的是，现有的知识迄今为止对遏制肥胖流行几乎没有帮助，世界上没有一个地方能够幸免于这一现象。在过去半个世纪中，全球范围内肥胖患病率呈上升趋势，并已达到相当高的流行水平。由于大大增加了2型糖尿病、脂肪肝、高血压、心肌梗塞、阻塞性睡眠呼吸暂停等疾病以及一些癌症风险，从而导致生活质量下降，寿命下降，肥胖是一个重大的健康挑战。尤其是肥胖合并T2DM的患者比重在单纯肥胖人群中比例增大，使得肥胖与T2DM成为社会广泛关注的公共卫生问题。肥胖与T2DM密切相关，体重增加是T2DM的独立危险因素，而肥胖特别是中心性肥胖容易造成胰岛素抵抗，促使胰岛*β*细胞高负荷运转，从而使胰岛功能受损，导致T2DM的发生。肥胖与T2DM之间的关系相当复杂，最近比较热门的研究越来越重视肥胖与T2DM之间的分子、信号通路、免疫以及基因水平。故本文就肥胖及T2DM之间的分子、信号通路以及其近来在肥胖外科治疗中的作用作一简要综述。

关键词

胰高血糖素样肽-1，肥胖，治疗

Progress in the Study of the Role of Glucagon-Like Peptide 1 (GLP-1) in the Surgical Treatment of Obesity

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文章引用: 玉苏普江·伊明江, 依力汗·依明, 买买提·依斯热依力, 艾克拜尔·艾力. 胰高血糖素样肽 1 (GLP-1)在肥胖外科治疗中的作用研究进展[J]. 临床医学进展, 2023, 13(2): 2811-2816. DOI: 10.12677/acm.2023.132396

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Received: Jan. 21st, 2023; accepted: Feb. 17th, 2023; published: Feb. 24th, 2023

Abstract

Obesity, traditionally defined as an excess of body fat leading to impaired health, is commonly assessed in clinical practice by the body mass index (BMI), expressed as the ratio of body weight in kilograms divided by height in square meters (kg/m²). Despite the large amount of research dedicated to understand the biology of obesity and energy balance, it is clear that the available knowledge has so far done little to curb the obesity epidemic, from which no part of the world is immune. The prevalence of obesity has been on the rise globally over the past half century and has reached considerable epidemic levels. Obesity is a major health challenge due to the greatly increased risk of diseases such as type 2 diabetes, fatty liver, hypertension, myocardial infarction, obstructive sleep apnea, and some cancers, which lead to reduced quality of life and decreased life expectancy. In particular, the proportion of patients with obesity combined with T2DM has increased in the population with simple obesity, making obesity and T2DM a public health problem of wide social concern. Obesity and T2DM are closely related, and weight gain is an independent risk factor for T2DM, while obesity, especially central obesity, tends to cause insulin resistance and contribute to high islet *β*-cell load, thus impairing islet function and leading to the development of T2DM. The relationship between obesity and T2DM is quite complex, and recent more popular studies have increasingly focused on the molecular, signaling pathways, immune, and genetic levels between obesity and T2DM. Therefore, this paper provides a brief review of the molecular and signaling pathways between obesity and T2DM and their recent role in the surgical treatment of obesity.

Keywords

Glucagon-Like Peptide-1, Obesity, Treatment

1. 胰高血糖素样肽-1 (glucagon-like peptide-1, GLP-1)

胰高血糖素样肽-1 (GLP-1)是起初被认为是肠内 L 细胞在进餐时分泌的一种促胰岛素激素，在血糖控制中起关键作用。它调节胰岛素和胰高血糖素的分泌、胃排空、食物摄入和血液流动[1]。随后的研究通过从胰腺α细胞抑制胰高血糖素分泌、延迟胃排空并介导饱足感应发现，GLP-1 也降低血糖[2]。因此GLP-1在餐后通过多种作用维持代谢稳态。十多年来，半衰期比内源性 GLP-1 长得多的 GLP-1 受体激动(glucagon-like peptide-1 receptor agonist, GLP-1RA)剂一直是 2 型糖尿病(diabetes mellitus type 2, T2DM)的有效治疗选择[3] [4]。有趣的是，近年来的研究还发现 GLP-1 对多种组织(例如心血管和神经系统)具有有

