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Evolution of the incretin system comprehension

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ABSTRACT

The incretin system plays a central role in the regulation of glucose homeostasis and is recognized as an important therapeutic target in modern endocrinology. This review outlines the evolution of scientific concepts related to incretins, from early observations of gut-derived factors enhancing insulin secretion to the identification of key incretin hormones, including glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). Particular attention is given to the incretin effect and its role in the regulation of postprandial glycemia. The molecular mechanisms underlying incretin action are discussed, including tissue-specific processing of proglucagon, secretion by intestinal L-cells, and receptor-mediated intracellular signaling pathways. The glucose-dependent nature of GLP-1–induced insulin secretion is emphasized as a critical factor ensuring a favorable safety profile with a low risk of hypoglycemia. Additional effects of incretins are also highlighted, including regulation of glucagon secretion, gastric motility, and feeding behavior. The review further addresses the translational progression from fundamental research to clinical application. The development of GLP-1 receptor agonists, including long-acting formulations resistant to degradation by dipeptidyl peptidase-4 (DPP-4), is considered, along with their clinical efficacy in glycemic control and body weight reduction. Current advances in incretin-based pharmacotherapy are discussed, including dual GLP-1/GIP receptor agonists and emerging multi-receptor agonists. Overall, the evolution of the incretin concept represents a successful integration of basic science and clinical medicine, leading to the development of effective therapeutic strategies for the treatment of type 2 diabetes mellitus and obesity.

Keywords: incretin system, GLP-1, GIP, DPP-4, GLP-1 receptor agonists, type 2 diabetes mellitus, obesity

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Развитие научных представлений об инкретиновой системе

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РЕЗЮМЕ

Инкретиновая система играет ключевую роль в регуляции гомеостаза глюкозы и рассматривается как важная терапевтическая мишень современной эндокринологии. В настоящем обзоре представлена эволюция научных представлений об инкретинах — от ранних наблюдений кишечных факторов, усиливающих секрецию инсулина, до идентификации основных инкретиновых гормонов, глюкозозависимого инсулинотропного полипептида (GIP) и глюкагоноподобного пептида-1 (GLP-1).

Особое внимание уделено феномену инкретинового эффекта и его роли в регуляции постпрандиальной гликемии. Рассматриваются молекулярные механизмы действия инкретинов, в том числе тканеспецифический процессинг проглюкагона, секреция кишечными L-клетками и рецептор-опосредованные сигнальные пути. Подчеркивается глюкозозависимый характер инсулинотропного действия GLP-1, определяющий высокий профиль безопасности терапии и низкий риск гипогликемии. Дополнительно освещаются эффекты инкретинов, связанные с регуляцией секреции глюкагона, моторики желудка и пищевого поведения.

Особое внимание уделено трансляции фундаментальных исследований в клиническую практику. Рассматривается разработка агонистов рецептора GLP-1, включая пролонгированные формы, устойчивые к деградации дипептидилпептидазой-4 (DPP-4), а также их клиническая эффективность в контроле гликемии и снижении массы тела. Обсуждаются современные направления инкретин-ориентированной терапии, такие как двойные агонисты рецепторов GLP-1/GIP и мультирецепторные агонисты. Таким образом, развитие инкретиновой концепции демонстрирует успешную интеграцию фундаментальной науки и клинической медицины, приведшую к созданию эффективных подходов к лечению сахарного диабета 2-го типа и ожирения.

Ключевые слова: инкретины, GLP-1, GIP, DPP-4, агонисты рецептора GLP-1, сахарный диабет 2-го типа, ожирение

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INTRODUCTION

Glucagon-like peptide-1 (GLP-1) receptor agonists are currently regarded as one of the most significant breakthroughs in clinical and experimental endocrinology, having substantially transformed the management of type 2 diabetes mellitus (T2DM) and obesity [1, 2]. However, the development of this therapeutic approach has been made possible only through the long-term evolution of scientific understanding of the humoral regulation of glucose metabolism and the discovery of the incretin phenomenon [3]. The history of incretins represents a paradigmatic example of the progressive advancement of fundamental physiology, peptide hormone biochemistry, and molecular pharmacology, ultimately leading to the emergence of a novel class of therapeutic agents.

