GLP-1R Agonists Therapy for Type 2 Diabetes

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Abstract: Glucagon-like peptide-1 receptor (GLP-1R) agonists are widely used for treating type 2 diabetes mellitus (T2DM) because of their glucose-lowering and weight-losing effects, and low risk of hypoglycemia. Hence, there is considerable interest in understanding the mechanism underlying the beneficial effects of GLP-1 and developing stable and effective GLP-1R agonists. Here, we summarize the presently known mechanism of GLP-1 actions, which are mainly through regulating cAMP-PKA signaling pathway; the latest developments in novel clinical GLP-1R agonists are also introduced, which are characterized with multiple properties, such as extended half-life, reduced side-effects, lower production costs and more convenient drug dosing mode. The potential risk of GLP-1-based therapeutics, an often-ignored fact, is also discussed.

Key words: glucagon-like peptide-1 receptor (GLP-1R); GLP-1R agonists; type 2 diabetes

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0 Introduction

Diabetes mellitus is a chronic metabolic disorder caused by defects in insulin secretion, insulin action, or both, which can lead to hyperglycaemia and glucosuria or even fat and protein metabolism disorder. Over 90% of cases of diabetes mellitus are type 2 diabetes mellitus (T2DM) [¹]. There has been a continuous rise in the prevalence of T2DM throughout the world and the number of diagnosed diabetes among adults (aged 20-79 years) is expected to increase to 439 million by 2030 [²], there is a strong demand for new agents that offer the benefits of glycaemic control while preserving β-cell function and the possibility of delaying or modifying the associated complications [³].

The action of glucagon-like peptide-1 (GLP-1), a hormone released by the gut enteroendocrine L cells in response to food, increases glucose-dependent insulin secretion by pancreatic β cells [⁴, ⁵]. GLP-1 exerts its function through binding and activating its receptor GLP-1R; recently, GLP-1R agonists have been widely used for treating diabetes because of their excellent glucose-lowering capacity. In the present review, the physiological functions of GLP-1 and the mechanism of GLP-1 action through regulating cAMP-PKA signaling pathway are described; the characteristics of three generation GLP-1R agonists and the potential risk of GLP-1-based therapeutics are also discussed.

1 Physiological Functions and Clinical Drawback of GLP-1

In vivo, GLP-1 has two bioactive forms, respec-
GLP-1(7-37) and GLP-1(7-36) amide, the latter is the main activity form of GLP-1. The physiological functions of GLP-1 encompass glucose-dependent stimulation of insulin secretion, suppression of glucagon secretion, inhibition of gastric emptying, and reduction of appetite and food intake [6] (Fig. 1). Studies in young rodents (aged ~1.5 months) have suggested that GLP-1 may induce an increase in $\beta$-cell mass through enhanced cellular regeneration and inhibition of apoptosis [5].

GLP-1R belongs to the G-protein-coupled receptor (GPCR) and is widely distributed in pancreatic islets, brain, heart, kidney, and the gastrointestinal tract [6, 7]. GLP-1R is the major target of incretin mimetic therapies for the management of T2DM. It has been proven that GLP-1 potentiates insulin secretion in a glucose-dependent manner mainly through regulating cAMP-PKA signaling pathway [8-11] (Fig. 1).

Fig. 1  GLP-1R is involved in regulating cAMP-PKA signaling pathway and then triggering relevant physiological effects

G$\alpha$ subunit of GLP-1R is categorized into one of several groups: $\alpha_s$, $\alpha_i/o$, $\alpha_q$, and $\alpha_{12/13}$, binding of an extracellular ligand to GLP-1R alters the conformation of the associated heterotrimeric G protein, causing dissociation of the $G_i$ and $G_o$ subunits and initiating a cascade of cellular events, $G_o$ activates adenylate cyclase, which stimulates adenosine triphosphate (ATP) to produce the second messenger cAMP. The inactive protein kinase A (PKA) holoenzyme is composed of four subunits, two of which are regulatory subunits named as R, the other two are catalytic subunits named as C. As the concentration of cAMP increases, cAMP binds to PKA and the regulatory subunits undergo a conformational change to release the catalytic subunits, and the free catalytic subunits then catalyze the phosphorylation of serine or threonine residues of PKA substrate to regulate secretion activity of PKA substrate, such as insulin [8-11]. By regulating cAMP-PKA signaling pathway, GLP-1 and its agonists exert relevant insulinomimetic effects, such as stimulating insulin secretion, suppressing of glucagon secretion, inhibiting of gastric emptying and reducing appetite and food intake. GLP-1 also can induce an increase in $\beta$-cell mass through enhanced cellular regeneration and inhibition of apoptosis [6].

Native GLP-1 has a rather short plasma half-life of a few minutes due to proteolytic degradation by the serine protease, dipeptidyl peptidase-IV (DPP-IV) (Fig. 2), which cleaves the N-terminal histidine and alanine residues from GLP-1(7-36) to generate GLP-1(9-36) amide with abolished biological activity [11]. The rapid inactivation of native GLP-1 restricts its clinical application; to overcome this obstacle, the incretin-based therapy has been developed in two directions [3]. The GLP-1R agonists that activate GLP-1R, and the DPP-IV inhibitors that raise the level of endogenous GLP-1. GLP-1R agonists play key roles in glucose homeostasis and have being highly valued therapies [6].

2  GLP-1R Agonists

There is a long history of the research and development of effective GLP-1R agonists [3]. Several GLP-1R