Is Glucagon-like peptide-1, an agent treating diabetes, a new hope for Alzheimer's disease?

Lin LI

Gerontology Institute, Shanxi Medical University, Taiyuan 030001, China

Abstract: Glucagon-like peptide-1 (GLP-1) has been endorsed as a promising and attractive agent in the treatment of type 2 diabetes mellitus (T2DM). Both Alzheimer's disease (AD) and T2DM share some common pathophysiologic hallmarks, such as amyloid β (A β), phosphorylation of tau protein, and glycogen synthase kinase-3. GLP-1 possesses neurotropic properties and can reduce amyloid protein levels in the brain. Based on extensive studies during the past decades, the understanding on AD leads us to believe that the primary targets in AD are the A β and tau protein. Combine these findings, GLP-1 is probably a promising agent in the therapy of AD. This review was focused on the biochemistry and physiology of GLP-1, communities between T2DM and AD, new progresses of GLP-1 in treating T2MD and improving some pathologic hallmarks of AD.

Keywords: glucagon-like peptide 1; type 2 diabetes mellitus; Alzheimer's disease

1 Introduction

Glucagon-like peptide (GLP) 1, a peptide of 30 amino acids with 50% sequence homology to glucagon, results from the expression of glucagon gene in the L cell of the distal intestinal mucosa^[1-3]. GLP-1 was found as an insulinogenic factor 20 years ago. Among all candidate incretins, GLP-1 was regarded as the most important physiological substance with dual gastrone and insulinotropic function^[4]. It exerts potent effects on glucose-dependent insulin secretion and insulin gene expression^[5]. The multifaceted actions of GLP-1 to regulate blood glucose include the following: 1) the stimulation of insulin secretion and its gene expression; 2) the inhibition of glucagon secretion; 3) the inhibition of food intake; 4) the proliferation and differentiation of β cells; and 5) the protection of β -cells from apoptosis^[6]. Although predominantly located in pancreatic islets, researches have demonstrated that GLP-1 and exendin-4, a naturally occurring more stable analogue of GLP-1 that binds at the GLP-1 receptor (GLP-1R), possess neurotrophic properties. They

can protect neurons against glutamate-induced apoptosis, and reduce levels of amyloid- β peptide (A β) in the brain^[7]. A extensive expression of GLP-1R in the brain has been documented^[8]. Therefore, GLP-1 is regarded as a new intervention peptide not only for type 2 diabetes mellitus (T2DM) but also for Alzheimer's disease (AD)^[9-11].

2 Synthesis and secretion of GLP-1

The biological active GLP-1 derives from a precursor with 36 amino acids. In the human genome, the nucleotide sequence encoding for the proglucagon gene is located on chromosome 17 and spans approximately 10 kb. The transcriptional unit of proglucagon consists of 6 exons and 5 introns. Four of the six exons encode distinct functional domains^[12]. It has been recognized that the post-translational processing of pre-proglucagon differs in a tissue-specific manner (Fig. 1). In the pancreas, the main GLP-1-related products are GLP-1 (1-36) amide and GLP-1 (1-37), while in the ileum and hypothalamus, they are GLP-1 (7-36) amide and GLP-1 (7-37)^[13].

Proglucagon is processed by proprotein convertase 2 in the pancreatic islet β -cells (to mainly release glucagon) and by proprotein convertase in the intestinal L cells (to mainly produce GLP-1 and GLP2)^[14]. The carboxyl-terminal amidation of GLP-1 entails the sequential enzymatic action by peptidylglycine α -monooxygenase and peptidylamidogly-

Corresponding author: Lin LI
Tel: 86-351-4934122
E-mail: linstrongling@yahoo.ca
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Fig. 1 Human proglucagon undergoes differential processing in pancreatic β cells and intestinal L cells. In the β cells, the major products released into plasma are glucicentin related polypeptide, glucagon, a minor and a major proglucagon fragment; whereas in the intestinal L cells, the major products released are glucicentin, GLP-1 and GLP-2. GRPP, glucicentin related pancreatic polypeptide; IP, intervening peptide. (According to Hui H *et al.*^[6])

colate lyase^[15]. Amidation of GLP-1 has been proposed to enhance its survival in the blood. Whether the amidated forms of GLP-1 might differentially affect nonpancreatic targets is not clear yet. GLP-1 is rapidly degraded *in vivo* by dipeptidyl peptidase-IV (DPP-IV), leading to its very short half-life (1–2 min)^[16,17]. Hence, future therapeutic agents would have to be more stable than GLP-1 in order to provide a lasting glucose-lowering effect.

