GLP-1 agonists in type 2 diabetes mellitus and beyond

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PRESENTACIÓN

La patogénesis de la diabetes mellitus de tipo 2 (DMT2) es un proceso complejo que aún no se conoce en su totalidad. El tratamiento de la DMT2 incluye la intervención dietética y la modificación del estilo de vida para promover la pérdida de peso, junto con la farmacoterapia para combatir la hiperglucemia y optimizar parámetros metabólicos como la presión arterial y los lípidos, y la cirugía metabólica. La intervención farmacológica sobre las hormonas incretinas **péptido 1 similar al glucagón** (GLP-1) y **polipéptido insulinotrópico dependiente de la glucosa** (GIP, antes conocido como polipéptido inhibidor gástrico) ha aportado importantes resultados beneficiosos para los pacientes con DMT2 y obesidad.

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RESUMEN

La intervención farmacológica sobre las hormonas incretinas GLP-1 y GIP para el tratamiento de la diabetes y también de la obesidad se ha estudiado exhaustivamente en los últimos años. Las investigaciones han señalado que los fármacos pueden actuar sobre la diana como agonistas y mejorar así la respuesta glucémica en pacientes que no pueden lograr el control con otras intervenciones. Las investigaciones sobre agonistas duales y triples de GLP-1 y GIP y también para la mejora de la respuesta del glucagón han demostrado que son fármacos prometedores en un futuro próximo para ayudar mejor a los pacientes de esas enfermedades graves. En el presente artículo analizamos algunos avances que se están produciendo en el abordaje de la DMT2 y la obesidad.

ABSTRACT

The pharmacological intervention on the incretin hormones GLP-1 and GIP for the management of diabetes and also obesity has been exhaustively studied in the past few years. Investigations have pointed out that the drugs can act on the target as agonists and then improving the glycaemic response in patients that cannot achieve control with other interventions. The researches on dual and triple agonists of GLP-1 and GIP and also for the improvement of glucagon response have shown that they are promising drugs in the near future for better helping the patients of those severe diseases. In the present article we discuss some advances that are being made in the approach for T2DM and obesity.

1. INTRODUCTION

The incretin concept has been made progress in the last decades, since gut hormones are recently been used as targets for the development of drugs for diseases with large numbers of patients, such as diabetes and obesity for instance. Although nowadays the lights are casted on two major peptides, namely GIP (originally "gastric inhibitory polypeptide," later renamed "glucose-dependent insulinotropic polypeptide") and GLP-1 ("glucagon-like peptide 1," now in its truncated (7–36) form), gastrointestinal endocrinology cannot just be summed up to those two important peptides (Rehfeld, 2018). In a perspective historic, it's important to remember that the seminal research and the very elegant results from the investigation by Bayliss and Starling (1902) first described the connection between the pancreas, the gut and incretin hormones in the early twentieth century and they probably have settled the basis for the future comprehension of the gastrointestinal physiology and endocrinology.

Nevertheless, the definition of incretin includes any gut hormone which under physiological circumstances stimulates or contributes to the stimulation of the secretion of pancreatic hormones such as insulin, glucagon, pancreatic polypeptide (PP), and pancreatic somatostatin.

