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REVIEW

GLP-1R agonists for the treatment of obesity: a patent review (2015-present)

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ABSTRACT

Introduction: Glucagon-like peptide-1 (GLP-1) is an endogenous peptide which is secreted by enteroendocrine L cells, GLP-1 receptor agonists (GLP-1 RAs) can exhibit glucoregulation by stimulating insulin release, promote satiety, delay gastric emptying, and reduce energy intake. Liraglutide is the only GLP-1 RA approved for the treatment of obesity. The phase III clinical study of semaglutide has completed and the result showed significant weight loss effect. GLP-1 RAs have been proven to be safe and effective in clinical trials, they are considered to be promising anti-obesity drugs.

Areas covered: This review provides an overview of recently published patents describing modified GLP-1 RAs, multi-agonists in the treatment or prevention of obesity from January 2015 to April 2020. Moreover, small molecule GLP-1 RAs, recombinant fusion proteins, combination of GLP-1 RAs with other drugs and the preparation of GLP-1 RAs are also covered.

Expert opinion: Currently, research on anti-obesity effect of modified GLP-1 RAs has grown significantly, liraglutide accounts for approximately 56% of the global obesity drug market. Long-acting analogues and multifunctional peptides showed good weight loss activity. As more and more clinical trials are carried out, we believe that GLP-1 RAs will occupy an important position in the market of obesity treatment.

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1. Introduction

1.1. Background of obesity and anti-obesity drugs

Nowadays, more than 10% adults worldwide suffer from obesity, which is mainly caused by high fat or carbohydrate food intake. In addition to high-calorie foods, physical stress, low self-esteem, eating disorders, and poor lifestyle can also lead to obesity [1]. Obesity is closely associated with many chronic diseases such as diabetes, nonalcoholic fatty liver disease, heart diseases, and cancer [2]. Several therapeutic approaches have been proposed to solve this epidemic problem over the last decades. As a result of the efforts worldwide, anti-obesity drugs such as Rimonabant® (Sanofi-Aventis), Sibutramin®(Abbott), Contrave®(Takeda), Orlistat®(Roche), etc. have been developed [3]. However, these drugs have drawbacks such as fatal adverse reactions or little efficacy in treating obesity. For example, Rimonabant® shows an adverse reaction of central nervous system disorder, Sibutramin® and Contrave® show adverse cardiovascular effects. Accordingly, there is an urgent need for safe and effective anti-obesity drugs [4].

1.2. GLP-1 receptor agonists and mechanism of anti-obesity effect

As such, active research has been conducted to develop a new pharmaceutical drug to resolve the problems of the conventional anti-obesity drugs. Recently, clinical trials showed that GLP-1 receptor agonists (GLP-1 RAs) can effectively reduce the body weight of the diabetic patients [5]. The available data strongly suggest that weight loss ensuing from GLP-1 R agonism in humans largely reflects reductions in food intake. The widespread distribution of GLP-1 R expression within the CNS as well as the autonomic and enteric nervous systems has spurred investigation into how physiological gut-derived GLP-1, as well as pharmacological activation of the GLP-1 R, controls appetite and body weight [6]. In-depth mechanism research displayed that the GLP-1 RAs have several physiological effects, with the anorexigenic (and insulinotropic) effects being the most important in the treatment of obesity [7]. The anorexigenic effect mediated by the GLP-1 RAs is exerted through central and peripheral pathways Figure 1. Centrally, GLP-1 RAs may pass the blood–brain barrier and bind with hypothalamic regions, particularly the arcuate nucleus and paraventricular nucleus. Twice-daily subcutaneous injection of liraglutide for 28 days in rats with diet-induced obesity increased Cart and reduced the relative expression of Npy, Agrp, Ghsr, and Lepr mRNA transcripts in the arcuate nucleus, which is a main reason to the decreasing of food intake [8]. Peripherally, gut-derived GLP-1 may communicate with the brain by accessing GLP-1 Rs within fibers innervating the portal vein or the nodose ganglion of the abdominal vagal nerve. GLP-1 RAs act on afferent vagal neurons and inhibit gastric and small bowel motility [9], additionally, the weight reduction effect of GLP-1 RAs was influenced by the diminished reduction in circulating leptin following GLP-1 RAs induced weight loss, which may further increase the anorexigenic effect.

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Article highlights

- Since the first GLP-1 receptor agonist liraglutide was approved in 2014 for the treatment of obesity, semaglutide has just completed its first phase III clinical trials with significantly weight loss effect during 68 weeks treatment, GLP-1 receptor agonists are considered to be promising to be the new choice for the overweight people.
- Some new strategies are tried to improve patient compliance and convenience, including the multi-agonists,combination of GLP-1RAs with other drugs, and oral preparation of the peptides. We reviewed patents relate to all above mentioned strategies as well as the traditional approaches used in the development of GLP-1 receptor agonists in this article.
- Small molecular GLP-1 receptor agonists showed excellent in vitro agonistic activity, but the development of these molecules has not received widespread attention, may be the in vivo effect is not so ideal.
- IAs the first oral preparation of GLP-1 receptor agonists semaglutide was approved in 2019, patents relate to the oral preparation or the controlled-release system have been increasingly applied, and the development of oral peptide preparation will increase in the future.

Evidence is currently inconsistent in demonstrating a change in energy expenditure by altering resting metabolic rate or diet-induced thermogenesis. Until now, clinically available GLP-1 RAs are exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, and semaglutide, all of which are approved to treat type 2 diabetes mellitus(T2DM) Figure 2. Only liraglutide is currently approved for the treatment of obesity, and semaglutide is under investigation which will be approved soon.

At present, the structural transformation of GLP-1 RAs is mainly proceeded in two aspects. One is resisting the hydrolysis of Dipeptidyl peptidase IV (DPP-4), mainly including the modification or replacement of the N-terminal and the extension, cyclization or glycosylation of the C-terminal of the endogenous GLP-1. The other aspect is slowing down the elimination rate in kidney, including PEGylation, fatty acid modification, coumarin modification, dimer formation structure or binding to fusion proteins Figure 3. Some small molecules mainly discovered by high throughput screening also showed excellent agonistic activity in vivo, which may offer another choice for obesity patients.

2. Mono-agonist of GLP-1 R

2.1. Endogenous GLP-1 RAs derivatives

Semaglutide is a GLP-1 derivative for once weekly administration which is developed by Novo Nordisk, this compound is firstly disclosed in WO2006097537 [10]. Comparing to endogenous GLP-1(7–37), the 8nd and the 35th amino acids of semaglutide peptide sequence are substituted to Aib (2-aminoisobutyric acid) and Arg, respectively, while an octadecanoic acid fatty chain is conjugated with Lys at position 26. Novo Nordisk also developed many new compounds on the basis of semaglutide. By introducing novel side chains to the Lys residue at position 34, 35, 36, 37, or 38 of the GLP-1 analogues, WO2016083499, WO2015000942 provide GLP-1 analogues with a satisfactory potency and make it possible for once-monthly administration [11,12]. WO2015000942 relates to the C-terminally extended derivatives of GLP-1 which comprise two side chains, one at a position 42 corresponding to native GLP-1(7–37), and the other at position corresponding to position 18, 23, 27, 31, 36, or 38 [12]. The side chain may comprise a C19, C20, or C22 diacid protracting moiety and optionally a linker [13]. Except for the above-mentioned examples of mono-acylated and di-acylated GLP-1 agonists, Novo Nordisk also developed novel acylating regents with the hydroxy group of 3,5-dichloro-2-hydroxybenzenesulfonic acid, which can improve the stability of GLP-1 analogues [14]. In addition, Novo Nordisk also applied a GLP-1 analogue with Trp at position 8 corresponding to GLP-1(7–37). These compounds are very stable against degradation by DPP-4, while maintaining the capability to activate the GLP-1 receptor [15].