In vivo, several metabolites of GLP-1 are generated by enzyme digestion. These products include GLP-1 (9–36), GLP-1 (7–35), and GLP-1 (7–34). GLP-1 (9–36) amide is the main catabolic product of GLP-1, and *in vivo* its concentration is 10-fold greater than the level of GLP-1 (7–36) amide, the biologically active form of this peptide^[18]. Isoforms of GLP-1 has different activity: the effect of GLP-1 (7–36) amide is 100 times more potent than GLP-1 (1–37) and GLP-1 (1–36) amide in stimulating [¹⁴C]-aminopyrine accumulation^[19]. GLP-1 (7–36) amide and GLP-1 (7–37) have similar effect and efficiency^[20]. GLP-1 (9–36) amide has no effect on β -cells and in some studies has been shown to be an antagonist of the adenylyl cyclase activity^[21]. GLP-1 (7–35) and GLP-1 (7–34) have clearly been shown to be agonists. GLP-1 (7–36) and GLP-1 (7–37) are two of the main naturally occurring GLP products present *in vivo* and have similar insulinotropic potency. The basic biochemical parameters of GLP-1 (7–36)

are listed in Tab. 1. The structural analysis of GLP-1 indicates that the first seven amino acid residues form a random coil structure, followed by a first helical region (7–14), then a linker region (15–17) and another helical region (18–29).

Plasma levels of GLP-1 rise rapidly after nutrient ingestion. Major regulators of GLP-1 secretion include pancreatic hormones (insulin and glucagon)^[22,23], nutrients (glucose and fatty acids), gastrointestinal hormones (gastric inhibitory polypeptide (GIP), gastrin-releasing polypeptide (GRP), gastric emptying^[24], satiety^[25], body weight^[26], and the vagal nerve-dependent release of acetylcholine^[27,28]. GIP is also a potent stimulator for GLP-1 release *in vitro*^[29].

Endocrine and neural pathways for GLP-1-mediated actions are shown in Fig. 2. GLP-1 is secreted by intestinal L cells. After diffusion into the lamina propria, GLP-1 reaches intestinal capillaries, where DPP-IV is expressed on the luminal surface of the endothelial cells. DPP-IV inactivates GLP-1 by cleavage of the N-terminal dipeptide. Consequently, only 25% of GLP-1 secreted enters the portal circulation in its intact form. Passage through the liver inactivates 40% of the remaining active GLP-1, thus only 10%–15% reaches the systemic circulation and the pancreas. GLP-1 can also stimulate the neural pathway by activating sensory efferent neurons from the nodose ganglion, the hepatportal region^[30,31], or the liver^[32], which can in turn

Tab. 1 Characteristics of human GLP-1 (7-36)

Sequence	HAEGTFTSDVSSVLEGQAAKEFIAWLVKGR
Number of amino acids	30
Molecular weight	3297.5
Estimated half-life	1 – 3 min (mammalian plasma, <i>in vivo</i>)
Instability index (II)	17.69
Aliphatic index	81.33
Grand average of hydropathicity	–0.047

