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GLP-1(28-36)amide, a Long Ignored Peptide Revisited

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Abstract : Glucagon-like peptide-1 (GLP-1), which has been extensively applied for treating type 2 diabetes mellitus (T2DM), is an incretin hormone that regulates glucose homeostasis. GLP-1(28-36)amide, a C-terminal nonapeptide (FIAWLVKGRamide) of GLP-1, is a major product derived from the cleavage of GLP-1 by the neutral endopeptidase (NEP). GLP-1(28-36)amide has long been regarded as a metabolically inactive byproduct, however, recent findings reveal that GLP-1(28-36)amide plays multiple novel roles in ameliorating hepatic metabolism, protecting β cells, improving glucose disposal and inhibiting weight gain. Here, we summarize the latest progress on the effects of GLP-1(28-36)amide with a focus on its roles in regulating the Wnt and mitochondrial-mediated signaling pathways.

Keywords: Diabetes, GLP-1(28-36)amide, GLP-1-related peptides.

INTRODUCTION

Diabetes mellitus (DM) is a progressive disease that is characterized by hyperglycemia, reduction in sensitivity to insulin and impaired β-cell function [1, 2]. There has been a continuous rise in the prevalence of diabetes mellitus worldwide and the number of diabetic patients may reach 300 million by 2030 [3]. The chronic hyperglycemia may cause multiple complications such as vascular diseases, obesity, hypertension and dyslipidemia [2]. Therefore, an ideal anti-diabetic agent would not only offer the benefit of achieving optimal glycemic control, but also preventing or alleviating associated complications.

Glucagon-like peptide 1 (GLP-1) is an incretin hormone that is secreted by the intestinal L-cells in response to food, which increases insulin secretion in a glucose-dependent manner [4]. GLP-1 exerts its biological actions through binding and activating its receptor (GLP-1R), which is widely distributed in pancreatic islets, heart, brain, kidney, and the gastrointestinal tract [1, 5, 6]. It is reported that native GLP-1 is rapidly released postprandially, peaking at 10-15 min followed by a sustained peak at 30-60 min [7]. GLP-1(7-36)amide, the N-terminally truncated products of native GLP-1, is the main active form in our body [8]. I*n vivo*, GLP-1(7-36)amide is rapidly inactivated due to proteolytic degradation by dipeptidyl peptidase-IV (DPP-IV), a serine protease that efficiently cleaves the GLP-1(7-36)amide to generate GLP-1(9-36)amide and a dipeptide [9]. This degradation restricts the clinical application of GLP-1 and two approaches have been developed to overcome this limitation. The first class of drug exploits GLP-1R agonists such as exenatide, liraglutide and lixisenatide, on the basis of GLP-1 sequence, exenatide is a synthetic peptide that shares approximately 50% of sequence identity to GLP-1 and liraglutide has two sequence modifications and an attached fatty acid side chain [10, 11]. Lixisenatide is a synthetic version of exenatide with its C-terminus modified with six lysine residues and deletion of one proline compared with exenatide [12]. The second class includes DPP-IV inhibitors that raise the plasma levels of endogenous GLP-1 [13, 14]. These two GLP-1-based therapeutic strategies have been widely applied in clinic for treating diabetes because of their excellent capacity of controlling post-prandial blood glucose, promoting pancreatic β cell survival, suppressing weight gain and reducing risk of hypoglycemia [6, 15, 16].

Different from DPP-IV, NEP, which cleaves GLP-1(7-36)amide or GLP-1(9-36)amide to generate GLP-1(28-36)amide, is widely distributed in endothelial cells, vascular smooth muscle cells, cardiac cells and renal epithelial cells [17]. As a neuropeptide degrading enzyme, NEP also possesses a number of organ-specific functions in both central nervous system and related peripheral tissues [18]. A major product of NEP digestion, GLP-1(28-36)amide, can be further metabolized in hepatocytes to generate two N-terminus cleavage products, GLP-1(29-36)amide and GLP-1(31-36)amide. Moreover, a recent *in vitro* study has demonstrated that the plasma half-life of GLP-1(28-36)amide is longer in human hepatocytes ($t_{1/2}$ = 24 min) than that in mouse hepatocytes ($t_{1/2}$ = 13 min) [19]. The physiological function of GLP-1(28-36)amide was previously unknown, however, recent studies have indicated GLP-1(28-36)amide with anti-diabetic effects involving Wnt and mitochondrial-mediated signaling pathways [20]. In this review, the novel

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beneficial effects of GLP-1(28-36)amide and its underlying mechanisms are summarized. Additionally, GLP-1-related peptides and molecules such as GLP-1(7-36)amide, GLP-1(9-36)amide, GLP-1R agonists and DPP-IV inhibitors which possess anti-diabetic effects similar to GLP-1(28-36)amide are also discussed.

