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Physiology and pharmacology of glucagon-like peptide-1 receptor

D.V. Kurkin[1,2], D.A. Bakulin[1], E.I. Morkovin[2], V.I. Petrov[2], A.V. Strygin[2], K.N. Koryanova[3], Yu.V. Gorbunova[1], Yu.A. Kolosov[1], O.V. Ivanova[1], E.V. Pavlova[1], M.A. Dzhavahyan[1], A.V. Zaborovsky[1], V.B. Saparova[1], I.E. Makarenko[1,4], R.I. Drai[4], A.N. Chumachenko[2]

[1] Russian University of Medicine,
Bld. 1, 20, Delegatskaya Str., Moscow, Russia, 127473
[2] Volgograd State Medical University,
1, Pavshikh Bortsov Sq., Volgograd, Russia, 400131
[3] Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University,
11, Kalinin Ave., Pyatigorsk, Russia, 357532
[4] Closed joint-stock company "Farm-Holding",
34A, Svyaz Str., Strelna Vil., St. Petersburg, Russia, 198515

E-mail: strannik986@mail.ru

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Modern approaches to the treatment of type 2 diabetes mellitus (T2DM) are aimed not only at glycemic control, but also at reducing cardiovascular risks. The increasing prevalence of the disease and the need for effective treatment options highlight the importance of glucagon-like peptide-1 (GLP-1) receptor agonists in the pharmacotherapy structure.

The aim of the work was to review the literature regarding the physiology of GLP-1 and the therapeutic potential and development trends of its agonists.

Materials and methods. The search for the review materials was carried out using the abstract databases of PubMed, Google Scholar and e-Library. The search was carried out for publications from 2000 to 2023, using the following keywords: "GLP-1"; "GLP-1R agonists"; "GIP"; "exenatide"; "liraglutide"; "dulaglutide"; "semaglutide"; "lixisenatide"; "albiglutide"; "taspoglutide" taking into account various spellings.

Results. The interaction of almost all food components with enteroendocrine cells of the intestine leads to the secretion of incretins (primarily GLP-1) into the blood, triggering a complex of physiological reactions aimed primarily at the rapid utilization of incoming glucose (regulation of insulin and glucagon secretion), as well as the central regulation of dietary behavior (slowing gastric emptying and the formation of a feeling of satiety). A wide distribution of the GLP-1 receptor in various tissues and organs, its connection with intracellular signaling cascades aimed at launching energy-consuming remodeling (recovery) processes in endothelial cells, heart, neurons, beta cells, etc., is the basis for a wide range of pleiotropic effects of GLP-1 unrelated to its hypoglycemic effect. The discovery of synthetic GLP-1 receptor agonists with a long period of action has made it possible not only to therapeutically influence various parts of carbohydrate metabolism disorders, but also to increase the functional reserves of the target diabetes organs, reducing the risk of developing complications of the disease. Incretin-like drugs are well tolerated, with nausea being the most common side effect. The factors limiting a wider use of the drugs include their high cost and the preferred form of a subcutaneous solution. The current research is focused on the development of long-acting, oral, dual and triple agonists, fixed-dose combinations, and small molecule drugs.

Conclusion. GLP-1 receptor agonists are a class of effective and safe drugs for the treatment of diabetes and obesity, which is rapidly developing in the most advanced areas of pharmacy. A further development of this group and the solution of the identified problems will open up new opportunities for the treatment of diabetes and its complications.

Key words: GLP-1; glucagon-like receptor-1 agonists; diabetes mellitus; incretins

Abbreviations: ECD – extracellular N-terminal domain; FDA – U.S. Food and Drug Administration; FGF21 – fibroblast growth factor 21; Gcg – preproglucagon; GRP – gastrin releasing peptide; NTS – nucleus tractus solitarius; PI3K – phosphatidylinositol 3-kinase; PKA – protein kinase A; PKB – protein kinase B; PVN – paraventricular nucleus of the hypothalamus; PYY – peptide YY; SGLT1 – sodium-glucose linked transporter 1; TMD – transmembrane domain; ATP – adenosine triphosphate; AD – Alzheimer's Disease; PD – Parkinson's Disease; GABA – gamma-aminobutyric acid; GIP – glucose-dependent insulinotropic polypeptide; GM – genetically modified; GLP-1 – glucagon-like peptide-1; GLP-1R – glucagon-like peptide-1 receptor; BBB – blood-brain barrier; DPP-4 – dipeptidyl peptidase 4; GIT – gastrointestinal tract; T2DM – type 2 diabetes mellitus; FFA – free fatty acids; cAMP – cyclic adenosine monophosphate; CNS – central nervous system.

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REVIEW

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Физиология и фармакология рецептора глюкагоноподобного пептида-1

Д.В. Куркин[1,2], Д.А. Бакулин[1], Е.И. Морковин[2], В.И. Петров[2], А.В. Стрыгин[2], К.Н. Корянова[3], Ю.В. Горбунова[1], Ю.А. Колосов[1], О.В. Иванова[1], Е.В. Павлова[1], М.А. Джавахян[1], А.В. Заборовский[1], В.Б. Сапарова[1], И.Е. Макаренко[1,4], Р.И. Драй[4], А.Н. Чумаченко[2]

[1] Федеральное государственное бюджетное образовательное учреждение высшего образования «Российский университет медицины» Министерства здравоохранения Российской Федерации, 127473, Россия, г. Москва, ул. Делегатская, д. 20/1

[2] Федеральное государственное бюджетное образовательное учреждение высшего образования «Волгоградский государственный медицинский университет» Министерства здравоохранения Российской Федерации, 400131, Россия, г. Волгоград, пл. Павших Борцов, д. 1

[3] Пятигорский медико-фармацевтический институт – филиал федерального государственного бюджетного образовательного учреждения высшего образования «Волгоградский государственный медицинский университет» Министерства здравоохранения Российской Федерации, 357532, Россия, г. Пятигорск, пр-кт Калинина, д. 11

[4] Закрытое акционерное общество «Фарм-Холдинг», 198515, Россия, г. Санкт-Петербург, пос. Стрельна, ул. Связи, д. 34

E-mail: strannik986@mail.ru

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Современные подходы к лечению сахарного диабета 2 типа (СД2) направлены не только на контроль гликемии, но и на снижение кардиоваскулярных рисков. Рост распространенности заболевания и необходимость в эффективных вариантах лечения подчеркивают важность агонистов рецепторов глюкагоноподобного пептида-1 (ГПП-1) в структуре фармакотерапии.

Цель. Анализ литературы, касающейся физиологии ГПП-1, а также терапевтического потенциала и тенденций развития его агонистов.

Материалы и методы. Поиск материала для написания обзора проводили с использованием реферативных баз PubMed, Google Scholar и e-Library. Поиск осуществляли по публикациям в период с 2000 по 2023 годы, с использованием следующих ключевых слов: «ГПП-1»; «агонисты ГПП-1Р»; «ГИП»; «эксенатид»; «лираглутид»; «дулаглутид»; «семаглутид»; «ликсисенатид»; «албиглутид»; «таспоглутид» с учетом различных вариантов их написания.

Результаты. Взаимодействие практически всех компонентов пищи с энтероэндокринными клетками кишечника приводит к секреции в кровь инкретинов (прежде всего ГПП-1), запускающих комплекс физиологических реакций, направленных, в первую очередь, на быструю утилизацию поступающей глюкозы (регуляция секреции инсулина и глюкагона), а также центральную регуляцию пищевого поведения (замедление опорожнения желудка и формирование чувства насыщения). Широкое распространение рецептора к ГПП-1 в различных тканях и органах, его связь с внутриклеточными сигнальными каскадами, направленными на запуск энергозатратных процессов ремоделирования (восстановления) в клетках эндотелия, сердца, нейронах, бета-клетках и др., является основой для широкого спектра плейотропных эффектов ГПП-1, не связанных с его гипогликемическим действием. Открытие синтетических агонистов рецепторов ГПП-1 с длительным периодом действия дало возможность не только терапевтически воздействовать на различные звенья нарушений углеводного обмена, но и увеличить функциональные резервы органов-мишеней СД, снижая риск развития осложнений заболевания. Инкретиноподобные препараты хорошо переносятся, самым распространенным побочным эффектом является тошнота. Факторы, ограничивающие более широкое использование препаратов, включают высокую стоимость и преимущественную форму – раствор для подкожного введения. Текущие исследования связаны с разработкой препаратов с пролонгированным действием, пероральной формы, двойных и тройных агонистов, фиксированных комбинаций, а также препаратов малых молекул.

Заключение. Агонисты рецепторов ГПП-1 представляют собой класс эффективных и безопасных лекарственных средств для терапии СД и ожирения, который стремительно развивается по самым передовым направлениям фармации. Дальнейшее развитие этой группы и решение обозначенных задач откроет новые возможности для лечения СД и его осложнений.

Ключевые слова: ГПП-1; агонисты глюкагоноподобного рецептора-1; сахарный диабет; инкретины

Список сокращений: ECD – внеклеточный N-концевой домен; FDA – Управление по санитарному надзору за качеством пищевых продуктов и медикаментов США; FGF21 – фактор роста фибробластов 21; Gcg – препроглюкагон; ГРП – гастрин-рилизинг пептид; NTS – ядро солитарного тракта; PI3K – фосфатидилинозитол-3-киназа; PKA – протеинкиназа A; PKB – протеинкиназа B; PVN – паравентрикулярное ядро гипоталамуса; PYY – пептид YY; SGLT1 – натрий-глюкозный котранспортер 1 типа; TMD – трансмембранный домен; АТФ – аденозинтрифосфат; БА – болезнь Альцгеймера; БП – болезнь Паркинсона; ГАМК – гамма-аминомасляная кислота; ГИП – глюкозозависимый инсулинотропный полипептид; ГМ – головной мозг; ГПП-1 – глюкагоноподобный пептид-1; ГПП-1Р – рецептор глюкагон-подобного пептида-1; ГЭБ – гематоэнцефалический барьер; ДПП-4 – дипептидилпептидаза 4; ЖКТ – желудочно-кишечный тракт; СД2 – сахарный диабет 2-го типа; СЖК – свободные жирные кислоты; цАМФ – циклический аденозинмонофосфат; ЦНС – центральная нервная система.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic and progressive metabolic disorder characterized by prolonged hyperglycemia, which increases the risk of developing macro- and microvascular complications. Between 80 and 90% of patients are overweight or obese at the time of T2DM diagnosis, so weight loss and a cardiovascular risk prevention are also key goals of T2DM treatment. At the same time, insulin and widely used drugs from the groups of thiazolidinedione and sulfonylurea derivatives contribute to the weight gain. Glucagon-like peptide-1 receptor (GLP-1R) agonists are incretin mimetics; they improve a glycemic control and are superior to other hypoglycemic drugs in many respects. GLP-1R agonists are recommended as one of the 2nd and 3rd line combination therapy options, primarily for patients with obesity and T2DM, and some (semaglutide and liraglutide) – to reduce the risk of cardiovascular events [1, 2].

Incretin mimetics (GLP-1R agonists and dipeptidyl peptidase-4 inhibitors – DPP-4) are well tolerated and do not cause hypoglycemia, but in 2013 the FDA (U.S. Food and Drug Administration) reported an increased risk of pancreatitis and precancerous cellular changes (metaplasia) of the ducts pancreas against the background of their use. At the same time, recent meta-analyses have shown that the incidence of acute pancreatitis increases with DPP-4 inhibitors, but not GLP-1R agonists. The inhibition of DPP-4 also affects the elimination of substrates other than glucagon-like peptide-1 (GLP-1): glucose-dependent insulinotropic polypeptide (GIP), some cytokines, growth factors and neuropeptides. DPP-4 (also called CD26) is also expressed on the surface of T-cells. Thus, DPP-4 inhibitors may have effects on the immune system and inflammation, which may also be influenced by genetic factors [3].

GLP-1R agonists are currently the drugs the effectiveness and safety of which have been confirmed by many clinical studies. Although they have a number of advantages over hypoglycemic drugs of other groups, a number of features limit their widespread use: nature, a method of production and, obviously, insufficient awareness of doctors and patients about modern antidiabetic drugs.

THE AIM of the work was to review the literature regarding the physiology of GLP-1 and the therapeutic potential and development trends of its agonists.

MATERIALS AND METHODS

The literature search (literature reviews, results of experimental and clinical studies) was carried out using the PubMed, Google Scholar and e-Library abstract databases. The search depth was 23 years – from 2000 to 2023. The list of keywords included (but was not limited to) various combinations and spellings: GLP-1 (GLP-1); GLP-1R agonists; GIP; exenatide; liraglutide; dulaglutide; semaglutide; lixisenatide; albiglutide; taspoglutide. The exclusion criteria included earlier publications and articles that did not directly address the topic of the work. 410 sources were analyzed and, after the systematization, the articles with similar information were removed. After screening, 120 sources were considered suitable for the inclusion in the review.

RESULTS AND DISCUSSION

Discovery of the preproglucagon family hormones

A timeline of major events related to the GLP-1 study is presented in Fig. 1.

At the beginning of the 20th century, when using insulin obtained from pancreatic extracts or in the form of crude preparations, the development of a hypoglycemic effect was preceded by an increase in glycemic levels (peak after 20 min), which was initially associated with a poor purification of the drug. In 1902, Ernest Bayliss and William Starling identified a substance produced by duodenal epitheliaL-cells upon contact with food components. This component stimulated the pancreas to secrete pancreatic juice when it entered the blood and was called secretin. In 1906, Benjamin Moore discovered that a repeated oral administration of porcine intestinal mucosal homogenate reduced glycosuria in diabetic patients, and also suggested that intestinal cells were able of secreting substances that stimulate an insulin secretion. In 1929, Edgard Zunz and Jean Labarre isolated a fraction from the intestinal extracts that reduced glycemic levels when administered to animals. It was called incretin, suggesting the ability to stimulate an insulin secretion. In 1923, Charles Kimball and John Murlin isolated a fraction of the pancreas that, when evaporated and reconstituted in water, had a potent hyperglycemic effect when administered to rabbits and dogs. The substance included in the fraction was called “glucose agonist” or “glucagon”. In 1965, Ellis Samols hypothesized that a glucagon-like intestinal material that stimulates the insulin secretion

might be related to the effect of incretin. The glucagon-like material isolated from the intestines consisted of proteins of several fractions and caused physiological effects opposite to those exerted by glucagon, which had been isolated from the pancreas. The concentration of the glucagon-like material in the blood increased in response to the entry of glucose into the intestine, but did not change when it was administered intravenously. Immunocytochemical studies showed that intestinaL-cells stained with antibodies to glucagon based on morphological and ultrastructural characteristics differed from pancreatic α-cells and were called "L-cells." Later, it was suggested that there is a large precursor molecule, proglucagon, which, during the translation, is split into several fractions differing in size and biological functions. Later, a 42-amino acid polypeptide that was capable of inhibiting gastric motility and hydrochloric acid secretion, was identified. It was named gastric inhibitory peptide or glucose-dependent insulinotropic polypeptide (GIP). It also increased the insulin secretion in a glucose-dependent manner, and its removal from intestinal extracts reduced the incretin effect by approximately 50% [4, 5].

