Proceedings of ICBioMed 2026 Symposium: Biomedical Engineering and Smart Medicine
DOI: 10.54254/2753-8818/2026.HZ37364

Structural Modifications of Semaglutide and GLP-1-Like

Peng Zeng

Department of Pharmacy, Southwest University, ChongQing, China
andsomezp@email.swu.edu.cn

Abstract. In China, the proportion of adults with type 2 diabetes (T2DM) is as high as 12%, and half of the population is overweight or obese. Currently, Glucagon-like peptide-1 (GLP-1) drugs have significant pharmacological effects in weight loss and the treatment of T2DM. In terms of drug development, progress is gradually moving from single-target injectables toward oral small molecules, GLP-1/GIP/glucagon multi-target agonists, combination formulations, and long-acting formulations. This article mainly studies how semaglutide is able to significantly extend its half-life through structural modification, allowing it to be administered once a week. Finally, the study concluded that semaglutide prevents cleavage by the DPP-4 enzyme through modification at position 8, increases circulation area beyond the glomerular filtration rate through albumin binding at position 26, and ensures receptor affinity and albumin binding at position 34 to maintain the effects of the modification at position 26. These three aspects together significantly regulate and greatly extend the half-life. This kind of research provides a basis for designing long-acting GLP-1 receptor agonists. In the future, this modification strategy could be used to develop multi-target agonists, helping to improve and upgrade drugs for metabolic disease treatment.

Keywords: Type 2 diabetes, Glucagon-like peptide-1 (GLP-1), gastric inhibitory peptide(GIP), Dipeptidyl peptidase (4DPP-4) enzyme

1. Introduction

According to the China Type 2 Diabetes (T2DM) Prevention and Treatment Guidelines (2020 edition), 12. 8% of Chinese adults have diabetes, and 90%-95% of them have T2DM [1]. According to a report from the National Health Commission of China, up to 50% of people in China are overweight or obese [1, 2]. Obesity is a whole-body metabolic disease and has been proven to be an independent risk factor for many other diseases [3, 4].

Currently, the treatment for obesity and T2DM mainly includes lifestyle changes, medication, and surgery. Although lifestyle changes can help improve blood sugar and some cardiovascular risk factors, it is hard to maintain long-term weight loss and reduce major cardiovascular events. As for medication, there are mainly two approaches right now: the traditional one, using metformin to treat T2DM, and the newer approach with GLP-1 receptor agonists (GLP-1RAs) that have clear heart and kidney protective effects. Surgery, on the other hand, comes with risks like being irreversible, surgical and anesthesia complications, and serious gastrointestinal side effects. Currently, GLP-

© 2026 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/2026.HZ37364

1RAs clearly have protective effects on the heart and kidneys, and it not only significantly reduces cardiovascular events but also work well for weight loss [5].

GLP-1 is a hormone made by L-cells in the gut. GLP-1 receptor agonists attach specifically to GLP-1. These drugs affect the pancreas using two paths called EPAC and PKA. This helps manage T2DM. They also slow down how the stomach empties. They make a person feel fuller. This effect helps with losing weight. The GLP-1RAs currently approved by the FDA mainly include liraglutide, semaglutide, dulaglutide, and tirzepatide. It is a dual-target receptor agonist for GIP (gastric inhibitory peptide) and GLP-1 when it comes to tirzepatide. Among them, semaglutide is the GLP-1RA drug with the most clinical research projects worldwide, covering the widest range of people and having the highest level of evidence. Its clinical exploration has expanded from initially lowering blood sugar and reducing weight to multidimensional metabolic protection, including heart and kidney health. The related research results support the ongoing expansion of its clinical applications.

This article mainly looks into the specific mechanism by which semaglutide achieves an extended half-life through structural modification. The main focus is on studying how GLP-1 is metabolized in the body and then modifying its structure to avoid being broken down too quickly by enzymes, so its half-life is greatly extended to have a therapeutic effect. It also provides new ideas for structurally modifying drugs for longer-lasting effects and multiple targets in future research, helping to improve and upgrade treatments for metabolic diseases.