Other than Novo Nordisk, many companies or universities actively modify GLP-1 with different methods. By simply mutating the Ser in position 13 to Pro, the application obtained a new peptide with better hypoglycemic activity than liraglutide [16]. Changing the C-terminal to Leu or Ile can also improve the duration time of GLP-1 [17]. CN104262481 discloses that by substituting the position 13, 20, 22, and 26 with Lys with chain decoration or Leu, Ser, and Trp can prolong the half-life of the peptide to up to 75 h [18]. The compounds disclosed by WO2019110981 particularly comprise an Aib residue at position 2 in conjugation with a His residue at position 3, the in vivo test on rats showed significant weight loss [19].

DPP-4 inhibitors can prevent endogenous GLP-1 from being degraded by enzymes. Directly conjugating the DPP-4 inhibitors to liraglutide by a linker can significantly prolong its half-life, and improve the compliance of diabetic patients on the premise of ensuring the efficacy and safety of medication [20].

Polyethylene glycol (PEG) technology is an applicable technology in the field of protein/peptide drug delivery. Generally, linear or branched PEG is used to modify the protein/peptide, which can improve the stability of the protein/peptide, significantly reduce the immunogenicity, and improve the ability of

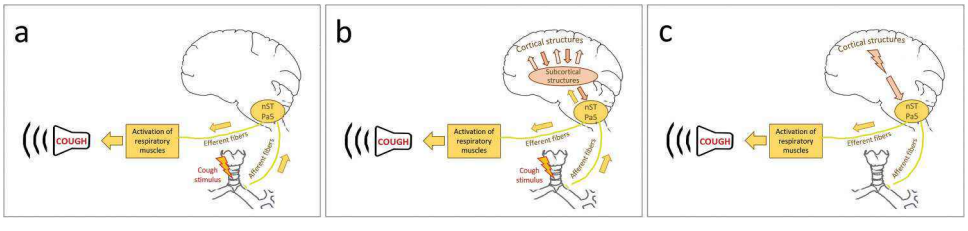

Figure 1. The potential mechanism of anti-obesity effect mediated by the GLP-1 agonists.

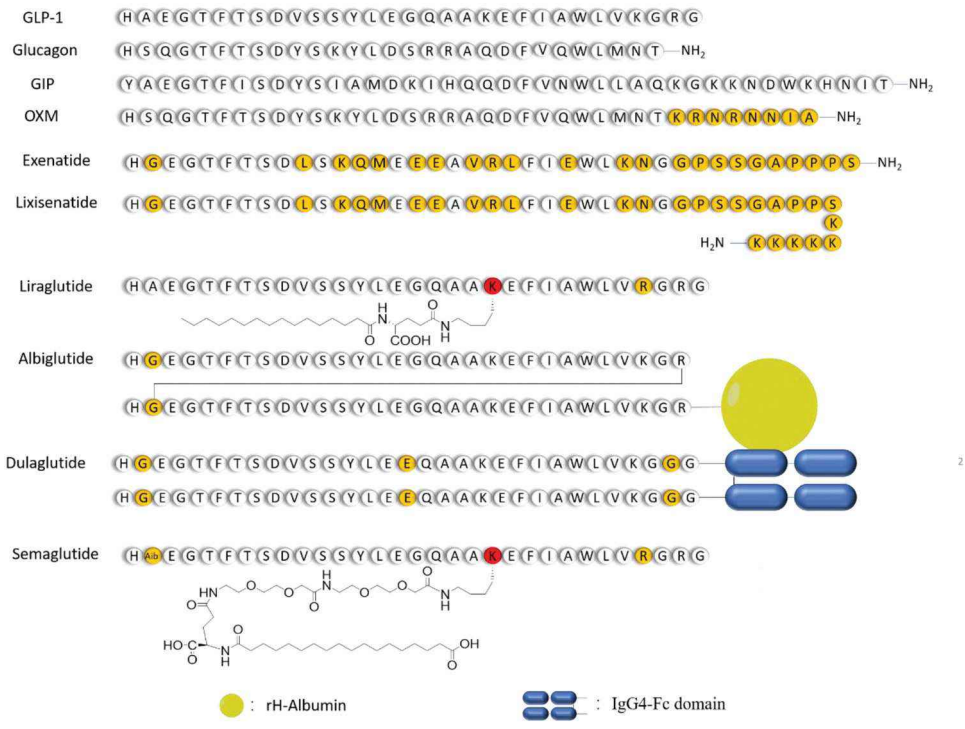

Figure 2. Sequences of GLP-1, glucagon, GIP, OXM, and clinically available GLP-1 receptor agonists.

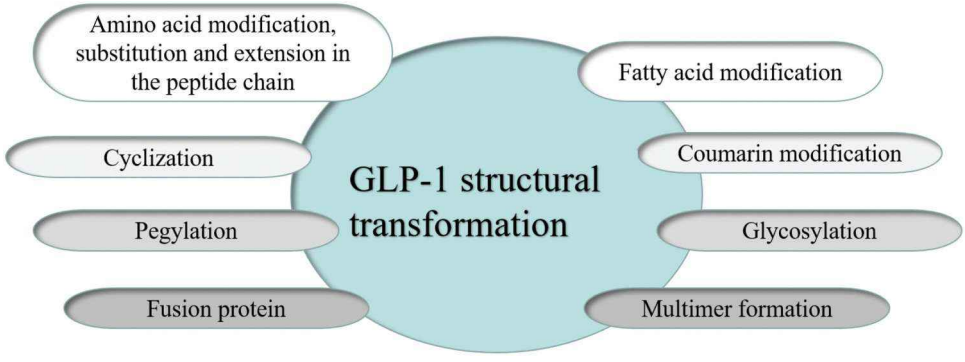

Figure 3. Different ways used in GLP-1 structural transformation.

resisting protease degradation [21]. A peptide sequence which is high homologous to endogenous GLP-1 with 4-arm PEG (40kD) can control the glucose level up to 144 h [22,23].

CN106699870 discloses a series of Xenopus laevis GLP-1 derivatives with PEGylated modification, the hypoglycemic duration of the preferred compound can be up to 48 h [24]. On the basis of that, a compound with duration time up to 72 h can be obtained by introducing a helix-promoting sequence at the C-terminus of Xenopus laevis GLP-1 [25]. The same effect as well as higher serum albumin binding ability to the peptide molecule can be obtained by directly conjugating cholic acid or mycophenolic acid to the above mentioned peptides [26,27]. CN107266555 relates a series of GLP-1 analogue dimers formed by the intermolecular disulfide bond between two GLP-1 analogue monomers, and the dimer can stabilize the blood glucose levels up to 96 h[28].

Until now, the long-acting GLP-1 analogues developed through modification by Fc or fatty acid are all limited to one week or less. CN107033234, CN109248323, and CN110386974 and WO2019201333 relate to a novel fatty acid conjugate of GLP-1 peptide analogues, the duration of the hypoglycemic activity in the body can be increased by about 1 time comparing with the currently recognized best technical product representatives dulaglutide/semaglutide [29–32]. In this new peptide, the 8th Ala, the 22nd Gly, and the 34th Lys are mutated to Val, Glu, and Arg, respectively.