益的生理作用，鉴于与T2DM相关的多种常见的诊断后并发症，这具有高度的临床相关性[3] [5] [6]。GLP-1通过与其受体GLP-1受体(glucagon-like peptide-1 receptor, GLP-1R)结合来介导其作用，GLP-1R是一种G蛋白偶联受体，大量存在于胰腺β细胞、肠道和中枢神经系统(CNS)中。除此以外肺、心脏、肾脏、血管和周围神经系统也存在GLP-1R [5] [6]。然而，研究报告称，尽管没有GLP-1R，GLP-1仍对某些胰腺外组织发挥作用，这意味着该激素也可能通过目前未识别的受体或机制起作用[7]。因此，鉴于不断出现的证据，人们已经接受GLP-1具有全身生理作用，并且该激素的作用不仅限于介导肠促胰素效应，尽管这仍然被广泛认为是GLP-1最重要的作用。

2. GLP-1与肥胖及T2DM的关系

2.1. GLP-1与肥胖的关系

肥胖与食欲增加、胃肠(gastrointestinal, GI)激素水平改变、脂肪量增加以及饱腹感和饱腹机制失调有关[8]，这些都是减肥药的目标。适口性、食物偏好和奖励功能因遗传和非遗传因素而异，并被认为在体重增加中发挥作用。此前已有研究表明，肥胖与对高能量食物的偏好之间存在关联[9]。对不同类型食物的渴望与肥胖有关[10] [11]，并可能预测对肥胖管理的反应[12] [13]。胰高血糖素样肽-1 (GLP-1)类似物或受体激动剂通过多种机制诱导体重减轻，包括可能对大脑食欲中心的直接中枢作用[14]，例如通过liraglutide (一种长效GLP-1类似物)激活GLP-1受体表达的谷氨酸能神经网络。GLP-1是一种肠促胰岛素激素，在控制能量摄入、延迟胃排空和抑制胰高血糖素分泌方面发挥作用[15]。GLP-1受体在大脑的多个部位表达，包括调节食欲的脑干和下丘脑核，利用大鼠模型进行的动物研究证实，控制食物摄入的下丘脑中心介导利拉路肽诱导的体重减轻[16]。

2.2. GLP-1与T2DM的关系

GLP-1是一种由30个氨基酸组成的肽，由肠道L细胞在进食时分泌[17] [18]。GLP-1受体在胰腺、胃肠道、肾脏、心脏和大脑[19]中表达。GLP-1在高血糖和正常血糖状态下的促胰岛素特性、降血糖作用已得到很好的证明。此外，该激素具有促进饱腹感，减少食物摄入，减缓胃排空作用[20]。2005年，FDA批准了第一个GLP-1受体激动剂艾塞那肽，随后有几项研究证明了它们在2型糖尿病患者中的有效性和安全性。事实上，这种药理学类别改善了葡萄糖稳态并降低了体重[21]，更有趣的是，大型心血管结局试验表明，GLP-1激动剂不仅耐受性良好，而且还降低了T2DM患者心血管和肾脏结局的风险。GLP-1在高血糖时抑制胰高血糖素[22] [23]，而在正常空腹血糖浓度时则不会[24]。已证明肠促胰岛素可间接影响肝脏和肌肉代谢，特别是通过改变胰岛素和胰高血糖素的循环浓度[25] [26]。此外，GLP-1是以葡萄糖依赖的方式与胰岛β细胞表面的GLP-1R结合后，通过环腺苷酸(cyclic adenosine monophosphate, cAMP)/ 磷脂酰肌醇-3激酶(phosphatidylinositol 3 kinase, PI-3K)信号通路增强β细胞胰岛素基因表达及β细胞增殖分化，从而减少β细胞凋亡并增多葡萄糖依赖性胰岛素的分泌，从而降低血糖防止T2DM的发生。