As early as the beginning of the 20th century, experimental evidence suggested the existence of gut-derived factors capable of stimulating insulin secretion [4]. Subsequent studies demonstrated that oral glucose administration induces a significantly greater insulin response compared with intravenous administration of an equivalent glucose load [5]. This phenomenon, termed the "incretin effect," served as the foundation for the identification of gastrointestinal hormones that enhance glucose-dependent insulin secretion [6]. It was not until the second half of the 20th century, with the advent of radioimmunoassay techniques and molecular biology, that two principal incretin hormones were identified: glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) [7, 8]. A major contribution to the development of this concept was the discovery of the proglucagon gene and the elucidation of tissue-specific processing of its products in pancreatic α-cells and intestinal L-cells, explaining the generation of multiple biologically active peptides from a single precursor [9].

Further investigation of GLP-1 structure, its receptor, and intracellular signaling pathways demonstrated that its effects are mediated via a specific G protein–coupled receptor, leading to activation of the adenylate cyclase system and potentiation of insulin secretion strictly under hyperglycemic conditions [10]. This glucose-dependent mechanism is of fundamental clinical importance, as it minimizes the risk of hypoglycemia, a major limitation of conventional glucose-lowering therapies. Additional studies have revealed the pleiotropic actions of GLP-1, including suppression of glucagon secretion, delayed gastric emptying, modulation of satiety centers in the hypothalamus, as well as cardioprotective and potential neuroprotective effects. Collectively, these findings have established the incretin system as a critical component of the integrated regulation of metabolic homeostasis.

The translation of fundamental discoveries into clinical practice required overcoming several pharmacological challenges, primarily related to the extremely short half-life of native GLP-1 due to its rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-4). The development of degradation-resistant analogues and GLP-1 receptor agonists represented a pivotal step in translating the incretin concept into therapeutic applications. Structural modifications enabling prolonged activity allowed for clinically meaningful duration of action and improved patient adherence. Consequently, GLP-1 receptor agonists have demonstrated not only effective glycemic control but also sustained weight reduction, improvement in blood pressure and lipid profiles, and a reduction in major adverse cardiovascular events, supporting their classification as agents with proven cardiometabolic benefits [11].

The current stage of incretin-based therapy is characterized by the continued evolution of pharmacological strategies. The development of oral semaglutide represents a significant advance in peptide drug delivery, demonstrating the feasibility of gastrointestinal absorption of biologically active peptides. In parallel, the concept of multi-receptor agonism has emerged, including the development of dual GLP-1/GIP receptor agonists such as tirzepatide, reflecting a shift toward more comprehensive modulation of metabolic regulatory pathways. In addition, triple agonists targeting GLP-1, GIP, and glucagon receptors are under investigation, offering the potential for more pronounced effects on body weight and energy metabolism.

Thus, the history of incretin discovery and the development of GLP-1 receptor agonists represents a compelling example of the successful integration of fundamental physiology, molecular biochemistry, and clinical medicine [1]. From the initial observations of the incretin effect to the development of innovative multi-target therapeutics, this field has undergone a long trajectory of scientific advances and technological innovation [2]. The rapid expansion of research activity in this area is illustrated by the increasing number of publications over time (Fig. 1). This review provides a systematic overview of the evolution of the incretin concept [3], examines the key stages in the development of GLP-1 receptor agonists [4, 5], critically evaluates evidence from major clinical trials [6,7], and highlights future directions in the field, including precision medicine approaches [8], multi-receptor agonism [9], and advances in drug delivery systems [10].