Examples of strengthening the interaction between the ligand and the receptor by forming dimers are widespread in nature [33,34]. Researchers also tried to use the drug dimer to increase the binding strength and efficacy between the GLP-1 analogues and the receptor. The product of two Exendin-4 molecules linked together by a small molecule is 3.5 times

Table 1. Some representative patents relate to GLP-1 R agonists derivatives.

Patent (Assignees)	Title	Feature modification based on GLP-1(7–37) sequence	Highlights
WO2016083499 (Novo Nordisk)	GLP-1 derivatives and uses thereof	Acylation at a Lys residue corresponding to position 34, 35, 36, 37, or 38 of human native GLP-l (7–37) with two acyl chains.	Potential for once-monthly administration
WO2015000942 (Novo Nordisk)	Derivatives of GLP-1 like peptides, and uses thereof	Comprising two side chains, one at a position 42 which corresponding to native GLP-1(7–37), and the other at a position corresponding to position 18, 23, 27, 31, 36, or 38.	Potential for once-monthly administration
WO2017149070 (Novo Nordisk)	GLP-1 derivatives and uses thereof	Substitution at position 8 with Trp.	Very stable against degradation by DPP-4
WO2020087305 (Suzhou Ruide Shengyue Pharmaceutical Technology Co., Ltd)	GLP-1 polypeptide with GLP-1 receptor agonist activity and application thereof	Substitution at position 13 with Pro.	Better hypoglycemic activity than liraglutide
CN107266557 (Tianjin Institute of Pharmaceutical Co., Ltd)	Glucagon-like peptide-1 analogue with modification of polyethylene glycol	PEGylation for GLP-1 analogues with PEG (40 kD)	Controlling the glucose level up to 144 h
CN104277103 (PegBio Co., Ltd)	Conjugate comprising polymer and biologically active molecule, and its application for weight loss	GLP-1 analog dimers formed by the intermolecular disulfide bond between two GLP-1 analog monomers	Controlling the glucose level up to 96 h

stronger than the binding strength of one Exendin-4 molecule alone to the receptor [35]. CN104277103 provides a compound formed by conjugating two or more Exendin-4 molecules with a divalent or more polymer can be particularly effective for weight loss and the preferred compounds can be effective up to one-month for each administration [36]. Table 1

2.2. Small molecule GLP-1 R agonists

The weight loss ability of small molecule GLP-1 agonists has yet to be studied, but it can be confirmed that some small molecules exhibited GLP-1 receptor agonistic activity comparable or even stronger than GLP-1 derivatives. In CA3045644 and CA2988721 [37,38], Pfizer designs a series of 6-carboxylic acids of benzimidazoles and 4-aza-, 5-aza-, and 7-aza-benzimidazoles as GLP-1 receptor agonists. And DIAST-X2 is one of the representatives, showing excellent GLP-1 R agonistic activity with EC50 of 0.99 nM and Emax of 99% which is relative to a saturating concentration of the full agonist GLP-1 (1 μM).

In GPCRs, the binding site of a natural ligand is called an orthosteric site, and a ligand that binds competitively with the natural ligand at this site is an orthosteric ligand. The binding pocket of the orthomorphic ligand is relatively conservative, usually located inside the 7th transmembrane helix near the extracellular side, and the binding site that is different in space and shape from the orthomorphic site is called an allosteric site. According to the different functions of allosteric modulators bound to allosteric sites, allosteric modulators are divided into positive allosteric modulators (PAM) and negative allosteric modulator of agonist effect (NAM). The diversity of allosteric site sequences and structures in a single GPCR subfamily provides a new idea for the development of selective GPCR modulators. Allosteric modulators target non-conserved allosteric sites and interact with normal ligands. They have unique advantages, including higher specificity and lower toxicity and represent an innovative strategy for drug discovery.

Positive allosteric modulators of GLP-1 R can exhibit no ligand bias and potentiate all endogenous forms of GLP. The compounds provide by WO2016094729 and WO2018200833 act as modulators or potentiators of GLP-1 receptor on their own [39,40], or with incretin peptides such as GLP-1(7–36) and GLP-1(9–36), or with peptide-based therapies, such as exenatide and liraglutide. WO2017117556 disclosed a series of positive allosteric modulators of the GLP-1 receptor showing good GLP-1 R agonistic activity. The EC50 of the molecule is 4.2 μm and the Emax is 56% which is relative to endogenous GLP-1, and the structure is shown in Figure 4.[41]

Another patent discloses a series of small molecule with benzenesulfonamide and phenylurea structure [42]. KR2018101671 discloses a heteroaryl substituted 2-phenylimidazo [1,2-a] pyridine derivative, these compounds have excellent ability to activate the GLP-1 receptor [43]. WO2018056453 provides compounds with an indole ring or a pyrrolo[2,3-b] pyridine ring and a pyrazolopyridine skeleton, the preferred compound has significant hypoglycemic activity at nanomolar level. While WO2019103060 relates to a series of condensed tricycle compounds [44]. OWL-833 is an oral non-peptide GLP-1 receptor agonist discovered by Chugai pharmaceutical and now developed by Eli Lilly. The molecule promoted cAMP accumulation to the same level achieved by GLP-1, and its EC50 values for human and cynomolgus monkey GLP-1 Rs were the same at 1.1 nmol/L [45]

3. Multi-agonists used to treat obesity

3.1. GLP-1 R/GCGR agonists

Glucagon is a hormone that is specifically expressed in the α cells of the pancreas, it can significantly increase the blood glucose level by promoting glycogen decomposition and gluconeogenesis. Glucagon can activate the phosphorylase of liver cells through the cAMP-PK system, it can also accelerate the entry of amino acids into liver cells and activate the enzyme system involved in the gluconeogenesis process, which enhances gluconeogenesis and promotes the metabolic breakdown of amino acids. Glucagon can also activate lipase, promote lipolysis, enhance the oxidation of fatty acids and increase the production of ketone bodies. A pharmacological

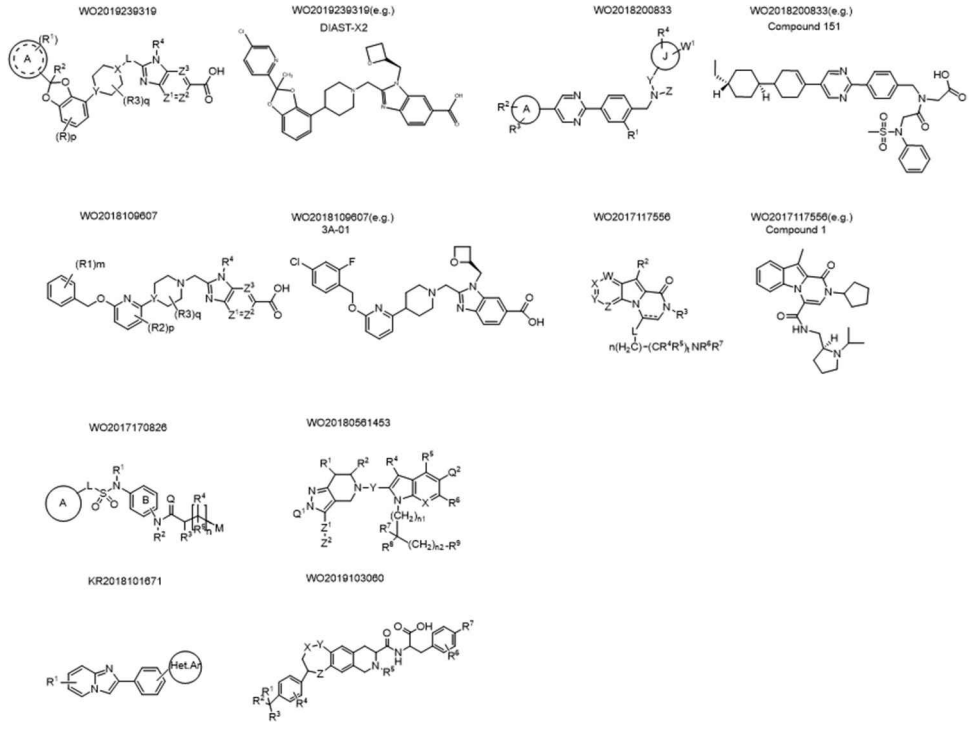

Figure 4. Small molecule GLP-1 agonists.

dose of glucagon can increase the cAMP content in myocardial cells, increase myocardial contraction and reduce weight to some extent [9,46,47].