An important discovery in the field of GLP-1R pharmacology was the isolation of exendin-4 (exenatide) by John Eng in 1992. Its clinical use became possible only in 2005 (AstraZeneca, UK). In 2006, Merck & Co (USA) received approval for the clinical use of sitagliptin, the first DPP-4 inhibitor, despite the fact that these enzymes were discovered back in 1966. Just 1 year later, in 2007, the same company registered the first combination drug from the group of incretin mimetics – a drug based on sitagliptin and metformin. In 2009, the first GLP-1R agonist with a high degree of homology to the human protein, liraglutide, appeared on the pharmaceutical market. In 2011, the first combination of an incretin mimetic and a non-hypoglycemic drug – a combination of sitagliptin and simvastatin – was registered. In 2014, incretin mimetics began to be registered for the first time for the indications not related to T2DM: liraglutide was registered as a drug for the treatment of obesity. In 2019, Novo Nordisk brought to the market the first oral GLP-1R agonist, semaglutide [4–6].

Expression of proglucagon family hormones

Preproglucagon (Gcg) is expressed in α-, β-cells of the pancreas, in enteroendocrine L-cells and in the brain [7, 8]. Specific enzymes – prohormone convertases, interacting with cleavage sites in the Gcg molecule, determine which peptide / hormone molecules are formed from it: glycentin (AK 1–69), the associated pancreatic polypeptide (GRPP; AK 1–30); glucagon (AK 33–61); oxyntomodulin (OXM; AK 33–69); the main fragment of proglucagon (MPGF; AK 72–158) and glucagon-like peptides 1 (GLP-1; AK 72–107/108) and 2 (GLP-2; AK 126–158) [9, 10]. These proglucagon fragments significantly influence a systemic metabolism, modulating food intake and satiety (GLP-1, glucagon, oxyntomodulin), maintaining fluid homeostasis (water intake and diuresis, GLP-1) [8, 11], thermogenesis (glucagon), metabolism lipids (GLP-1, glucagon, GLP-2), gastrointestinal motility (glucagon, GLP-1, GLP-2) and gastric emptying (glucagon, GLP-1, GLP-2). Glucagon and GLP-1, formed from the same precursor (preproglucagon, Gcg), are secreted by different cells and have opposite effects on blood glucose concentrations. This is achieved by cell-specific processes that determine a different expression and cleavage of proglucagon into fragments by enzymes from the group of convertases, i.e. prohormone convertase 1 (PC1 or PCSK1 or PC1/3) or 2 (PC2 or PCSK2). PC1 is expressed in brain and intestinal cells, participating in the formation of GLP-1, GLP-2, glycentin, oxyntomodulin and the intermediate peptide IP2. PC2 is expressed in the pancreas and determines the formation of glucagon, pancreatic polypeptide (GRPP), major proglucagon fragment (MPGF) and intermediate peptide (IP1) [4, 12].

The distribution (expression) of these enzymes in tissues is quite conservative under physiological conditions, but can change during hyperglycemia. In particular, the activity and/or expression of PC1 in α-cells (or isolated islets) is detected when cultured in a medium with a high concentration of glucose [13], which also leads to an increase in GLP-1 levels. An increased expression of PCSK1 in α cells leads to an increased production and secretion of GLP-1, an insulin and islet survival [14]. It has been noted that in the mice knockout for the glucagon receptor, the level of GLP-1 in α-cells is higher, therefore such animals are less sensitive to the toxic effects of streptozotocin [15]. Research findings suggest an important role for α cells in compensating for a high functional activity of β cells during the insulin resistance, pregnancy, and a cellular stress by modulating an intraislet GLP-1 production. Some studies note that to maintain adequate functioning of the islet apparatus, a communication

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of α- and β-cells is important, and glucagon, the main peptide, proglucagon-derived peptides (PGDP), being also a GLP-1R agonist, stimulates an insulin secretion, acting on β-cells [12]. In islets isolated from the mice with a β-cell-specific deletion of the glucagon receptor GcgR ($GcgR^{\beta cell-/-}$), a stimulation of the insulin secretion by glucagon is preserved but attenuated by treatment with the GLP-1R antagonist exendin (9–39), and in the islets isolated from GLP-1R knockout mice, a glucagon-dependent insulin secretion is reduced [4, 16].

GLP-1, GLP-2, glucagon, GIP, secretin and somatoliberin belong to the group of structurally related peptides capable of binding to structurally similar receptors of the GPCR class B family. The receptors of this family are named on the basis of its single and unique endogenous ligand (GLP-1, GLP-2, Gcg, GIP and somatoliberin), but under physiological conditions there is no significant cross-reactivity between peptide ligands and receptors of this family [17]. However, in the pancreas, glucagon is known to have a physiologically relevant cross-reactivity with GLP-1R with an EC_{50} of 36.4±0.22 nmol/L, but GLP-1 has no affinity for the glucagon receptor. It can be assumed that the interaction of glucagon with GLP-1R plays an important role for the insulin secretion [4, 18].

Proteins of the GLP-1 family are formed by processing from proglucagon. They differ in their ability to enhance the insulin secretion and are divided into GLP-1 (1–37) (or 1–36 amide), GLP-1 (7–36 amide) (“amidated” GLP-1) and GLP-1 (7–37) (“glycine-extended GLP-1”).

In humans, almost all circulating GLP-1 is one of the truncated forms, ~80% corresponds to GLP-1 (7–36 amide) and ~20% corresponds to the glycine-extended GLP-1 (7–37). The relative abundances of GLP-1 (7–36 amide), GLP-1 (7–37), and GLP-1 (1–37) vary among species. Longer and shorter forms of GLP-1 were found in the textracts of rat intestines and pancreas. GLP-1 (7–36 amide) and GLP-1 (7–37) equally effectively stimulate the secretion of insulin and C-peptide, exceeding the activity of GLP-1 (1–37). GLP-1 (amide 7–36) is rapidly metabolized to GLP-1 (amide 9–36), which is considered a weak partial agonist of the GLP-1 receptor, but relative to its parent structure, its plasma concentration may be five to ten times higher [4, 19, 20].

A cell-type selective Gcg expression is regulated by more than a dozen transcription factors that selectively bind to cis-acting elements in Gcg promoter and enhancer regions to stimulate or inhibit the Gcg expression. In addition to a number of homeodomain proteins, the Gcg expression is also stimulated by protein kinase A (PKA) in response to high levels of cAMP. Insulin stimulates the Gcg expression in the intestine and suppresses it in α cells. Some effectors of the Wnt pathway enhance the Gcg expression in the intestine but not in the pancreas [4, 21].

Glucagon receptor and GLP-1

Typically, all the effects of endogenous GLP-1 are realized through GLP-1R, a transmembrane receptor containing 463 amino acids associated with a G protein (GPCR). Like other class B GPCRs, GLP-1 receptors contain an extracellular N-terminal domain (ECD, an extracellular N-terminal domain or NTD, an N-terminal domain) of more than 100 amino acid residues, and a transmembrane domain (TMD), consisting of seven helices connected by extracellular and intracellular loops. The extracellular N-terminal domain of family B GPCRs contains a common fold stabilized by three disulfide bridges, which is essential for mediating the binding affinity of the receptor to the ligant peptide. GLP-1 binds to both the extracellular N-terminal domain (ECD) and the extracellular half of the TMD. The structure-activity relationship studies of the GLP-1R activation have revealed an extensive interaction of the GLP-1 C terminus with the peptide-binding groove of the N-terminal extracellular domain (ECD) of the receptor. Binding of GLP-1 to the ECD brings the N-terminus of the GLP-1 peptide closer to the TMD, and their interaction causes a conformational change in the helical bundle, allowing an interaction of the intracellular half of the TMD with the G protein. The key insulinotropic effect of GLP-1 through the G-protein coupled receptor B is through the formation of cyclic adenosine monophosphate (cAMP), which, in combination with elevated Ca^{2+} levels, promotes exocytosis of insulin-containing vesicles [20, 22, 23]. In addition to pancreatic islet cells, GLP-1R is also expressed in the brain, kidney, stomach, liver, skeletal muscles, and adipose tissue. In the pancreas, the maximum level of GLP-1R expression is observed in β-cells, less in acinar cells and minimum in ductaL-cells. This receptor was also found in the walls of the kidneys and lungs arteries, the sinus node of cardiomyocytes (limited to the sinoatrial node), and the duodenum (in the Brunner’s gland). A low expression of GLP-1R was noted in parietal and smooth muscle cells of the stomach and in the intestinal plexus [4, 24, 25].

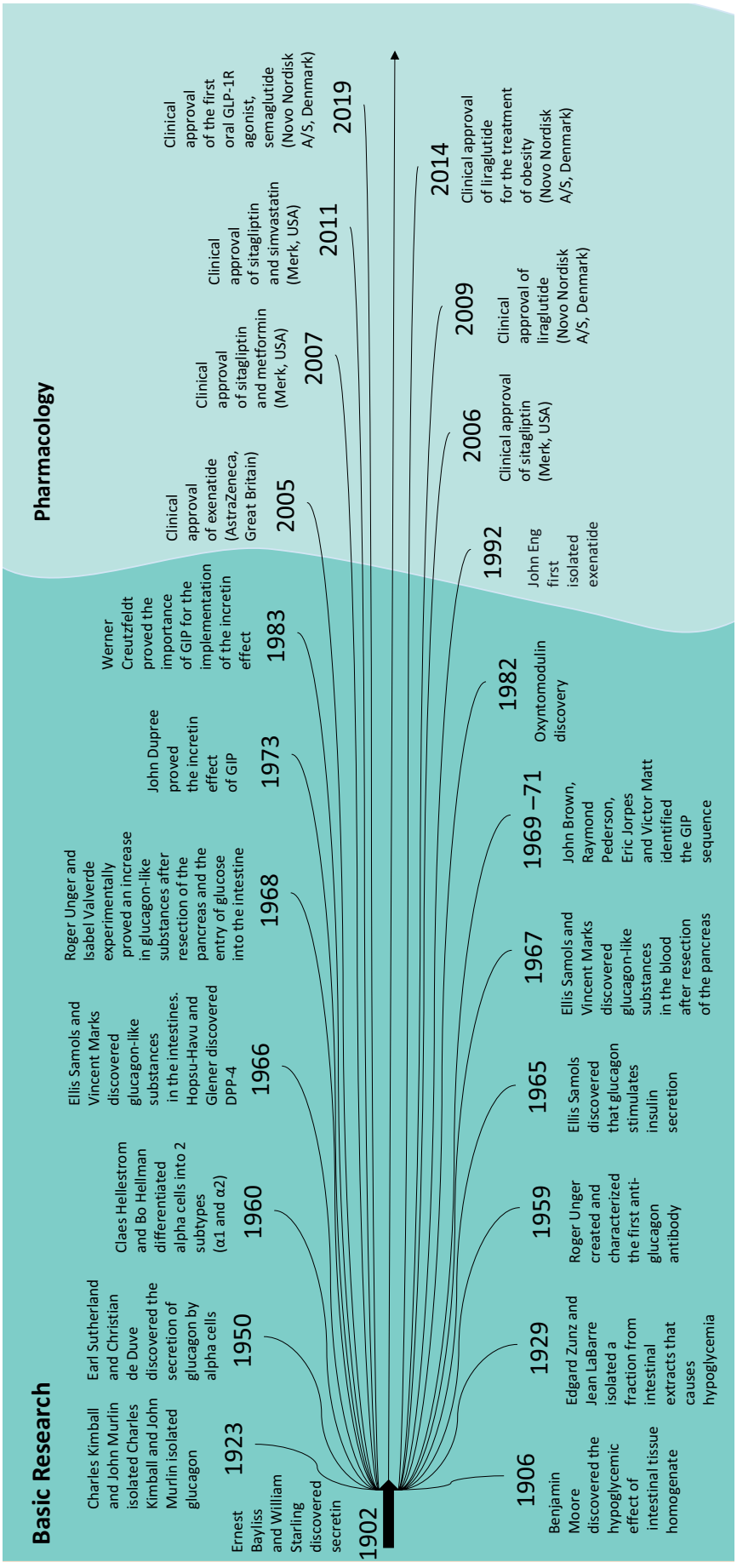

Figure 1 – Key dates of discoveries related to the development of GLP-1R agonists

Note: GIP – glucose-dependent insulinotropic polypeptide; GLP-1R – glucagon-like peptide-1 receptor; DPP-4 – dipeptidyl peptidase 4.

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	Sales volume of agonists GLP-1 (packages, A)			Sales volume of agonists GLP-1 (rubles, B)			Sales volume of agonists GLP-1 (rubles, C)		
Exenatide (Bayeta)	7110 (26.26%)	2786 (1,97%)	827 (0.44%)	31137 (13.57%)	16499 (1.08%)	4887 (0.24%)	4235.0 (10.15%)	6594.2 (11.16%)	8314.5 (9.48%)
Lixisenatide (Lixumia)	507 (1.87%)	86 (0.06%)	17 (0.001%)	1885 (0.82%)	299 (0.02%)	81 (0.001%)	4135.6 (9.91%)	4089.3 (6.92%)	4975.1 (5.67%)
Insulin glargine and lixisenatide (Soliqua SoloStar)	–	3543 (2.50%)	7925 (4.18%)	–	17628 (1.15%)	27586 (1.36%)	–	5006.8 (8.47%)	3679.1 (4.20%)
Liraglutide (Victoza)	19404 (71.68%)	72630 (51.31%)	74408 (39.26%)	194952 (84.99%)	630084 (41.05%)	638013 (31.57%)	10025.2 (24.03%)	8827.2 (14.93%)	9609.2 (10.96%)
Liraglutide (Saxenda)	50 (0.18%)	20097 (14.20%)	29156 (15.38%)	1411 (0.62%)	449220 (29.27%)	648294 (32.07%)	23316.2 (55.90%)	23996.5 (40.60%)	22030.9 (25.12%)
Insulin degludec and liraglutide (Sulfotai)	–	–	23 (0.001%)	–	-	421 (0.02%)	–	–	19362.4 (11.30%)
Dulaglutide (Trulicity)	–	42399 (29.96%)	64258 (33.91%)	–	421130 (27.44%)	575917 (28.49%)	–	10594 (17.92%)	9910.70 (11.30%)
Semaglutide (Ozempic)	–	–	12898 (6.81%)	–	-	126004 (6.23%)	–	–	9804.78 (11.18%)

Figure 2 – Market of GLP-1R agonists in the Russian Federation

Note: the data was officially purchased from the DSM Group, based on them, calculations were made and diagrams were presented; data are presented in Russian rubles.
As of August 1, 2022, 1 US dollar (USD) corresponded to 61.3 Russian rubles (RUB).