EFFECTS OF GLP-1(28-36)AMIDE *IN VITRO* AND *IN VIVO*

Recent studies have indicated GLP-1(28-36)amide might be a bioactive and insulinomimetic peptide similar to GLP-1(7-36)amide and GLP-1(9-36)amide [21]. GLP-1(28-36)amide has been reported to play multiple beneficial roles in ameliorating hepatic metabolism, protecting β cells, improving glucose disposal and inhibiting weight gain or even exerting direct cardioprotective effects [21-27]. We summarize the current progress on the beneficial effects of GLP-1(28-36)amide in pancreas and extra-pancreatic tissues or cell lineages.

Ameliorating Hepatic Metabolism

The effects of GLP-1(28-36)amide on ameliorating hepatic metabolism are first demonstrated in the suppression of oxidative stress in isolated mouse hepatocytes. GLP-1(28-36)amide (100 nM) treatment on hepatocytes for 24 hours directly modulates mitochondrial oxidative metabolism, such as gluconeogenesis in mitochondria of hepatocytes [22]. Another study indicates the administration of GLP-1(28-36)amide at a rate of 18.5 nmol/kg BW/day for 9 weeks to diet-induced obese mice diminishes the development of hepatic steatosis [21].

Protecting Pancreatic β cells

GLP-1(28-36)amide plays an important role in modulating cell growth and function not only in the rat pancreatic INS-1 cell line, but also in dispersed human islet cells. This nonapeptide is demonstrated to promote β-cell survival and improve β-cell functions in a study of 10 μM treatment for 18 hours against cytotoxicity induced by glucolipotoxicity media [23]. A recent study also suggests that the intraperitoneal injection of 18 nmol/kg GLP-1(28-36)amide once daily for 9 weeks show cytoprotective effect on pancreatic β cells by increasing mass and promoting proliferation in a β-cell injury diabetic mouse model [24].

Improving Glucose Disposal

GLP-1(28-36)amide administration effectively improves glycemic control. An *in vivo* study in high-fat diet-fed mice indicates that a six-week administration of 18.5 nmol/kg GLP-1(28-36)amide improved hepatic glucose disposal, which is associated with increased cAMP levels and phosphorylation of PKA target. Furthermore, the glucose disposal is drastically attenuated after GLP-1(28-36)amide injection during pyruvate tolerance test [25]. GLP-1(28-36)amide also regulates glucose levels in a streptozotocin-induced diabetes mouse model. Once-daily intraperitoneal injection of GLP-1(28-36)amide (18 nmol/kg) for nine weeks significantly reduced fasting glucose levels from nearly 17 mM to 12 mM compared with their PBS control group [24]. Another recent study showed that injection of GLP-1(28-36)amide to high fat-fed mice prevents the development of both fasting hyperglycemia and hyperinsulinemia [21].

Inhibiting Weight Gain

GLP-1(28-36)amide treatment provides a significant reduction in body weight gain approximately four-fold higher than that of the control vehicle in response to high-fat diet-fed mice [25]. A study that infuses GLP-1(28-36)amide for 9 weeks in diet-induced obese mice effectively inhibits the rate of weight gain [21]. In addition, the average change in body weight gain per week of mice receiving GLP-1(28-36)amide was 50% less than that of the mice receiving control vehicle [21].

Cardioprotective Effects

GLP-1(28-36)amide has been found to exert important biological effects on the cardiovascular system. In a study that administered GLP-1(28-36)amide for 20 min to male C57BL6/J mice (10-12 week old), then isolated hearts underwent 30 min of global ischemia and 40 min of reperfusion, the recovery of left ventricular developed pressure (LVDP) was significantly greater in GLP-1(28-36)amide group compared to vehicle-treated hearts [26]. The cardioprotection effect of GLP-1(28-36)amide is also suggested in the reduction of infarct size in a myocardial infarction (MI) model [26].