Gastrin-regulating peptide also known as OXM, is a 37-amino acids peptide whose sequence includes 29 amino acids of glucagon and 8 amino acids at the C-terminus called IP-1 (intervening peptide-1). OXM is quickly secreted after meals, and the main physiological functions include reducing gastric acid and pancreatic exocrine secretion, and delaying gastric emptying. In addition, OXM can also reduce food intake and increase energy consumption. OXM is a natural GLP-1 R/GCGR dual agonist in vivo, which is structural modified by several patents in recent years [48]. Beijing Hanmei Pharmaceutical constructed new OXM analogues by substituting Ser to the unnatural amino acid Aib at position 2. At the same time, the negatively charged amino acid residues Glu in the side chain substituted at position 16 and 21 can help to form salt bridges to fix the α-helix configuration. These strategies can significantly prolong the pharmacokinetic properties of the compounds in the body [49,50].

Balanced GCGR and GLP-1 R activity refers to a compound that has affinity for GCGR and GLP-1 R in vitro binding assay that is close to 1:1, Glucagon peptide analogs and derivatives modified to have various degrees of activity at the GLP-1 R and GCGR have been disclosed in WO2020019813, WO2019060660, WO2019016306, US20170008944, WO2016055610, WO2016198604, WO2016198628, WO2015086731, WO2015086732, WO2015086733 [51–60]. US20170008944, WO2015086731, WO2015086732, and WO2015086733 relate to a series of compounds based on Exendin-4 which were applied by Sanofi [54,58–60].

To achieve a balanced activation of the two receptors, our group adopted fixed point replacement such as Ala and Cys to modify the structure of glucagon. This strategy is a good way to overcome the glycemic effect caused by the activation of GCGR, and obtains GLP-1 R/GCGR dual agonists with better weight loss effect and good hypoglycemic effect [61]. We also tried to introduce the substitution of Exendin-4, GLP-1 and lixisenatide partial C-terminal peptide sequences to the natural OXM C-terminal, respectively, and obtained OXM analogues with better pharmacological activity [62–65]. In WO2020019813 [51], we hybridize the peptide sequences of OXM and Exenatide and increase its resistance to DPP-4 enzyme degradation. After conjugating with the fatty acid chain, the compounds exhibit a longer pharmacological action and better weight loss effect. These hybrid peptides not only showed good affinity and agonistic activity for GLP-1 R, but also maintain moderate GCGR agonistic activity. In the long-term administration experiment on male C57bl/6 mice for 56 consecutive days, all tested hybrid peptides show good weight control effect, which is significantly better than OXM.

Novo Nordisk applied stable and protracted GLP-1 derivatives which are GLP-1 R/GCGR agonists in 2014. The GLP-1 derivatives comprise a lipophilic moiety and at least two negatively charged moieties, one of the negatively charged moieties is distal of a lipophilic moiety; and the polypeptide optionally comprises a C-terminal amide [55]. WO2015055801 and WO2016166289 provide novel acylated glucagon analogue peptides with increased selectivity for the GLP-1 receptor comparing to human glucagon [66,67].

The long-acting co-agonists of GLP-1 R and GCGR by Merck have better body weight loss effect than liraglutide and

semaglutide [68,69]. WO2017153575 provides GLP-1 R and GCGR co-agonists for the treatment of obesity, the result showed that G730 at a dose of 20 nmol/kg are more effective than liraglutide 26.6 nmol/kg. CN108341879 and CN108341880 relate to chimeric peptides obtained by PEG conjugation with modified OXM dimer or hybrid peptide of GLP-1 R/GCGR have a better weight loss effect than liraglutide [70,71].

Relative to GLP-1, exendin-4 is resistant to cleavage by DPP-4 resulting in a longer half-life in vivo[72]. Among the exendin-4 derivatives described in WO2015086731, WO2015086732 and US20170008944, several of the underlying residues are different from OXM [54,58,59]. In particular residues Tyr10 and Tyr13, which are known to contribute to the fibrillation of glucagon are replaced by Leu in position 10 and Gln in position 13. This replacement, especially in combination with Ile in position 23 and Glu in position 24, leads to exendin-4 derivatives with potentially improved biophysical properties as solubility or aggregation behavior in solution[73]. The nonconservative replacement of an aromatic amino acid with a polar amino acid in position 13 of an exendin-4 analogue surprisingly enhance the activity of the peptides on the GCGR. In WO2015086733[60], Sanofi changes the 13th position to Leu as well as the 10th position, which also has the same effect. All tested compounds showed a statistically significant weight loss compared to vehicle DIO mice in daily body weight beginning on day 6 and continuing through the end of the study. These benefits resulted from an initial decrease in food consumption and was maintained although food consumption recovered during prolonged study period. In WO2016198628, Exendin-4 is modified with d-Ser at position 2, Gln at position 3 and position 17, Arg at position 18, Ala at position 19 and Ile at position 27, and these modifications lead to potent GLP-1 and glucagon receptors activity [57].

WO2017178829 discloses compounds that are analogues of exendin-4, GLP-1 and OXM which have a modified ligand bias and therapeutically useful characteristics [74]. WO2016209707 discloses that removal of the residues of the C-terminal sequence of OXM, KRNRNNIA, may improve solubility, which is attributable to the removal of the Arg residue [75]. Certain compounds with a GPSSG C-terminal sequence exhibited improved in vivo potency, and also improved stability and solubility of the compounds Table 2.

3.2. GIPR/GLP-1 R agonists

Glucose-dependent insulinotropic polypeptide (GIP) is a 42 amino acids peptide that released from intestinal K-cells following food intake. GIP and GLP-1 are the two gut enteroendocrine cell-derived hormones accounting for over 70% of the insulin response to an oral glucose challenge. Native GLP-1 and GIP were proven in humans following co-infusion to interact in an additive manner with a significantly increased insulinotropic effect compared to GLP-1 alone [76]. Designing hybrid molecules with dual agonist on the GLP-1 R and GIPR offers the therapeutic potential to achieve significantly better reduction of blood glucose levels, increase insulin secretion and an even more pronounced effect on body weight reduction compared to the marketed GLP-1 agonist liraglutide [77].