2. Pathology of T2DM and the pharmacological mechanism of GLP-1

2.1. Pathological mechanism

The core pathological mechanism of T2DM is insulin resistance with a steady decline of pancreatic β-cell function involving the combined abnormalities of metabolic pathways, cytokines, and signaling pathways in many tissues. After insulin binds to receptors on target cells, insulin normally triggers metabolic effects through the IRS-PI3K-Akt pathway; in a state of insulin resistance, insulin receptor substrate (IRS) is abnormally phosphorylated on serine, leading to insufficient activation of this pathway. In muscles, Akt (serine protein kinase)-mediated translocation of GLUT4 (glucose transporter 4) is blocked, which suppresses glucose uptake and glycogen synthesis pathways. The blockage of Akt-mediated translocation of GLUT4 prevents muscles from breaking down glucose, in the body leading to more glucose being stored in the blood and causing blood glucose levels to rise. Lastly, in the liver, the pathways that normally suppress carboxykinase and glucose-6-phosphatase become weaker, which overactivates gluconeogenesis and glycogen breakdown. The weakening of the pathways that suppress carboxykinase and glucose-6-phosphatase makes the liver store more glucose, and because the signaling pathways are messed up the liver does not stop producing glucose, leading to higher blood glucose levels. So, it's because, on one hand, sugar can't be broken down, and on the other hand, sugar keeps being produced, and under this double effect, the pancreatic cells gradually lose function due to compensatory action.

2.2. Mechanism of action of GLP-1

2.2.1. Regulating pancreatic function

GLP-1 can increase glucose-dependent insulin release from pancreatic cells, keep glucagon levels down, and help avoid low blood sugar as much as possible. In incretins, after GLP-1 binds to GLP-

DOI: 10.54254/2753-8818/2026.HZ37364

1R, it activates GTP-binding proteins and stimulates adenylyl cyclase (AC) to produce cAMP. Then cAMP activates the exchange protein EPAC and protein kinase PKA, which further increases calcium levels, boosting insulin secretion. Also, this situation only gets activated when blood sugar is high, because when it's low or normal, the ATP/ADP ratio is low, the K-ATP channels on the cell membrane stay open, potassium ions flow out, the cell membrane hyperpolarizes, and the calcium channels close. Activating the GLP-1R signaling pathway can not only boost the biosynthesis and secretion of insulin, but also, since activating transcription factor 4 (ATF4) is a key effector in the cellular integrated stress response, GLP-1 can help relieve endoplasmic reticulum stress in β cells by enhancing ATF4 translation in a cAMP-dependent way, which might help maintain or even improve β cell function. Finally, after GLP-1 binds to its receptor, it can also promote SMS release and act on SSTR2 on the surface of pancreatic alpha cells, directly inhibiting glucagon secretion [6].

2.2.2. Regulation in other aspects

GLP-1 can change how food a person eats in two different ways. One way is that it stops the stomach and the small intestine from moving much as they usually do. The exact connections in the brain that make this happen are not fully understood. Also, this effect tends to go quickly. This is believed to be because many different signals in the body are working together, such as the PI3K-Akt-mTOR pathway. Another way GLP-1 works is by turning on brain cells called pro-opiomelanocortin or POMC. These brain cells help stop the body from wanting to eat. They also stop a signal called neuropeptide Y or NPY, which makes people want to eat more. GLP-1 also makes high-calorie foods less rewarding by changing how the brain's dopamine system works. This helps people eat less impulsively and snack less [6]. Glucagon is not working well as it should, so it can't attach to the receptors on liver cells. Through the cAMP/PKA path it makes the liver break down its stored sugar. At the time, insulin is not working as much as it should. This helps keep the liver from getting too full of fat [7].

