Peptides 100 (2018) 190–201

Contents lists available at ScienceDirect

Peptides

journal homepage: www.elsevier.com/locate/peptides

Gut hormone polyagonists for the treatment of type 2 diabetes

Sara J. Brandt[a,1], Anna Götz[a,b,c,1], Matthias H. Tschöp[a,d,e], Timo D. Müller[a,d,*]

[a] Institute for Diabetes and Obesity, Helmholtz Diabetes Center at Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Business Campus Garching, Parkring 13, 85748 Garching, Germany
[b] Department of Internal Medicine I, University Hospital RWTH Aachen, Aachen, Germany
[c] Institute for Diabetes und Regeneration, Helmholtz Diabetes Center, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Business Campus Garching, Parkring 13, 85748, Garching, Germany
[d] German Center for Diabetes Research (DZD), Neuherberg, Germany
[e] Division of Metabolic Diseases, Department of Medicine, Technische Universität München, Munich, Germany

ARTICLE INFO

Keywords:
GLP-1/Glucagon Co-agonism
Polypharmacology
Type 2 diabetes
Gip

ABSTRACT

Chemical derivatives of the gut-derived peptide hormone glucagon-like peptide 1 (GLP-1) are among the best-in-class pharmacotherapies to treat obesity and type 2 diabetes. However, GLP-1 analogs have modest weight lowering capacity, in the range of 5–10%, and the therapeutic window is hampered by dose-dependent side effects. Over the last few years, a new concept has emerged: combining the beneficial effects of several key metabolic hormones into a single molecular entity. Several unimolecular GLP-1-based polyagonists have shown superior metabolic action compared to GLP-1 monotherapies. In this review article, we highlight the history of polyagonists targeting the receptors for GLP-1, GIP and glucagon, and discuss recent progress in expanding of this concept to now allow targeted delivery of nuclear hormones via GLP-1 and other gut hormones, as a novel approach towards more personalized pharmacotherapies.

1. Introduction

Diabetes mellitus is a devastating metabolic disease that has reached epidemic proportions worldwide. Type 2 diabetes (T2D) is the most common form of the disease, affecting 90–95% of diabetic patients, with 415 million affected individuals. Estimates suggest that by 2040 this number will rise to 642 million [1]. This rise in diabetes has severe economic consequences, since approximately 12% of the global health expenditure ($673 billion) is spent on diabetes and its complications, which includes hospital, outpatient, and therapeutic interventions [1]. This economic burden will continue to increase as the rates of diabetes are growing rapidly, especially in low- and middle-income countries, where more than 75% of diabetic individuals live [2–4]. Tragically, the World Health Organization (WHO) estimates that diabetes resulted in 1.6 million deaths in 2015, making it the 6th leading cause of death [5].

Diabetes mellitus is characterized by pathological failure to buffer against prolonged episodes of hyperglycemia, which ultimately leads to diabetes related complications. Microvascular complications include damage of the eyes (retinopathy), the nervous system (neuropathy) and the kidney (nephropathy), while macrovascular complications include coronary artery disease, cerebrovascular and peripheral vascular disease [6].

Cardiovascular disease is perhaps the most dangerous consequence of diabetes, despite the ravaging impact that neuropathy, nephropathy and retinopathy can have on diabetic individuals. The major contributor to type 2 diabetes is obesity, which is also gaining global prevalence [7,8].

Type 2 diabetes is managed with non-pharmacological interventions and various pharmacological treatment options. While lifestyle changes in diet and physical activity are the primary approach to treat individuals with diabetes, pharmacological options are usually required to meet target levels of blood glucose and glycolysated hemoglobin (HbA1c).

