Biomedicine & Pharmacotherapy 108 (2018) 952–962

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

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

Review

Recent updates on GLP-1 agonists: Current advancements & challenges

Dilip Sharma, Suril Verma, Shivani Vaidya, Kiran Kalia*, Vinod Tiwari*

Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research (NIPER)-Ahmedabad, Gandhinagar 382355, Gujarat, India

ARTICLE INFO

Keywords:
Incretins
GLP-1 agonists
Type-2 diabetes mellitus
DPP-4 inhibitors

ABSTRACT

Glucagon-like peptide (GLP)-1 is an incretin hormone exhibiting several pharmacological actions such as neuroprotection, increased cognitive function, cardio-protection, decreased hypertension, suppression of acid secretion, increase in lyposis, and protection from inflammation. The most potent actions are glucose-dependent insulinotropic and glucagonostatic actions, stimulation of β-cell proliferation, enhanced insulin secretion and reduced weight gain in patients with type-2 diabetes pertaining to blood glucose control. Despite all these actions, its short half-life (around 2 ~ min) and degradation by a dipeptidyl peptidase-4 enzyme (DPP-4) limits the therapeutic utility of GLP1. In this review, we have discussed DPP IV-resistant analogs of GLP-1 currently present in clinical trials such as Exenatide, Liraglutide, Semaglutide, Efpeglenatide, Exenatide ER, Ittca 650 (Intarcia), Dulaglutide, Albiglutide, and Lixisenatide. Moreover, we have also discussed in detail the pharmacology, signaling mechanisms, and pharmacokinetic properties (Cmax, Tmax, $T_{1/2}$, Vd, and Bioavailability) of DPP IV-resistant analogs of (GLP-1). Interestingly, GLP-1 agonist drugs have shown better potential to treat type-2 diabetes mellitus (T2DM) as compared to currently used drugs in clinics without causing the side effects of hypoglycemia and weight gain.

1. Introduction

Diabetes is among the most common and prominent disease in various countries of the world and on top of that, type-2 diabetes is prevalent in 90% of the population suffering from diabetes [1]. Currently available drug therapies such as thiazolidinediones (TZD; insulin sensitizers), sulphonylureas, and insulin (insulin secretagogue) have a major drawback that includes hypoglycemia and weight gain due to an insulin-dependent mechanism of action [2]. Oral intake of glucose secretes more insulin compared to injected glucose due to the presence of the gut hormone called “incretins” or “glucoincretins” and their glucose-dependent mechanism of action [3]. Gastrointestinal peptide (GIP) and Glucagon-like Peptides (GLP-1, GLP-2) are two incretins that are released upon ingestion of food in a biphasic manner to overcome postprandial hyperglycemia by increasing insulin secretion from β-cell [4] and reducing glucose excursion and glucagon secretion [5,6]. The incretin hormones also decrease gastric motility, inhibit β-cells apoptosis, and induce their proliferation [7,8]. The diminished activity of GIP along with the reduced effect of GLP-1 has been observed as one of the pathophysiological features of T2DM along with β-cell resistance, obesity, etc [9,10]. GLP-1 has a half-life of only 2-min because of rapid degradation by the dipeptidyl peptidase 4 (DPP-4) enzyme. To overcome the drawback of the short half-life of endogenous GLP-1 and to achieve the therapeutic advantages, two approaches are being practiced. The first is to use DPP-4 inhibitors (sitagliptin, vildagliptin), which prevents the breakdown of native GLP-1, and the second, is the synthesis of DPP-4 resistant GLP-1 analogs (exenatide, liraglutide, exenatide LAR, albiglutide, Dulaglutide, lixisenatide) [11].

2. Methods

In this review, we have discussed the release and regulation of GLP-1 and how it controls the insulin secretion from pancreatic β-cells. In the second part of this review, we have discussed the detailed pharmacology of currently available GLP-1 agonists along with new drugs under clinical trials. The present paper is based upon recent review articles, research articles, clinical trials, meta-analysis, press release and oral/poster presentations published in the area of GLP-1R agonists. Literature survey has been done by searches in Google, Google Scholar, Science direct and PubMed using the terms “GLP-1R agonist”, “Exenatide”, “Liraglutide”, “Semaglutide”, “Efpeglenatide”, “Exenatide”ER, “Ittca 650(Intarcia)”, “Exenatide LAR”, “Albiglutide”, “Dulaglutide”, “Lixisenatide”, “short-acting GLP-1RA”, and “long-acting GLP-1RA”. Additionally, manual searches based upon the names of clinical trials, physiology of GLPs, pathophysiology of type-2 diabetes and reference lists in relevant papers have been performed [12].

