Glucagon-like Peptide-1 Receptor Agonists

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Type 2 diabetes mellitus (T2DM) is a heterogeneous, chronic, progressive metabolic disease accounting for 90–95% of all diabetes. Glucagon-like peptide-1 (GLP-1) receptor agonists are a new class of antihyperglycemic drugs that enhance appropriate pancreatic β-cell secretion, pancreatic α-cell (glucagon) suppression, decrease liver glucose production, increase satiety through their action on the central nervous system, slow gastric emptying time, and increase insulin action on peripheral tissue. They are effective in the management of type 2 diabetes mellitus and have a favorable effect on weight loss.

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1. Incretin System

It was shown that oral glucose stimulates insulin secretion more than intravenous glucose infusion, even when the same plasma glucose concentration profiles are achieved. This is the so-called incretin effect. Incretins, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (previously called gastric inhibitory polypeptide) (GIP), are part of the endocrine system and are involved in postprandial stimulation of insulin secretion and the physiological regulation of glucose homeostasis [1].

GLP-1 is a 37 amino acid long polypeptide secreted from specialized L cells primarily located in the brush border of the small and the large intestine. Small amounts of GLP-1 are continuously cleaved from proglucagon and excreted, but excretion rises rapidly after mixed meal ingestion. Degradation of GLP-1 is mediated by the enzyme dipeptidyl-peptidase 4 (DPP-4) in the portal vein and liver. Only 1015% of GLP-1 enters the systemic circulation. GLP-1 is also secreted as a neurotransmitter from neurons in the brainstem that project in areas related to the regulation of energy homeostasis [2].

GLP-1 acts through a receptor (GLP-1R) that belongs to the B subfamily of the G protein-coupled receptor family. It consists of seven transmembrane domains in the form of alpha-helices, which are interconnected by six loops, of which three are intra- and three extracellular [3]. GLP-1 first contacts the N-terminal domain and then all three extracellular loops of GLP-1R [4]. Signal transmission operates via a signaling cascade that ultimately increases the cell’s cyclic adenosine monophosphate (cAMP) [3].

GLP-1 receptors (GLP-1R) are expressed not only on pancreatic β-cells but also on a subset of pulmonary epithelial cells, atrial cardiac myocytes, cells lining the gastric pits and small intestinal mucosa, and neurons in several brain regions. They are also located on the nodular ganglion of the vagal nerve, whose central branches

terminate in the solitary nucleus in the brainstem. Information from the nucleus is transmitted to the hypothalamus, thalamus, and hemispheres [2][5].

The secretion of incretins is controlled by a series of integrated mechanisms that include direct interaction with distinct chemosensors on the brush border of K and L cells in the gut and multiple indirect neuro–immuno–hormonal loops [6].

GLP-1 increases the synthesis and release of insulin from pancreatic β-cells. GLP-1 regulates the gene expression of pancreatic β-cells, inhibits apoptosis of β-cells, protects them from glucolipotoxicity, and improves their function. In addition, GLP-1 also reduces glucagon secretion by pancreatic α-cells. This reduces glucose production in the liver, reflected in lower blood glucose levels. GLP-1 may additionally act through the activation of visceral afferent neurons. On the other hand, it centrally regulates food intake, energy consumption, and the functioning of the digestive system, thus slowing down gastric emptying and reducing acid secretion, resulting in decreased appetite and body weight. GLP-1 also lowers blood lipoproteins, systolic blood pressure, and inflammation [7][8].

According to meta-analyses, there are no systematic differences in nutrient-induced GLP-1 secretion between healthy and T2DM subjects despite significant inter-individual variance in secretory responses. However, patients with advancing stages of T2DM may have reduced levels of active GLP-1. On the other hand, physiological and pharmaceutical GLP-1 concentrations cause insulinotropic (and glucagonostatic) effects in patients with T2DM [6].

