CLINICAL IMPLICATIONS OF BASIC RESEARCH

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Discovery of GLP-1–Based Drugs for the Treatment of Obesity

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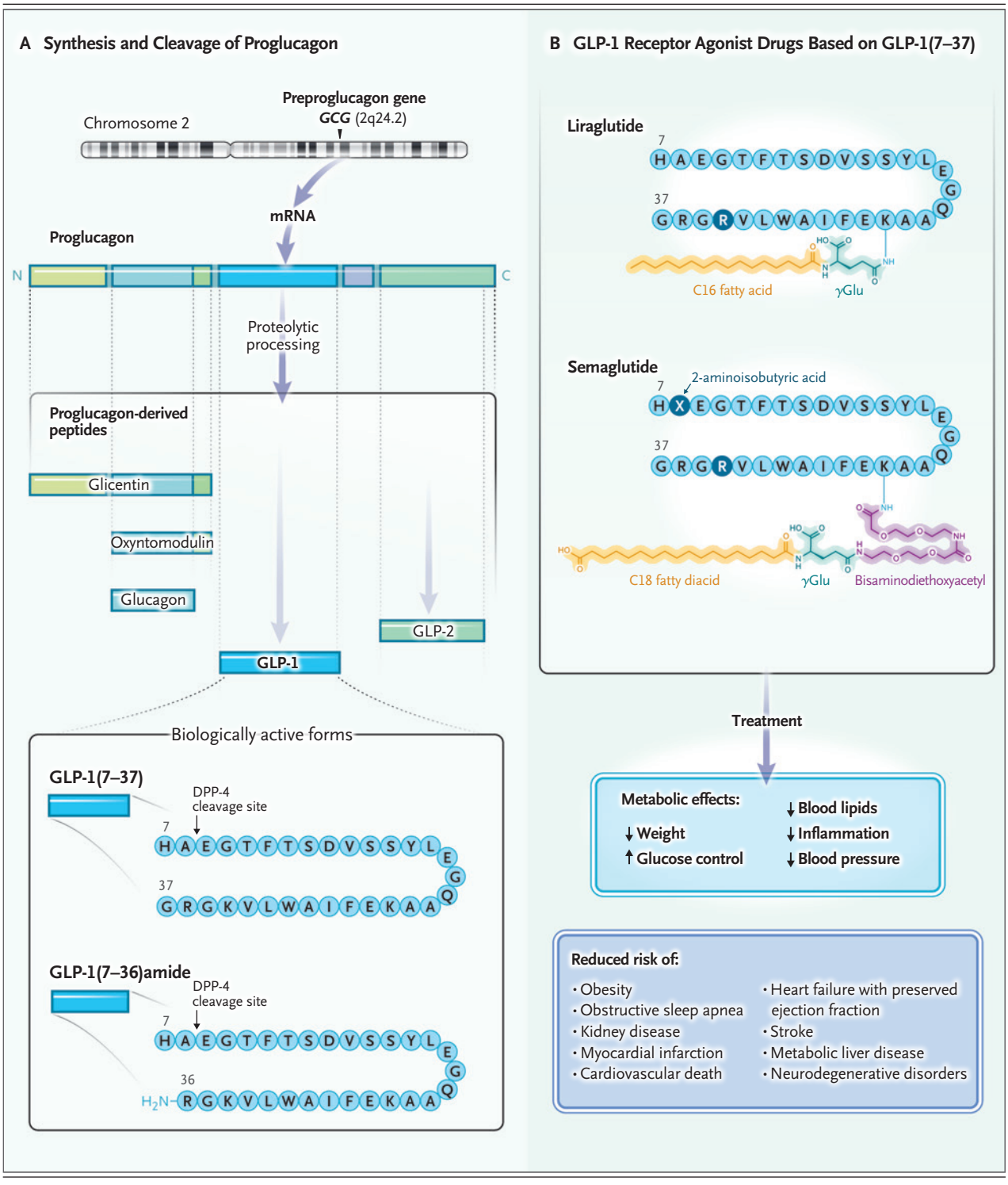
Since the pioneering discovery of secretin-like activity by Bayliss and Starling in 1902, scientists have pursued the mysteries of gut-hormone biology, such that the peptide hormone–secreting enteroendocrine-cell system is now understood to be the largest endocrine system, contributing dozens of peptide hormones that regulate hunger, satiety, gut motility, and barrier and immune function, as well as the absorption, digestion, and assimilation of ingested energy. It is fitting, then, that the 2024 Lasker–DeBakey Clinical Medical Research Award recognizes Joel Habener, Svetlana Mojsov, and Lotte Bjerre Knudsen for their scientific achievements that have enabled the discovery and development of glucagon-like peptide-1 (GLP-1) receptor agonists, medicines that have revolutionized the treatment of obesity.

