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Review Article

Glucagon-like peptide-1 receptor agonists for the treatment of type 2 diabetes: Differences and similarities

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ABSTRACT

Glucagon-like peptide-1 (GLP-1) is a gastrointestinal hormone, secreted in response to ingestion of nutrients, and has important effects on several of the pathophysiological features of type 2 diabetes (T2D). The effects include potentiation of insulin secretion, suppression of glucagon secretion, slowing of gastric emptying and suppression of appetite. In circulation, GLP-1 has a half-life of approximately 2 min due to rapid degradation by the enzyme dipeptidyl peptidase 4 (DPP-4). Because of this short half-life GLP-1 receptor (GLP-1R) agonists, resistant to degradation by DPP-4 have been developed. At the moment four different compounds are available for the treatment of T2D and many more are in clinical development. These compounds, although all based on the effects of native GLP-1, differ with regards to structure, pharmacokinetics and size, which ultimately leads to different clinical effects. This review gives an overview of the clinical data on GLP-1R agonists that have been compared in head-to-head studies and focuses on relevant differences between the compounds. Highlighting these similarities and differences could be beneficial for physicians in choosing the best treatment strategy for their patients.

1. Introduction

Worldwide the number of patients with type 2 diabetes (T2D) increases as economic development and urbanization lead to lifestyle changes encompassing reduced physical activity and increased food intake resulting in obesity. In 2013 the International Diabetes Federation (IDF) estimated the number of people with diabetes worldwide, to be 382 million, a number expected to approach 590 million in 2035, with T2D accounting for up to 95% [1,2]. T2D is progressive and characterised by insulin resistance, a steady decline in glucose-induced insulin secretion, and inappropriately high glucagon levels, which in combination leads to high blood glucose concentrations [3]. Over time T2D results in complications that broadly can be classified as microvascular (neuropathy, nephropathy and retinopathy) or macrovascular (atherosclerotic manifestations such as myocardial infarction and stroke). In 2012 it was estimated that almost 5 million deaths worldwide were attributable to diabetes, obesity and its complications [1,4,5]. The ultimate goal of glucose lowering drugs is to control glucose homeostasis as tight as possible to prevent the development of micro- and macrovascular complications and early death [6,7]. In order to reach this, a treatment regimen combining several glucose-lowering drugs is often needed. However, several treatment modalities are associated with a number of shortcomings: hypoglycaemia (sulphonylureas (SUs) and insulin); weight gain (SUs, insulin and thiazolidiones (TZD)); gastrointestinal side effects (metformin, bile acid sequestrants and α-glucosidase inhibitors); increased risk of genital and urinary tract infections (sodium-glucose co-transporter 2 inhibitors); and increased risk of bone fractures and heart disease (TZD) [8–11]. In addition to side effects none of these glucose-lowering drugs target the multifaceted pathophysiology of T2D.

In 2005, the glucagon-like peptide-1 (GLP-1) receptor (GLP-1R) agonists were introduced into clinical practise, and since 2009 they have been part of the joint position statements on treatment of T2D by the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) [12,13]. The GLP-1R agonists target a broad spectrum of the multifaceted pathophysiology of T2D. Thus, they improve glucose homeostasis without risk of hypoglycaemia, facilitate body weight loss, and exert effects on cardiovascular parameters of potential benefit. Naturally, the introduction of the GLP-1R agonists has generated substantial clinical interest. However, many physicians and other healthcare providers have limited experience with this novel therapy, and as several GLP-1R agonists are emerging, it has become apparent that there are clinical relevant differences between them, which make the therapeutic field challenging to navigate within. This review provides an overview of the current clinical

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data on GLP-1R agonists that have been compared in head-to-head studies and focuses on relevant differences between the compounds.

2. Methodology

Literature searches were performed by using the MEDLINE database with key words: “glucagon-like peptide-1”, “glucagon-like peptide-1 receptor agonists”, “exenatide”, “lixisenatide”, “liraglutide”, “exenatide once-weekly”, “albiglutide”, “dulaglutide”, “semaglutide”. Additionally published abstracts from the ADA and EASD were searched. Furthermore manual searches including scanning of reference lists in relevant papers and specialist journals have been performed.