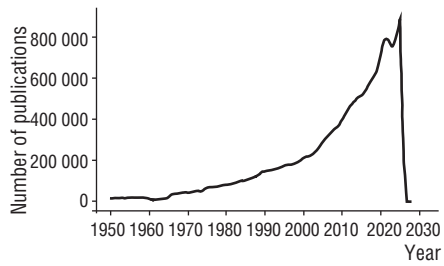

Fig. 1. Temporal dynamics of the number of publications on "GLP-1" in PubMed since 1950. (the drawing prepared by the authors). ***Note.*** From the 1950s to the 1970s, publication activity remained low and relatively stable. A steady increase in the number of publications began in the late 1980s. After 2000, the growth became exponential, reflecting the rapid expansion of incretin research and the clinical implementation of GLP-1 receptor agonists. The peak of publication activity has been observed in recent years (up to 2025)

Рис. 1. Линейный график динамики числа публикаций по запросу «GLP-1» в PubMed, начиная с 1950 г. *(*рисунок составлен авторами). ***Примечание.*** В 1950–1970-х гг. наблюдается низкий и относительно стабильный уровень публикационной активности. С конца 1980-х гг. начинается устойчивый рост числа работ. После 2000 г. рост становится экспоненциальным, что отражает активное развитие исследований инкретиновой системы и клиническое внедрение агонистов рецептора GLP-1. Пик публикационной активности приходится на последние годы (до 2025 г.)

EARLY YEARS (1902–1975)

The maintenance of glucose homeostasis is a fundamental prerequisite for health, whereas chronic episodes of hypo- and/or hyperglycemia are associated with severe microvascular complications, metabolic disturbances, coma, and death. Prior to the discovery and clinical implementation of insulin in the 1920s, type 1 diabetes mellitus, characterized by absolute insulin deficiency, was essentially a fatal disease, with patient survival limited to only a few years after diagnosis.

The identification of insulin and the confirmation of its hypoglycemic effects fundamentally changed the prognosis of the disease, transforming type 1 diabetes from a lethal condition into a manageable chronic disorder. However, at the early stages of introduction of insulin therapy, when preparations were derived from pancreatic extracts [1] or were insufficiently purified [2], a paradoxical effect was observed: a transient increase in blood glucose levels, peaking approximately 20 minutes after injection, followed by a subsequent decrease. This transient hyperglycemia was hypothesized to result from a toxic fraction associated with inadequate purification methods [2]. The same impurity likely contributed to local skin reactions and abscess formation observed in some patients [2]. These clinical observations prompted improvements in insulin extraction and purification techniques from pancreatic tissue homogenates, ultimately enhancing the safety and predictability of its therapeutic use.

In an effort to develop a rapid and cost-effective method for industrial insulin purification, Charles Kimball and John Murlin in 1923 isolated a pancreatic fraction which, after evaporation and reconstitution in water, produced a pronounced hyperglycemic effect when administered to rabbits and dogs [3]. As this fraction did not lower blood glucose levels, the researchers proposed that its effect was mediated by a factor antagonizing the hypoglycemic action of insulin. This factor was subsequently named “glucagon” (initially referred to as a “glucose agonist”) [3].

In the following decades, considerable efforts were directed toward elucidating the molecular mechanisms regulating carbohydrate metabolism by two functionally opposing pancreatic hormones [4]. One of the key findings was that the hyperglycemic action of glucagon is primarily mediated in the liver through the stimulation of glycogenolysis and gluconeogenesis [5, 6]. At the same time, a paradoxical effect of glucagon was identified — its ability to stimulate insulin secretion in humans, as described by Ellis Samols in 1965 [7].

In the early 1950s, Earl Sutherland and Christian de Duve demonstrated that glucagon production in the pancreas is abolished when islet α-cell function is impaired by cobalt or synthalin A, but remains preserved following alloxan-induced damage to exocrine acinar cells and pancreatic β-cells [8, 9]. These findings confirmed that glucagon is synthesized in pancreatic α-cells.

Subsequent histological studies by Claes Hellerström and Bo Hellman enabled the differentiation of pancreatic α-cells into α1 and α2 subtypes. However, it was not until the early 1960s that convincing evidence was obtained demonstrating that α2-cells are the primary source of glucagon [10]. This conclusion was based on a reduction in the number of α2-cells in rats and guinea pigs following administration of exogenous glucagon [11], as well as on the intense staining of these cells for tryptophan, an amino acid present in the glucagon molecule. Later, Bo Hellman and Åke Lernmark showed that α1-cells produce a factor that inhibits insulin secretion [12], which was subsequently identified as somatostatin.