In WO2015035419, Roche provides a GIPR/GLP-1 R co-agonist peptide for human administration, the dosage ranges from about 0.75 mg to about 2.5 mg per day [78]. In WO2015086728 [79], the inventor points out that by modifying the selective GLP-1 R agonist exendin-4 by Leu in position 10 and Gln in position 13, a peptide with potentially improved biophysical properties as solubility or aggregation behavior in solution can be obtained. The non-conservative replacement of an aromatic amino acid Tyr with a polar amino acid in position 13 also surprisingly leads to peptides with high activity on the GIPR. Another series of patents applied by Sanofi discloses that α, α-dialkylated amino acids with a basic side chain in position 20 of exendin-4 can maintain high activity at GLP-1 R/GCGR. The incorporation of the unnatural amino acid also increases enzymatic stability of the peptides and potentially improves the pharmacokinetic properties. Compounds comprising Leu in position 10 and 13 are also more resistant to cleavage by neutral endopeptidase and DPP-4 [58–60,80,81]. Unnatural amino acids may also have a positive effect on the balance of agonist activity between GIP and GLP-1. Moreover, the length, composition, position of fatty acid chains and the linker may have unexpected effects of agonist activity balance of GIP and GLP-1 [82]. Eli Lilly discloses their GIP/GLP-1 coagonists in US20200024322 [83], the composition for oral administration is also disclosed. Tirzepatide or LY3298176 is the most advanced GLP-1/GIP coagonists which has completed its phase II clinical trial and the phase III is in progress. Although this compound has significant effects in reducing blood glucose and weight loss, the high dose causes gastrointestinal side effects [84]. In another patent by Sanofi, the exendin-4 derivatives were modified at position 28 with a β-Ala. These new compounds have reduced activity on the GIP receptor which may avoid the frequent episodes of hypoglycemia relate to high levels of GIP [56]. What's more, compounds carrying an Aib at position 27 and 34, Pro at position 32 and Lys at position 35 and 39 also showed reduced activity on the GIP receptor [54].

3.3. GLP-1 R/GCGR/GIPR agonists

Bhat et al, Gault et al and Finan et al described triple agonists by combining the agonistic actions of GLP-1, glucagon and GIP in one molecule leads to a therapeutic principle with antidiabetic action and a pronounced weight lowering effect superior to pure GLP-1 agonists, which glucagon-receptor mediated increased satiety and energy expenditure as well as GIP receptor mediated increased insulin secretion [85–88].

The first triple receptor agonist, a hybrid of GIPR/GLP-1 R/GCGR tri-agonist, was developed by Richard Di Marchi and Matthias Tschöp [88]. Currently, WO2015067716 describes glucagon analogs with triple agonist activity [89], and WO2016198604 describes analogs of exendin-4 itself having triple agonistic activity [56]. US20180155406 and WO2018100135 applied by Sanofi disclose triple receptor agonists based on exendin-4, the peptides they obtained have balanced agonistic activity on the three receptors [90,91]. These peptides are derived from exendin-4 wherein at least the amino acid at position 14 bears a side chain for a prolonged half-life. WO2019229225 relates to a hyaluronic

Table 2. Some representative patents relate to GLP-1 R/GCGR agonists.

Patent (Assignees)	Title	Feature modification	Highlights
WO2016090628 (Beijing Hanmi Pharmaceutical Co., Ltd)	Oxygen regulating peptide (OXM) analogues, their synthesis and application	OXM analogues comprising substitutions of the 2nd Ser to Aib, the 16th and Ser and the 21st Asp to Glu	Prolonging the pharmacokinetic properties
WO2020019813 (China Pharmaceutical University)	Preparation of oxyntomodulin (OXM) hybrid peptide for reduction of blood glucose	Conjugation of a fatty acid chain with hybrid of OXM and Exenatide	Longer pharmacological action and greater weight loss effect
WO2016166289 (Zealand Pharma A/S)	Acylated glucagon analog peptides with increased selectivity for GLP-1 receptor for treatment of obesity, diabetes and other associated metabolic disorders.	Glucagon analogues with acylation	Increasing selectivity for the GLP-1 receptor comparing to GCGR
WO2015086731 (Sanofi)	Exendin-4 peptide analogs as dual GLP-1/GIP receptor agonists and their therapeutic use	OXM analogues comprising substitution of Tyr to Leu at position 10, Tyr to Gln at position 13	Improving biophysical properties as solubility or aggregation behavior in solution
WO2017074798 (Merck Sharp & Dohme Corp.)	Long-acting coagonists of the glucagon and GLP-1 receptors.	GLP-1(7–36) analogues comprising substitutions of the 3rd Glu to Gln, the 15th Glu to Asp, the 17th Gln to Arg, the 23rd Ile to Val, the 29th Gly to Thr	Blood serum half-life of a week
CN108341879 (Tianjin Institute of Pharmaceutical Research Co., Ltd.)	Chimeric polypeptide and application thereof	Conjugation of PEG with modified OXM dimer or hybrid peptide of GLP-1 R/GCGR	Better weight loss effect than liraglutide

acid conjugate which provides a GLP-1 R/GCGR/GIPR triple agonist release from a subcutaneous depot in an active form over the time period of at least 6 days after administration [92]. This helps patients to reduce the frequency of injections, while being able to maintain optimal control of the plasma levels and consequently blood glucose. Additionally, the conjugate according to this invention may release the triple receptor agonist in a release profile resulting in a very flat pharmacokinetic profile of the agonist leading to a lower risk of Cmax-related side effects. WO2019125929 and WO2019125938 applied by Eli Lilly disclose incretin analogs with balanced activity of the GIPR, GLP-1 R and GCGR, which allows for administration of doses that provide sufficient activity at each receptor to provide the benefits of agonism of those receptors while avoiding unwanted side effects [93,94]. The incretin analogs can result in enhanced glucose control, metabolic benefits such as body weight lowering and/or improved body composition, lipid benefits such as proprotein convertase subtilisin/kexin type 9 (PCSK9) lowering.

WO2015067716 provides GLP-1 R/GCGR/GIPR triple agonists which are superior to existing GLP-1 analogues by improving glycemic control and enhancing body weight loss which is possibly due to the better preservation of islet and β-cells [89]. WO2017116204 provides another series of triple activators which may contain intramolecular bridges (e.g. covalent or non-covalent bridges), especially in the form of rings between amino acids 16 and 20 of the peptide [95]. The inventors also conjugated the triple agonists with IgG Fc fusion protein to get persistent conjugate [96]Table 3.

4. Patents related to the fusion protein

Fusion proteins are products of fusion genes, and can also be obtained by fusing one or two proteins through biological or chemical methods. Generally, in order to obtain an ideal drug, GLP-1 needs to select different proteins for fusion. To address the shortcomings of GLP-1 being rapidly cleared by DPP-4 in vivo and lack of effectiveness, one of the strategies is fusing GLP-1 analogues with antibody. Currently, the longest-acting of GLP-1 agonists dulaglutide which is a fusion of an IgG4-Fc fragment to the GLP-1 analogues can be administered once per week. The antibody used for fusion has the biological activity of specifically recognizing GLP-1 R without hindering the binding of GLP-1 receptor. Its high affinity and stability with the receptor can activate GLP-1 receptor for a long time, consequently, the effective time and potency of its binding to the receptor promote greatly.

WO2015000413 discloses an anthropogenic GLP-1 recombinant protein molecule fused with an anthropogenic immune globulin subtype (IgG2) Fc section. The fusion protein has preserved biological activity of GLP-1, and prolonged half-life in vivo [97]. In order to overcome the problems regarding potential immunogenicity and effect or activity associated with the use of GLP-1-Fc fusions, the fusion protein of the invention have multiple amino acid residue substitutions in the GLP-1 portion and Fc portion, these substitutions provide potential increase in vivo stability, reduce immunogenicity and eliminate effects or functions. WO2015021871 discloses an antibody that can specially bind to GLP-1 R [98]. In this patent, the GLP-1 portion is fused to the light and heavy chains of the antibody via a peptide linker rich in Gly and Ser. These two amino acids have smaller side chains, the linker sequence has considerable flexibility which allows GLP-1 to interact freely with GLP-1R. At the same time, the alternately appear of Gly and Ser can avoid excessive and repetitive introduction of unnecessary immunogenicity into the fusion protein. Another exendin-4 derivative fusion protein uses IgG2 Fc variant in the hinge region of human IgG2 containing mutations of Pro 331

Table 3. Patents relate to GLP-1 R/GCGR/GIPR receptor agonists.