Obesity has been shown to reduce the incretin effect even in the absence of impaired glucose tolerance or T2DM [6]. Novel therapeutic approaches for T2DM and obesity treatment rely on the incretin effect of GLP-1R agonists on both pancreatic β-cells and other peripheral and central mechanisms of action.

2. Pharmacological Properties of GLP-1 Receptor Agonists

GLP-1 receptor agonists (GLP-1 RAs) are polypeptides injected subcutaneously, similar to insulin. According to their structure, they can be grouped into exenatide and human-like GLP-1. Depending on the time of receptor activation, they are divided into two groups. Short-acting compounds provide short-term activation of the GLP1 receptor, they reach peak concentration in a few hours, and after 6–10 h, their concentrations fall sharply or even to zero. Long-acting compounds activate the receptor continuously, for a long time, and can be administered once a day or once a week [9].

2.1. Short-Acting GLP-1 RAs

Exenatide was the first incretin analog approved for clinical use, and it has also been the longest studied. Exenatide shares approximately 50% of the amino acids with human GLP-1 and has a similar affinity for GLP-1 receptors. Due to its half-life (t ½) of 2.4 h, it should be administered twice daily. It is mainly excreted through the kidneys. Early research has shown that after 30 weeks of treatment twice daily, the therapy improves fasting and postprandial glucose levels [9].

The second short-acting GLP-1 RAs was lixisenatide, which can be administered daily. It is designed as a C-terminal modification with six lysine residues and the absence of one proline, allowing physiological degradation by DPP-4. The drug binds strongly to the receptor. Approximately 55% of lixisenatide is bound to proteins. Its half-life (t ½) is 3 h. Lixisenatide is eliminated by glomerular filtration followed by tubular reabsorption [9].

2.2. Long-Acting GLP-1 RAs

The long-acting agonist liraglutide is a modified form of GLP-1 obtained by replacing the amino acid serine with arginine and adding the C16 palmitoyl fatty acid side chain on lysine binding to serum albumin and thus increases resistance to degradation by DPP-4. Following subcutaneous injection of liraglutide, plasma concentrations are stable for up to 13 h after administration once a day, and 24-h blood glucose monitoring is achieved. More than 98% of liraglutide is bound to plasma proteins. Liraglutide is metabolized similarly to large proteins, so no organ is considered the primary route of excretion [9].

Exenatide LAR is released biphasically from microparticles. The initial fast peak is followed by a slower release. It can be administered independently of food intake and meals at any time of the day. The full therapeutic effect is achieved in two weeks [9].

Dulaglutide consists of two identical GLP-1 analog peptide chains, approximately 90% homologous to native human GLP-1 and linked to the heavy chain of the immunoglobulin G4 (IgG4). The addition of IgG4 increases the peptide's size, which helps reduce the rate of renal clearance. At the same time, the Fc fragment (crystallizable region) of IgG4 prevents the formation of antibodies and reduces the potential for immune cytotoxicity. Peak plasma concentrations are reached within 48 h. It is degraded via the general protein breakdown pathways into amino acids [9].

Semaglutide is another long-acting GLP-1 RA. In healthy adults, subcutaneous administration of 0.5 mg semaglutide reached the maximum concentration (Cmax) in 24–56 h [10][11]. Semaglutide has 94% amino acids identical to native GLP-1. Still, it has three-tier modifications that make it less susceptible to degradation. In this way, its half-life is extended by one week to be used once a week. As more than 99% of semaglutide is bound to plasma albumin, systemic removal is slower, and absorption is delayed. Semaglutide had a greater volume of distribution (0.102 L/kg) than liraglutide and a slower body clearance (0.0016 L/h/kg) [11]. Semaglutide is metabolized by proteolytic cleavage of the peptide backbone and b-oxidation of the fatty acid side chain to six different metabolites, primarily excreted in urine and feces. On the other side, the excretion of the intact drug in the urine is minimal, so renal dosing is not necessary [10][11].