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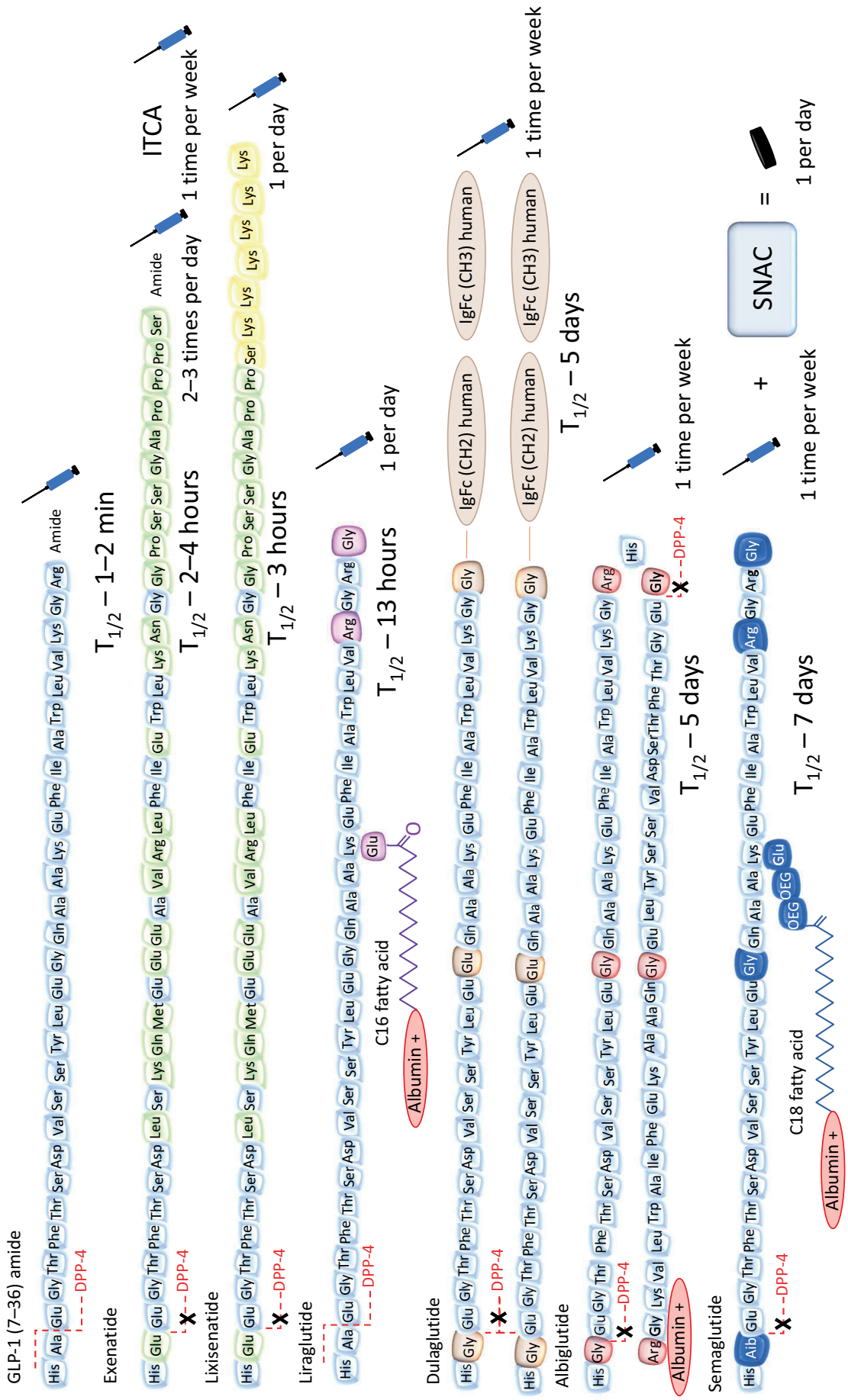

Figure 3 – Structure and features of drugs based on GLP-1 analogues

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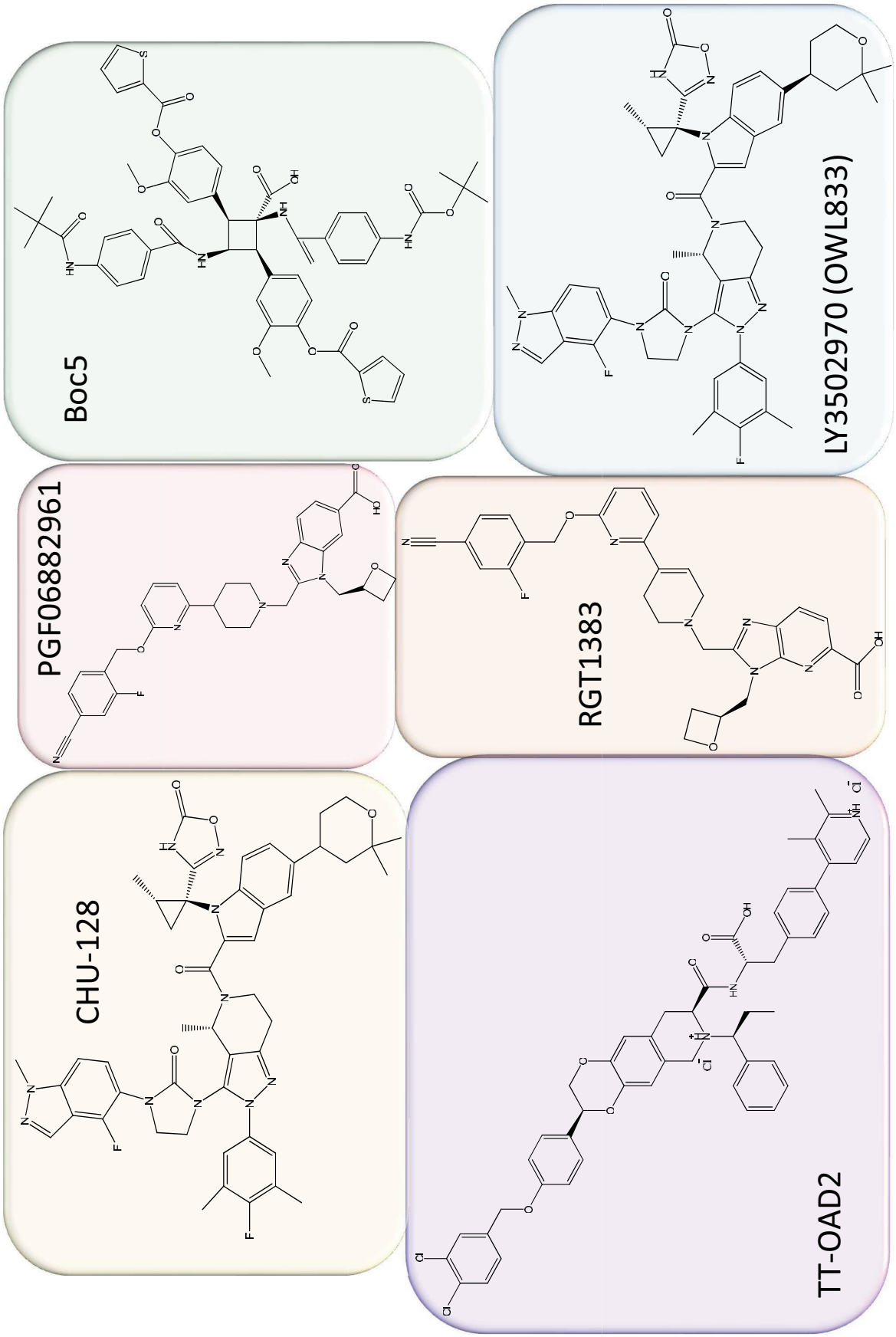

Figure 4 – Structures of non-peptide GLP-1R agonists

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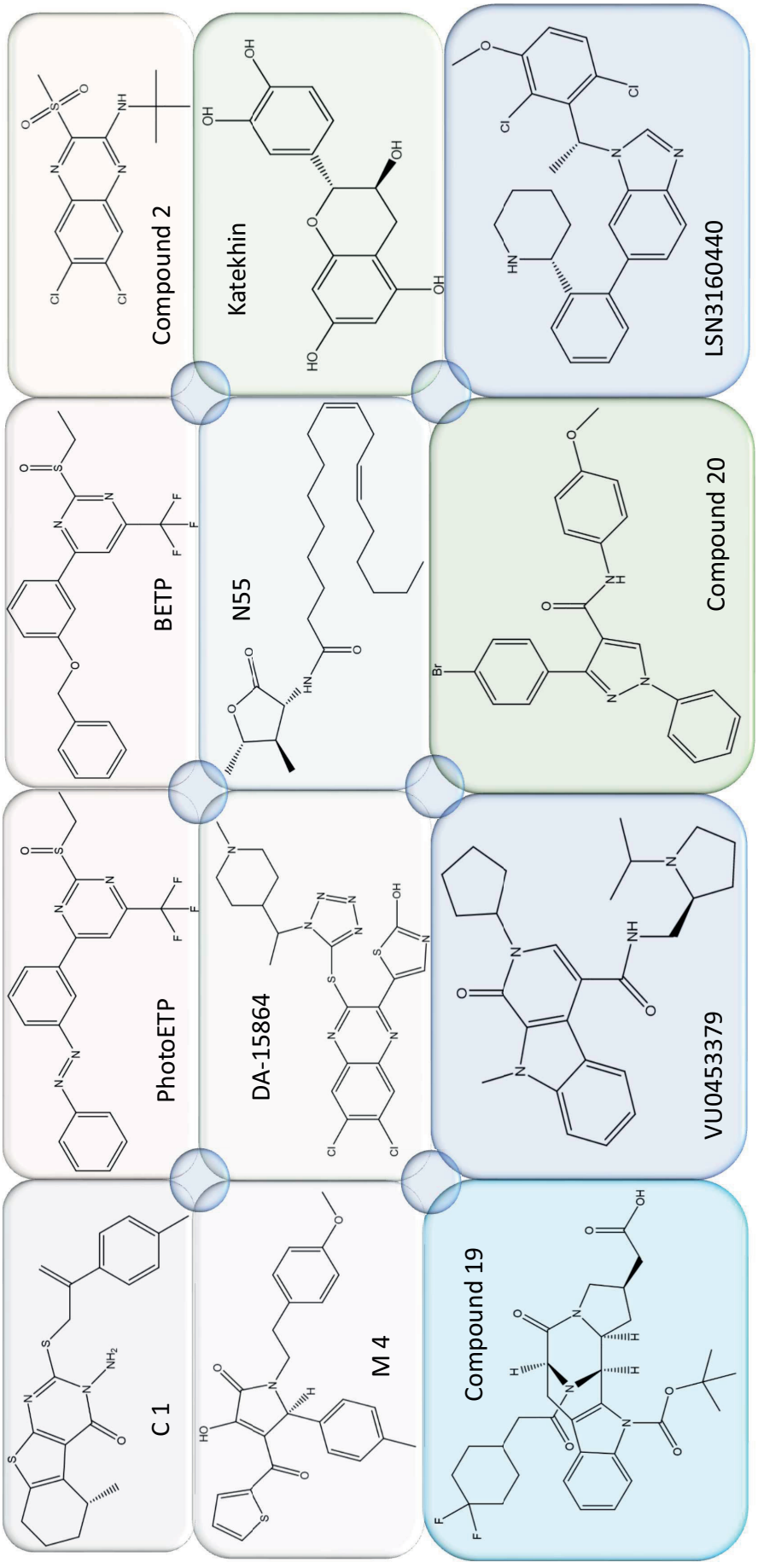

Figure 5 – Allosteric modulators GLP-1R

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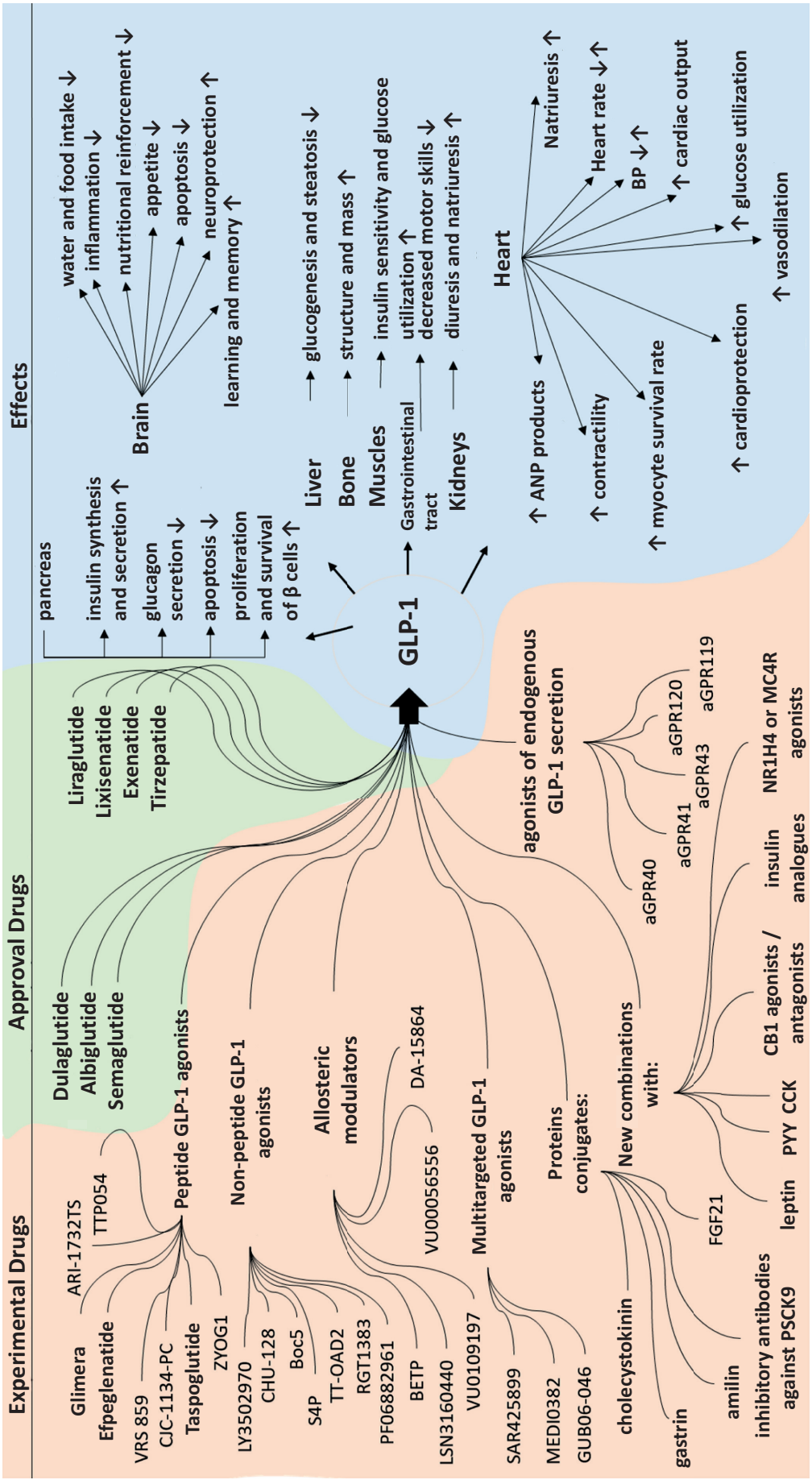

Figure 6 – Approaches to the creation of GLP-1R agonists and their effects
Note: BP – blood pressure; GLP-1 – glucagon-like peptide-1.

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Table 1 – Localization and function of receptors GPR40, GPR41, GPR43, GPR119, GPR120 [35, 36]

Receptor	Localization	Physiological effect upon activation	Agonist
GPR40 (FFA1, FFAR1)	L- and K-cells of the intestine, beta cells of the pancreas	↑ secretion of incretins and glucose-stimulated insulin secretion, improvement of regenerative abilities and ↓ apoptosis of beta cells	medium- and long-chain fatty acids, saturated and unsaturated (C10–C22)
GPR41 (FFA3, FFAR3)	L-cells, monocytes, neutrophils, adipocytes, alpha- and beta-cells	↑ secretion of incretins and leptin, physiological effects have not been fully studied	short chain fatty acids (C3=C4=C5>C2=C1)
GPR43 (FFA2, FFAR2)	L- and K-cells, adipocytes, leukocytes, Alpha- and beta-cells	↑ secretion of incretins and leptin, ↓ intestinal motility, ↑ secretion of GLP-1, ↓ activation of leukocytes, ↓ lipolytic activity in adipose tissue and ↓ plasma levels of free fatty acids; physiological effects have not been fully studied	short chain fatty acids (C2=C3>C4>C5=C1)
GPR119	L- and K-cells, beta-cells	↑ incretin secretion and glucose-stimulated insulin secretion, improved regeneration and ↓ apoptosis of beta-cells	fatty acid amide derivatives and phospholipids
GPR120 (FFA4, FFAR4)	L-cells, adipocytes, macrophages	↑ secretion of incretins, ↑ glucose uptake by adipocytes and acquisition of an anti-inflammatory phenotype by tissue macrophages	medium- and long-chain saturated (C14-C18) and unsaturated (C16–C22) fatty acids

The studies performed on transgenic animals with a controlled expression of green fluorescent protein (GFP) have established the presence of its activity in pancreatic β- and δ-cells, vascular smooth muscles, atrium, gastric antrum, intestinal neurons, vagal ganglia and dorsal roots. [25, 26].