The pancreatic hormone glucagon, which is produced predominantly in pancreatic islets, was discovered in 1923. Glucagon acts as a counterregulatory hormone, opposing insulin action and maintaining glycemia in the fasting state. The subsequent detection of immunoreactive proteins related to glucagon that have a higher molecular weight, such as glicentin, in the circulation system and the gut, was intriguing. These proteins were presumed to originate from enteroendocrine cells, and their discovery foreshadowed that of the extrapancreatic glucagon-related peptides. Working initially with anglerfish and later with rats, Habener and colleagues elucidated the sequence of the complementary DNAs and genes encoding glucagon, further clarifying the relationship between glucagon and glicentin and identifying entirely new sequences of two structurally related peptides, which were designated GLP-1 and GLP-2 (glucagon-like peptide-2).[1]

Svetlana Mojsov, a peptide chemist at the Massachusetts General Hospital, set out to study the post-translational processing of proglucagon by synthesizing different putative forms of GLP-1 and developing antibodies and radioimmunoassays to detect the glucagon-like peptides. These efforts enabled collaborative research that uncovered multiple forms of GLP-1 in the rat pancreas and gut, including the discovery that a truncated form of GLP-1 — GLP-1(7–37) — was abundant in gut extracts.[2] An important finding was that N-terminally truncated forms of GLP-1, such as GLP-1(7–37) and GLP-1(7–36), but not GLP-1(1–37), showed insulinotropic activity when tested in perfused pancreas systems and in islet cells.[3-5] The translational importance of these preclinical studies was rapidly established by the demonstration that GLP-1(7–36)amide rapidly increased levels of circulating insulin and decreased glucagon levels in healthy human participants, thereby lowering the peak glycemic response to intravenous glucose infusion.[6] The biologic activity and pharmacologic benefits of GLP-1 are shown in Figure 1.

Figure 1 (facing page). Derivation of Glucagon-like Peptide-1 (GLP-1) and the Biologic Actions of GLP-1 Medicines.

As shown in Panel A, the mammalian proglucagon-derived peptides are derived by means of post-translational processing from a larger proglucagon precursor encoded by *GCG*. Glucagon is synthesized in and secreted from the endocrine pancreas, whereas biologically active GLP-1 (7–37) and GLP-1(7–36)amide, together with several structurally related proglucagon-derived peptides — principally glicentin, oxyntomodulin, GLP-1, and glucagon-like peptide-2 (GLP-2) — are synthesized by gut endocrine cells and secreted into the circulation. Proglucagon-derived peptides are also produced within brain-stem neurons. As shown in Panel B, GLP-1 medicines pharmacologically mimic the actions of native GLP-1 and produce multiple metabolic benefits. These actions include a reduction in the incidence of obesity-associated complications, often independent of weight loss.[12] The abbreviation γGlu denotes γ-glutamate, DDP-4 dipeptidyl peptidase 4, and mRNA messenger RNA.