Fig. 2 Endocrine and neural pathways for GLP-1-mediated actions. FFA, free fatty acids. (-) indicates inhibition; (+) or ↑ indicates stimulation; ↓ indicates delayed. (According to Combettes MM^[34])

activate the solitary tract nucleus in the brain^[33]. In response, descending impulses are generated, thereby stimulating vagal motor neurons that send impulses (inhibitory or stimulatory) to peripheral tissues, such as the stomach and pancreas. GLP-1 is a powerful candidate for the treatment of T2DM, but its rapid degradation by DPP-IV and its renal clearance have limited the use of the native peptide in the clinical setting. Exendin 4I, a naturally occurring long-acting GLP-1R agonist with a resistance to DPP-IV-mediated inactivation, is even more potent than the native GLP-1^[35]. The design of DPP-IV-resistant GLP-1-analogs, conjugated forms of GLP-1, as well as the DPP-IV inhibitors, have been explored by various research teams, and various agonists of the GLP-1R have been developed and tested in animal models of T2DM^[6]. Some GLP-1 mimic have been in clinical phase II and III, even launched in the US^[34]. GLP-1 binds a specific cell membrane receptor, termed GLP-1R, a member of the seven-membrane-spanning G-protein-coupled family of receptors (GPCR) (Fig. 3). GLP-1R

is localized on chromosome 6 and contains 12 introns and 13 exons^[36]. GLP-1R have been identified in brain, lung, pancreatic islets, stomach, hypothalamus, heart, intestine, and kidney^[37,38]. GLP-1R consists of 463 amino acids (with a molecular weight of 65 kDa), and contains 8 hydrophobic domains (Fig. 3). The N-terminal hydrophobic segment is probably a signal sequence, whereas the others are membrane-spanning hydrophobic motifs^[39]. GLP-1R efficiently couples adenylyl cyclase to stimulate insulin secretion^[40].

3 Commonality between T2DM and AD

Since the early 1960s, insulin action in the central nervous system (CNS) has been under investigation^[41]. Although insulin is unable to regulate glucose uptake in neuronal tissue, it directly affects the CNS: both insulin and its receptor are expressed throughout the mammalian brain^[42,43]. The finding that there are commonalities between neurons and β-cells offers a reasonable explanation to the common risk and prevent factors between T2DM and AD. There are speculations that the pathogenetic mechanism is jointly

shared between T2DM and AD. Researches have shown some common risk factors between T2DM and AD, such as higher cholesterol, dysmetabolism, cardiovascular disorder, oxidative stress, inflammation, apolipoprotein 4, apoptosis, etc. The finding that treatment with GLP-1 offers some beneficial effects to a number of the therapeutic targets associated with AD open a new area of research. The commonality between T2DM and AD may contribute to the explanation of GLP-1 as a promising peptide to treat T2DM and AD.

AD is characterized by intracellular neurofibrillary tangles (NFTs), containing an abnormal hyperphosphorylated form of tau protein, and extracellular senile plaques (SPs), which are mainly composed by fibrillar A β peptide. Both of the hallmarks are involved, more or less, in T2DM. Age-related degenerative diseases, AD and T2DM, are associated with the accumulation of amyloid fibrils^[44]. Glycogen synthase kinase-3 (GSK-3), an important kinase in the insulin signaling pathway, is involved in phosphorylated of tau protein in the AD brain^[45]. Another commonality is that both diseases extensively involve in cell loss and degenerative change. AD is by far the most common neurodegenerative disease with an extensive neuron loss. T2DM is also a degenerative disease that results from the

selective destruction of pancreatic β -cells^[46].

Amyloid protein deposits are commonly observed in pancreatic islets of diabetic patients. These deposits consist of islet amyloid polypeptide (IAPP)^[47,48]. Given the pathogenetic similarities and the fact that A β precursor protein and IAPP have a 90% structural similarity^[49], it is not surprising that AD seems to predispose for insulin resistance^[50], insulin hypersecretion^[50], and T2DM^[49,50]. Conversely, individuals suffering from T2DM show an increased prevalence of dementia^[51,52]. This effect is perhaps explained by the elevation in serum insulin levels (as observed in prediabetes and early T2DM), which has been associated with impaired cognitive function^[53]. This might be due to elevated A β levels, which are associated with elevated serum insulin content^[54].