The most commonly used medicinal approaches to treat T2D include biguanides, sulfonylureas, thiazolidinediones, insulin, inhibitors of the sodium glucose cotransporter 2 (SGLT 2) or the dipeptidyl peptidase-4 (DPP-IV) enzyme, or mimetics targeting the receptor for glucagon-like peptide 1 (GLP-1) [9]. While all of these pharmacotherapies improve glucose handling, albeit with varying efficacy [10–12], many of these options have undesirable effects and some even possess a dose-dependent risk of causing hypoglycemia, such as insulin and

* Corresponding author at: Institute for Diabetes and Obesity, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Neuherberg, Business Campus Garching – Hochbrück, Parkring 13, 85748 Garching, Germany.
E-mail address: timo.mueller@helmholtz-muenchen.de (T.D. Müller).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.peptides.2017.12.021
Received 30 October 2017; Received in revised form 21 December 2017; Accepted 21 December 2017

sulfonylureas [13–16]. Other side effects, such as weight gain, are also commonly described for the use of sulfonyluresas, insulin and thiazolidinediones, which limit their overall use in already obese individuals [16]. Collectively, there is a great demand for the development of safe and effective anti-diabetic agents with accompanied weight reduction and cardiovascular safety. In this review, we report recent advances in the development of unimolecular polyagonists, describe the underlying mechanisms identified in preclinical studies, and discuss potential translational relevance of these novel pharmacotherapies.

2. Physiology and pharmacology of GLP-1, GIP and glucagon

2.1. Glucagon-like peptide 1 (GLP-1)

Insulin secretion is controlled not only by glucose directly but also by insulinotropic factors like the incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) [17].

Glucagon-like peptide 1 is synthesized and secreted primarily from the intestinal L-cells after post- translational processing of proglucagon by prohormone convertase 1/3 (PC1/3). The proglucagon gene is not only expressed in the L-cells of the intestine, but also in the α-cells of the endocrine pancreas and neurons located in the caudal brainstem and hypothalamus [18]. GLP-1 is secreted in response to nutrient ingestion and acts as an insulinotropic hormone in a glucose-dependent fashion [19]. GLP-1 binds to the GLP-1 receptor (GLP-1R), a seven transmembrane G-protein-coupled receptor with high expression in pancreatic islets, the central nervous system and enteric neurons [20], but also in the lung, kidney, lymphocytes, macrophages [21], heart [22], and human coronary endothelial cells [23].

In addition to its insulinotropic effects, GLP-1 also inhibits glucagon secretion from pancreatic α-cells [24], delays gastric emptying [25], enhances β-cell proliferation while inhibiting β-cell apoptosis in rodents [26], decreases gluconeogenesis in the liver [27] and reduces hepatic lipid content [20]. GLP-1 also decreases body weight via centrally regulated inhibition of food intake, and GLP-1 fails to affect food intake in mice with CNS-specific deletion of the GLP-1 receptor [28–30]. In addition, GLP-1 has neuroprotective effects with pharmacological potential for the treatment of neurodegenerative diseases such as Alzheimer's [31] and Parkinson's disease (PD) [32–34]. Exendin-4 has further been shown to have neuroprotective effects in animal models of cerebral ischemia [35] and amyotrophic lateral sclerosis [36]. Moreover, GLP-1 has cardioprotective effects and exerts metabolic benefits in cardiomyocytes, blood vessels, immune cells, leading to attenuated development of atherosclerosis, beneficial reductions in systolic and diastolic blood pressure, reduced cholesterol plasma levels, and reduced ischemia-reperfusion injury [37–40]. Additionally, GLP-1R mRNA transcripts are also expressed in the kidney and GLP-1 agonism in rodents with diabetic nephropathy reduces proteinuria and produces functional and histological improvement in the diabetic kidney [41]. Clinical data of pooled registration trials and results of large-sized cardiovascular outcome studies indicate that use of GLP-1R agonists, in addition to standard care, modestly improve albuminuria in T2D, beyond the effects of glycaemic control [42]. Especially the use of liraglutide in patients with T2D and high cardiovascular risk has resulted in lower rates of the development and progression of diabetic kidney disease than placebo [43]. GLP-1R mRNA was also detected at high levels in the rat lung and binds to receptors on the submucosal glands of the trachea and the smooth muscle of the pulmonary arteries, causing a significant increase in mucous secretion and pulmonary smooth muscle relaxation [44,45].