The pursuit of medicines that mimic the actions of native GLP-1 for the treatment of type 2 diabetes was challenged by the rapid degradation and clearance of native GLP-1, together with the induction of nausea, diarrhea, and vomiting when too much GLP-1 was infused rapidly. Remarkably, after more than a decade of effort to circumvent these challenges, in 2005, a structurally related lizard salivary gland protein, exendin-4 (exenatide), became the first GLP-1–based medi-

cine to be approved for type 2 diabetes. Although exenatide is relatively resistant to enzymatic inactivation by dipeptidyl peptidase 4 (DPP-4), it requires twice-daily administration and does not provide the continuous, 24-hour activation of the GLP-1 receptor that was shown to be effective for improving glycemic control. Lotte Knudsen and her team in Copenhagen set out to remedy these limitations and developed liraglutide, the first human GLP-1 analogue that was relatively DPP-4–resistant. Liraglutide, through acylation, bound noncovalently to albumin, further restricting the extent of degradation by DPP-4 and prolonging the circulating half-life, thereby providing the first long-acting GLP-1 medicine approved for type 2 diabetes that has a true 24-hour profile of pharmacologic GLP-1–receptor activation.

Glucagon-secreting tumors, designated glucagonomas, often manifest clinically with marked weight loss, an outcome consistent with observations that glucagon reduces food intake and augments energy expenditure. Some of these tumors also produce high levels of GLP-1. In 1996, three studies showed that intracerebroventricular administration of GLP-1 rapidly reduced food intake by rats and mice, actions that were shown to be mediated by the canonical GLP-1 receptor.[7-9] Although modest weight loss of 1 to 3% of the baseline body weight had been observed with doses of exenatide or liraglutide used to treat type 2 diabetes, concerns regarding their side-effect profile limited enthusiasm for testing higher doses. Despite considerable hesitation within the pharmaceutical industry at the time regarding the commercial viability of obesity therapeutics, Knudsen and her team tested higher doses of 2.4 mg and 3 mg of liraglutide once daily, ultimately achieving substantially more weight loss in persons with obesity than had been observed with the 1.8-mg daily dose in persons with type 2 diabetes.[10] In 2014, liraglutide became the first GLP-1 medicine approved for a weight-loss indication.[10] With the subsequent introduction of semaglutide, a more DPP-4 resistant, highly efficacious GLP-1 medicine suitable for once-weekly administration, and more recently, tirzepatide, the first GLP-1 coagonist, it is now possible to achieve a mean weight loss of 15 to 20% or more in persons with obesity or in those who are overweight and have one or more weight-related medical complications.[11]

The development of weight-loss therapeutics has been periodically set back by safety issues, with imbalances in the rates of neuropsychiatric or cardiovascular events or cancer leading to the withdrawal of medicines from the market. The use of long-acting GLP-1 medicines in persons with type 2 diabetes who either are at risk for or have established cardiovascular disease is supported by the findings from multiple studies showing reduced rates of myocardial infarction and stroke and reduced cardiovascular and all-cause mortality.[12] In 2023, semaglutide was shown to reduce the rates of major adverse cardiovascular events by 20% among persons with a history of atherosclerotic cardiovascular disease and obesity or in persons with overweight and one or more weight-related complications. In separate studies, semaglutide and tirzepatide markedly reduced symptoms and associated coexisting medical complications in persons with obesity and heart failure with preserved ejection fraction. Moreover, semaglutide reduced the rates of renal and cardiovascular disease among persons with type 2 diabetes who were at risk for chronic kidney disease, and tirzepatide reduced the apnea–hypopnea index and improved sleep-related outcomes in persons with obstructive sleep apnea and obesity.[12]

The development of more-effective GLP-1 medicines and the expansion of therapeutic benefits beyond weight loss (Fig. 1) has sparked a resurgence of interest in drug-development activity surrounding GLP-1–based therapeutics. Although most innovative efforts are centered on improving the extent of achievable weight loss, GLP-1 medicines, principally combinations of GLP-1 and one or more additional peptides, are also being studied in persons with metabolic liver disease, peripheral artery disease, Parkinson's disease, Alzheimer's disease, and a variety of neuropsychiatric and dependence-related disorders. Perhaps we have witnessed only the first moments of a new era of enteroendocrine biology and GLP-1 medicines, with waves of innovation yet to crest.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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This article was published on September 19, 2024, at NEJM.org.

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DOI: 10.1056/NEJMcibr2409089