Patent (Assignees)	Title	Feature modification based on exendin-4 sequence	EC_{50}(pM)		
			GLP-1 receptor	GCG receptor	GIP receptor
US20180155406 (Sanofi)	New compounds as peptidic trigonal GLP1/glucagon/GIP receptor agonists	Gly2′ Aib; Gln3′ His; Gln13′ Leu; Met14′ Lys[gGlu-gGlu-Palm]; Glu17′ Gln; Ala18′ Arg; Val19′ Gln; Leu21′ Glu; Asn28′ Ala; Ser32′ Pro; Gly34′ Aib; Ala35′ Lys; Ser39′ Lys.	1.4	2.3	2.1
WO2018100135 (Sanofi)	New compounds as peptidic GLP1/glucagon/GIP receptor agonists	Gly2′ Aib; Gln3′ His; Met14′ Leu; Glu15′ Asp; Glu17′ Gln; Ala18′ Leu; Val19′ Ala; Leu21′ Asp; Lys27′ Ile; Asn28′ Ala; Ala35′ Lys; Ser39′ Lys.	2.6	24.7	5.6
WO2016198604 (Sanofi)	Exendin-4 Derivatives as Dual GLP-1/Glucagon Receptor Agonists	Gly2′ Aib; Gln3′ His; Met14′ Leu; Glu15′ Asp; Glu17′ Gln; Ala18′ Leu; Val19′ Ala; Leu21′ Asp; Lys27′ Ile; Asn28′ Ala; Ala35′ Lys; Ser39′ Lys.	2.1	7.9	680
WO2019125929 (Eli Lilly)	Incretin Analogs and Uses Thereof	His1′ Tyr; Ala2′ Aib; Glu3′ Gln; Phe6′ αMeF(2 F); Leu10′ Tyr; Lys12′ Ile; Gln13′ Leu; Met14′ Leu; Glu15′ Asp; Glu16′ Lys; Glu17′ Lys-fatty acid; Val19′ Gln; Arg20′ His; Leu21′ Ala; Trp25′ Tyr; Lys26′ Leu; Asn27′ Glu;	29.3	34.9	11.5
WO2019125938 (Eli Lilly)	Incretin Analogs and Uses Thereof	His1′ Tyr; Ala2′ Aib; Glu3′ Gln; Leu10′ Tyr; Lys12′ Ile; Gln13′ αMeL; Met14′ Leu; Glu15′ Asp; Glu16′ Lys; Glu17′ Lys-fatty acid; Val19′ αMeK; Arg20′ His; Leu21′ Ala; Trp25′ Tyr; Lys26′ Leu; Asn27′ Glu;	22.6	75.7	147

to Ser, Thr 250 to Gln, and Met 428 to Leu to further reduce its immunogenicity [99]. Another patent shows that Fc mutant is preferably modified by changing Asn 434 to Ala [100]. The higher safety of the peptide can also be used at higher doses, which greatly reduces the frequency of administration. WO2017062334 relates a fusion protein comprising an antibody conjugated to a glucagon analogues which have been modified to be resistant to cleavage by DPP-4, have long half-life in vivo and enable to active both GLP-1R and GCGR [101].

Amylin is a peptide hormone which can aid in the digestive process by helping to control the rate of digestion [102]. CN104558198 and CN108424460 provide a fusion protein of GLP-1 analog fusing with amylin analog, which has dual physiological activities of GLP-1 and amylin with long-acting function that can achieve synergistic hypoglycemia accompanying weight loss [103,104]. Human serum albumin (HSA) is a soluble monomeric protein that makes up half of the total protein in the blood. CN105884901 provides a new drug which is a recombinant HSA/GLP-1 fusion protein, this fusion can significantly increase the stability of the therapeutic protein in serum and achieve the long-term effect of protein drugs [105].

The terminal peptide of human chorionic gonadotropin B chain (CTP) also has the effect of prolonging the half-life of certain proteins in vivo. It is found that fusion of CTP peptide and Fc fragment at the C-terminus of exendin-4 and its analogues can bring a synergistic effect to resist renal clearance. In particular, CTP at the N-terminus of Fc also has a relatively stable three-dimensional conformation, which promotes the independent folding of exendin-4 analogues and the Fc segment to form a more ideal three-dimensional conformation indicating that CTP is working as a part of the linker peptide. The obtained compounds exhibit a longer half-life and higher biological activity and milder adverse effect than dulaglutide [106].

Fc fusion proteins are often homo-dimers, however, heterodimers can also be constructed. WO2016077806 discloses a fusion protein comprising two polypeptides, and the peptides which are randomly chosen from a GLP-1 analogue, a glucagon analogue, a GIP analogue or an OXM analogue [107]. The fusion protein provided by WO2020048494 is found for the first time existing in the form of a tetramer, which is more stable than a homodimer Fc fusion protein and effectively prolongs the in vivo half-life [108]. The efficacy obtained from a dual receptor agonist is synergistically improved in comparison to either the native protein agonist or a construct single receptor. WO2018166461, CN110128525, and CN109836486 provide a dual-target fusion protein containing GLP-1 and fibroblast growth factor 21 (FGF21) linked through an immunoglobulin Fc portion, these new compounds have better stability and significantly prolong half-life, and exhibit synergistic effects in reducing blood glucose, lipid, and body weight [109–112].

To further strengthen the weight loss effect of GLP-1 derivatives, Novo Nordisk constructs a new compound targeting areas in the brain involved in the regulation of body weight and an allosteric ligand to receptor located in the blood-brain barrier such as the transferrin receptor. Exemplary fusions exhibit an increased binding to brain regions expressing the GLP-1 receptor as compared to fusions or conjugates with inactive control Fab's. In vivo mice studies confirm increased reduction in food intake as well as weight loss for the active construct compared to the inactive one [113]. The above-mentioned structures are summarized in Table 4.

5. Patents related to the preparation and association with other drugs

In order to improve the solubility and stability of the drug, it is often necessary to modify the structure of the drug or use drug excipients [114]. CN104587453 provides a GLP-1 derivatives particle complex which is stable and has a slow-release effect to realize the long-term hypoglycemic and better control of the body weight [115]. WO2016127887 discloses a stabilized solution preparation of a pharmaceutical GLP-1R antibody fusion protein, which comprises a final concentration of about 0.1–100 mg/ml of GLP-1R antibody fusion protein, a concentration of 5–30 mM citrate buffer, and a final concentration of 0.01% – 0.2% Tween-80 and L-Arg with a final concentration of 80–200 mM, and a pH of 5 – 8 [116]. This stable formulation improves the solubility of the GLP-1R antibody fusion protein and its stability under the special circumstances, such as at high temperatures.

Nowadays, the marketed products of GLP-1 injection require to store at 2–8°C, in order to improve patients' convenience and shipment logistics, there is a need to improve the stability of compositions of GLP-1RAs. WO2018115901 discloses an aqueous solution composition comprising a GLP-1RA as an active ingredient and multivalent anions having a charge of at least minus 2 as stabilizing agent, the peptide can be stable at 30°C for 9–14 weeks[117]. WO2018210919 relates to compositions comprising liraglutide and thiol-containing excipient to improve the storage stability [118]. Also, phenol can stabilize the liquid preparation in some extent. WO2016077220 provides pharmaceutical compositions comprising GLP-1/GIP co-agonist peptide, phenol, Histidine, trehalose, and water for injection [119]. In WO2019038412 and WO2020084126, histidine and phenol were used for stabilizing semaglutide. Thus, the composition comprising stabilizers have improved chemical and/or physical stability. The improved stability results in benefits for the patient in form of a longer shelf-life and a longer in-use period [120–122].