The insulinotropic and cardioprotective actions of GLP-1 make it a useful pharmacological tool in the fight against T2D. However, the therapeutic value of native GLP-1 is hampered by a relatively short half-life, less than two minutes in humans [46], due to degradation by dipeptidyl peptidase-4 (DPP-IV), which cleaves GLP-1 at its second N-terminal alanine 2 residue, thus yielding an inactive GLP-1_{9-36} amide or GLP-1_{9-37} [46–48]. In addition, neutral endopeptidase (NEP) has also been shown to deactivate GLP-1 in vivo [49,50]. To overcome the susceptibility for rapid DPP-IV degradation, synthetically-designed GLP-1 derivatives have been developed which possess a longer half-life due to amino acid substitutions at the N-terminus, or the addition of fatty acids which extend the half-life of GLP-1 through delayed clearance from the circulation [51]. These synthetic analogs are currently very popular in the treatment of diabetes.

Between 2005 and 2016, the FDA approved six synthetic GLP-1R agonists available for use in the United States to treat T2D: exenatide (Bayetta®, AstraZeneca, USA), liraglutide (Victoza®, Novo Nordisk), exenatide long-acting release (Bydureon®, AstraZeneca, USA), albiglutide (Tanzeum®, GlaskoSmithKline), dulaglutide (Trulicity®; Eli Lilly & Co), and lixisenatide (Lyxumia®, Sanofi). These analogs have extended biological half-lives and confer little to no risk of hypoglycemia. Chronic treatment of patients with T2D patients over 12–52 weeks with these different GLP-1 receptor analogs, such as liraglutide and exenatide, leads to a reduction in glycolysated hemoglobin (HbA1c) of 1.1-1.6% and up to 5% reduction in body weight [52–57]. Besides the glucose lowering effect of all GLP-1 analogs, in 2017, the FDA approved liraglutide (Saxenda®, 3 mg) for a second indication as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in overweight and obese adult patients [58]. Also in 2017, the FDA approved a new indication for liraglutide (Victoza® 1,2/1,8 mg), for reducing the risk for myocardial infarction, stroke, and cardiovascular death in adults with type 2 diabetes who have established cardiovascular disease. Based on the results from the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation) trial, liraglutide reduced the risk of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke by 13% compared with placebo ($p = 0.01$), with an absolute risk reduction of 1.9% [59].

Currently, a new drug application for once-weekly semaglutide (Novo Nordisk) was submitted to the FDA in December 2016. Semaglutide is a fatty-acylated GLP-1 analog that has been shown to decrease body weight and to improve glycemia in preclinical trials with patients with type 2 diabetes [60]. Semaglutide is also under review by the European Medicines Agency, and the Japanese Pharmaceuticals and Medical Devices Agency [61].

Unfortunately, GLP-1 and its analogs induce adverse events, mostly of gastrointestinal character, such as nausea, vomiting and diarrhea [62]. These side effects occur in a dose-dependent manner, which generally limits the use of higher doses to drive greater weight loss [63]. An observed slight increase in heart rate in humans when treated with liraglutide and exenatide long-acting release (LAR) led to required cardiovascular outcome studies to demonstrate cardiovascular (CV) safety via randomized, controlled trials.

In light of the dose-limiting side effects, there is a desire for safer and more effective GLP-1 based analogs. In this review, we discuss the advantages of GLP-1 agonism in conjunction with other hormones, such as GIP and glucagon.

2.2. Glucose-dependent insulinotropic polypeptide (GIP)

Glucose-dependent insulinotropic polypeptide (GIP) is synthesized in and secreted from enteroendocrine K- cells of the proximal small intestine in response to dietary lipids [64–66]. Additionally, CNS production of GIP has also been described in rodents [67], and GIP transcripts have been localized in pancreatic α-cells of rodents and humans [68]. Encoded by a proGIP precursor, post-translational processing by the prohormone convertase enzymes 1 and 3 (PC1/3) yields a mature 42 amino acid protein (GIP 1–42) [69]. In pancreatic α-cells and a subset of enteroendocrine K-cells however, differential processing of proGIP by PC 2 and C-terminal amidation by peptidyl-glycine α-amidating monooxygenase results in a 30 amino acid protein (GIP 1–30).