The density of GLP-1R expression in different organs can vary greatly between humans and animals. For example, thyroid C cells in rodents express GLP-1R at very high densities (more than 10 000 times higher than in humans), and a chronic administration of GLP-1R agonists to rodents caused a marked proliferation of thyroid C cells and hypersecretion of calcitonin. It appears that in rodents a gastrointestinal stimulus (gastrin, GLP-1) is required for a normal calcitonin secretion, whereas in humans, this function has disappeared. Numerous clinical studies have reported no increase in the calcitonin secretion or the incidence of C-cell carcinoma during therapy with GLP-1R agonists [19]. However, the labeling of some drugs, such as tirzepatide (a GIP and GLP-1 receptor agonist), contains warnings about the risk of C-cell thyroid tumors in certain categories of patients.

The activation of GLP-1R through Gs stimulates the synthesis of cAMP, through the Gq/11 pathway it increases intracellular Ca^{2+} and through the recruitment of β-arrestin it promotes the activation of the ERK signaling pathway [27, 28]. A ligand-dependent functional selectivity of GLP-1R leading to the launch of signal transduction pathways specific for various ligands (relative to the endogenous hormone), causing diverse cellular responses, has been proven. This was revealed by analyzing a cAMP production, Ca^{2+} accumulation, β-arrestin recruitment and $ERK_{1/2}$ phosphorylation. Exendin-4 (exenatide) and oxyntomodulin, unlike GLP-1, are biased for β-arrestin signaling, which also promotes the cell proliferation and survival through mechanisms involving the $ERK_{1/2}$ activation [27, 28]. This property of GLP-1R is important because different ligands, by modulating specific signaling pathways, can have different pharmacological effects.

GLP-1 secretion

L-cells are distributed with an increasing gradient along the length of the gastrointestinal tract, occurring at low frequency in the duodenum (proximal-distal neuronal and/or humoral signals providing the early phase of GLP-1 secretion during meals), increasing in the jejunum, reaching a maximum in the ileum and colon gut. GLP-1 immunoreactive cells are also located in the gastric mucosa, although in small numbers [7]. The apical surface of the L-cell faces the intestinal lumen and, upon a contact with chyme (with lipids and carbohydrates), secretes GLP-1 [25, 29]. Distal L-cells may play an important role in slowing the passage of chyme as it reaches the ileum and colon through the “ileal brake” mechanism (a negative feedback mechanism for slowing an intestinal transit in response to the increased levels of undigested nutrients in the ileum). This phenomenon is also reproduced by a proximal ileal transposition or the use of α-glucosidase inhibitors, where the exposure of more L-cells to undigested nutrients leads to a greater GLP-1 secretion [7, 30].

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Incretins are broken down quite quickly after the secretion. Within the intestine, 75% of active GLP-1 is destroyed, half of the passing GLP-1 is broken down in the liver, and only 10–15% of active GLP-1 reaches the pancreas [31]. Fasting plasma levels of GLP-1 are in the range of 5–10 pmol/L and increase after meals to 15–50 pmol/L (half-life for GLP-1 is 2 min). The level of GIP in this case varies from 20–30 to 300 pmol/L after a meal, returning, like GLP-1, to the initial level within 3 h (half-life for GIP is 5–7 min) [32].

In the portal vein, total GLP-1 concentrations peak approximately 15 min after an intragastric infusion of a liquid meal and return to the baseline levels within 90 to 120 min. There is a controversy as to whether a glucose-induced GLP-1 secretion is impaired in patients with T2DM, but a clinical trial showed that GLP-1 response to oral glucose was reduced in patients with prediabetes or T2DM, but a meta-analysis of 22 clinical trials did not confirm this [33].

Proteins, fats, and carbohydrates influence the GLP-1 secretion through different mechanisms. Accordingly, more GLP-1 is released after the ingestion of a mixed meal [26].

Effect of carbohydrates on GLP-1 secretion

The cellular mechanisms of a glucose stimulation of the GLP-1 secretion by L-cells partially coincide with the mechanisms underlying the insulin secretion by pancreatic islets. Glucose and fructose dose-dependently increase the secretion of GLP-1 by enteroendocrine cells through a universal mechanism – the closure of ATP-sensitive $K-_{ATP}$ channels, which is accompanied by a membrane depolarization, the opening of voltage-dependent Ca^{2+} channels (VDC), an increase in Ca^{2+} influx and the triggering of vesicular exocytosis with the secretion of GLP-1 into the bloodstream. Sulfonylureas, by inhibiting the $K-_{ATP}$ activity, increase the insulin secretion, but there is no clear evidence that they affect the GLP-1 secretion. In addition, glucose (even in low concentrations) stimulates the electrical activity of L-cells, promoting the secretion of GLP-1 through the induction of small inward currents dependent on the sodium-glucose cotransporter (SGLT1). Sucralose and other sweeteners did not affect the GLP-1 secretion in primary L-cell cultures or in humans [26, 30, 34].

Effect of lipids on GLP-1 secretion

L-cells, like other enteroendocrine cells, react through specific receptors with a decreasing efficiency (as listed) to the following free fatty acids: α-linolenic (C18:3), docosahexane (C22:6), palmitoleic (C16:1), oleic (C18:1), stearic (C18:0) and octanoic (C8:0) acids. In humans, saturated fatty acids are less effective than unsaturated fatty ones. The induction of the GLP-1 secretion by free fatty acids (FFAs) is strongly dependent on the cytosolic Ca2+ concentration. FFAs increase the GLP-1 secretion by stimulating the influx of extracellular Ca2+ through Ca2+ channels on the cell surface [26, 35, 36].

In response to FFA, the secretion of GLP-1 is mediated by receptors for long-chain FFA – GPR40 (FFAR1) and GPR120 (FFAR4), short-chain FFA – GPR41 (FFAR3) and GPR43 (FFAR2), as well as for the derivatives of fatty acid amides and phospholipids GPR119 [37, 38]. In the animals knockout for these receptors, the secretory response of GLP-1 to FFA is significantly reduced, and the use of agonists to different receptors (with different secondary messengers) leads to the development of a synergistic effect on the GLP-1 secretion [26, 27, 30].

Effect of amino acids on GLP-1 secretion

The secretion of GLP-1 can be stimulated by proteins, tri- and dipeptides and amino acids. This was observed in the experiments on the cultures of primary L-cells of the mice colon, in GLUTag cells, the isolated perfused ileum, as well as *in vivo* in mice, rats and humans [26, 39]. Glutamine, asparagine, phenylalanine and glycine have a stimulating effect on the GLP-1 secretion, with glutamine and glycine being the most active. In the studies on NCI-H716 cells, the stimulating effect of leucine, isoleucine, valine, skim milk, casein and whey on the GLP-1 secretion was proven. The release of GLP-1 is stimulated by L-arginine (also an insulin secretagogue), which has been demonstrated in the experiments in the isolated rat intestines and when administered orally. These effects were absent in the GLP-1R knockout mice [26, 30].

In response to proteins or individual amino acids, the stimulation of the GLP-1 secretion is based on the activation of Ca^{2+} calmodulin-dependent kinase II [26], i.e. the peptide-mediated GLP-1 secretion is a Ca^{2+}-sensitive process and involves L cell signaling through the Ca^{2+}-sensing receptor (CaSR) and peptide transporter 1 (PEPT1). The stimulation of GLP-1 secretion from purified murine L-cell cultures by glycine-sarcosine (Gly-Sar) is blocked in the absence of extracellular Ca^{2+} and is inhibited by the treatment of L-type Ca^{2+} channels with nifedipine. The oligopeptide stimulation of GLP-1

release is reduced in cultured L-cells treated with a CaSR antagonist and increased in the peptide transporter 1 (PEPT1)-deficient mice [4, 26].

Effect of endocrine stimuli on GLP-1 secretion

The specific distribution of L-cells in the intestine suggests the existence of a proximal-distal coordination loop in which neuronal and/or endocrine factors arising in the upper intestine, influence the secretion of GLP-1 by L-cells in the distal region [7, 29]. However, the putative shunt (if it exists) is likely important during the early postprandial phase, when L-cells of the distal intestine are not yet in direct contact with nutrients in the intestinal lumen. L-cells are found in close proximity to both enteric neurons and intestinal microvessels [7], suggesting a possible role for a neuroendocrine regulation of the GLP-1 secretion. The presence of the neuroendocrine regulation of the GLP-1 secretion is confirmed by the results of studies in rodents, in which a direct contact of L-cells in this part of the intestine with nutrients in its lumen is excluded. The introduction of glucose or fat into the duodenum of such rodents very quickly causes the secretion of GLP-1 by L-cells at the level comparable to that observed when they were introduced into the ileum [7, 40].

Neurotransmitters from vagal and intestinal neurons (including acetylcholine and gastrin-releasing peptide) increase the GLP-1 secretion. Acetylcholine receptors, including the muscarinic receptors M1, M2, and M3, are expressed in rat L-cells and human NCI-H716-cells. A nonspecific muscarinic receptor antagonist (atropine) or a selective M1 antagonist (pirenzipine) suppressed the lipid-induced GLP-1 secretion in rats, which was not observed for M2 or M3-selective antagonists [7]. In NCI-H716 cells, the GLP-1 secretion is stimulated by bethanechol (an M2 agonist), which is blocked by the pretreatment with pirenzipine or gallamine (an M2 antagonist) [41]. Together, these data indicate the involvement of muscarinic receptors M1 and M2 in GLP-1 secretion by L cells [4,7].

In the isolated perfused porcine ileum, the GLP-1 secretion is inhibited by the administration of norepinephrine. This effect is blocked by the co-infusion of a non-selective α-adrenergic receptor antagonist (phentolamine) [41]. The GLP-1 secretion is stimulated by a β-adrenergic agonist (isoprenaline) and this effect is blocked by the co-infusion of a β-adrenergic antagonist (propranolol) [41]. These data suggest that the intestinal GLP-1 secretion is stimulated by cholinergic and β-adrenergic receptors signaling but they are inhibited by an α-adrenergic receptor activation.

Gastrin-releasing peptide (GRP) is produced and released by GRP-ergic neurons of the intestinal nervous system and also stimulates the secretion of GLP-1, which was blocked by the administration of a GRP antagonist (BW10). The ability of GRP to increase the GLP-1 secretion has been demonstrated in rat L-cell cultures and in rat ileal preparations. Using the isolated perfused canine pancreas, it was found that GRP also directly stimulates the insulin secretion and delays gastric emptying. The GLP-deficient mice had a decreased glucose tolerance, the first-phase insulin secretion, and GLP-1 in response to oral glucose [42].

Thus, the secretion of GLP-1 is carried out by the L-cells located in the proximal small intestine after the hummus has just left the pylorus. Postprandial glucose concentrations may exceed the absorptive capacity of the proximal intestine, resulting in glucose reaching distant L-cells more quickly. Neuroendocrine reflexes may be involved in the regulation of the GLP-1 secretion. The local increase in GIP stimulates the vagal afferent transmission with a subsequent activation of its efferent and intestinal neurons, which release acetylcholine and/or GLP, which stimulate the secretion of GLP-1 from the distal region [7].

Other factors influencing the GLP-1 secretion include the activation of the olfactory receptor OR51E1 by nonanoic acid, which stimulates the secretion of GLP-1 and PYY in L-cells [43]. Ghrelin stimulates the GLP-1 secretion in L-cell cultures. The peripheral administration of ghrelin enhances the glucose-stimulated GLP-1 secretion, which is not observed in the GLP-1R knockout mice and is blocked by the administration of a ghrelin receptor antagonist (GHRP6) [40].

Effects of GLP-1

Insulinotropic effects of GLP-1

Binding of GLP-1 to its receptor in β-cells activates adenylate cyclase, increasing the concentration of cAMP and activating PKA (phosphorylates the SUR1 subunit of K_{ATP}-channels, shifting the balance towards their closure and depolarization of the cell membrane, which leads to the opening of voltage-gated Ca^{2+} channels (VDC) and exocytosis insulin granules), as well as enhancing signaling through metabolic proteins directly activated by cAMP (Epac) [27, 34, 44]. Up to 50% of GLP-1-induced insulin secreted depends on signaling through Epac, members (Epac1 and Epac2; expressed in β-cells) which contain an

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evolutionarily conserved cAMP-binding domain, allowing them to regulate various biological functions in a cAMP-dependent manner. Epac proteins stimulate the release of Ca^{2+} from the endoplasmic reticulum, increasing the insulin secretion by increasing the pool of intracellular Ca^{2+} [27, 44]. During hyperglycemia, the Ca^{2+} influx into β-cells through VDC channels is significantly increased; Epac2 opens RYR Ca^{2+} channels in the endoplasmic reticulum, further increasing an intracellular Ca^{2+} concentration and, consequently, insulin exocytosis. A calcium-induced calcium release (CICR) determines the dependence of the insulinotropic effect of GLP-1 on the glucose concentration. Therefore, in isolated perfused rat pancreas, at the glucose concentrations <2.8 mmol/L, GLP-1 cannot stimulate an insulin release, which changes when it increases (>6.6 mmol/L) [21, 34, 45]. GLP-1-stimulated insulin exocytosis is partially inhibited by a PKA inhibitor (H89) and is completely blocked by the combination of H89 with anti-Epac2 antiserum (cAMP-GEFII) [4, 45].

In addition to the distinct effect of GLP-1 on the insulin secretion, GLP-1R, by activating PKA, stimulates insulin synthesis in β-cells, which probably occurs due to an increase in the expression of Pdx1 (insulin promoter factor 1) [46].

Effect of GLP-1 on β-cell proliferation and apoptosis

As the age increases, the rate of β-cell replication decreases. In the experimental studies, it was noted that GLP-1R agonists increase the β-cell mass by stimulating their proliferation and inhibiting apoptosis [6, 47, 48]. GLP-1R agonists, by activating the transcription factor CREB, stimulate the expression of the insulin receptor substrate 2 (Irs2, a substrate of insulin-like growth factor 1 and insulin receptor tyrosine kinases), which promotes the growth and survival of β-cells. In mice deficient in Irs2 [47], the β-cell destruction and increased apoptosis were observed. They were accompanied by severe hyperglycemia, which was not eliminated even with a long-term administration of exendin-4, which, by enhancing the CREB phosphorylation, improves the Irs2 function. Streptozotocin-induced β-cell apoptosis was reduced by the administration of GLP-1R agonists, which reduced the oxidative stress and increased the β-cell survival by stimulating anti-apoptotic signaling mechanisms – a PI3-kinase-dependent phosphorylation of protein kinase B (PKB), leading to the inactivation of the proapoptotic protein BAD and the suppression of FoxO1 [44, 49, 50]. Thus, after the activation of GLP-1R in the β-cell, multiple signaling pathways are triggered. They can preserve the mass of β-cells under pathological conditions (the activation of PKA, PKB, CREB, the expression of Pdx1 and Irs2, the inactivation of BAD, etc.). However, according to many authors, the inhibition of apoptosis has a greater therapeutic potential, since the β-cell proliferation decreases with the age and is less pronounced in humans compared to laboratory animals [4, 44, 48, 51].