3. GLP-1在外科治疗中的作用

尽管通过生活方式干预和药物策略做出了巨大的努力，但减肥手术仍然是严重肥胖患者最有效的治疗方法[27] [28]。除体重减轻外，减肥手术还能迅速改善血糖，对许多患者来说，还能解决2型糖尿病(T2DM)和其他肥胖相关的合并症。其中腹腔镜Roux-en-Y胃搭桥术(LRYGB)与腹腔镜袖胃切除术(LSG)是最为常见的手术方式。LSG因操作相对简单、安全，并发症发生率较低、对机体胃肠道正常结构破坏较小，近年来迅速发展成为主流减重手术方式。胃泌素是由胃和十二指肠内分泌细胞分泌的，是唯一一种消化道分泌的肽，当外源性给药时，会在餐后减少并增加进食[29]。鉴于LRYGB和LSG的大部分胃

被绕过或切除，预计术后胃泌素水平会下降。然而，LRYGB 术后将胃组织留在腹腔内似乎足以维持胃泌素水平，因为多项研究表明，与 LRYGB 相比，LSG 术后空腹胃泌素水平的下降幅度明显更大[30] [31]。胃泌素的减少是否重要是个问题，因为遗传上缺乏胃泌素的小鼠在 LSG 时体重下降正常，葡萄糖耐量也有改善，这表明胃泌素的减少对 LSG 后的代谢改善不是必需的[32]。T2DM 的典型特征是为补偿全身的胰岛素抵抗而夸大胰岛素分泌，随后胰岛 β 细胞功能逐渐衰竭。虽然这种疾病被认为是慢性和进行性的，但鉴于上述胰岛素分泌和敏感性的改善，许多患者的 T2DM 同时得到缓解也就不奇怪了。虽然餐后 GLP-1 反应可能是减肥手术后胰岛素和葡萄糖反应所必需的，但 GLP-1 是否是解决 T2DM 的原因尚不清楚。尽管一项研究发现，营养素诱导的 GLP-1 反应是 LRYGB 术后 T2DM 缓解的最佳预测因素之一[33]，但另一项研究发现，无论患者是否术后缓解、复发或 T2DM 缺乏或缓解，LSG 术后 2 年的患者对混合餐的 GLP-1 反应是相似的[34]。这些受试者在使用 GLP-1 拮抗剂后也有胰岛素分泌受损，但糖耐量的恶化有限，这表明 LSG 后长期 GLP-1 分泌的增强对于维持 T2DM 受试者的正常糖耐量既不充分也不关键。虽然 GLP-1 在减肥手术后解决 T2DM 中的因果作用在人类中很难区分，但其他预测因素，如疾病的持续时间，以及手术前 β 细胞的破坏程度，可能对确定这些 β 细胞是否能充分恢复以解决 T2DM 更为关键[35]。

4. 总结与展望

肥胖症及糖尿病成为流行性疾病，减重代谢外科应运而生并逐渐成为肥胖和 T2DM 的主要治疗方式。减肥手术后一个主要的生理变化是餐后各种肠道分泌肽的大量增加。这些肽已被发现是食欲、能量消耗、葡萄糖和脂质代谢的关键生理调节因子，使它们成为改善手术后代谢的良好机制候选者。然而，任何单一肽的增加在多大程度上是减肥手术效果的唯一机制是有争议的。减肥手术现在被认为是代谢手术，在这种手术中，减肥对代谢稳态的独立影响与手术中的减肥成分同等重要。术后血糖改善是多种因素共同作用的结果，这些因素可能因所研究患者组的手术程序、啮齿动物种类和潜在生物学(即性别、遗传、血糖状态等)而有所不同。医疗保健适用性、经济限制和手术侵入性等障碍阻碍了减肥手术的广泛实施，因此，为了找到一种更简单的减肥和代谢健康策略解决全球范围内的肥胖流行，继续进行临床前和临床研究是必要的。

基金项目

国家自然科学基金项目(82060166)；新疆维吾尔自治区区域协同创新专项(上海合作组织科技伙伴计划及国际科技合作计划)项目(2020E01014)；新疆维吾尔自治区引进高层次人才天池百人计划项目(201939)。

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