Recent research suggests that high-cholesterol could promote the synthesis of A β , and lower cholesterol by blocking the 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibits the A β production^[55]. Thus the HMG-CoA reductase inhibitors, termed statins, may offer an alternative therapeutic strategy for AD. The similar positive regulation of cholesterol to A β also can be seen in the T2DM^[56]. Several transgenic mouse models overexpressing

Fig. 3 Schematic representation of the structure of the rat GLP-1R. The GLP-1 receptor contains an NT, three EC and IC loops, seven TM domains, and a carboxy-terminal (CT) tail. Amino acids are identified by the one-letter code. (According to Hui H *et al.*^[6])

IAPP have been generated. These mice generally develop T2DM subsequent to amyloid deposits^[57,58]. Conversely, targeted disruption of IAPP leads to enhanced insulin secretion and improved glucose tolerance^[59]. Of interest, disruption of insulin-degrading enzymes causes increased amyloid plaque formation and glucose intolerance accompanied by hyperinsulinemia^[60].

Freude^[61] proved significantly increased tau phosphorylation at Ser²⁰² in the brain within 10 min after 1-mU insulin injection and an even further increase after injection of 4 U of insulin, indicating a correlation between tau phosphorylation and peripheral insulin levels *in vivo*. Further, Freude demonstrated that insulin receptor signaling and tau phosphorylation were completely abolished in the brains of the mice lacking the brain insulin receptor (NIRKO) under hyperinsulinemic conditions, indicating that the cerebral insulin receptors are a direct target of peripheral administered insulin.

GSK-3 is a serine/threonine kinase that phosphorylates glycogen synthase in the rate-limiting step of glycogen biosynthesis^[62]. GSK-3 have been implicated in the formation of neurofibrillary tangles^[63,64]. GSK-3 inhibition is an attractive target identified to be useful in the treatment of diseases such as T2DM and AD.

Neuroectoderm-derived neural cells and pancreatic β -cells derived from endoderm tissue share many features. A common substance to both β -cells and neurons is the enzyme glutamic acid decarboxylase, involved in the synthesis of β -aminobutyric acid, the main inhibitory neurotransmitter in the brain. Likewise, tyrosine hydroxylase and dopa decarboxylase are common biosynthetic enzymes. Thyrotrophin-releasing hormones as well as both the low and high affinity P75 nerve growth factor (NGF) receptors are shared attributes of both neuronal tissues and β -cells. Finally, β -cells resemble neurons in that they are electrically excitable and respond to hormonal stimuli and glucose by depolarization and exocytosis, in a process that resembles neurotransmitter release from synaptic vesicles. Although derived from different germ layers in the embryo, these two cell types clearly share many similarities and as such, it is reasonable to assume that common signaling mechanisms occur in response to similar physiological responses, such as proliferation and differentiation^[9].

4 GLP-1, a strong intervenor of T2DM and AD

The pharmacological actions of GLP-1 on glucose

metabolism, including stimulation of insulin release, suppression of glucagon release, and inhibition of gastric emptying, have provided the rationale for its assessment as a therapeutic agent for T2DM^[65]. Recent research focusing on intervening AD showed that GLP-1 is also a strong intervenor of AD^[9-11].

GLP-1 regulates insulin secretion and insulin gene expression via its action on the pancreas following binding at the G-protein coupled GLP-1R. The GLP-1R signaling has been demonstrated to inhibit glucagon secretion^[66]. It has been demonstrated that there is commonality of GLP-1R expression in both rat and human brains^[9]. Within the CNS, GLP-1 and several analogs that bind to the GLP-1R possess neurotropic properties and offer protection against glutamate-induced apoptosis and oxidative injury in cultured neuronal cells^[7]. Moreover, GLP-1 can modify processing of A β protein precursor in cell cultures, and can reduce A β -peptide levels in the brain *in vivo*^[67].