Effect of GLP-1 on glucagon secretion

The GLP-1 receptor is present in only 10% of pancreatic α-cells [25] and most authors are inclined to believe that GLP-1 inhibits the glucagon secretion not through GLP-1R, but through endocrine mechanisms. GLP-1 stimulates the secretion of somatostatin, which, through paracrine mechanisms, reduces the release of glucagon. This effect was blocked by a somatostatin 2 receptor antagonist (CYN154806) [21, 25]. The effect of GLP-1 on the glucagon secretion can be mimicked by forskolin-induced changes in cAMP. Low concentrations of forskolin (1–10 nmol/L) suppress the glucagon secretion by up to 60%, while high concentrations (0.1–10 μmol/L), on the contrary, stimulate it. The PKA inhibitor (8-Br-Rp-cAMPS) attenuates the glucagon secretion-inhibitory effect of GLP-1. The blockade of N-type Ca2+ channels by ω-conotoxin, but not L-type Ca^{2+} channels by nifedipine, reduces the stimulation of the glucagon secretion by glucose and blunts the effects of GLP-1. Thus, GLP-1 may inhibit the glucagon secretion from α-cells through the PKA-dependent modulation of the N-type Ca^{2+} channel activity in addition to the paracrine action of somatostatin [52]. In addition to the above, GLP-1 indirectly suppresses the glucagon secretion due to its insulinotropic effect (increases the secretion of insulin, amylin, zinc and GABA). Insulin inhibits the glucagon release by activating phosphatidylinositol 3-kinase (PI3K). In α-cells, insulin further enhances the translocation of GABA-A receptors, and when released from β-cells, it enhances the inhibition of the glucagon secretion by glucose. Insulin co-crystallizes with Zn^{2+} in the secretory granules of β-cells and is co-secreted with it during hyperglycemia, and in this case, Zn^{2+} plays an important role in the suppression of the glucagon secretion by insulin [4, 51].

Thus, GLP-1 inhibits the glucagon secretion through several mechanisms involving somatostatin, insulin, Zn^{2+}, GABA and amylin. The significant involvement

of the GLP-1 receptor on α-cells in this process is not supported by all authors.

Cardiovascular effects of GLP-1

The expression of GLP-1R has been noted in blood vessels, as well as in the atria, ventricles, endocardium, endothelium, and smooth muscle cells of coronary vessels [25, 32]. Many studies have revealed the cardioprotective effects of GLP-1R agonists, which are associated with improvements in the endothelial function and myocardial metabolism, as well as the cardiomyocyte survival. In a myocardial ischemia-reperfusion injury, the cytoprotective effect of GLP-1 is associated with the activation of a number of RISK-pathway kinases (Reperfusion Injury Salvage Kinase / RISK / Pathway) – protein kinase A, phosphoinositol 3-kinase (PI3K), protein kinase B and $ERK_{1/2}$, which contributed to a decrease in the permeability of the mitochondrial membrane, protecting cardiomyocytes from apoptosis during the reperfusion injury [53]. Some researchers associate a cardioprotective effect with a GLP-1R-mediated activation of the transcription factor Nrf2 (GLP-1R / PKA(PKB) / CREB / Nrf2), which regulates the expression of antioxidant enzyme genes (glutathione-S-transferase, UDP-glucuronyltransferase, heme oxygenase-1 and etc.) [49]. There is a hypothesis about the vasoactive and cardioprotective role of the GLP-1 metabolite, which is not supported by all researchers.

In healthy volunteers, a single administration of GLP-1, its metabolite or exenatide does not affect the blood flow in the mesenteric or renal arteries, but causes vasodilation of the abdominal cavity and internal organs, which underlies the hypotensive effect of GLP-1 [54]. A meta-analysis of 60 clinical studies found that GLP-1R agonists reduced a diastolic blood pressure by 1.84 to 4.60 mmHg. Art. and increase the heart rate by 2–3.35 beats/min [55].

The mechanisms underlying the effect of GLP-1 on the blood pressure, are not fully understood, but may include vasodilation caused by the nitric oxide secretion, the ability to stimulate the urine and sodium excretion through the kidneys [11, 19].

Effect of GLP-1 on food intake and body weight

GLP-1R is expressed at high densities in the frontal cortex, hypothalamus, thalamus, hippocampus, amygdala, cerebellum, and substantia nigra. These regions are key in the central regulation of the energy homeostasis and autonomic functions [56, 57].

In the hypothalamus, the receptor is mainly distributed in the following nuclei: arcuate (ARC, arcuate nucleus of the hypothalamus, associated with the regulation of appetite), lateral (LHA, lateral hypothalamic area – a hunger center), paraventricular (PVN, paraventricular nucleus of the hypothalamus) – secretes oxytocin, which suppresses appetite entering the ventromedial nucleus (VMH, ventromedial nucleus of the hypothalamus – a saturation center), as well as somatostatin – slows down a gastric motility, dorsomedial (DMH, dorsomedial hypothalamic nucleus – regulation of the blood pressure and the heart rate) and suprachiasmatic (SCN, suprachiasmatic nucleus – circadian rhythms) [8, 57, 58].

The receptor is found in the dorsal complex of the vagus nerve, in the nucleus of the solitary tract (NTS, nucleus of the solitary tract) – one of the nuclei of the medulla oblongata, the processes of its neurons are part of the facial, glossopharyngeal and vagus nerves. The NTS is the entry point for sensory nerves from the internal organs, serves as a switch for vagal reflexes and, due to its connections with the hypothalamus, is a link in the formation of appetite. The peripheral administration of leptin or gastric distension activates GLP-1-producing neurons in the NTS [21, 58].

GLP-1R is expressed at a lower density in the periventricular zones: the subfornical organ and *area postrema* (AP, “posteriormost field,” “chemoreceptor zone” of the brain stem, responsible for the gag reflex). As a neuropeptide, GLP-1 can regulate many autonomic and neuroendocrine functions. It has been shown experimentally and clinically that GLP-1, by inhibiting the activity of the vagus nerve, reduces a gastric motility and the secretion of gastric glands and pancreatic juice [7, 57].

The central regulation of food intake by GLP-1 agonists is not limited to GLP-1R signaling in the hypothalamus and hindbrain. GLP-1 also influences the nutrition by affecting areas of the brain involved in reward, motivation, and addiction, such as the ventral tegmental area (VTA), the nucleus accumbens (NAcc, or Nac, *nucleus accumbens,* a group of neurons in the ventral striatum (belongs to the basal ganglia of the brain), involved in the processes associated with reward, pleasure, addiction, aggression, fear and the placebo effect), lateral septum (LS, lateral septum – a brain area connecting CA3 with the ventral tegmental area for communication reward signals with the context in which they arise) [4, 57, 58].

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There are different opinions about the ability of endogenous GLP-1 to cross the blood-brain barrier (BBB). The studies using radiolabeled GLP-1 have demonstrated its rapid uptake by brain through the endothelium that expresses GLP-1R on its surface. Other authors suggest the passage of GLP-1 into the brain tissue in certain areas with an incomplete BBB, i. e. in the area of the periventricular organs of the brain stem, also known for its high density of GLP-1 receptors. A similar tropism was observed with synthetic GLP-1R agonists (liraglutide and semaglutide). Interestingly, at these sites, the agonist accumulation (required for imaging) is lower in GLP-1R knockout animals. Thus, these experiments also reveal the site of the first activation of the agonist receptor. The large molecule GLP-1R agonists (dulaglutide and albiglutide) are expected to have a low ability to cross the BBB, resulting in less central side effects and less influence on appetite. However, the capillary fenestrae in the pancreatic islets appear to be wide enough to provide an access to these large molecules [19, 59].

Mice with global GLP-1R deficiency had a normal body weight and showed no apparent metabolic abnormalities when maintained on a standard *ad libitum* diet, except mild hyperglycemia during fasting and glucose loading. With an experimental nonspecific blockade of GLP-1R, a specific deletion or GLP-1R inactivation in the central nervous system (including only in the nucleus of the solitary tract – NTS), as well as vagotomy, GLP-1 lost its hypophagic effect [7, 58, 60]. In contrast, a direct intraparenchymal administration of subthreshold doses of GLP-1R agonists into the NTS, the ventral tegmental area (VTA), a paraventricular nucleus (PVN), a lateral nucleus (LN), a ventromedial nucleus (VMN), dorsomedial (DMN), nucleus accumbens (NAcc), ventral hippocampus and lateral septum reduces the food intake, which is blocked by the GLP-1R antagonist exendin (9-39) [58, 61]. The anorexigenic effect of liraglutide is blunted by the genetic removal of GLP-1R from glutamatergic neurons, but is completely preserved when it is removed from GABAergic neurons [62].

The administration of GLP-1R agonists causes the neuronal activation (measured by the cFos activation) in the paraventricular nucleus (PVN), amygdala, area postrema (AP), nucleus tractus solitarius (NTS), and arcuate nucleus (ARC) [7, 51]. The GLP-1R-induced neuronal activation is accompanied by an increased phosphorylation of PKA and MAPK with a corresponding decrease in the AMPK activity (which increases during fasting, inhibits glycolysis, and stimulates food intake). At the same time, the PKA / MAPK activity inhibition by the administration of Rp-cAMP or UO126 weakens the effects of GLP-1R agonists [56, 63].

The activation of GLP-1R inhibits a variety of reward-related behaviors in rodents, such as the amphetamine-associated operant behavior, alcohol consumption and seeking, and place preference (Amp-CPP) test. This is not observed in mice with a CNS-specific deletion of GLP-1R [57, 64]. The activation of the nucleus accumbens (NAcc) by GLP-1R reduces food intake by reducing food palatability. Fed rats given a choice between a regular or high-fat diet and given exendin-4 preferred the regular diet [60]. The injection of exendin (9–39) into the NAcc increases the amount of the energy-dense food eaten and increases the frequency of licking during the first meal, which is an indicator of strong palatability [51, 57, 58, 65]. Thus, GLP-1R agonism reduces homeostatic and hedonic feeding, and modulates food intake not only through the hypothalamus and hindbrain, but also through signaling in the mesolimbic system, in which the GLP-1R activation influences the behavior related to reward and taste perception. .

A direct electrical stimulation of the nucleus tractus solitarius (NTS) induces glutamatergic excitatory postsynaptic currents (EPSCs) in Gcg^+ positive neurons. Leptin induces a rapid depolarization of Gcg+ neurons in the NTS, as detected by voltage and current measurements in the whole-cell horizontal or coronal sections of the brainstem, impairing its ability to directly stimulate the central GLP-1 secretion. Hindbrain Gcg^+ neurons do not have GLP-1R and cannot be directly activated by GLP-1. The administration of PYY, melanotan II, or ghrelin did not stimulate these neurons in isolated NTS brain slices, but they responded to the stimulation by leptin, cholecystokinin, and epinephrine [8, 66]. The leptin receptor expression was detected in GLP-1-secreting NTS neurons. This may mean that peripheral endocrine stimuli (e.g., leptin), through this mechanism, may trigger the central activation of GLP-1-secreting NTS neurons.

A cholecystokinin-induced activation of NTS Gcg^+ neurons is blocked by the glutamate receptor antagonist (DNQX) or the inhibition of the α1-adrenergic signaling [66], these neurons perceive various peripheral signals and, in response to them, regulate the energy balance. A permanent blockade of GLP-1R in the central nervous system or its viral knockdown is accompanied by an increase in body weight in rats, while a chemogenetic stimulation of Gcg^+ neurons, on the contrary, caused

a decrease in food consumption [67]. An acute chemogenetic inhibition of these neurons did not increase food intake, but did increase it after stress-induced hypophagia [68]. Thus, glutamatergic GLP-1-producing neurons in the NTS are activated by a number of peripheral signals and regulate many aspects of feeding behavior.

Effect of GLP-1 on energy homeostasis

Non-shivering thermogenesis requires a functional brown adipose tissue, so it is reasonable to believe that GLP-1R contributes to the control of the energy expenditure by regulating the activity of brown adipose tissue through the receptors in the CNS, since it is expressed in brain nuclei involved in the control of brown adipose tissue metabolism. The administration of GLP-1 into the dorsomedial nucleus of the hypothalamus (DMH) increased thermogenesis in brown adipose tissue, and the disruption of local GLP-1R expression on rat DMH neurons led to an increase in body weight, which was accompanied by a decrease in the heat production by brown adipose tissue [58, 69].

Thus, GLP-1Rs of brain are involved in the control of the energy expenditure, primarily by regulating food intake and also regulating the energy expenditure. But the studies of these GLP-1 effects are limited due to their low penetration ability through the BBB and their distinct effect on the appetite and gastrointestinal motility, as well as the physiology of GLP-1R in rodents.

Effect of GLP-1 on gastric emptying

The activation of GLP-1a leads to a decrease in gastric motility and the hydrochloric acid secretion, both when administered peripherally and centrally. The observed effect was not reproduced in GLP-1R knockout mice, or after vagotomy in humans, and blocking the GLP-1 receptor, on the contrary, led to the accelerated gastric emptying [63]. However, with a long-term administration, GLP-1R agonists have a reduced effect on gastric motility due to developing tachyphylaxis [70].

Effect of GLP-1 on hypothalamic-pituitary-adrenal axis

Nucleus tractus solitarius (NTS) neurons are involved in regulating the hypothalamic-pituitary-adrenal axis in response to stress, and GLP-1R signaling in the brain plays an integral role in the acute CNS response to stress. Preproglucagon-positive NTS neurons have dense projections to the PVN area of the hypothalamus, where they innervate corticoliberin-releasing neurons [4, 51, 57, 58]. GLP-1R is also expressed in PVN neurons, which are colocalized with corticoliberin [71]. The administration of GLP-1 into the CNS of rats and mice activates the hypothalamic-pituitary-adrenal axis and increases the corticosterone secretion. In rodents and humans, peripherally administered GLP-1R agonists transiently stimulate the hypothalamic-pituitary-adrenal axis and increase concentrations of corticosterone, aldosterone, and ACTH [59]. Mice with a PVN-selective deletion of GLP-1R have an impaired stress-induced activation of the hypothalamic-pituitary-adrenal axis, which prevents stress-induced weight loss, reduces cardiovascular responses and anxiety [71]. The combined administration of dexamethasone and exendin-4 leads to a greater anorexigenic effect and weight loss than the GLP-1 agonist alone. By the administration of anti-dopamine-β-hydroxylase-saporin (DSAP), the ablation of catecholamines in hindbrain neurons blunts the ability of exendin-4 to increase the corticosterone secretion but potentiates the hypophagic effect of exendin-4.

Effects of GLP-1 on learning, memory and neuroprotective effects

The GLP-1 receptor is expressed in the hippocampus, an area of the brain involved in spatial learning and memory. The central GLP-1R agonism improves some aspects of learning and memory in the Morris water maze and increases latency in the passive avoidance test. The improvement in learning and memory by the GLP-1 administration is blocked by the pre-administration of exendin (9–39) and is absent in GLP-1 receptor-deficient mice [72].

Central GLP-1R signaling is neuroprotective. GLP-1 and exendin-4 enhance the differentiation and neurite outgrowth in rat pheochromocytoma (PC12) and human neuroblastoma SK-N-SH cells. The effect of GLP-1R agonists is blocked when PC12 cells are co-incubated with exendin (9–39). GLP-1 and exendin-4 protect cultured hippocampal neurons from glutamate-induced apoptosis [56, 73]. The duration and severity of seizures induced by the systemic administration of the neurotoxin kainic acid was greater in GLP-1R knockout mice than in wild-type mice and shorter in the mice that had undergone the targeted restoration of the GLP-1R expression in the hippocampus using an adeno-associated virus (AAV).