3. Conformation of semaglutide

3.1. Insufficiency of natural GLP-1

Natural GLP-1 is released by L-cells in the distal intestine and the lining of the colon. It is a peptide from the incretin group, but it gets broken down and removed from the body very quickly, so it cannot be used directly as a treatment. Dipeptidyl peptidase 4 (DPP-4) is a protease that is found on cell surfaces. It is present in the epithelium, the vascular endothelium, the kidneys, and immune cells, with the most activity in the intestines. This enzyme can specifically find the alanine residue at position 8 of the N-terminal of the GLP-1 molecule. It. Removes the N-terminal dipeptide structure, which makes GLP-1 lose its ability to connect with the GLP-1 receptor. This is the way that GLP-1 is turned off in the body. Besides enzymatic degradation, the kidneys are another key organ for clearing GLP-1. A small amount of active GLP-1 that isn't broken down in the circulation can pass freely through the glomeruli. After it enters the tubules, the renal tubules reabsorb it. Then the tubule epithelial cells break it down using enzymes inside the cells. Only a small amount of the substance leaves the body in urine in its original form. Because of this clearance mechanism, GLP-1 has a plasma half-life of only about 2 minutes in the body. Almost half of the GLP-1 that comes out after meals gets turned off by DPP-4 in the gut before the GLP-1 ever reaches the blood. This means GLP-1 cannot stay at a high enough level in the blood to keep metabolism regulated. That's why natural GLP-1 probably can't be used directly as a drug [8].

DOI: 10.54254/2753-8818/2026.HZ37364

3.2. Structure modification process and results of semaglutide

3.2.1. The eighth modification process and result

The eighth residue of GLP-1 is alanine, and this alanine sits exactly at the DPP-4 enzyme's specific cleavage site. When the DPP-4 enzyme recognizes this alanine, the peptide chain is cut between the ninth amino acids, and GLP-1 immediately loses its ability to activate the GLP-1 receptor. To stop this cut while keeping GLP-1 affinity high, the Novo Nordisk team first tried mutations, such, as alanine-to-glycine, alanine-to-valine, and alanine-to-leucine. The results showed that although some resistance to degradation was achieved, the GLP-1 receptor affinity was greatly reduced and activity dropped, so all were discarded. They eventually chose a non-natural amino acid, α-amino isobutyric acid (Aib), as the substitute. The unique structure of Aib, with two methyl groups attached to its α-carbon, creates enough steric hindrance at the binding interface with DPP-4. This effectively blocks the enzyme's catalytic pocket from grabbing and cleaving the peptide bond between residues 8 and 9 [9-11].

3.2.2. The 34th modification process and result

In the GLP-1 (7-37) sequence, the amino acid at position 34 is lysine. Lysine at position 34 also carries a free amino group on its side chain. If lipidation is performed directly on the lysine at position 26 the chemicals in the reaction will also react with the amino group of lysine at position 34. This reaction creates by-products, such as double modifications and positional isomers of single modifications. These by-products make purification harder. Seriously lower the uniformity of the final drug quality. To avoid this problem, Novo Nordisk first tried a series of trial-and-error changes. They changed lysine at position 34 to alanine. The lysine-to-alanine change disturbed the charges and the shape of the peptide chain, which greatly reduced receptor affinity. That version was discarded. Next they changed lysine at position 34 to acid. The lysine-to-glutamic acid change reversed the charge disrupted the protein-binding shape and caused loss of activity. That version was also discarded. Finally, the Novo Nordisk research team replaced lysine at position 34 with arginine. Because arginine and lysine are both positively charged and have side-chain lengths, this replacement kept the charge pattern in that region unchanged and did not hurt GLP-1 receptor binding. Moreover, arginine's side chain has a guanidino group, not an amino group like lysine, and the guanidino group is much less chemically reactive than the amino group, meaning it cannot form stable covalent bonds with the lipidation reagent. This means that during the subsequent lipidation process, the reagent can only bind to lysine at position 26, completely eliminating the possibility of non-specific reactions at position 34 [9-11].

3.2.3. The 26th modification process and result

In the design, both the length of the fatty acid chain and the polarity of the linker arm affect receptor affinity and albumin binding. To find the optimal combination, the Novo Nordisk research team created different combinations of fatty acid chains of varying lengths and linkers of different structures, testing over 50 combinations for in vitro activity and pharmacokinetics. They attached a C18 fatty chain to the side-chain amino group of lysine at position 26 through a hydrophilic linker. This C18 fatty diacid chain can bind repeatedly to albumin. This binding makes the whole molecule larger, so it goes past the glomerular filtration threshold. The C18 fatty diacid chain also takes advantage of albumin's time in the blood, giving the molecule a much longer half-life [9-11].