In 1959, Roger Unger developed and characterized the first antibodies against glucagon, enabling the establishment of a radioimmunoassay (RIA) for the measurement of glucagon in blood and tissues [13]. In 1966, Ellis Samols and Vincent Marks demonstrated that glucagon-like immunoreactivity is present not only in the pancreas but also in extrapancreatic tissues, particularly in the intestine [14–16]. Moreover, circulating glucagon-like material was detected in pancreatectomized patients and dogs, thereby excluding the pancreas as its sole source. In 1968, Unger further demonstrated that intraduodenal, but not intravenous, administration of glucose increased circulating glucagon-like immunoreactivity [17], indicating an intestinal origin of this factor.

The intestinal glucagon-like material was found to be heterogeneous, comprising multiple fractions with different molecular weights and biological properties distinct from pancreatic glucagon [17, 18]. Unlike pancreatic glucagon, intestinal forms did not induce hyperglycemia in dogs and lacked glycogenolytic activity in the isolated perfused rat liver [17]. However, similarly to glucagon, they were capable of stimulating insulin secretion, suggesting the existence of multiple molecular forms or related peptides [18].

Immunocytochemical studies demonstrated that intestinal cells exhibiting glucagon-like immunoreactivity differ morphologically and ultrastructurally from pancreatic α-cells [19]. These cells were classified as L-cells [20]. Subsequently, higher molecular weight glucagon-like material was also identified in the pancreas of dogs [21], as well as in the islets of birds [22] and guinea pigs [23]. Collectively, these findings led to the conclusion that glucagon is synthesized as part of a larger precursor molecule that undergoes post-translational proteolytic processing to generate peptides of varying length and biological activity.

Immunoprecipitation analysis of rat pancreatic islets identified this precursor as a protein with a molecular weight of approximately 18 kDa, named proglucagon [24]. In the pancreas, proglucagon is cleaved to produce mature glucagon and an additional fragment of approximately 10 kDa that does not contain the glucagon sequence, referred to as the major proglucagon fragment (MPGF) [24, 25].

DISCOVERY AND CHARACTERIZATION OF GLP-1 (1983–1990)

In the early 1980s, it was demonstrated that the major form of glucagon-like immunoreactive material in the intestine — glicentin — contains the complete amino acid sequence of glucagon [26, 27]. Since glicentin was also detected in the pancreas [28], it was hypothesized that it represents a fragment of proglucagon. Initially, glicentin was believed to consist of approximately 100 amino acids; however, its subsequent purification from porcine intestine revealed that it is a 69-amino-acid peptide. These findings demonstrated that intestinal proglucagon

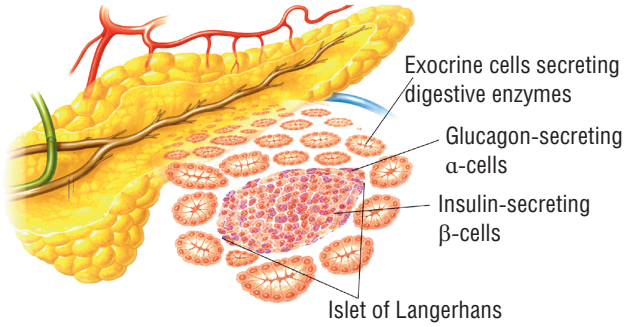

Fig. 2. Structure of the islets of Langerhans: a modern view (the drawing prepared by the authors)

Рис. 2. Строение островков Лангерганса: современное представление (рисунок составлен авторами)

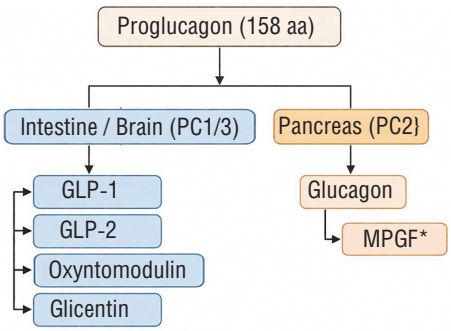

Fig. 3. Tissue-Specific Processing of Proglucagon (PC1/3 and PC2) (the drawing prepared by the authors)

Рис. 3. Тканеспецифическая протеолитическая обработка проглюкагона (PC1/3 и PC2) (рисунок составлен авторами)

undergoes proteolytic processing to generate peptide products distinct from those derived in the pancreas (Fig. 2).