The interest in developing the class of compounds that is called GLP-1 agonists arose after pioneers works from some laboratories that have identified several highly conserved glucagon-like peptides (GLPs) (Unger *et al.*, 1966; Samols *et al.* 1966). Such molecules were related in structure to glucagon, a pancreatic peptide hormone that regulates carbohydrate, fat, and protein metabolism. Early Investigations on novel glucagon-like peptides have described that they are processed from the glucagon prohormones (Bell *et al.*, 1983). The decoding of the glucagon gene has uncovered two glucagon-like peptides encoded in proglucagon, the glucagon precursor polypeptide, both expressed in the gut. One of these peptides, glucagon-like peptide I, is processed from proglucagon into at least two forms, 37 amino acids GLP-1 (1-37), and 31 amino acids GLP-1 (7-37). Indeed, Drucker *et al.* (1987) have reported that GLP-I (7-37) increases cAMP levels (dose range: 50 pM–5 nM) , insulin mRNA transcripts (25mM) and insulin release (25mM) in rat insulinoma cells. Experimental purification from gut extracts has demonstrated that GLP-1 is also synthetized in a truncated (7-36) form (Mojsov *et al.*, 1986). Interestingly, the GLP-1 (7-36) was demonstrated to, in slightly supraphysiological doses, stimulate insulin secretion, lower glucagon concentrations, and normalize elevated fasting plasma glucose concentrations in type II diabetic patients (Nathan *et al.*, 1992; Nauck *et al.*, 1993). Wetterglen *et al.* (1993) have infused intravenously synthetic truncated GLP-1 in patients in a plasma concentration of 110 +/- 14 pmol/L. They have shown that the infusion peptide has reduced the postprandial gastric acid secretion, the gastric emptying rate, and the postprandial trypsin and lipase outputs. Considering the postprandial insulin and glucagon concentrations and blood glucose levels, results have implied a significant reduction in glucose concentration, therefore indicating that GLP-1 stimulated insulin secretion and inhibited glucagon secretion. Authors have concluded that truncated GLP-1 acts as a physiological inhibitor of gastric and pancreatic functions in humans. Hvidberg *et al.* (1994) have infused synthetic GLP-1 at rates of 25 and 75 pmol/kg/h into healthy volunteers after an overnight fast and measured plasma concentrations of glucose, insulin, and glucagon and glucose turnover. During the infusions Authors have reported significantly results for a decrease in plasma glucose level, a decrease in plasma glucagon level, a reduction in glucose rate of appearance and an increase in glucose clearance. Authors have concluded for a potential role of GLP-1 in the control of hepatic glucose production and glucose clearance through its effects on the pancreatic glucoregulatory hormones. Notably, Creutzfeldt *et al.* (1996), have performed experiments in fasting type-1 diabetic patients tested by intravenously infused GLP-1(7-36 amide) at concentration 1.2 pmol/kg/min or placebo; they have measured the glucagon and plasma glucose and also C-peptide. Authors have concluded that GLP-1 lowered fasting glycemia also in type-1 diabetic patients by reducing glucagon plasma concentration.

2. DEVELOPMENT OF GLP-1 AGONISTS

Once the physiological role for the incretins GIP and GLP-1 in regulating glycemia was disclosed, it turned indispensable to find a pharmaceutical dosage form for the incretins that could bring to patients a medicine with pharmacokinetic and pharmacodynamic suitable characteristics, since the short half-life of the native GLP-1 limited its therapeutical potential (Deacon *et al.*, 1995). The very first GLP-1 receptor agonist approved for clinical use was exenatide (synthetic exendin-4) (Nielsen *et al.*, 2004), a peptide originally isolated from Heloderma suspectum lizard venom (Eng *et al.* 1992). In mammals, exendin-4 is resistant to degradation by dipeptidyl peptidase-IV (DPP-IV) and has a much longer plasma half-life than GLP-1, which is degraded by DPP-IV with a half-life of less than 2 min. Exendin-4 and GLP-1 share many glucoregulatory actions that the known pancreatic GLP-1 receptor may mediate (figure 1); interestingly, when they were added together to insulinoma-derived cells, they showed a synergistic effect on rising intracellular AMPc concentration (Goke *et al.*, 1993).

Among several approaches employed for the development of GLP-1 agonists to extend the half-life of native GLP-1, the albumin binding was applied in the development of the human GLP-1 analog liraglutide once daily and, subsequently, semaglutide once weekly (Knudsen and Lau, 2019). The albumin binding approach has been extensively studied to improve the pharmacokinetic properties of small peptides, such as the extending of their half-lives (Dennis *et al.*, 2002). For instance, using such method Jonassen *et al.* (2012) have demonstrated an improvement of the time-action profile for insulin deglutec, with a duration of blood-glucose lowering action extended beyond 42 h.

