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

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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 (Aβ), 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 Aβ 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 T2DM 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 regard 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 (Aβ) 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-monoxygenase and peptidylamidogly-
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). 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. Isoforms of GLP-1 have 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. GLP-1 (7-36) amide and GLP-1 (7-37) have similar effect and efficiency. GLP-1 (9-36) amide has no effect on β-cells and in some studies has been shown to be an antagonist of the adenyl cyclase activity. 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), nutrients (glucose and fatty acids), gastrointestinal hormones (gastric inhibitory polypeptide (GIP), gastrin-releasing polypeptide (GRP), gastric emptying), satiety, body weight, and the vagal nerve-dependent release of acetylcholine. GIP is also a potent stimulator for GLP-1 release in vitro.

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 hepatoportal region, or the liver, which can in turn...