DOI: 10.54254/2753-8818/2026.HZ37364

Novo Nordisk's research team found that as the fatty acid chain length gradually extends from C12 to C18, the derivatives show a significant increase in albumin affinity; however, when the chain length continues to extend to C20 or even C22, the increase in albumin affinity starts to decline. This is because excessively long chains disrupt the molecule's lipophilic-hydrophilic balance, leading to unstable molecular aggregates in an aqueous physiological environment. The terminal carboxyl group of a dicarboxylic acid can form extra electrostatic interactions with the positively charged residues inside albumin's fatty acid binding pockets, whereas a monocarboxylic acid's methyl group cannot create such interactions [9-11].

The research team also found that directly attaching C18 dicarboxylic acid to Lys26 makes the molecule too hydrophobic, which interferes with GLP-1R binding and causes loss of efficacy. So, a hydrophilic flexible linker is needed. The linker keeps the GLP-1 receptor and fatty acid chain properly spaced, preventing the hydrophobic chain from messing with the peptide's binding to the receptor and losing receptor affinity. In semaglutide, the linker structure is γGlu-2xOEG. At the beginning, the Novo Nordisk team tried connecting with several OEGs. Using 0 or 1 OEG made the fatty acid too close to the peptide chain, causing a lot of hindrance. This steric hindrance seriously inhibited receptor binding, drastically increased the IC50, and made the drug less effective, so that approach was discarded. Using 3 OEGs made the linker too long and flexible; the fatty acid then had much freedom to move, preventing it from fitting stably into the albumin pocket, significantly reducing albumin affinity and losing long-acting properties, so that option was also discarded. In the end, they settled on a linker structure with two OEGs. Among them, γGlu forms an amide bond with the amino group of lysine at position 26 through its γ-carboxyl side chain, which keeps the albumin-binding group and the receptor-binding domain spatially separated. The carboxyl group of γGlu ionizes to a negative charge in physiological conditions, enhancing the molecule's overall water solubility. During the process of binding to albumin, the flexible structure of OEG allows the fatty acid chain to freely adjust its conformation, making it more compatible with albumin's fatty acid binding pocket. At the same time, the hydrophilic OEG unit balances the hydrophobicity of the fatty acid chain, preventing a drop in water solubility and ensuring good absorption after subcutaneous injection [9-11]. Ultimately, the γGlu-2xOEG connecting arm was coupled with a C18 fatty diacid chain, enabling the construct to avoid glomerular filtration while maintaining receptor affinity and albumin-binding capacity.

3.3. Pharmacokinetics and safety of semaglutide

Semaglutide is used for injection because this lets the drug be absorbed at a rate that matches long-acting pharmacokinetics. The drug is released slowly under the skin and is taken up gradually. It stays in the body longer [12, 13]. Its strong binding to albumin also slows how fast it breaks down and leaves the body. It is best to change the injection site each time, using the abdomen, thighs, or upper arms. This helps the drug absorb evenly and keeps its effect steady. Smeglutide has a half-life of 7 days, so it is injected once a week. The injection does not depend on food. The amount absorbed is the same whether you take it before or after a meal [14, 15]. Studies show that giving exenatide daily can drop HbA1c by 0. 8% to 1. 0% and help people lose 2 to 3 kilograms. This effect is weaker than weekly semaglutide, which can lower HbA1c by about 1. 5% and cause weight loss of more than 15%. Because exenatide must be taken times a day and it has strong stomach side effects, fewer than 40% of patients keep using it, much lower than the adherence for once-weekly semaglutide. Doctors usually use exenatide for short-term treatment when blood sugar after meals is very high. The common side effects of semaglutide are stomach problems such, as nausea, vomiting,

DOI: 10.54254/2753-8818/2026.HZ37364

diarrhea, constipation and stomach pain. These usually happen at the start of treatment. Get better with time.