As described above, current investigations of GLP-1(28-36)amide have mainly focused on its hepatic, pancreatic and cardiac effects, however, compared with GLP-1R agonists and DPP-IV inhibitors which have been thoroughly investigated or even commercially available, our knowledge on GLP-1(28-36)amide remains limited. On the other hand, accumulating evidence strongly support that GLP-1-based therapies cause undesired gastrointestinal tract reactions, such as nausea, vomiting, and diarrhea [28, 29]. Moreover, there has been ongoing debate about the association between GLP-1-based agents and pancreatic injury such as pancreatitis and pancreatic cancers, while the potential risk of GLP-1(28-36)amide remains unknown and awaits further exploitation [30, 31].

MECHANISMS OF GLP-1(28-36)AMIDE'S BENEFICIAL EFFECTS

Previous studies showed that the cellular mechanisms underlying the effects of GLP-1 is mainly mediated by cAMP-PKA signaling pathway [32]. The activated GLP-1R is involved in this signaling pathway and then triggers relevant physiological effects. However, GLP-1(28-36)amide has been shown to exert its effects in insulin-sensitive tissues such as liver where there is no detectable expression of GLP-1R [22]. The mechanism of GLP-1(28-36)amide on regulating hepatic metabolism is associated with a GLP-1R independent mitochondrial-mediated pathway. Studies suggest that this nonapeptide is uptaken by hepatocytes and targeting mitochondria, modulates oxidative phosphorylation through lowering reactive oxygen species levels, inhibiting the accumulation of liver triglycerides, and suppressing

excessive gluconeogenesis [21, 22, 25]. Further-more, in a high-fat diet (HFD) induced obese mouse model, GLP-1(28-36)amide treatment suppressed excessive gluconeogenesis of primary hepatocytes mainly through decreasing the gluconeogenic genes expression of Pck1, G6pc and Ppargc1a [25].

GLP-1(28-36)amide is proposed to modulate the growth and function of pancreatic β cells, with a mechanism involves mitochondrial-mediated signaling pathways [23]. Increasing experimental evidence implicate that oxidative stress plays a key role in opening of the mitochondrial permeability transition (MPT) pore and the loss of mitochondrial membrane potential [23]. GLP-1(28-36)amide, a cell-permeable nonapeptide, appears to act as an antioxidant and targets to mitochondrion, inhibits MPT, preserves membrane potential, and thus effectively suppresses β cell apoptosis and promotes β cell survival [24, 27]. Another presently known mechanism of GLP-1(28-36) amide effects on β cells is related to the PKA/β-catenin (β-cat) signaling pathway [24, 27]. The bipartite transcription factor β-cat/TCF, a key effecter of Wnt signaling pathway, is formed by free β-cat and a member of the TCF protein family [33, 34]. The Wnt signaling pathway was previously known for its role in tumor and subsequently extensive investigations have found that several key components of the Wnt signaling pathway are involved in pancreas development, islet function, and insulin production and secretion [35]. Furthermore, it has been shown that GLP-1 and its agonist, exendin-4, induce Wnt signaling in both isolated islets and INS-1 cells [36]. GLP-1 and exendin-4 are known to promote β cells survival *via* GLP-1R, while GLP-1(28–36)amide exerts cytoprotective actions on β cells in a GLP-1R independent manner [23]. In a recent *in vitro* investigation on β cells, GLP-1(28-36)amide has been demonstrated to stimulate β-cat Ser^{675} phosphorylation, leading to Wnt signaling pathway activation, which is associated with the activation of cAMP/PKA signaling cascade [24].

It has been suggested that GLP-1(28-36)amide significantly reduced fasting glucose levels due to increased basal insulin levels and the alleviated insulin resistance [24]. This nonapeptide also effectively suppresses hepatic glucose production both *in vivo* and *in vitro* settings, mainly through inhibiting the expression of two gluconeogenic enzymes and the gluconeogenic transcriptional coactivator PGC-1α [25].

In diet-induced obese mice model, the underlying mechanisms of GLP-1(28-36)amide effect on body weight gain remain controversial. One possible mechanism of this nonapeptide on suppressing weight gain is closely related with increased energy expenditure [21], whereas another study indicates that the GLP-1(28-36)amide treatment inhibits the rate of weight gain which is associated with improved tolerance to pyruvate challenge *in vivo* [25]. Since the mechanisms underlying the weight-loss effects of GLP-1 is associated with inhibiting gastric emptying, and reducing appetite and food intake [4], which suggests a possibility that GLP-1(28-36)amide may promote weight loss in obese and diabetic individuals through the same mechanisms as that of GLP-1.