Nevertheless, some of the GLP-1-derived agonists with DPP-IV resistance appear to be rapidly cleared from the plasma by renal clearance. The clinical studies of full name exendin-4 showed that daily administration or combination therapy with oral anti-diabetic agents was required to normalize blood glucose level. It is a motivated effort to develop the longer-acting molecules that retain the native GLP-1 actions. It is also clear that a gene therapy approach exerting long lasting effects would have advantages over parenteral protein drug delivery. A new gene therapy agent GLP-1/IgG1-Fc fusion construct developed by Kuma *et al.*^[68] showed a unique advantage. They generated a plasmid by fusing active human GLP-1 and mouse IgG1 heavy chain constant regions (GLP-1/Fc). An IgK leader peptide-driven secretable fusion protein of the active GLP-1 and IgG1-Fc was constructed for mammalian expression. The researches *in vivo* and *in vitro* showed that the bivalent GLP-1/Fc fusion protein is an effective approach for the therapy of T2DM.

In clinical treatment, GLP-1 based therapies for T2DM is in progress. Therapy strategies related to GLP-1 include injected DPP-IV-resistant GLP-1 mimetics or orally active DPP-IV inhibitors^[69-71]. The GLP-1 enhancers, DPP-IV inhibitors pre-registered by US Food and Drug Administration (FDA) are Vildagliptin (LAF237) and Sitagliptin (MK-0431). Those in clinical phase III programs are Denagliptin, SYR 322 and Saxagliptin (BMS477118). Those in clinical phase II are Ro-0730699, PSN 9301 and TA 6666. GLP-1 mimetic and Byetta-Exenatide have been launched in the

US (2005). GLP-1 mimetics in clinical phase III programs is Liraglutide NN2211. Those in clinical phase II programs are ZP-10, BIM-51077, Exenatide-LAR, and CJC-113^[34].

The stimulus for neuronal GLP-1-transmission within the CNS is unclear. One possibility is that GLP-1-containing neurons or receptors are implicated in other neuropeptide-containing CNS pathways or down-stream from classic neurotransmitter systems such as noradrenalin, serotonin or dopamine. An alternative possibility is that peripheral GLP-1 acts on vagal afferent fibers^[72], where it could influence GLP-1 neuronal transmission in the CNS. Emerging evidence suggests that stimulation of neuronal GLP-1 receptors plays an important role in regulating neuronal plasticity and cell survival^[10]. It was recently reported that GLP-1 and exendin-4 possess neurotrophic properties and can protect neurons against glutamate-induced apoptosis. Perry^[7] showed that GLP-1 can reduce the levels of A β in the brain *in vivo* and can reduce levels of amyloid precursor protein (APP) in cultured neuronal cells. GLP-1 and exendin-4 protect cultured hippocampal neurons against death induced by A β and iron, an oxidative insult. Collectively, this data suggests that GLP-1 can modify APP processing and protect against oxidative injury.

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胰高血糖素样多肽 1 — 治疗糖尿病的多肽，是治疗阿尔茨海默病的新希望？

李琳

山西医科大学，老年医学研究所，太原 030001

摘要 胰高血糖素样多肽 1 (Glucagon-like peptide, GLP) 已被证明是有前景的 II 型糖尿病 (Type 2 diabetes mellitus, T2DM) 治疗剂。阿尔茨海默病 (Alzheimer's disease, AD) 和 T2DM 具有在淀粉样蛋白 β (Amyloid β , A β), tau 蛋白磷酸化和葡萄糖合成酶 3 等方面的共同的病理生理特征。GLP-1 具有神经营养特性，并能降低脑淀粉样蛋白水平。过去几十年对 AD 的广泛研究使我们认识到对其治疗应针对 A β 和 tau 蛋白。总结这些之后发现，GLP-1 可能有希望用于治疗 AD。本文综述了 GLP-1 的生物化学和生理学特征，T2DM 和 AD 的共同的病理生理特征，以及 GLP-1 在治疗 T2MD 和改善 AD 某些病理变化方面的新进展。

关键词：胰高血糖素样多肽 1；II 型糖尿病，阿尔茨海默病