4. Other GLP-1 RAs

4.1. Exenatide

Exenatide is a natural 39-peptide derived from the saliva of the Gila monster, with only 53% homology to human GLP-1, and there are two key natural optimizations. First, the second position at the N-terminus is glycine, replacing the eighth position alanine in human GLP-1. Because its spatial conformation doesn't fit the DPP-4 catalytic pocket, it can naturally resist DPP-4 degradation. Next, the serine-rich sequence from positions 30 to 39 on the C-terminal forms a unique secondary structure, naturally resisting DPP-4 enzyme degradation, with a half-life of about 2. 5 hours. This molecule has no fatty acid modification or linker arm, making it a pure native peptide. Because the non-human sequences don't fit well with the human GLP-1 receptor, their absolute affinity is much lower than that of liraglutide and semaglutide. Also, because it lacks an albumin-binding structure, the drug is completely free in the blood, has no long-lasting anchoring ability, and has a short half-life [12, 13]. Clinical studies have shown that injecting exenatide twice a day can lower HbA1c by 0. 8% to 1. 0% and help lose 2-3 kg, but its effectiveness is noticeably weaker than the weekly semaglutide formulation (which can lower HbA1c by about 1. 5% and lead to over 15% weight loss). And because it requires frequent dosing and has obvious gastrointestinal side effects, patients' long-term adherence is less than 40%, much lower than once-weekly semaglutide, so clinically it's mostly used for short-term intensive situations where post-meal blood sugar fluctuates a lot.

4.2. Liraglutide

Liraglutide, as the first-generation once-daily long-acting GLP-1 receptor agonist, uses a design approach with amino acid modifications and fatty acid side chain modifications to extend its half-life and improve resistance to enzymatic breakdown while keeping receptor affinity. Replacing the 8th alanine with α-aminoisobutyric acid can block the DPP-4 enzyme's catalytic pocket with the dimethyl group's steric hindrance, making it resistant to enzyme breakdown while keeping the human GLP-1 receptor affinity. Next, a C16 palmitic acid chain is attached to the lysine residue at position 26, which can reversibly bind to albumin through hydrophobic interactions, extending the half-life to about 13 hours. But this molecule doesn't have a hydrophilic linker or any other structural optimizations. Its receptor affinity is higher than exenatide, but albumin binding only relies on the hydrophobic effect of the 26th fatty acid, so the binding is limited and easily dissociates, making it not long-acting [11]. Clinical studies have shown that taking 1. 8mg of this molecule daily can lower HbA1c by 1. 1% to 1. 6% and help lose about 2 to 3 kg. The once-weekly semaglutide formulation performs significantly better in both lowering blood sugar and weight loss, and the weekly dosing schedule greatly improves patients' long-term adherence to medication.

In short exenatide is a peptide that comes from the saliva of Gila monsters that live in the Americas. Because of its properties exenatide can resist the breakdown by the enzyme DPP-4. Exenatide has no fatty acid additions and only lives in the body for 2. 5 hours. Therefore exenatide must be taken twice each day. Both liraglutide and semaglutide are made from the hormone GLP-1. They have been changed by putting an amino acid called Aib at the 8th spot to stop enzyme damage. Liraglutide adds a chain called C16 palmitic acid, at the 26th spot so it can stick to albumin. This gives liraglutide a life of 13 hours so liraglutide can be taken once a day. Semaglutide instead uses a

DOI: 10.54254/2753-8818/2026.HZ37364

C18 fatty diacid and a water-friendly linker to bind albumin stronger. This makes semaglutide about 7 days so semaglutide only needs to be taken once a week.

5. Conclusion

This article mainly studies the core pathological mechanisms of type 2 diabetes and the regulatory pathways of GLP-1 receptor agonists, and also how the substitution of Aib at position 8 in semaglutide's structural modification can better prevent it from being broken down by DPP-4. Replacing Lys with Arg at position 34 reduced the production of side reactions, improved production efficiency, and kept receptor affinity largely unaffected. The 26th compound uses a γGlu-2×OEG hydrophilic linker to attach a C18 fatty diacid for high-affinity albumin binding. Together, these three features extend the molecule's half-life to about 7 days, allowing for the clinical benefit of once-a-week dosing. This study provides new ideas for the rational molecular design of long-acting GLP-1 receptor agonists, offers approaches for modifying multi-target drugs, and also gives reusable technical insights for optimizing the structures of drugs for treating metabolic diseases. This article mainly focuses on molecular structure analysis, and there's still limited discussion on the details of GLP-1's signal regulation. Also, the specific side effects of GLP-1 haven't been clearly explained. Future research could take a closer look at how GLP-1 actually regulates various signaling pathways and thoroughly figure out the mechanisms behind its side effects, to avoid tragedies similar to the Fen-Phen incident.