CN106074376 relates to a GLP-1 sustained release nano preparation which is formed by distearoylphosphatidylethanolamine-polyethylene glycol (DSPE-PEG) nano micelles [123]. Encapsulating GLP-1 into micelles can avoid GLP-1's rapid kidney filtration and inactivation of enzyme metabolism so that prolong the half-life time in vivo to 48 h. Dhal et al reported hyaluronic acid as a suitable carrier for drug conjugates [124]. Kong et al reported an exendin-4-hyaluronic acid conjugate which showed a glucose lowering effect over 3 days in mice [125]. On the basis of above-mentioned patents, Sanofi have applied its invention relates a crosslinked hyaluronic acid which has a longer residence time as a local depot at the application site. This conjugate can keep a GLP-1/GCGR agonist in an active form for at least 6 days [126].

The oral route is desirable for administration due to its noninvasive nature and has a great potential to decrease the patient's discomfort related to administration. However, oral administration of GLP-1 agonists is challenged by poor bioavailability. So far, oral semaglutide tablets are the first approved GLP-1 agonist. Novo Nordisk applied for the tablets comprising GLP-1 agonists and an enteric coating in 2016. One invention relates to solid pharmaceutical compositions orally comprising a GLP-1 agonist, an absorption enhancer which is a salt of medium-chain fatty acid, and an enteric coating. The bioavailability of the GLP-1 agonist is about 2.7% in dogs [127]. Another invention relates to pharmaceutical compositions comprising a tablet core and an immediate release coating, while the tablet core comprises a GLP-1 peptide and an absorption enhancer [128]. Novo Nordisk also applied a solid composition comprising a GLP-1 derivative and dapagliflozin or with or without a salt of NAC to further improve its pharmaceutical composition for oral administration of GLP-1 peptide [129–131].

Another oral GLP-1 preparation constructs recombinant probiotic bacteria containing GLP-1 mutants, which can be prepared into various types of solid and liquid preparations to realize oral administration, and avoid the pain of long-term injection of patients. At the same time, after human take it orally, the genetically engineered probiotic bacteria can survive and colonize the human intestine and become a functional in vivo bioreactor, which continuously produces and secretes GLP-1 mutant polypeptides, thereby playing a role of continuous hypoglycemic effect and treatment of obesity [132–134].

Co-administration is one of the strategies to better exert the therapeutic effect of GLP-1RAs. US20200155487 discloses a combination treatment of obesity with Liraglutide and seladelpar which is an orally active, potent agonist of PPARδ(2 nM) [135]. CN109010310 provides a nanoparticles composition comprising orlistat, GLP-1RAs and a copolymer [136]. The composition can realize the combined oral administration of orlistat and GLP-1RAs, and has a good weight loss effect. CN110759991 introduces small molecular derivatives of gefilozil which have high serum protein binding rate and high lipid-lowering effect, resulting in high-glycemic activity, high stability and long-acting hypoglycemic GLP-1 derivatives [137].

Macrophage inhibitory cytokine-1 (MIC-1) is a distant member of the TGF-beta super family. Accumulating evidences support the therapeutic utility of MIC-1 in metabolic disorders such as obesity [138]. Transgenic mice overexpress MIC-1 gain less weight and body fat both on a normal low-fat diet and on a high-fat diet [139]. WO2019048660 discloses a method of prevention or treatment of obesity, wherein a MIC-1 compound is administered simultaneously, separately or sequentially with a GLP-1 compound [140]. WO2019139934 discloses compositions comprising satiety peptides (PYY, GLP-1, OXM, and cholecystokinin) and DPP-4 inhibitors to treat obesity [141].

Administration of FGF21 compounds can decrease the body weight, blood glucose and plasma lipids as well as improve insulin sensitivity [142,143]. Sanofi applied for a combination of an FGF21 compound and a GLP-1RA. FGF21 and GLP-1 exert their pharmacological effects at different plasma concentrations. So, comparing to the fusion peptide of FGF21 and GLP-1, it may be more appropriate to take the two compounds separately [144,145]. Table 5

6. Conclusion

Obesity is an increasing problem worldwide and requires new and improved treatment options. Mimicking gut hormones mark a new era of anti-obesity drugs. So far, GLP-1-based therapy in the form of liraglutide has overall tolerable risks and mainly mild and transient adverse events. The efficacy of liraglutide is comparable to that of other anti-obesity drugs and significantly increases the chance of achieving and maintaining clinically meaningful weight loss. The strategy of designing and synthesizing long-acting analogs, multifunctional agonists, and combination drugs to improve patient's compliance and enhance therapeutic effects has been continuously attempted. Review of recent patents and the preclinical/clinical compounds indicates that several different approaches have been used to further enhance the anti-obesity effect of GLP-1RAs. One of the approaches is to modify the peptide by amino acid substitution and conjugate it with fatty acid or PEG, which can promote half-time in vivo. Another approach is to develop dual/triple agonists, these kinds of compounds exhibit synergistic effect by simultaneously stimulating multiple receptors, but attention should be paid to the balance of agonistic activity between receptors. It is confirmed that some small molecules have GLP-1 receptor

Table 4. Patents of recombinant fusion proteins of GLP-1.

Patent (Assignees)	Title	Fused molecules	Highlights
WO2020048494 (Zhejiang Palo Alto Pharmaceuticals)	Long-acting recombinant GLP1-Fc-CD47 protein and its preparation and use thereof	GLP-1 agonist, Fc region of human IgG4 and CD47 signal polypeptide	More stable in tetramer and reducing macrophage clearance
WO2019243502 (Novo Nordisk)	Novel compounds for treatment of obesity	GLP-1 agonists and transferrin	Targeting to blood-brain barrier (BBB)
WO2018024162 (Sunshine Lake Pharma)	GLP-1 fusion protein comprising mutated immunoglobulin Fc portion	A GLP-1 agonist and Fc region of human IgGl, IgG2, IgG3 or IgG4	An increased half-life
WO2018166461 (Sunshine Lake Pharma)	Dual-target fusion proteins comprising the Fc portion of an immunoglobulin	An FGF21 compound, a GLP-1 agonist and Fc region of human IgG4	Dual-target fusion protein
WO2017074123 (Yuhan Corporation)	Dual function proteins and pharmaceutical composition comprising same	An FGF21 compound a, a GLP-1 agonist and the Fc region of immunoglobulin	High stability; avoiding potential Adverse effects
WO2015000413 (Genor Biopharma Co., Ltd.)	Long-acting hypoglycemic fusion protein	GLP-1 and Fc region of human IgG1	An increased half-life
WO2015021871 (Gmax Biopharm LLC)	Antibody specifically binding to GLP-1R and fusion protein thereof with GLP-1	GLP-1 antibody and GLP-1 agonist	Immunogenicity reducing
CN109836486 (Beijing Shuangyin Biotechnology Co., Ltd.)	Fusion protein of fibroblast growth factor 21 variant and its use thereof	An FGF21 compound, a GLP-1R agonist and Fc region of human IgG4	Dual-target fusion protein
WO2019154189 (Guangdong East Sunshine Pharmaceutical)	Fusion protein of fibroblast growth factor 21 variant and its use thereof	An FGF21 variant, a GLP-1R agonist and Fc region of human IgG4	Dual-target fusion protein
CN104558198 (Chengdu Beite Biotechnology)	Preparation and use of fusion protein of GLP-1 analogue and amylin analogue	A GLP-1 agonist, amylin analogues and Fc region of human IgGl, IgG2, IgG3 or IgG4	Helping to control the rate of digestion
CN106279430 (Shanghai anyuan Biotechnology)	Exendin-4 analog fusion protein, its preparation method and thereof	Exendin-4 analogs and Fc region of human IgG2	Immunogenicity reducing
CN108424460 (Chengdu Beite Biotechnology)	Preparation and application of fusion protein of GLP-1 analogues and davalintide analogues	GLP-1 analogues and davalintide analogues	Helping to control the rate of digestion
CN105884901 (Beijing meifuyuan Biotechnology)	Recombinant human serum albumin/glucagon peptide fusion protein with function of continuously controlling blood sugar level	A GLP-1 agonist and r Human Serum Albumin	Continuously controlling blood glucose level
CN106117370 (Shanghai anyuan Biotechnology)	Fusion protein of highly glycosylated Exendin-4 and its analogs, preparation method and use thereof	Exendin-4 analogs, at least 1 human chorionic gonadotropin β subunit terminal peptide rigid unit and human immunoglobulin Fc fragment	Better activity and an increased half-life
WO2016077806 (Askgene pharm)	Fusion proteins with dual receptor agonist activities	Two of GLP-1R agonistic peptides and two of Fc region	Dual receptor agonist activities
WO2017062334 (Merck)	Antibody peptide conjugates that have agonist activity at both the glucagon and glucagon-like peptide-1 receptors	An antibody peptide and a GCGR/GLP-1R coagonist peptide	Dual receptor agonist activities