In 1982, a shorter intestinal form was identified — a 37-amino-acid peptide containing the complete 29-amino-acid sequence of glucagon and an additional C-terminal octapeptide similar to that found in glicentin. Due to its ability to act on the oxyntic glands of the stomach, this peptide was named oxyntomodulin [29]. These findings established that proglucagon undergoes tissue-specific differential post-translational processing: in the intestine, glicentin and oxyntomodulin are produced, whereas in the pancreas, glucagon and the N-terminal fragment of glicentin (MPGF) are generated (Fig. 3) [30].

Using molecular cloning techniques and cDNA analysis of preproglucagon, Joel Habener in the early 1980s demonstrated that its sequence encodes additional glucagon-related peptides [31, 32]. Subsequently, two such peptides were identified in the proglucagon structure of rats [33], hamsters [34], cattle [35], and humans [36], and were named glucagon-like peptide-1 and glucagon-like peptide-2 (GLP-1 and GLP-2).

Further radioimmunoassay studies in tissues from rats, pigs, and humans confirmed differences in the profile of peptides derived from proglucagon in the pancreas and intestine. In the pancreas, glucagon and the major proglucagon fragment (MPGF) are predominantly produced, whereas in the intestine, shorter immunoreactive peptides, including GLP-1, are released.

In subsequent years, the search for intestinal factors with insulinotropic activity was hindered by the lack of reliable methods for quantitative insulin measurement in tissues and blood. With the introduction of radioimmunoassay (RIA) for insulin in the 1960s [37], it was demonstrated that intestinal mucosal extracts stimulate insulin secretion in healthy individuals, whereas this effect is absent in patients with type 1 diabetes mellitus [38]. At approximately the same time, it was shown that oral glucose administration induces a significantly greater insulin response than parenteral administration [39]. This enhanced insulin secretion following oral glucose intake was observed both in individuals with normal body weight and in those with obesity and was termed the “incretin effect” [40, 41].

Between 1969 and 1971, studies by John Brown and Raymond Pederson, in collaboration with peptide chemists Erik Jorpes and Viktor Mutt [42], led to the identification of a 42-amino-acid peptide, gastric inhibitory polypeptide (GIP), named for its ability to inhibit gastric motility and hydrochloric acid secretion [43]. In 1973, John Dupré demonstrated that intravenous administration of GIP at near-physiological concentrations, in combination with glucose, enhances immunoreactive insulin secretion and improves glucose tolerance in healthy volunteers, thereby confirming the contribution of GIP to the incretin effect [44]. It was later established that the insulinotropic action of GIP is mediated through a direct effect on pancreatic β-cells, enhancing glucose-stimulated insulin secretion, as demonstrated in isolated rat islets [45], as well as in the perfused pancreas of dogs [46] and humans [47].

However, studies from the laboratory of Werner Creutzfeldt (1983) demonstrated that immunoprecipitation of GIP from intestinal extracts reduced the incretin effect by less than 50% [48], indicating the presence of additional insulinotropic factors. Clinical observations in patients following resection of various segments of the small intestine revealed no direct correlation between circulating GIP levels and the magnitude of the incretin effect; rather, the latter depended largely on the integrity of the ileum [49].

Given the ability of glucagon to stimulate insulin secretion, attention was subsequently directed toward recently identified glucagon-like peptides sharing approximately 50% sequence homology with glucagon. Analysis of proglucagon cDNA in fish and mammals revealed sequences homologous to both glucagon and GIP, suggesting their potential insulinotropic activity. However, the predicted forms GLP-1 (1–36 amide) and GLP-2 did not exhibit insulinotropic effects. It was later demonstrated that a truncated form of GLP-1, isolated from the intestine of humans and pigs, markedly enhances insulin secretion in various experimental models [50], and subsequently in clinical studies [51]. Thus, GLP-1 was identified as a key hormone of the incretin system.

Between 1985 and 1987, the definitive identification of GLP-1 as a physiologically relevant and potent incretin hormone resulted from parallel and complementary studies conducted by academic and industrial research groups (Fig. 4, 5).