References

[1] Chinese Diabetes Society of Chinese Medical Association. (2021). Guideline for the prevention and treatment of type 2 diabetes mellitus in China (2020 edition). *Chinese Journal of Diabetes Mellitus, 13*(4), 315–409. (In Chinese)

[2] National Health Commission of the People's Republic of China. (2020). Report on the nutrition and chronic disease status of Chinese residents (2020). National Health Commission of the People's Republic of China. (In Chinese)

[3] Chinese Society of Endocrinology, Chinese Society of Surgery, & Chinese Society of Nutrition. (2024). Guidelines for the diagnosis and treatment of obesity (2024 edition). *Chinese Journal of Endocrinology and Metabolism, 40*(12), 1001–1048. (In Chinese)

[4] International Agency for Research on Cancer. (2018). *IARC handbooks of cancer prevention: Volume 16. Body fatness*. International Agency for Research on Cancer.

[5] Li, J., Li, F., Niu, L., et al. (2024). Research progress on the mechanisms and effects of semaglutide in diabetic cardiomyopathy. *Journal of Medical Research, 53*(3), 26–30. (In Chinese)

[6] Drucker, D. J. (2018). Mechanisms of action and therapeutic application of glucagon-like peptide-1. *Cell Metabolism, 27*(4), 740–756. https://doi.org/10.1016/j.cmet.2018.03.001

[7] Armstrong, M. J., Gaunt, P., Aithal, G. P., et al. (2016). Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): A multicentre, double-blind, randomised, placebo-controlled phase 2 study. *The Lancet, 387*(10019), 679–690. https://doi.org/10.1016/S0140-6736(15)00803-X

[8] Tian, Q., & Hong, T. P. (2020). Advances in the mechanisms of action and clinical applications of glucagon-like peptide-1 receptor agonists. *Chinese Journal of Diabetes Mellitus, 12*(8), 622–625.

[9] Lau, J., Bloch, P., Schäffer, L., et al. (2015). Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. *Journal of Medicinal Chemistry, 58*(18), 7370–7380. https://doi.org/10.1021/acs.jmedchem.5b00726

[10] Knudsen, L. B., Nielsen, P. F., Huusfeldt, P. O., et al. (2000). Potent derivatives of glucagon-like peptide-1 with pharmacokinetic properties suitable for once daily administration. *Journal of Medicinal Chemistry, 43*(9), 1664–1669. https://doi.org/10.1021/jm9909645

[11] Knudsen, L. B., & Lau, J. (2019). The discovery and development of liraglutide and semaglutide. *Frontiers in Endocrinology, 10*, 155. https://doi.org/10.3389/fendo.2019.00155

[12] DeFronzo, R. A., Ratner, R. E., Han, J., et al. (2005). Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care, 28*(5), 1092–1100.

DOI: 10.54254/2753-8818/2026.HZ37364

https://doi.org/10.2337/diacare.28.5.1092

[13] Eng, J., Kleinman, W. A., Singh, L., et al. (1992). Isolation and characterization of exendin-4, an exendin-3 analogue, from Heloderma suspectum venom: Further evidence for an exendin receptor on dispersed acini from guinea pig pancreas. *Journal of Biological Chemistry, 267*(11), 7402–7405. https://doi.org/10.1016/S0021-9258(18)42531-8

[14] Weiskirchen, R., & Lonardo, A. (2025). Semaglutide from bench to bedside: The experimental journey towards a transformative therapy for diabetes, obesity and metabolic liver disorders. *Medical Sciences, 13*(4), 265. https://doi.org/10.3390/medsci13040265

[15] Pillarisetti, L., & Agrawal, D. K. (2025). Semaglutide: Double-edged sword with risks and benefits. *Archives of Internal Medicine Research, 8*(1), 1–13. https://doi.org/10.26502/aimr.0189