agonistic activity comparable to or even stronger than GLP-1 derivatives. But the weight loss ability of small molecule GLP-1RAs has yet to be studied. Designing recombinant fusion proteins is also a useful way to prolong the circle time in the body, but the immunogenicity emerges inevitably. Recent patents indicate that it is also a good choice to combine GLP-1 analogues with other weight-loss drugs or lipid-lowering drugs. Until now, there is still a lack of effective, long-term, noninvasive treatment for obesity, 'one treatment fits all' approach to obesity may associated with highly variable efficacy and outcomes.

7. Expert opinion

Nowadays, when people's strong desire to lose weight is in great contradiction with the existing diet drugs with poor efficacy, developing GLP-1RAs is a good choice. At present, GLP-1RAs occupy a large market share in the field of diabetes treatment, while only liraglutide has been approved for the treatment of obesity. Semaglutide is now under phase III clinical trials for the treatment of obesity, and preliminary research results indicate that it is promising to be the next drug approved for weight loss.

Chemical conjugation and fusion proteins strategies are widely used to enhance the plasma half-life and thus reduce the frequency of injection, but these compounds cannot provide a controlled release system for a more extended duration of action. Therefore, appropriate pharmaceutical preparation strategies can not only extend the preservation time of the peptides, but also achieve a controlled release in vivo.

Achieving a certain weight loss effect requires a dose several times higher than the dose of hypoglycemic of GLP-1RAs. Combining GLP-1 derivatives with other compounds may lower the potential risk of GLP-1-mediated adverse effects. As the semaglutide tablets approved by FDA in 2019 is the first orally

Table 5. Patents of Dosage form of GLP-1 agonists.

Patent (Assignees)	Title	Dosage form and content	Highlights
WO2020084126 (Novo Nordisk)	Stable semaglutide compositions and uses thereof	Liquid compositions of the GLP-1 peptide semaglutide comprising a stabilizer such as histidine.	The improved stability results in benefits for the patient in form of a longer shelf-life and a longer in-use period.
WO2019038412 (Novo Nordisk)	GLP-1 compositions and uses thereof	Liquid Composition comprising semaglutide, no more than 0.01%(w/w) phenol, at least 60%w/w water, and optionally one or more pharmaceutically acceptable excipients.	Higher stability and can be for parenteral administration.
WO2019149880 (Novo Nordisk)	Solid compositions comprising a GLP-1 agonist, a salt of n-(8-(2-hydroxybenzoyl) amino) caprylic acid and a lubricant	Solid tablet, sachet or capsule composition comprising a GLP-1 receptor agonist and a salt of N-(8-(2-hydroxybenzoyl) amino) caprylic acid	Accelerating absorption of the GLP-1 agonist within 15–30 minutes after administration and thereby improved exposure of the GLP-1 agonist by oral administration
WO2019215063 (Novo Nordisk)	Solid compositions comprising a GLP-1 agonist and a salt of n-(8-(2-hydroxybenzoyl) amino) caprylic acid	Solid tablet, sachet or capsule composition comprising a GLP-1 receptor agonist, a salt of N-(8-(2-(hydroxybenzoyl)amino) caprylic acid and a hydrotrope	Accelerating absorption of the GLP-1 agonist within 15–30 minutes after administration and thereby improved exposure of the GLP-1 agonist by oral administration
WO2018210919 (Novo Nordisk)	GLP-1 compositions and uses thereof	Liquid compositions comprising the GLP-1 peptide liraglutide and a thiol-containing excipient, at least 90%(w/w) water	Improving storage stability
WO2018224689 (Novo Nordisk)	Solid compositions for oral administration	Solid tablet, sachet or capsule composition comprising (i) a GLP-1 derivative and dapagliflozin, or (ii) a GLP-1 derivative and a salt of NAC in combination with a sodium glucose linked transporter 2 (SGLT2) inhibitor.	Accelerating absorption of the GLP-1 agonist within 15–30 minutes after administration and thereby improved exposure of the GLP-1 agonist by oral administration
WO2018115901 (Arecor limited)	Glucagon-like peptide 1 (GLP-1) receptor agonist compositions	Liquid solution composition comprising a GLP-1 receptor agonist and multivalent anions having a charge of at least minus 2.	(i) Longer shelf-life, (ii) higher in-use temperature, and (iii) storage at room temperature
WO2016120378 (Novo Nordisk)	Tablets comprising GLP-1 agonist and enteric coating	Solid tablet composition comprising a GLP-1 receptor agonist, an absorption enhancer and an enteric coating.	Enteric coated solid dosage forms pass through the stomach and release the drug substance when the target pH/site is reached in the intestine.
WO2016120380 (Novo Nordisk)	Pharmaceutical composition for oral GLP-1 administration comprising a tablet core and immediate release coating	Solid tablet composition comprising a GLP-1 receptor agonist, an absorption enhancer and an enteric coating.	Enteric coated solid dosage forms pass through the stomach and release the drug substance when the target pH/site is reached in the intestine.
CN106074376 (Jiangsu Normal University)	GLP-1 sustained-release nano preparation, preparation method and application	Nano sustained-release composition comprising a GLP-1 receptor agonist and matrix of Distearoylphosphatidylethanolamine-polyethylene glycol	(i) Avoiding GLP-1's rapid renal filtration and inactivation by enzyme metabolism. (ii) Prolonging the half-life and bioactive time in vivo.
CN104587453 (East China Normal University)	GLP-1 derivative particle complex and its preparation method and application	Particle complex comprising a GLP-1 receptor agonist and modified polymer of γ -PGA-L-PAE	Stable in solution (ii) Resisting the degradation of GLP-1 derivatives by DPPIV enzyme. (ii) Prolonging the circulation time of the body with slow-release effect

administration of GLP-1RA, converting injection into oral preparations will also be a right direction of scientific researchers and pharmaceutical companies. After all, long-term continuous injections bring great inconvenience to patients. So, orally administered GLP-1RAs have the potential to dramatically affect the market.

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Declaration of interest

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