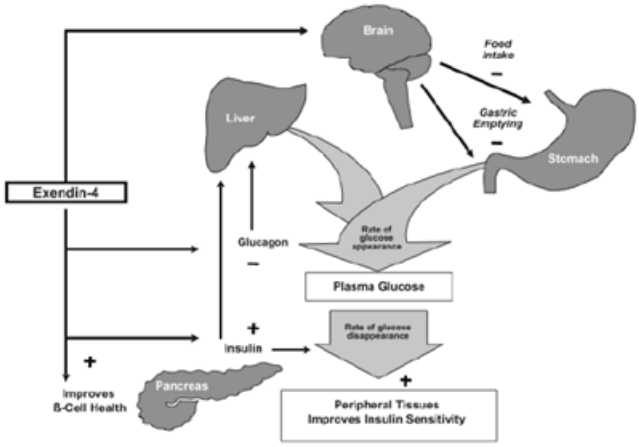

Figure 1. *Extracted from: Göke R, et al., 1993. (see reference list for full citation). Theoretical overview of the mechanisms of action for exendin-4 (exenatide).*

In their drug discovery program, Knudsen and Lau (2019) employed human GLP-1 as the starting point for experiments aimed at increasing the intravenous half-life of GLP-1 beyond that which could be obtained with dipeptidyl peptidase IV (DPP-IV) stabilization as prior demonstrated by Deacon *et al.*, 1998. Their strategy was based on fatty-acid derivatization to prepare analogs that could reversibly bind to albumin and, thereby, protect the peptide from both DPP-IV degradation. Using such approach, they have performed numerous experiments and they have attained important results that were made available in plenty of publications (i.e., Knudsen *et al.*, 2000). Such results have allowed them to select liraglutide as the first GLP-1-based analog suitable for once-daily (OD) dosing. In the sequence of their investigation, they have searched for an effective GLP-1 analog that could be administered once weekly, to avoid the inconvenience of daily administration and to improve the therapeutic for the patients. The original idea was to build up a molecule that could act as an agonist on GLP-1R with suitable potency to cause a reduction in glucose blood concentration but at the same time without spoiling the binding characteristics to albumin, not impairing the desired pharmacokinetic (PK) and pharmacodynamic (PD) profile (Knudsen and Lau, 2019). In the screening program, Authors have tested abundantly substituted GLP-1 and liraglutide analogs in diverse in vivo and in vitro experimental protocols to achieve the semaglutide molecule (figure 2).

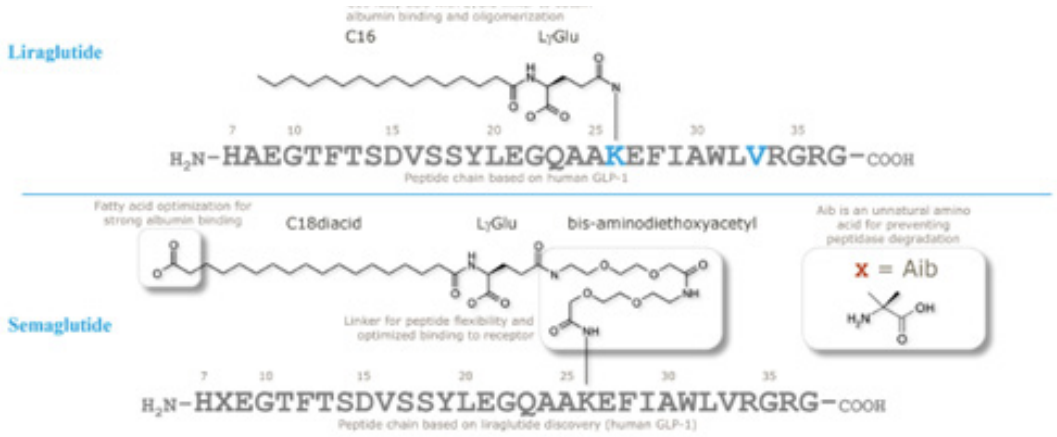

Figure 2. *Extracted from Knudsen LB and Lau J (2019) (see reference list for full citation). Chemical structures of liraglutide and semaglutide.*