A pivotal contribution was made by the work of Svetlana Mojsov and Joel Habener (Massachusetts General Hospital, Harvard Medical School), who, based on cDNA analysis of preproglucagon, proposed the existence of biologically active forms of GLP-1 distinct from the full-length 37-amino-acid peptide [52]. Their studies demonstrated that tissue-specific post-translational

Fig. 4. Svetlana B. Mojsov — one of the pioneers in the discovery of the insulinotropic form of GLP-1

Рис. 4. Светлана Б. Мойсов — одна из первооткрывателей инсулинотропной формы GLP-1

Fig. 5. Joel F. Habener — a co-discoverer of the active form of GLP-1 and its insulinotropic function

Рис. 5. Джоэл Ф. Хабенер — соавтор открытия активной формы GLP-1 и ее инсулинотропной функции

processing of proglucagon in the intestine generates a truncated form of GLP-1 — GLP-1 (7–36) amide. This form, rather than the full-length GLP-1 (1–37), exhibited potent insulinotropic activity in vitro in pancreatic islet preparations. Furthermore, GLP-1 (7–36) amide was shown to enhance glucose-dependent insulin secretion, fulfilling the defining criterion of an incretin hormone [53].

In parallel, the group led by Lotte Knudsen at Novo Nordisk conducted studies aimed at the chemical synthesis and functional characterization of various forms of GLP-1. Their work confirmed the biological activity of the truncated peptide and established its pharmacological properties. Of particular importance was the demonstration that the insulinotropic effect of GLP-1 is strictly glucose-dependent, distinguishing it from sulfonylureas and minimizing the risk of hypoglycemia-an essential consideration for its therapeutic application [54].

Collectively, these studies demonstrated that the biologically active form of the hormone is GLP-1 (7–36) amide (and the closely related GLP-1 (7–37)); that GLP-1 enhances insulin secretion only under conditions of elevated glucose levels; that the peptide is produced in intestinal L-cells via tissue-specific processing of proglucagon; and that GLP-1 fulfills the functional criteria of an incretin hormone.

Thus, by the late 1980s, GLP-1 had been recognized, alongside GIP, as a physiological incretin. However, unlike GIP, it retained its insulinotropic activity under conditions of metabolic dysfunction, which subsequently established its predominant role in the development of therapies for type 2 diabetes mellitus.

EVOLUTION OF LONG-ACTING THERAPEUTICS (2007–2019)

In 2007, a research group at Novo Nordisk introduced the concept of developing long-acting analogues of human GLP-1 based on principles of rational protein engineering [55]. The resulting compound, liraglutide, incorporated an amino acid substitution of arginine with lysine at position 34 and the attachment of a palmitic acid (C16) moiety, enabling reversible binding to plasma albumin and thereby extending the half-life to approximately 13 hours [56] (Fig. 6). This modification allowed for once-daily administration. The LEAD clinical program, which included more than 8,000 patients across six randomized trials, demonstrated high efficacy of liraglutide. In particular, in the LEAD-2 study, liraglutide showed superiority over glimepiride in reducing HbA1c (–1.1% vs –0.7%) [57]. Across the LEAD program, sustained reductions in HbA1c of 1.0–1.5% were observed, accompanied by weight loss of 2–4 kg. In January 2010, the FDA approved liraglutide, establishing it as the first GLP-1 receptor agonist with a once-daily dosing regimen.

Between 2012 and 2014, Eli Lilly implemented an alternative pharmacological engineering strategy, leading to the development of dulaglutide — a hybrid molecule composed of two modified GLP-1 fragments covalently linked to the Fc fragment of human immunoglobulin G4. The increased molecular size and Fc-mediated recycling via the neonatal Fc receptor resulted in a half-life of approximately 90 hours, enabling once-weekly administration. Within the AWARD clinical program, which enrolled more than 9,000 patients, dulaglutide demonstrated consistent superiority in glycemic control compared with several standard therapeutic approaches [58]. Its FDA approval in September 2014 effectively established once-weekly GLP-1 receptor agonist therapy as a new clinical standard.