3. The physiology and antidiabetic actions of GLP-1

During a meal, plasma-levels of GLP-1 rise within minutes and return to very low levels in the fasting state [14]. GLP-1 asserts its effects through binding to the GLP-1Rs expressed in the pancreas and a variety of other tissues including: lung, heart, blood vessels, gastrointestinal tract, kidney, breast and central nervous system (CNS) [15–17]. In the pancreatic beta cell, receptor-binding of GLP-1 in the presence of elevated glucose concentrations leads to stimulation of insulin secretion [14]. In the pancreatic alpha cell GLP-1 robustly inhibits glucagon secretion through a direct mechanism [18] or mediated by local stimulation of insulin and somatostatin [19,20]. Furthermore, GLP-1 decreases gastrointestinal motility and thereby induces delayed and protracted entry of nutrients to the absorbing parts of the gastrointestinal tract [21,22]. This effect is a key mediator for the normalisation of postprandial glucose (PPG) excursions, and potentially more important than the insulinotropic effects of GLP-1 for maintaining PPG homeostasis [23]. GLP-1 also promotes satiety [24] presumably mediated by a combination of central (GLP-1 can access the brain via leaks in the blood–brain barrier) and peripheral (possibly by affecting vagal afferent fibres) mechanisms [25,26]. Additionally GLP-1 has been shown to increase resting energy expenditure and lower plasma concentrations of free fatty acids [27]. Furthermore, GLP-1 seems to reduce systolic blood pressure and may even exert protective effects on the myocardium. All of these GLP-1 effects (summarized in Fig. 1) are potentially beneficial for patients with T2D, and have been sought exploited clinically with the development of GLP-1R agonists.

4. GLP-1R agonists

One of the challenges in developing GLP-1R agonists is that native GLP-1 is very rapidly degraded by the enzyme dipeptidyl peptidase 4 (DPP-4) resulting in a half-life of approximately 2 min [28]. To overcome this problem GLP-1R agonists resistant to degradation by DPP-4 have been developed by two different strategies. One strategy exploits the structure of native GLP-1, with a few amino acid alterations that protect the molecule from being degraded by DPP-4 (Fig. 2). The other strategy exploits a naturally occurring protein, exendin-4 (originally isolated from the saliva of the lizard *Heloderma suspectum*), which activates the GLP-1R with equal potency as native GLP-1. The GLP-1R agonists, available or in late clinical development, are, however, different not only based on their structure but also based on their pharmacokinetic profiles and can largely be divided into short-acting or continuous-acting GLP-1R agonists. The short-acting GLP-1R agonists (exenatide and lixisenatide) are despite being resistant to degradation by DPP-4 still subject to renal elimination, which confers a plasma half-life of approximately 2 to 4 h for these agents [29,30]. They are administered once or twice-daily. Due to their somewhat short half-life administration of short-acting GLP-1R agonists results in relatively large fluctuations in plasma concentrations during the day, which in turn results in intermittent activation of the GLP-1Rs. With regards to the continuous-acting peptides, different modifications have been applied in order to obtain an even longer duration without changing

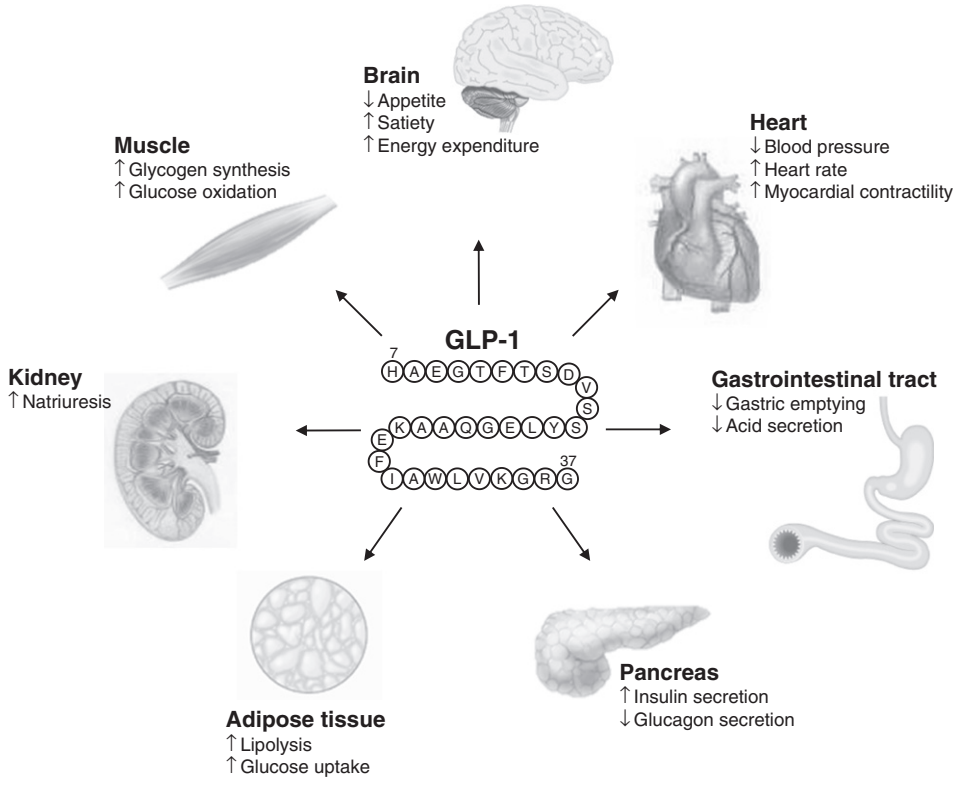

Fig. 1. Effects of GLP-1 or GLP-1R agonists. Illustrates the pleiotropic effects of GLP-1 on various tissues. Abbreviations: GLP-1R, glucagon-like peptide-1 receptor.