Efpeglenatide is an exendin analog containing single amino acid modification linked to a crystallizable (Fc) fragment of human immunoglobulin G for slower clearance and once-weekly dosing. The geometric mean t ½ varies between 135 and 180 h. In the single dosage study, the maximum serum concentration (t_{max}) of efpeglenatide ranged from 72 to 144 h. Compared to liraglutide and dulaglutide, efpeglenatide is associated with faster dissociation from the GLP-1R and allows more cell surface receptors to remain available for signaling.

Efpeglenatide leads to a more significant accumulation of cyclic adenosine monophosphate and insulinotropic activity after chronic exposure [12].

3. Clinical Efficacy of GLP-1 RAs

Differences in the duration of action of GLP-1 RAs lead to differences in their effect on blood glucose regulation. Short-acting GLP-1 RAs more strongly delay gastric emptying, resulting in a more significant impact on postprandial blood glucose. On the other hand, the longer half-life of long-term GLP-1 RAs allows better regulation of glucose concentrations, including fasting plasma glucose. If GLP-1 RAs are administered as monotherapy, they can reduce the HbA1c levels by 0.7–1.51. In combination with other oral antihyperglycemics or as part of triple therapy, further reduction in HbA1c levels by 0.4–1.9 may be reached. In addition to the beneficial effect on glucose levels, body mass may also decrease by an average of 0.2–4 kg. The highest levels of body mass reduction are achieved in patients with a body mass index (BMI) above 30 kg/m^2 [9].

4. Side Effects of GLP-1 RAs

The most common side effects, which usually occur immediately upon initiation of therapy, are nausea (8–44%), vomiting (4–18%), and diarrhea (6–20%). It is not yet clear whether these side effects impact digestive function or have indirect effects on the central nervous system, either through access to the brain through areas without a blood–brain barrier or indirectly through receptors on branches of afferent parasympathetic nerves. Nausea and vomiting are less common when using prolonged-release forms. Although they belong to the same group, side effects also depend on the composition, dose, and basic antihyperglycemic therapy (metformin) [13]. GLP-1 RAs are associated with a very low risk of hypoglycemia, but caution should be exercised when used in combination with other antihyperglycemic agents, such as sulfonylurea [14].

T2DM patients are three times more likely to develop acute pancreatitis than healthy individuals, but the mechanisms have not been elucidated. In mouse models, they found that GLP-1 RAs increase acinar cell mass in the pancreas, enhancing amylase and lipase synthesis [15]. The ELIXA (Evaluation of LIXisenatide in acute Coronary Syndrome) study showed that the number of acute pancreatitis in the lixisenatide group was lower than in the placebo group [16]. However, acute pancreatitis has been reported in post-marketing studies in individual exenatide users. T2DM patients with semaglutide and dulaglutide have elevated pancreatic enzymes [15]. Pancreatic malignancy occurred in studies with exenatide and placebo groups in equal numbers. GLP-1 RAs were associated with a lower risk of prostate, lung, and colon cancer, but a higher risk of thyroid cancer [17]. FDA has recommended that patients at increased risk for medullary adenoma or thyroid adenocarcinoma and with multiple endocrine neoplasia syndrome 2 should not be treated with GLP-1 RAs [18]. GLP-1 receptors were found to be expressed in neoplastic and hyperplastic lesions of thyroid C cells and on follicular derived papillary thyroid cancer cells [19]. However, dulaglutide treatment was not found to increase calcitonin levels in the reported case of a patient with pre-existing medullary thyroid cancer [20]. Although the cardiovascular outcomes trial did not find an association between GLP-1 RAs and thyroid cancers [21], the recent FDA Adverse Event Reporting System

(FAERS) database analysis confirmed a higher risk of thyroid cancer [17]. Among other side effects, semaglutide treatment was associated with more vitreous hemorrhages, blindness, or conditions that required photocoagulation therapy (p = 0.2) [10].

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