Further advancement of the long-acting concept was achieved by Novo Nordisk in 2015 with the development of semaglutide. In this molecule, the C16 fatty acid used in liraglutide was replaced with a longer C18 chain, enhancing albumin binding and further slowing drug clearance [55]. These structural modifications resulted in a half-life of approximately 7 days. The SUSTAIN clinical development program included over 9,000 patients. In the SUSTAIN-7 trial, semaglutide administered once weekly at doses of 0.5 and 1.0 mg produced greater reductions in HbA1c (–1.5% and –1.8%, respectively) compared with dulaglutide 1.5 mg (–1.1%), as well as more pronounced weight loss (6.5 kg vs 3.0 kg) [59]. In December 2017, the FDA approved semaglutide, marking a new stage in enhancing the therapeutic efficacy of this drug class.

In 2019, Novo Nordisk achieved a technological breakthrough in peptide drug delivery by developing an oral formula-

tion of semaglutide in combination with the absorption enhancer sodium N-(8-[2-hydroxybenzoyl]amino)caprylate (SNAC) [21]. The mechanism of SNAC involves local pH elevation and enhanced transcellular absorption in the stomach. Despite relatively low systemic bioavailability (approximately 1%), the oral formulation demonstrated clinical efficacy comparable to injectable GLP-1 receptor agonists, as confirmed in the PIONEER clinical program (Table 1) [60]. In September 2019, the FDA approved oral semaglutide, providing patients with the first effective alternative to injectable administration of this drug class.

THE ERA OF MULTI-AGONISTS (2020–2025)

In 2020, tirzepatide developed by Eli Lilly represented a paradigm shift as a dual agonist of GLP-1 and GIP receptors [61]. The rationale for this approach was based on evidence that activation of GIP receptors preserves beneficial effects on adipose tissue metabolism and energy expenditure [62]. The SURPASS clinical program demonstrated that tirzepatide is among the most effective glucose-lowering agents developed to date [63]. In the SURPASS-2 trial, a head-to-head comparison with once-weekly semaglutide 1 mg showed reductions in HbA1c of 2.0, 2.4, and 2.3% with tirzepatide at doses of 5, 10, and 15 mg once weekly, respectively, compared with a 1.9% reduction with semaglutide. The weight-loss effects were equally remarkable: tirzepatide produced dose-dependent reductions of 7.1, 10.3, and 12.9 kg, compared with 5.7 kg for semaglutide [30]. FDA approval of tirzepatide (Mounjaro) for the treatment of type 2 diabetes in May 2022 further validated the dual-agonist approach.

In 2023, the SURMOUNT-1 trial evaluating tirzepatide for obesity treatment reported the most pronounced pharmacological weight reduction observed to date. The study included 2,539 adults with obesity and demonstrated that tirzepatide administered once weekly at doses of 5, 10, or 15 mg resulted in mean body weight reductions of 16.0, 21.4, and 22.5%, respectively, compared with 2.4% with placebo over 72 weeks. At the highest dose, 91% of participants achieved at least 5% weight loss, while 57% achieved substantial reductions of 20% or more [63].

FDA approval of tirzepatide (Zepbound) for obesity treatment in November 2023 coincided with the development of retatrutide, the first triple agonist targeting GLP-1, GIP, and glucagon receptors [64]. Early phase II clinical trial results for retatrutide demonstrated even greater metabolic effects, with some participants achieving weight reductions exceeding 25%.

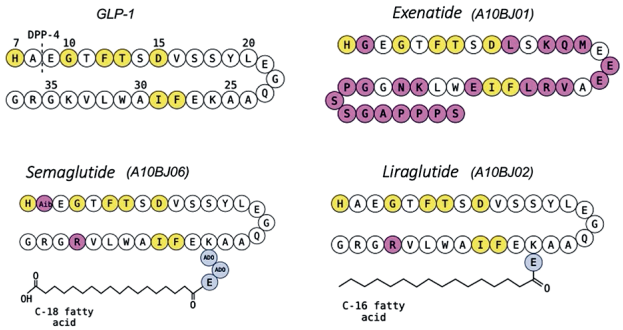

Fig. 6. Structural features of endogenous GLP-1 and molecular modifications of GLP-1 receptor agonists (the drawing prepared by the authors)