The neuroprotective effects of the central GLP-

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1R agonism are mediated by the ability to increase the formation of cAMP and enhance the activation of PI3-kinase and ERK. The GLP-1R agonism increases cAMP levels in cultured hippocampal neurons and PC12 cells. The pharmacological inhibition of either PI3-kinase or ERK blocks the stimulatory effect of GLP-1 and exendin-4 on neurite outgrowth in PC12 cells. In PC12 cells, the stimulation of the axonal growth by GLP-1 is partially suppressed by the PKA inhibitor (H89), suggesting the cAMP-mediated activation of PI3K and ERK after the GLP-1R agonism and is not entirely dependent on PKA signaling [56].

The impaired insulin sensitivity may be a causative factor in the neurodegeneration in Huntington's disease patients [74]. The overexpression of mutant huntingtin protein disrupts insulin signaling and stimulates neuronal apoptosis in human neuronal SK-N-MC cells, and liraglutide improves the insulin sensitivity and increases the viability of such cells by mechanisms including: reducing neuronal glucotoxicity, oxidative stress and mutant protein aggregation through the stimulation of AMPK-mediated autophagy [73, 74].

In a neurodegeneration rat model, GLP-1 and exendin-4 reduced an ibotenic acid-induced depletion of cholinergic neurons of the basal forebrain, which was reflected in the greater preservation of the choline acetyltransferase immunoreactivity of these cells. The administration of GLP-1R agonists into the hippocampus prevents learning and memory impairment caused by the administration of amyloid β [75]. GLP-1R agonists, when administered to mice, reduce the progression of Alzheimer's disease (AD) [76, 77]. In asthma, a glucose transport across the BBB is reduced, and a 6-month administration of liraglutide in asthma patients largely neutralized this process [78]. In another study, a 12-week treatment with liraglutide in the patients at risk of AD did not affect cognitive processes, as no differences had been noted between cohorts [79]. Clinical studies of the neuroprotective effects of GLP-1R agonists in AD are ongoing [80].

GLP-1 analogues have shown some effectiveness in the treatment of Parkinson's disease (PD), which is characterized by the degeneration of dopaminergic neurons, which is experimentally achieved by administering the dopaminergic neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). In the mice treated with this toxin, a 7-day infusion of exendin-4 into the lateral ventricle significantly reduced the damage to the dopaminergic system and the development of motor disorders [81]. Similar neuroprotective effects of GLP-1 agonists have been noted in various models of PD [82]. In primary cultures of neurons treated with the dopaminergic toxin 6-hydroxydopamine (6-OHDA), exendin-4 increased their survival and levels of tyrosine hydroxylase, a key enzyme in dopamine synthesis [81]. Several clinical studies have confirmed the ability of GLP-1R agonists to improve clinical symptoms of PD, as well as motor and cognitive functions [83].

The administration of liraglutide or semaglutide in a model of ischemia-reperfusion injury of the brain led to a dose-dependent reduction in the infarct size by up to 90% (and, accordingly, a neurological deficit after 24 hours) after a 90-minute (a moderate severity of ischemia) occlusion of the middle cerebral artery. However, a preliminary administration of the GLP-1R antagonist exendin (9–39) reduced the protective effect of the drugs, and the neuroprotective effect of GLP-1 agonists was significantly reduced when choosing a more severe type of ischemia – for 120 or 180 min [84].

Effect of GLP-1 on water intake and kidney function

In humans, GLP-1R has been identified in proximal tubule cells and preglomerular vascular smooth muscle cells. GLP-1 has a dose-dependent effect on the renal function by reducing water intake and stimulating a urine and sodium excretion (stimulation of proximal tubular natriuresis) for a short time after its intracerebroventricular or intraperitoneal administration. Moreover, the effect was centrally mediated and did not depend on food intake, and was blocked by exendin (9–39). GLP-1 probably induces natriuresis and diuresis by inhibiting sodium-hydrogen exchanger 3 (NHE3), located on the brush border of renal proximal tubular cells. This effect may partly explain the hypotensive effect of GLP-1R agonists. Through the modulation of cAMP/PKA signaling, GLP-1 influences the inflammation, including the kidney and blood vessels, likely protecting the kidney from the oxidative damage [11, 85].

In clinical trials, GLP-1R agonists primarily reduced the incidence of albuminuria in the absence of a clear evidence of an effect on severe renal outcomes [11, 19, 85].

Effect of GLP-1 on bone tissue

In addition to glucose homeostasis, incretins are involved in the regulation of the energy-consuming

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process of bone remodeling: they inhibit the resorption and stimulate the bone tissue formation. The existence of an enteroendocrine-bone axis is indicated by the accumulated data on the influence of factors such as long-term parenteral nutrition, bariatric surgery, and a hereditary dysfunction of the GIP on the incidence of osteoporosis [30, 86]. In the animals' knockout for receptors for two incretins, $GIPR^{-/-}$ and $GLP\text{-}1R^{-/-}$, a decrease in the bone strength and a slowdown in collagen synthesis were observed [87].

The GLP-1 receptor is expressed in some human osteoblast cell lines (MG-63 and TE-85), which, however, has not been observed for the Saos-2 line. At the same time, GLP-1 increased the viability of MG-63 and TE-85 cells. GLP-1 receptor knockout mice suffer from osteopenia and have increased skeletal fragility. Liraglutide slowed bone loss in the rats with glucocorticoid-induced osteoporosis and in ovariectomized diabetic rats. It should be noted that, unlike in humans, in rodents, the activation of GLP-1R in thyroid C cells promotes the release of calcitonin, which inhibits the bone resorption. This somewhat reduces the translational potential of the studies results of GLP-1R agonists obtained at the preclinical stage [86]. GLP-2, which is co-secreted with GLP-1, also plays an essential role in functioning of the enteroendocrine-bone axis. The GLP-2R receptor (GLP-2R) is widely expressed in human osteoclasts and can regulate their activity. In clinical studies, GLP-2 was shown to reduce markers of the bone resorption in healthy and postmenopausal women [10, 86].

Most of the data in the literature are on the GIP effect on bone tissue remodeling. It dose-dependently reduced the differentiation and the bone resorptive activity of murine and human osteoclasts and also inhibited the parathyroid hormone-induced increase in the bone resorption. GIP also reduced apoptosis in the human bone marrow mesenchymal stem cells and Saos-2 osteoblastic cells. The administration of GIP to healthy people led to a decrease in the level of type I collagen C-telopeptide (CTX I), a marker of the bone tissue resorption, and an increase in the level of type 1 procollagen N-terminal propeptide (P1NP), a marker of the bone matrix formation. Thus, GIP may have an anabolic effect on the bone in addition to the inhibiting bone resorption [86].

GIP and GLP-2 are key regulators of postprandial bone remodeling in humans in the enteroendocrine-bone axis. Their combined administration to healthy people resulted in an additive reduction in the bone resorption, exceeding the effect of each hormone separately. Coagonists of the GIP and GLP-2 receptors being developed are considered a promising approach for the treatment of osteoporosis [9], but currently published results are contradictory. Thus, the GIP/GLP-1/GLP-2 receptors may become promising pharmacological targets for the prevention of fractures in the patients with osteoporosis and possibly also other bone diseases, such as patients with diabetes [88].

Pharmacology of GLP-1

In the structure of the pharmaceutical market of hypoglycemic agents in the Russian Federation, GLP-1R agonists in 2016 accounted for 0.09% (27 071) in packages and 2.3% (229.3 million) in rubles, and in 2019 and 2020, these figures were significantly higher than 0.3% (141 541), 4.41% (189 512) and 8.55% (1.5 billion), 10.56% (2 billion), respectively (Fig. 2 A, B). Moreover, the cost of such drugs is the highest on the market (Fig. 2 B). It should be noted that in 2016 there were only 4 drugs on the market – exenatide (Bayeta®, Astra Zeneca, UK), lixisenatide (Lixumia®, Sanofi, France), liraglutide (Victoza® and Saxenda®, Novo Nordisk A/S, Denmark), and in 2020, dulaglutide (Trulicity®, Eli Lilly and Company, Switzerland), semaglutide (Ozempic®, Novo Nordisk A/S, Denmark) and combinations with insulin analogues (degludec or glargine) were added. Considering the data presented (Fig. 2), the market for hypoglycemic drugs containing GLP-1R agonists can be considered rapidly developing. Currently, the modification of degradation-resistant GLP-1R agonists is mainly aimed at improving pharmacokinetic parameters.

GLP-1R agonist drugs

Exenatide is a synthetic peptide of 39 amino acids (Fig. 3) (first discovered as exendin-4 in the saliva of the Arizona common snake *(Heloderma suspectum),* the first 30 of which are 53% homologous to the mammalian GLP-1. Exenatide has glycine at the second amino acid position. on the N- end, which protects the peptide from the DPP-4-mediated degradation and inactivation. They also differ in a number of amino acids in the central and C-terminal domains, which include Leu10, Lys12, Gln13, Met14, Glu16, Glu17, Tyr19, Arg20, Leu21, Glu24, Lys27, Asn28 and Gly30. The C terminus of exendin-4 is 9 amino acids larger than GLP-1, which maintains the secondary structure through a tryptophan cage formation and increases the selectivity for GLP-1R [89–

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91]. The exendin-4 of half-life in rats is 18–41 minutes after intravenous, 125–174 min after intraperitoneal and 90–216 minutes after the subcutaneous administration, its bioavailability is higher than that of GLP-1 (7–36 amide) and GLP-1, plasma clearance is 4–8 ml/min. The mode of application is twice a day. Amylin Pharmaceuticals has developed a once-weekly formulation of exenatide under the brand name Bydureon® (AstraZeneca, marketed since 2012). In this formulation, exenatide is formulated in a sustained-release microsphere containing a 50:50 poly(D,L-lactide-glycolide) polymer (37.2 mg per dose) along with sucrose (0.8 mg per dose) [6, 90, 92].

At the time of its introduction, exenatide was a promising treatment for T2DM, the significant drawback of which was the requirement for 2 daily injections. Therefore, Intarcia Therapeutics developed the ITCA 650 device – an osmotic mini-pump the size of a match (4x44 mm), implanted subcutaneously into the abdominal wall and delivering microdoses of exenatide into the body for up to 6 months. Four clinical trials showed significant reductions in HbA1c and body weight, but the FDA denied its approval in 2017 due to manufacturing issues [6, 90], and in 2021, the FDA again denied the approval for this approach due to the increased risk development of vascular diabetes complications on the use of ITCA 650.

VRS 859 (exenatide-XTEN, Versartis Inc., USA) is a combined protein, with a uniform and stable absorption, containing exenatide and a hydrophilic end of 864 amino acids (XTEN technology, Amunix Inc), which increased the half-life from 2.4 to 139 h in humans and should theoretically lead to the long-lasting glycemic control [90]. The studies of this compound in mice have shown that after the intraperitoneal administration of the drug at a dose of 120 nmol/kg, the glucose tolerance persists for up to 48 hours (after the administration of exenatide, a similar improvement lasts up to 1 hour). It is suggested that a single subcutaneous dose of 100 mg of VRS-859 can provide plasma drug levels sufficient to provide a glycemic control for 1 month [92].

Efpeglenatide (HM11260C, Langlenatide, LAPS-Exendin, LAPS-Exd4). In this drug, exendin-4 is coupled to the non-glycosylated Fc fragment of human immunoglobulin through a non-peptide linker (unlike dulaglutide, which has only one peptide variant fused to the Fc carrier) to reduce the immunogenic potential. Efpeglenatide has a half-life of >150 h and is in phases II and III of clinical trials (a weekly or monthly dosage) [90]. In obese nondiabetic patients, in a 20-week study, efpeglenatide (4, 6, 8 mg once every 7 or 14 days) significantly reduced body weight (6.2–7.8 kg *vs* placebo –0.8 kg), no serious adverse events were observed [6, 51].

Albenatide (CJC-1134-PC, ConjuChem, USA) is exendin-4 linked to the C-terminus of recombinant human albumin, forming a special conjugate complex (Preformed Conjugate-Drug Affinity Complex, PC-DAC) through a linker with a maleimide terminal, which is used for a chemical conjugation with a single cysteine residue in albumin. In humans, the half-life of CJC-1134-PC is approximately 8 days. The results of clinical trials have not yet been published [6, 31, 92].

Thus, despite the fact that exenatide was the first registered drug from the group of GLP-1R agonists and its relatively small similarity (in terms of the amino acid sequence) with the human hormone, it continues to be studied and modified, new dosage forms / combinations are being developed; they prolong and simplify its application and increase its efficiency.

Lixisenatide is an analogue of exenatide in which the proline at position 38 is omitted and six consecutive lysine residues with pharmacokinetic characteristics comparable to exenatide, are added to the C-terminus. Used once a day; increasing the administration frequency does not increase the effectiveness of a hyperglycemia control [6, 92]. In Russia, a fixed combination solution for a subcutaneous administration of lixisenatide (33 and 50 μg/ml)+insulin glargine (100 U/ml) is registered.

Liraglutide is designed on the native GLP-1 sequence (7–37) with a (conservative) substitution of lysine at position 28 for arginine. At the second position from the N-terminus, alanine is retained, but the lysine at position 20 is linked through a gamma-glutamic acid spacer to palmitic acid (C16:0), which, by binding to albumin, makes the drug less sensitive to DPP-4 proteolysis. Liraglutide is 97% homologous to GLP-1. The molecule modification contributed to the increased bioavailability, and its half-life increased to ~ 12 h. Used once daily at doses of 0.6–1.8 mg/day, and at a dose of 3 mg/day, liraglutide has been approved for the treatment of obesity since 2014 [92 ,93].

Semaglutide is an analogue of liraglutide, 94% homologous to GLP-1. The DPP-4-sensitive alanine at the second N-terminal position in liraglutide is replaced by aminoisobuturic acid (Aib), and the palmitic (C16:0) fatty monoacid in liraglutide is replaced by dicarboxylic

stearic acid (C18:0). These chemical modifications extend the half-life of semaglutide to 160 hours. It is used once a week. High-dose semaglutide is undergoing clinical trials for efficacy in obesity without T2DM. Based on semaglutide, the first oral GLP-1R agonist was created – drug Rebelsas® (Novo Nordisk A/S, Denmark), the effects of which are comparable to GLP-1R agonists administered subcutaneously. To facilitate the absorption in the gastrointestinal tract (to increase lipophilicity) and protect the peptide drug from the enzymatic destruction, the absorption enhancer N-(8-[2-hydroxybenzoyl]amino) sodium caprylate was used [89, 93].

Dulaglutide consists of two identical disulfide-fused GLP-1 molecules that are linked by a polypeptide chain (glycine and serine spacer) to a heavy chain fragment (Fc) of modified human immunoglobulin G4 (IgG4) to reduce an immunogenic potential. The GLP-1 fragments of dulaglutide are 90% homologous to the native one (some fragments of native GLP-1 are replaced by parts of exendin-4). Glycine at the second N-terminal position protects the molecule from DPP-4 inactivation, while glutamic acid at position 16 stabilizes the secondary structure and improves its potency. The glycine substitution at position 30, along with the native glycine at the C terminus of GLP-1 (7–37), serves as a leading sequence for the spacer that anchors the Fc fragments of IgG4. Such modifications improve the bioavailability, slow down the renal clearance and reduce the immunogenic potential. It is to be used once a week [6, 92].

Albiglutide is a head-to-tail tandem of two GLP-1 molecules, in which the C-terminus of the first molecule is fused to the N-terminus of the second. Each of the two GLP-1 molecules is replaced by glycine in the DPP-4-sensitive fragments. The C-terminus of the second GLP-1 is covalently fused to human albumin, which slows down renal clearance, increasing the half-life to ~120 h in humans [92]. It is to be appied once a week.