* Corresponding authors.
E-mail addresses: kirankalia@gmail.com (K. Kalia), vinodtiwari1980@gmail.com (V. Tiwari).

https://doi.org/10.1016/j.biopha.2018.08.088
Received 24 April 2018; Received in revised form 4 August 2018; Accepted 15 August 2018

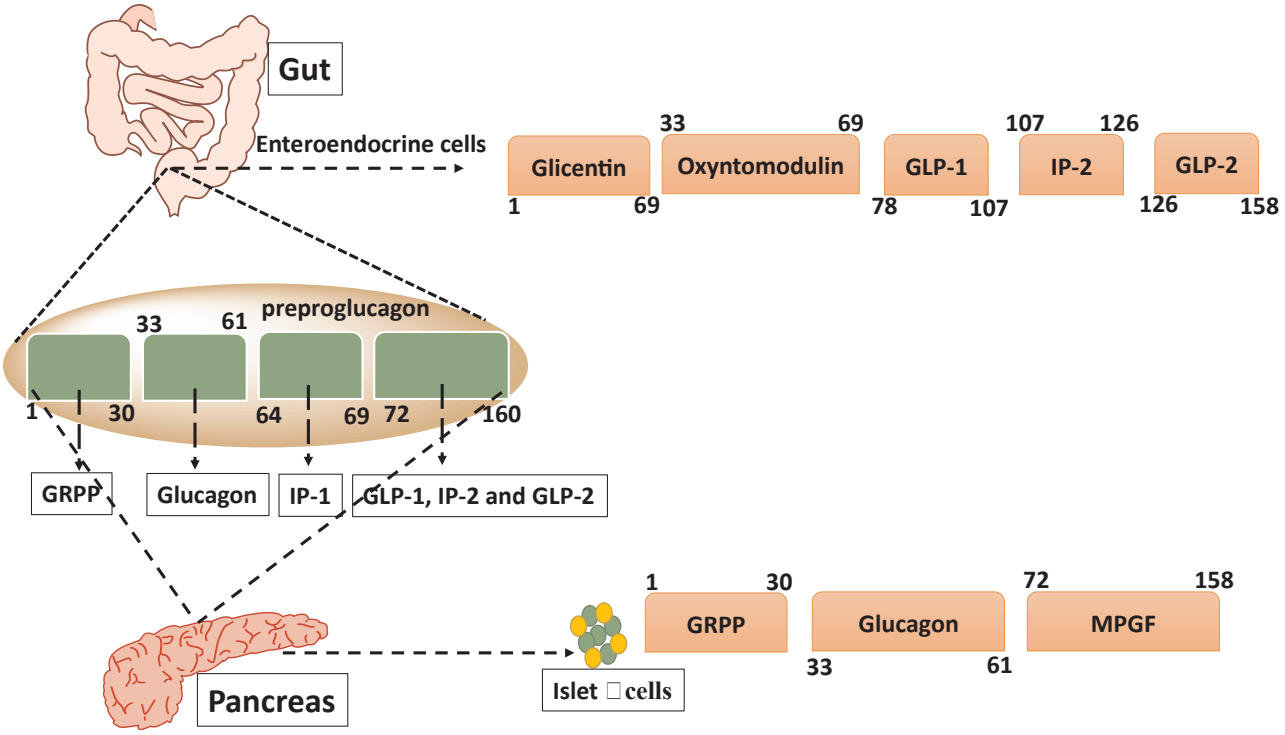

Fig. 1. Schematic representation of production of GLP-1: Production of preproglucagon in intestinal enteroendocrine L-cells and Pancreatic α-cells. GLP-1 peptide drived from Posttranslational processing of preproglucagon by prohormone convertases 1/3 in intestinal L-cells and GLP-2, oxyntomodulin, glicentin, and IP2 also drived in L-cells. In the α-cells of the pancreatic islet, glucagon, glicentin-related pancreatic polypeptide (GRPP) and major proglucagon fragment (MPGF) derived from preproglucagon cleaved by, prohormone convertase 2.