Liraglutide and semaglutide are now well established compounds to treat type 2 diabetes. They both are long-acting GLP-1R agonists that have PD effects for 24 h/day (Degn *et al.*, 2004; Jensen *et al.*, 2017). Liraglutide was developed for OD administration, with a dose of up to 1.8 mg, whereas semaglutide is available as once week (OW) injection of up to 1.0 mg. Liraglutide is additionally approved for the treatment of obesity, at a dose of 3.0 mg (Pi-Sunyer *et al.*, 2015). To its turn, once-weekly subcutaneous semaglutide 2.4 mg is also approved as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adults with an initial Body Mass Index of ≥ 30 or ≥ 27 kg/m2 in the presence of ≥ 1 weight-related comorbid condition (Bergman *et al.*, 2023). Furthermore, oral semaglutide was the first oral glucagon-like peptide 1 (GLP-1) receptor agonist approved for the treatment of adults with T2D. Semaglutide has been co-formulated with the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate to improve bioavailability. Oral semaglutide has been shown to have efficacy and safety profiles similar to those of other GLP-1R agonists (Kane *et al.*, 2022). Besides, several recent clinical trials have shown that the drugs can also reduce the symptoms of heart failure and the risk of heart attack and stroke. For all those entirely results the periodic Science has named GLP-1 drugs the breakthrough of the Year (Frankel, 2023).

3. DEVELOPMENT OF DUAL OR TRIPLE AGONIST

Nauck et el. (1993) have demonstrated that in humans healthy volunteers the combination of GIP and GLP-1 led to B-cell responses that were significantly higher than those with either hormone alone. GIP and GLP-1 can interact in an additive manner in normal man. The GIP and GLP-1 receptor agonism were described by Finan *et al.* (2013) who developed an unimolecular dual agonist of GIP and GLP-1 receptors, referred to as a "twincretin". Coskun *et al.* (2018) have developed a dual GIP and GLP-1 receptor agonist, LY3298176, that later was named tirzepatide. The molecule was formulated as a synthetic linear peptide containing 39 amino acids, based on the native GIP sequence. It is attached to a 20-carbon fatty diacid moiety, which binds to albumin, prolonging its half-life to 5 days and thus enabling once weekly dosing. Tirzepatide has a comparable GIP receptor binding affinity to native GIP and five times lower GLP- 1 receptor affinity than that of native GLP-1. Similar to the others the GLP-1 Receptor Agonist (RA) tirzepatide is also administered subcutaneously. The reported clinical trials for the drug have shown its efficacy, safety and tolerability in humans in placebo controlled studies and also in active comparators, such as GLP-1 RAs (dulaglutide and semaglutide), long-acting insulin analogues (glargine and degludec) or short-acting insulin analogue (lispro) (Min and Bain, 2020). The degree of HbA1c reduction and weight reduction observed in pre-clinical, phase 1 and 2 clinical trials has not previously been observed in diabetes clinical trials. Furthermore, the side effect profile is comparable to that of a GLP-1 receptor agonist. The most frequently observed adverse events were related to the gastrointestinal system. Nausea, diarrhea, and vomiting were the most common adverse reactions. The reduced appetite was also reported as a noted adverse event.

Recently, Urva et al (2022) have described the LY3437943 molecule. It is a 39 amino acid single peptide conjugated to a C20 fatty diacid moiety that possesses agonist activity at the glucagon, GIP, and GLP-1 receptors. LY3437943, later named retatrutide, is less potent at the human glucagon and GLP-1 receptors compared with native glucagon and GLP-1, and more potent at human GIP compared with native GIP and exhibits an extended pharmacokinetic half-life while providing desired pharmacological properties. The authors reported their results for a multiple-ascending dose phase 1 clinical trial, providing initial evidence of the safety and efficacy of the triple GLP-1, GIP, and glucagon receptor agonist LY3437943 in participants with type 2 diabetes.

Additionally, more recently phase 2 clinical trials for retatrutide have been conducted (Rosenstock *et al.*, 2023; Jastreboff *et al.*, 2023). In both trials the findings were consistent with the yet reported phase 1 clinical trials, i.e., once-weekly treatment with retatrutide resulted in substantial weight reduction at 24 and 48 weeks, with dose-dependent efficacy. Robust bodyweight reduction is increasingly recognized as a crucial component of type 2 diabetes treatment, which points to a promise of future pharmacological and therapeutic use for the molecule. The safety profile of retatrutide in the studies was consistent with that of tirzepatide and GLP-1 receptor agonists in patients with type 2 diabetes.

4. CONCLUSION

The GLP-1 RA's and the dual or triple agonists seems at least to add new understanding for the pathologies of diabetes and obesity. Neverthless, despite the widespread use of these drugs, there are still few reports in the literature about adverse events and recommendations for use in specific situations.

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