Taspoglutide (R1583/BIM51077; Hoffmann-La Roche, Switzerland) is a long-acting analog of human GLP-1 containing aminoisobutyric acid, 10% (Aib 8–35) of human GLP-1 (7–36 amides) with 93%. homology to the native polypeptide. In a phase III study, it effectively reduced HbA1c and body weight when administered weekly subcutaneously at doses of 10 and 20 mg. However, undesirable reactions such as nausea, vomiting and allergic manifestations occurred more often than when taking exenatide at a dose of 10 mcg twice a day. The development of taspoglutide was discontinued in 2010 [89].

Glymera (Glymera, PB1023, PhaseBio Pharmaceuticals, USA) is a recombinant analogue of GLP-1, a polypeptide consisting of 636 amino acids, genetically fused with a physiologically inert polymeric elastin-like peptide of E. coli, and is administered subcutaneously once a week (in phase III clinical trials). The efficacy of weekly doses (50, 70 and 100 mg) was compared with once-daily liraglutide and placebo in a phase IIb study (600 patients with T2DM, 20 weeks). The effectiveness of the glymera administration was inferior to liraglutide [90].

Common adverse reactions to GLP-1 analogs are nausea, vomiting, and diarrhea. These effects are dose-dependent, and in some cases are perceived as potentially beneficial by reducing meal frequency and quantity, thereby promoting weight loss. Compared with short-acting GLP-1 analogues (such as exenatide), long-acting ones are less likely to cause nausea and vomiting, but more often cause diarrhea [51].

In the literature, there is also limited information about the developed peptide GLP-1R agonists ZYOG1 (Zydus Cadila, India) and ARI-1732TS (Arisaph Pharmaceuticals, USA), the studies of which are at phase 1 and the preclinical stage, respectively [90].

According to the information available in the State Register of Medicines, the following GLP-1R agonists and their combinations – INN (trade name – name of the holder or owner of the registration certificate of the medicinal product) are registered in Russia:

– exenatide (Bayeta®, Astra Zeneca, UK);

– lixisenatide + insulin glargine (Soliqua SoloStar®, Sanofi Winthrop, France);

– liraglutide (Victoza®/Saxenda® – Novo Nordisk A/S, Denmark; Quinliro® – Biokhimik JSC, Russia; Enligria® – Promomed Rus LLC, Russia);

– liraglutide+insulin degludec (Sultophy® – Novo Nordisk A/S, Denmark);

– dulaglutide (Trulicity® – Swix Healthcare LLC, Russia);

– semaglutide solution for the subcutaneous administration; (Ozempic® – Novo Nordisk A/S, Denmark; Quincenta® – Promomed Rus LLC, Russia; Semavik® – GEROPHARM LLC, Russia),

– semaglutide tablets (Rebelsas® – Novo Nordisk A/S, Denmark).

As part of the import substitution of foreign drugs with Russian analogues, GLP-1R agonists are of great

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interest to domestic pharmaceutical companies. A particular attention is drawn to the most studied drug, liraglutide, as well as semaglutide, a GLP-1R agonist with a long period of action [94, 95]. At the same time, as for liraglutide, taking into account a relatively small size of the peptide and its lack of tertiary structure, it is considered expedient to produce API through chemical synthesis, which is assessed as a highly productive, scalable and commercially viable process that can produce a high-purity product. The results of a comparative study of liraglutide obtained in this way (Enligria®, a solution for a subcutaneous administration 6 mg/ml, Promomed RUS LLC, Russia) showed similar to the original drug (Saxenda®, a solution for a subcutaneous administration 6 mg/ml, Novo Nordisk A/S, Denmark) physicochemical and biological properties [94].

Non-peptide GLP-1R agonists

As stated above, the activation of GLP-1R by endogenous GLP-1 requires an extensive action on the receptor complex, including the interaction of the C terminus of GLP-1 with the peptide-binding groove of the N-terminal extracellular domain (ECD) of the receptor, followed by the approach and interaction of the N terminus of the peptide GLP-1 with a transmembrane domain (TMD). This allows the interaction of the intracellular half of the TMD with the G protein, a signal transmission, and ultimately leads to exocytosis of insulin-containing vesicles. Mimicking the initial multiple extensive interactions with the ECD and TMD of the GLP-1 receptor seemed unrealistic for non-peptide small molecules, for which, in addition, different features of interactions with the receptor complex had been proposed [20, 22, 23]. However, several non-peptide agonists are currently in clinical trials: PF 06882961 (Pfizer, USA), TTP-273 (vTv Therapeutics/Huadong Medicine, China) and OWL-833 (Chugai/Eli Lilly, USA), which indicates significant progress in overcoming this problem [96].

The non-peptide agonists LY3502790, PF-06882961 and CHU-128 (Fig. 4) are characterized by a specific interaction with the GLP-1 receptor: the activation of the G-protein signaling activity only in the GLP-1 receptor with Trp33 (ECD). This was an unexpected finding because primate-specific Trp33 (ECD) served as a critical point for binding small molecules, but not native GLP-1. Non-peptide agonists induce changes in the GLP-1R conformation through van der Waals interactions and hydrogen bonds of Trp33 (ECD) with extracellular loops ECL 1 and ECL2 instead of a direct interaction of the peptide with ECL2 [96]. TTP-273 has unique kinetic and signaling properties and has a distinct binding mode compared to GLP-1 [97].

TTP273 (Transtech Pharmaceuticals (TTP), later renamed as vTv Therapeutics, USA) is being developed as an oral GLP-1R agonist with a half-life of about 6 hours. Its 2-week administration caused a pronounced dose-dependent decrease in glycemic levels, the blood pressure (systolic by 8 mm Hg, placebo – 2 mm Hg, diastolic up to 5 mm Hg, placebo – 1 mm Hg), triglyceride levels (by 2.8 mmol/L compared with placebo 1,7 mmol/L) and body weight: by 2 kg compared to placebo – 0.6 kg. In a 12-week multicenter study, T2DM patients receiving metformin additionally received TTP273 (150 mg once or twice daily) or placebo. While taking TTP273, the following placebo-adjusted values were observed: HbA1c –0.86 and –0.71%, respectively (placebo – HbA1c +0.15%). A weight reduction was observed by an average of 0.9 and 0.6 kg when taking TTP273 once and twice daily, respectively. Study 2, LOGRA (aLlosteric Oral GLP-1R Agonist), assessed the safety and efficacy of TTP273 in T2DM patients at a stable dose of metformin, but the results have not yet been published. TT-OAD2 is a weaker analogue of TTP273 from the same developer with slow kinetics, but a revealed structure. In HEK293 cells (with a high density of GLP-1R), the compound affects cAMP without recruiting β-arrestin-1 [20, 90, 97, 98].

Compound RGT1383 is a full GLP-1R agonist, comparable to GLP-1, increases cAMP with an EC50 value of about 0.2 nmol/L and a partial agonist of the β-arrestin recruitment at the level of ~ 30%. RGT1383 binds to the orthosteric binding pocket through an inward movement of the extracellular loop of ECL3 and the extracellular end of TM7. In addition, the Trp33 extracellular N-terminal domain (ECD) plays a critical role in binding RGT1383 to the human GLP-1 receptor [20, 97].

Danuglipron (PF-06882961, Pfizer Inc, USA) is a member of a series of pyrimidine derivatives that, in *in vitro* studies, exhibits a GLP-1R agonism higher than that of some closely related peptides (exendin-4, liraglutide and endogenous oxyntomodulin). PF-06882961 increases cAMP production (EC_{50}=13 nM) and partially increases Ca^{2+} levels, pERK1/2 recruitment and β-arrestin. The binding sites for PF-06882961 and LY3502970 or CHU-128 largely overlap, although each occupies a different position. This significant overlap

explains the species specificity of compounds PF-06882961 and LY3502970 [99]. Orforgliprone LY3502970 (OWL833, Chuai Pharmaceutical, Japan and Eli Lilly, USA) is a non-peptide partial agonist of GLP-1R for the oral use. In efficacy studies, the oral administration of this compound reduced glucose levels in humanized GLP-1R transgenic mice, as well as insulinotropic and hypophagic effects in non-human primates, at levels comparable to exenatide [20, 22]. The analysis of seven randomized controlled trials of orforgliprone and danuglipron showed significant reductions in body weight and HbA1c levels with a low risk of hypoglycemia, but a high incidence (more than 50%) of gastrointestinal adverse events (nausea and vomiting) may significantly limit the prospects of such drugs [100].

Some of the first non-peptide GLP-1R agonists described are substituted cyclobutane compounds, exemplified by the compounds Boc5 (a full agonist) and S4P (a partial agonist). These compounds do not activate cells without GLP-1 receptors or cells expressing glucagon receptors (GcgR) or GLP-2 receptors, and their agonism is blocked by exendin (9–39). Despite a high degree of mimicking the effects of peptide GLP-1R agonists, the Boc5 compound and its more active derivative have not received any further development as oral drugs [20].

Allosteric modulators of GLP-1R are being developed as drugs that, by binding to various allosteric sites of the receptor, can enhance the action of endogenous peptide agonists of the GLP-1 receptor (Fig. 5). The first compounds exhibiting a similar pharmacological activity were developed by Novo Nordisk (based on quinoxalines). The compound synthesized by this company is a complete and highly selective GLP-1R agonist (exendin (9–39), the effect is absent in the animals knockout for the target receptor), increases the binding affinity of GLP-1 to the receptor, but not its activity. The designated compound is less active than GLP-1, exenatide or liraglutide in stimulating the insulin secretion by BRIN-BD11 cells. Quinoxaline derivatives require the optimization to improve their chemical stability and pharmacokinetics. The 2-thio-quinoxaline analog compound DA-15864 increases a glucose-stimulated insulin secretion and acts synergistically with GLP-1, significantly increasing peak plasma insulin levels. It has also been reported that the combined use of quinoxaline-based allosteric modulators with exendin-4 has a pronounced neuroprotective effect, which was mediated by the stimulation of GLP-1R through the cAMP-PKA-CREB signaling pathway [20].

The pharmaceutical company Domain Therapeutics has developed a series of quercetin-like flavonoids (flavones, isoflavones and catechins), which are allosteric modulators of GLP-1R [20], but have not been developed as drugs.

Eli Lilly (USA) has released a number of agonists and positive allosteric modulators of GLP-1R based on pyrimidine, which are optimized to increase the affinity for GLP-1R and the effectiveness of inactive GLP-1 (9–36) – the main metabolite of GLP-1(7–36). The BETP activity is not blocked by exendin-4 (9–39); in *in vivo* studies, the compound stimulates an insulin secretion in rats and the oxyntomodulin-stimulated insulin secretion, indicating its ability to initiate biased signaling through oxyntomodulin-mediated GLP-1R. Competitive binding studies showed that LSN3160440 cooperatively modulates the binding affinity and efficiency of GLP-1 (9–36) to activate the GLP-1 receptor. The compound LSN3160440 in *in vitro* and *in vivo* studies enhanced the activity and effectiveness of GLP-1 (9–36) in activating its receptor. Co-addition of LSN3160440 and GLP-1(9–36) to isolated mouse β-cells or the administration to Wistar rats significantly increased a glucose-dependent insulin secretion (at the levels comparable to GLP-1). This compound is the only reported allosteric receptor modulator that simultaneously interacts with both the orthosteric ligand and the receptor [20, 101].

Malik F. et al. developed an innovative high-throughput screening system that identified compounds VU00056556 and VU0109197 with a common hexahydroquinolone carboxylate core that interacted with GLP-1R more tightly than native GLP-1. Once the lead compound was identified, its structure was optimized, resulting in VU0453379, which exhibits a biased GLP-1R agonism (a highly selective agonist) and weakly affects a β-arrestin recruitment, with an acceptable metabolic and pharmacokinetic profile. This compound is the first to cross the BBB, which may be important for the development of central GLP-1R agonists [20].

Compounds HIT-465 and HIT-736 (their structure has not been disclosed) have a high bioavailability and a long half-life and are biased modulators of GLP-1R, but the allosteric binding site is different from that of the compound developed by Novo Nordisk A/S [20].

Ethanolic extracts from fenugreek seeds (*Trigonella foenum-graecum* L.) enhance GLP-1 signaling, and their fractionation and purification led to the isolation of compound N55 (N-linoleoyl-2-amino-γ-butyrolactone).

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In *in vitro* studies, this compound promotes a GLP-1-dependent cAMP accumulation and dose-dependent endocytosis of GLP-1 receptors. Compound N55 has a unique mechanism of action – instead of binding to the allosteric site of GLP-1R, like other known modulators, N55 directly binds to GLP-1(7–36)NH_2. Binding of N55 to GLP-1 may induce conformational changes in GLP-1 (7–36)NH_2, thereby inhibiting its degradation and exposure to trypsin. Therefore, N55 represents a new class of allosteric modulators of GLP-1R, and similar effects on GLP-1 may have a potential to control the activity of this receptor [20, 102].

A group of scientists from Sanofi-Aventis Deutschland GmbH developed compound N14 based on 3,4,5,6-tetrahydro-1H-1,5-epiminoazocino[4,5-b] indole, which is the most potent non-covalent allosteric modulator of GLP-1R, it stimulates an insulin secretion and has acceptable pharmacokinetic and pharmacodynamic characteristics [20].

All known non-peptide GLP-1R agonists bind to it predominantly in the helical bundle of the receptor, with a binding pocket that overlaps with that of GLP-1 in a manner that is either similar or completely different. The multiple active conformations of GLP-1R result in varying efficacy and biased agonism of the substances. Allosteric binding sites for GLP-1R are located at several locations throughout its structures – on the GLP-1 peptide itself and in intra- and extracellular areas – and allosteric modulators influence the affinity and effectiveness of orthosteric ligands.

Combination therapy based on GLP-1

Currently, combination forms with insulin degludec (Sultophy®, Novo Nordisk A/S, Denmark) or glargine (Soliqua SoloStar®, Sanofi, France) are used. The creation of such combinations is logical and understandable from the point of view of increasing the effectiveness of hypoglycemic therapy (due to the synergy in the action of insulin and GLP-1R agonists) and marketing (expanding the product portfolio by combining two of the company's drugs into one). Combining GLP-1R analogues with basal insulin reduces HbA1c faster and more significantly compared to monotherapy [103].

Various approaches to combining GLP-1R agonists include their combination with amylin, glucagon [104], leptin, salmon calcitonin, PYY, cholecystokinin, melanocortin-4 receptor (MC4R) agonists [105], various insulin analogues [103], adrenomedullin [107] and β3-adrenergic receptor agonists [108], cannabinoid receptor 1 (CB1) agonists/antagonists [109], and bile acid receptor agonists (farnesoid-x (FXR), NR1H4) [110].

Multitarget molecules based on GLP-1

The creation of multitarget molecules that will interact with multiple receptors is potentially more attractive than monotherapy or combinations of individual drugs for several reasons. First, it is easier to obtain a marketing authorization for a molecule than for a combination. Second, each substance in the combination has unique pharmacokinetic profiles that are equalized when the molecules are fused, limiting an interindividual variability in metabolism and pharmacokinetic interactions of individual structures. At the same time, the activity of one molecule is constant, and in combination it can be titrated by changing the ratio of the components in the mixture, which is especially important if one of them has a narrow therapeutic window.

The possibility of using glucagon as part of a multifunctional molecule with hypoglycemic effects was not initially considered, but its catabolic properties (lowering lipid levels) are attractive, especially if its hyperglycemic effects can be reduced. One possible candidate that interferes with or compensates for the counterinsular action of glucagon is GLP-1, while at the same time providing the full range of effects inherent to this hormone. Thus, the co-administration of GLP-1 and glucagon led to a decrease in food intake and an increase in the energy expenditure. A long-term administration of selective monoagonists in combination to obese primates caused a greater reduction in body weight compared to the use of these drugs alone [111].