Рис. 6. Структурные особенности эндогенного глюкагоноподобного пептида-1 и модификации агонистов рецептора GLP-1 (рисунок составлен авторами)

CONCLUSION

Thus, the scientific quest to understand the incretin system, which began with early observations of gut-derived factors

Table 1. Pharmacokinetic and physicochemical properties of GLP-1 receptor agonists

Таблица 1. Фармакокинетические и физико-химические характеристики агонистов рецепторов GLP-1

Drug (ATC)	Homology to human GLP-1	Half-life	Molecular weight	Absorption and distribution	Metabolism	Elimination	Regulatory status
Exenatide (A10BJ01)	~53%	≈2,4 h	≈4200 Da	Rapid absorption, moderate Vd	Proteolysis (DPP-4, endopeptidases)	Renal	Approved (T2DM)
Lixisenatide (A10BJ03)	~50%	≈3 h	≈4900 Da	Rapid attainment of Cmax	Non-specific proteolysis	Renal	Approved (T2DM)
Liraglutide (A10BJ02)	~97%	≈13 h	≈3750 Da	Delayed absorption, albumin binding	Proteolytic degradation	Renal/intestinal	Approved (T2DM, obesity)
Semaglutide (A10BJ06)	~94%	≈168 h	≈4100 Da	Subcutaneous/ oral, high albumin binding	Proteolysis and β-oxidation	Renal/intestinal	Approved (T2DM, obesity)
Dulaglutide (A10BJ05)	~90%	≈ 4 days	≈59 700 Da	Slow absorption	Protein catabolism	Amino acid pool	Approved (T2DM)
Albiglutide (A10BJ04)	~97%	4–7 days	≈73 000 Da	Limited distribution	Protein catabolism	No data available	Previously approved
Tirzepatide (A10BX16)	–	≈5 days	≈4800 Da	Subcutaneous, albumin binding	Proteolysis and fatty acid metabolism	Renal/intestinal	Approved (T2DM, obesity)

The table was compiled by the authors / Таблица составлена авторами

influencing glucose metabolism in the early 20th century and reached an apparent milestone with the identification of GLP-1 as a key incretin hormone in the late 1980s, is still far from its final stage. Rather than representing a completed chapter, the development of incretin biology exemplifies a continuously evolving field at the intersection of fundamental physiology, molecular endocrinology, and translational medicine. Over the past decades, advances in peptide biochemistry, receptor pharmacology, and drug design have enabled the transformation of basic physiological insights into highly effective therapeutic strategies. The emergence of GLP-1 receptor agonists has not only redefined the management of type 2 diabetes mellitus but also expanded therapeutic possibilities in obesity and cardiometabolic disorders. Importantly, these agents have demonstrated that targeting endogenous regulatory systems can yield both efficacy and safety superior to traditional pharmacological approaches.

However, the incretin system itself is far more complex than initially anticipated. Ongoing research continues to uncover additional layers of regulation, including interactions between incretin hormones, central and peripheral signaling pathways, and their integration within broader neuroendocrine and metabolic networks. The recent development of dual and triple receptor agonists underscores a paradigm shift from single-target interventions toward multi-dimensional modulation of metabolic homeostasis. Future directions in this field are likely to be shaped by advances in precision medicine, enabling more individualized therapeutic strategies based on genetic, metabolic, and phenotypic characteristics of patients. In parallel, innovations in drug delivery systems, including oral peptide formulations and long-acting compounds, will further improve treatment adherence and clinical outcomes.

In this context, the evolution of the incretin concept should be viewed not as a completed success story, but as an ongoing scientific trajectory. Continued integration of experimental and clinical research will be essential for unlocking the full therapeutic potential of incretin-based approaches and for addressing the growing global burden of metabolic diseases.

ADDITIONAL INFORMATION

Author contributions. All authors contributed to the conception, literature analysis, drafting, and critical revision of the manuscript, and approved the final version.

Conflict of interest. The authors declare no competing interests.

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли равный вклад в разработку концепции, анализ литературы, подготовку и редактирование рукописи и одобрили её окончательный вариант.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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