EFFECTS OF OTHER GLP-1-RELATED PEPTIDES AND MOLECULES

GLP-1-related peptides and molecules, such as GLP-1(7-36)amide, GLP-1(9-36)amide, GLP-1R agonists and DPP-IV inhibitors, also possess anti-diabetic effects similar to GLP-1(28-36)amide.

GLP-1(7-36)amide

GLP-1(7-36)amide exerts multiple glucoregulation effects such as glucose-dependent stimulating insulin secretion, suppressing glucagon secretion, inhibiting gastric emptying, and reducing appetite and food intake [14-16, 37]. Furthermore, GLP-1(7-36)amide induces an increase in pancreatic β-cell mass by stimulating pancreatic β-cell proliferation, enhancing β-cell neogenesis, and suppressing β-cell apoptosis [1, 38, 39].

GLP-1(9-36)amide

GLP-1(7-36)amide can be degenerated by enzyme action of DPP-IV into GLP-1(9-36)amide, which is used to be regarded as an inactive metabolite [40]. However, there have been several studies which demonstrate that GLP-1(9-36)amide retain biological activity in insulin-sensitive target tissues such as the heart and liver [41, 42]. Administration of GLP-1(9-36)amide is also shown to inhibit weight gain in diet-induced obese mice, as well as to reduce postprandial glycemia independent of plasma insulin levels in humans [43, 44].

GLP-1R Agonists

GLP-1R agonists, such as exenatide, liraglutide and lixisenatide, improve glycaemic control and β-cell function with much longer half time, are currently available in the market [10]. GLP-1R agonists also exert effects beyond glycaemic actions owing to the wide expressing of GLP-1R in extra-pancreatic tissues [45, 46]. For example, GLP-1R agonists have been shown to have cardioprotective effects [47]. It is reported that exenatide reduces myocardial infarct size and protected against deterioration of cardiac function in a porcine model of ischemia and reperfusion injury [48]. In a mouse model of myocardial infarction (MI), liraglutide improves cardiac output and reduces infarct size and mortality from cardiac rupture [49]. Moreover, GLP-1R agonists are reported to optimize the selection of therapeutic agents for the treatment of diabetic patients with cardiovascular disease [50, 51]. Additionally, GLP-1R agonists have also been shown to play neuroprotective roles in rodent models of stroke, Alzheimer's disease and Parkinson's disease [27].

DPP-IV Inhibitors

Since native GLP-1 can easily be digested by DPP-IV, DPP-IV inhibitors have also been developed against diabetes *via* increasing the half life of endogenous incretin hormone [14, 40]. Compared with control group, DPP-IV inhibitors have been shown to reduce the level of glycated hemoglobin and plasma glucose without causing obvious adverse effects [52].

ABBREVIATIONS

GLP-1	=	Glucagon-like peptide-1
T2DM	=	Type 2 diabetes mellitus
GLP-1R	=	GLP-1 receptor
NEP	=	Neutral endopeptidase
DPP-IV	=	Dipeptidyl peptidase-IV
DM	=	Diabetes mellitus
LVDP	=	Left Ventricular Developed Pressure
MI	=	Myocardial infarction
CNS	=	Central nervous system
HFD	=	High-fat diet
β-cat	=	β-catenin
MPT	=	Mitochondrial permeability transition

SUMMARY AND DISCCSSION

The novel physiological effects of GLP-1(28-36)amide, such as inhibiting weight gain and attenuating glucose levels, and showing effects on β cells and hepatocytes, suggest that GLP-1(28-36)amide could be highly attractive as an add-on treatment in therapy of T2DM. On the other hand, the unique mitochondrial targeting property of GLP-1(28-36)amide is rather different form its precursor GLP-1 or GLP-1R agonists [53], such phenomenon will be of great interest to be further understood. Further studies to define whether GLP-1(28-36)amide activates a new receptor or possesses other action modes are also necessary. Moreover, the downstream metabolites such as GLP-1(29-36)amide or GLP-1(31-36)amide, may also worth being studied further.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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