The structural similarity of GLP-1 to glucagon allows their pharmacological effects to be integrated by combining them into a single molecule. Preclinical studies of GLP-1/glucagon coagonists confirmed the feasibility of this approach, which led to the creation of a large number of similar molecules (based on glucagon, oxyntomodulin, etc.), which are currently undergoing clinical trials. The most notable compounds are SAR425899 (Sanofi-Aventis Deutschland GmbH) and MEDI0382 (AstraZeneca), which have shown promising results in their effectiveness in reducing hyperglycemia and body weight. Compound SAR425899 was also found to cause dose-dependent severe gastrointestinal side effects, which may limit its use in relation to compound MEDI0382. The research on these two compounds is ongoing [92, 104, 112].

Novo Nordisk A/S has developed several long-acting dual agonists (NN1177, NN1151, NN1359) that differ in their affinity for the GLP-1 and glucagon receptors. These compounds have been successfully tested in preclinical trials, but several systemic problems have been identified due to the species specificity and a number of receptors involved, making it difficult to optimally select the GLP-1 / glucagon activity ratio of these compounds. The pharmacodynamic effects of coagonists vary among species and are dependent on the compound exposure and study duration (a tolerance development), making the identification of an optimally balanced clinical candidate difficult [104, 113].

The compound GUB06-046 is a coagonist to the secretin receptor (SCTR) and GLP-1; its use significantly reduces body weight, increases glucose utilization and increases β-cell mass [114].

The creation of monomolecular GLP-1 and GIP agonists is advisable from the point of view of enhancing insulinotropic effects. GIP is also involved in the regulation of a bone tissue remodeling and has a therapeutic potential for osteoporosis. The question of the therapeutic value of stimulation or receptors inhibition for GIP remains open, since in T2DM patients, the sensitivity of tissues to GIP decreases, which can be restored against the background of normalization of glycemia [51, 104, 115].

Tirzepatide (LY3298176) is an experimental GIP analogue and is a linear polypeptide of 39 amino acids. The dibasic fatty acid portion (eicosandioic acid) is linked via glutamic acid to two (2-(2-aminoethoxy) ethoxy)acetic acid units to the side chain of a lysine residue. This arrangement provides a much longer half-life, increasing the time between the doses due to its high affinity for albumin. The drug is administered weekly subcutaneously. Phase 3 trials were completed worldwide in 2021. Tirzepatide has a greater affinity for GIP receptors than for GLP-1 receptors, resulting in a greater reduction in hyperglycemia compared to the selective GLP-1R agonists. Tirzepatide mimics the actions of natural GIP, in relation to the GLP-1 receptor it stimulates an increase in cAMP, but not β-arrestin, and it also increases the levels of adiponectin, an adipokine involved in the regulation of glucose and lipid metabolism, with a maximum increase of 26% (10 mg dose) from the baseline at 26 weeks [93].

In May 2022, the FDA approved of Mounjaro™ injection (tirzepatide, Eli Lilly and Company, USA) for once-weekly dosing (the six doses are: 2.5, 5, 7.5, 10, 12.5, and 15 mg) at as an adjunct to diet and exercise to improve a glycemic control in T2DM adults. It is the first and the only FDA-approved GIP and GLP-1 receptor agonist which has been demonstrated to be effective and safe through the SURPASS program. The effects of the drug were compared with a semaglutide injection 1 mg, insulin glargine and insulin degludec. The efficacy of the drug was evaluated at doses of 5 mg, 10 mg and 15 mg, used alone or in combination with metformin, SGLT2 inhibitors, sulfonylureas and insulin glargine. In a SURPASS study (SURPASS-4, NCT03730662), compared with the baseline HbA1c (8.5%), the drug reduced it by an average of 2.1% (5 mg), 2.3% (10 mg), and 2.4% (15 mg) compared to 1.4% for insulin glargine. It also reduced patients' weight from the baseline of 90.3 kg by an average of 6.4 (5 mg), 9 (10 mg) and 10.4 kg (15 mg) compared with an increase of 1.8 kg for insulin glargine [112, 116].

Based on the encouraging efficacy of the GLP-1/glucagon and GLP-1/GIP coagonists, it was hypothesized that a single molecule with a triple agonism at all three of these receptors could provide a greater efficacy than the corresponding coagonists. In such a molecule, the glucagon fragment is responsible for the modulation of lipid metabolism [104, 106], the GLP-1 and GIP fragments compensate for the hyperglycemic effect of glucagon, have an insulinotropic effect and jointly promote weight loss. The monomeric peptide exhibits a triple agonism at the GLP-1, GIP, and Gcg receptors, which reduces body weight more significantly than the corresponding coagonists and monoagonists in preclinical studies [105]. Clinical studies of such drugs are ongoing.

Retatrutide (LY3437943) is an agonist of GLP-1, GIP and glucagon receptors. In phase II clinical trials, the patients with a body mass index higher than 30, experienced a 17.5% reduction in body weight after 24 weeks of the treatment and a 24.2% reduction after 48 weeks, indicating a significant potential of triple agonists in the treatment of excess body weight [117].

An alternative to producing chimeric or hybridized peptides with scrambled sequences is fusion molecules or conjugates. As noted above, the sequences similarity of the proglucagon peptide family and the structures of their receptors make it possible to construct chimeric peptides with an agonism at multiple receptors with the sizes comparable to native peptides. In particular, the results of the compounds studies obtained by fusion of the GLP-1 molecule with gastrin, amylin, cholecystokinin, FGF21 and inhibitory antibodies against PCSK9 have

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already been published. The GLP-1 / gastrin molecule (also active against the related intestinal hormone xenin) has the potential to restore β-cells [118]. The GLP-1/amylin molecule and GLP-1 / cholecystokinin significantly reduce food intake and blood glucose levels [104]. The fusion of GLP-1 with FGF21 or GLP-1 with anti-PCSK9 led to a more pronounced (than after the use of GLP-1R agonists) normalization of dyslipidemia and body weight [119]. In a phase I clinical trial, the treatment of overweight and obese patients with a GLP-1 / anti-PCSK9 drug reduced LDL cholesterol but did not improve glucose metabolism [120].

Despite the promising results of preclinical studies of various GLP-1 conjugates, it is necessary to establish the cellular mechanisms of their effects, pharmacokinetic parameters and compatibility / reliability of the data translation into clinical practice.

Approaches to the development of GLP-1R agonists and their effects are shown in Fig. 6.

Stimulators of endogenous GLP-1 secretion

In addition to the above-mentioned pharmacological approaches to influencing the GLP-1 receptor, leading pharmaceutical companies are trying to realize the possibility of increasing the secretion of incretins by enteroendocrine cells of the intestine by stimulating a special group of receptors localized on them. Under normal conditions, their physiological activators are FFAs supplied with food or formed as a result of fermentation of dietary fiber under the influence of intestinal microbiota. These receptors (GPR40, GPR41, GPR43, GPR119 and GPR120) were discovered during the implementation of the Human Genome Project, and subsequently their significant role in the regulation of incretin biosynthesis and carbohydrate metabolism was established. The activation of GPR40 receptors, in addition to incretin-mediated effects, has hepato- and neuroprotective effects, GPR41 and GPR43 affect the leptin metabolism, an adipocyte differentiation, the nervous and immune systems [35, 36]. The metabolic and pleiotropic effects of GPR119 [35, 37] and GPR120 agonists are being actively studied [26, 27, 30].

CONCLUSION

Thus, the peptide, discovered due its ability to stimulate the insulin secretion, has evolved into a class of drugs with a pronounced effectiveness against the progression of diabetes and overweight / obesity. The generally accepted description of its role is as follows: GLP-1 is released from the intestine into the bloodstream after eating to increase the insulin secretion and suppress the glucagon secretion to effectively utilize the intestinal glucose and reduce glycemia to normal values (incretin effect), and GLP-1 also acts on afferent neurons of the vagus nerve and/or directly to the brain to suppress appetite and create satiety. In addition, a wide distribution of the GLP-1 receptor in various tissues and organs, its connection with intracellular signaling cascades aimed at launching energy-consuming anabolic processes, provides cardio-, endothelial- and neuroprotective effects of GLP-1, unrelated to its hypoglycemic effect. The use of more potent synthetic GLP-1R agonists has revealed the significant therapeutic potential of these pleiotropic properties of GLP-1, with a confirmation in clinical studies. GLP-1R agonists are a class of medications that provide not only areliable glycemic control and weight loss for patients, but are also accompanied by a reduction in the risk of developing cardiovascular complications of diabetes. GLP-1 agonists stimulate insulin biosynthesis and the β-cell proliferation, and also inhibit their apoptosis. Incretin-like drugs are well tolerated, and the most common side effect of this class is nausea, which is due to the central effect of GLP-1 on the gastric tone.

In addition to the described examples, the development of new incretin mimetics continues: GLP-1R agonists (VRS 859, efpeglenatide, CJC-1134-PC, taspoglutide, glymera, TTP054, ZYOG1, ARI-1732TS), including the non-peptide nature (LY3502970, CHU-128, Boc5, S4P, TT-OAD2, RGT1383, PF06882961), allosteric receptor modulators (DA-15864, BETP, LSN3160440, VU00056556, VU0109197), new combinations (with leptin, salmon calcitonin, PYY, cholecystokinin, insulin analogues, adre nomedullin, agonists β3-adrenergic receptor, cannabinoid receptor 1 (CB1) agonists / antagonists, MC4R agonists and NR1H4 agonists), molecules based on GLP-1R agonists with a multi-target mechanism of action (SAR425899, MEDI0382, GUB06-046, Tirzepatide), including in the form conjugates with other proteins (gastrin, amylin, cholecystokinin, FGF21 and inhibitory antibodies against PCSK9).

GLP-1R agonists are consistently increasing their presence on the Russian pharmaceutical market. Thus, from 2016 to 2020, their share increased from 0.09 to 0.41% or from 2.3 to 10.56% of sold hypoglycemic agents of all groups in physical (packaging) and value (rubles) terms, respectively. The dominant position is occupied

by the pharmaceutical company of Denmark, in whose product portfolio for 2020 there were 5 positions, which allows this company to occupy more than 50% of the market in volume terms and almost 70% in value terms.

Thus, GLP-1R agonists represent a class of not only effective and safe drugs for the treatment of T2DM and obesity, but also rapidly developing in the most advanced areas of pharmacy.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Denis V. Kurkin – idea and planning of the structure of the work, design of graphic material, editing and approval of the final version of the manuscript; Dmitry A. Bakulin, Yuliya V. Gorbunova, Valeria B. Saparova, Ksenia N. Koryanova, Anastasia N. Chumachenko, Olga V. Ivanova, Elizaveta V. Pavlova – collecting materials and writing a draft manuscript; Evgeniy I. Morkovin, Andrey V. Strygin, Yuriy A. Kolosov – collecting materials and editing the final version of the manuscript; Marina A. Dzhavakhyan, Andrew V. Zaborovsky, Igor E. Makarenko, Roman V. Drai, Vladimir I. Petrov – consultations on highly specialized issues, approval of the final version of the manuscript.

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AUTHORS

Denis V. Kurkin – Doctor of Sciences (Pharmacy), Asistant Professor, Head of the Scientific and Educational Institute of Pharmacy named after. K.M. Lakina of Russian University of Medicine; Professor of the Department of Clinical Pharmacology and Intensive Care of Volgograde State Medical University. ORCID ID: 0000-0002-1116-3425. E-mail: strannik986@mail.ru

Dmitry A. Bakulin – Candidate of Sciences (Medicine), Head of the Interdepartmental Scientific and Educational Center of Pharmacy of Scientific and Educational Institute of Pharmacy named after. K.M. Lakina of Russian University of Medicine. ORCID ID: 0000-0003-4694-3066. E-mail: mbfdoc@gmail.com

Evgeniy I. Morkovin – Candidate of Sciences (Medicine), Assistant Professor, Head of the Laboratory of Neuropsychopharmacology of Volgograd State Medical University. ORCID ID: 0000-0002-7119-3546. E-mail: e.i.morkovin@gmail.com

Vladimir I. Petrov – Doctor of Sciences (Medicine), Professor, Academician of RAS, Head of the Department of Clinical Pharmacology and Intensive Care of State Medical University; Chief Freelance Specialist, Clinical Pharmacologist of the Ministry of Healthcare of the Russian Federation, Honored Scientist of the Russian Federation, Honored Doctor of the Russian Federation. ORCID ID: 0000-0002-0258-4092. E-mail: brain@sprintnet.ru

Andrey V. Strygin – Candidate of Sciences (Medicine), Assistant Professor, Deputy Director of Research Center for Innovative Medicines of Volgograd State Medical University. ORCID ID: 0000-0002-6997-1601. E-mail: drumsav@mail.ru

Ksenia N. Koryanova – Candidate of Sciences (Pharmacy), Associate Professor of the Department of Pharmacology with a Course of Clinical Pharmacology, Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University. ORCID ID: 0000-0003-1571-9301. E-mail: kskor-16@mail.ru

Yuliya V. Gorbunova – Candidate of Sciences (Medicine), Head of Laboratory of Scientific and Educational Institute of Pharmacy named after. K.M. Lakina of Russian University of Medicine. ORCID ID: 0000-0002-1116-3425. E-mail: yvgorbunova@yandex.ru

Yuriy A. Kolosov – Candidate of Sciences (Medicine),

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Assistant Professor, Deputy Director for Academic Affairs of the Scientific and Educational Institute of Pharmacy named after. K.M. Lakina of Russian University of Medicine. ORCID ID: 0000-0003-1506-2565. E-mail: tronk79@gmail.com

Olga V. Ivanova – Candidate of Sciences (Pharmacy), Senior Researcher of the Scientific and Educational Institute of Pharmacy named after. K.M. Lakina of Russian University of Medicine. ORCID ID: 0000-0003-4333-322X. E-mail: ovivanova134@mail.ru

Elizaveta V. Pavlova – junior researcher of the Scientific and Educational Institute of Pharmacy named after. K.M. Lakina of Russian University of Medicine. ORCID ID: 0000-0003-0651-3205. E-mail: lizapavlova1609@yandex.ru

Marina A. Dzhavakhyan – Doctor of Sciences (Pharmacy), Assistant Professor, Deputy Director for Implementation and Development of the Scientific and Educational Institute of Pharmacy named after. K.M. Lakina of Russian University of Medicine. ORCID ID: 0000-0003-2673-6203. E-mail: akopovamarina13@mail.ru

Andrew V. Zaborovsky – Doctor of Sciences (Medicine), Assistant Professor, Head of the Department of Pharmacology of Russian University of Medicine. ORCID ID: 0000-0002-7923-9916. E-mail: azabor@mail.ru

Valeria B. Saparova – researcher of the Scientific and Educational Institute of Pharmacy named after. K.M. Lakina of Russian University of Medicine. ORCID ID: 0000-0002-8445-1129. E-mail: Valeriya.Saparova@geropharm.com

Igor E. Makarenko – Candidate of Sciences (Medicine), – researcher of the Scientific and Educational Institute of Pharmacy named after. K.M. Lakina of Russian University of Medicine; Head of the Medical Department of Farm-Holding. ORCID ID: 0000-0003-2308-0608. E-mail: Igor.Makarenko@geropharm.com

Roman V. Drai – Candidate of Sciences (Medicine), Director of Farm-Holding. ORCID ID: 0000-0003-4594-6097. E-mail: roman.drai@geropharm.com

Anastasia N. Chumachenko – student-researcher of Volgograd State Medical University. ORCID ID: 0000-0002-7756-3827. E-mail: nastya11386@icloud.com