3. Physiology of glucagon-like peptide-1 (GLP-1)

In T2DM, the activity of incretin hormones is diminished, but the insulinotropic effect of GLP-1 is preserved [13,14]. GLP-1 (36 amino acid) is produced in enteroendocrine L-cells of the distal small bowel and colon. It is active in two forms, GLP-1(7–36) amide and GLP-1(7–37), both are equipotent but the earlier one is abundant in nature (Fig. 1) [14]. Their concentrations are low (5–10 pmol/L) during fasting conditions and high (15–50 pmol/L) after meals. Alanine, at the second residue of incretins, is the site of cleavage by DPP-4 enzymes, restricting its half-life to only ~2 min by producing inactive GLP-1(9–36) amide or GLP-1(9–37) [15]. Only 10–15% of secreted GLP-1 finally reaches the systemic circulation [16].

GLP-1 analogs and DPP-4 inhibitors are included as a second line treatment in type-2 diabetes as per the guidelines of European Association for the Study of Diabetes (EASD) and American Diabetes Association (ADA) [17].

3.1. Regulation of GLP-1 secretion

GLP-1 releases in a biphasic manner, rapidly within 15–30 min of nutrient ingestion followed by a second minor peak at 90–120 min. Brubaker et al. (2006) have proposed that the rapid rise of GLP-1 after meals is due to the proximal-distal link regulated by neurotransmitters (Ach), neuropeptide (GRP), and subsequent secretion due to the transit of nutrients down the lumen with direct interaction with distal L-cells. The fat, rather than glucose that transits to the lumen, is a more important physiological regulator of GLP-1 release [18]. Also, GABA and glycine are reported to secrete GLP-1 from GLUTag cell lines. In rats, GLP-1 is secreted by GIP through a neuronal pathway but in humans the mechanism is different. Somatostatin has an inhibitory effect upon GLP-1 secretion and the inhibition of somatostatin by immunoneutralization leads to increase in GLP-1 secretion up to eight fold (Fig. 2) [19].

3.2. Regulation of insulin secretion by GLP-1

Binding of GLP-1 to its receptors activates adenylate cyclase, hence, cAMP levels are elevated followed by PKA and cAMP-regulated guanine nucleotide exchange factor 2 (cAMP-GEF2), also known as Epac2 [20]. PKA causes closure of ATP sensitive K^+ (K_{ATP}) channels and membrane depolarisation with activation of L-type voltage-dependent calcium channel (VDCC), followed by generation of the action potential and Ca^+ influx [21]. PKA-dependent closure of delayed rectifying K^+ channels results in prolongation of the duration of the action potential. PKA also leads to Ryanodine receptors (RYR) and inositol 1,4,5-trisphosphate (IP3) mediated Ca^{+2} release. Epac2 activates Rap1 with the formation of IP3 and DAG, which further leads to CICR (Calcium-induced calcium release), from Ryanodine receptor (RyR) and inositol-3-phosphate receptor (IP3R) respectively [22]. All these pathways ultimately increase cytoplasmic Ca^{+2} that induce mitochondrial ATP synthesis and exocytotic release of insulin from insulin granules (Figs. 2 and 3).

4. Glucagon-like Peptide-1 agonists: pharmacology and current status

4.1. Exenatide

Exenatide is a synthetic form of the naturally occurring peptide Exendin-4 present in Gila monster [23]. It has 50% sequence homology with native GLP-1 with the substitution of amino acid Arg with Gly at 2nd position, which provides resistance against DPP-4 and a half-life of ~2-4 h. It is administered 60 min before breakfast and dinner, with a predominant effect of reduction in postprandial glucose (PPG) [24]. Exenatide is rapidly absorbed following subcutaneous administration and eliminated through the kidneys after proteolytic degradation by dipeptidyl peptidase IV [25].