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## Mechanisms of action of glucagon-like peptide 1 in the pancreas

Máire E. Doyle a,b, Josephine M. Egan c,\*

Department of Pathology, Immunology & Laboratory Medicine, College of Medicine, University of Florida, Gainesville, FL, USA
 Department of Oral Biology, College of Dentistry, University of Florida, Gainesville, FL, USA
 Diabetes Section, National Institute on Aging/NIH, Baltimore, MD 21224, USA

#### Abstract

Glucagon-like peptide 1 (GLP-1) is a hormone that is encoded in the proglucagon gene. It is mainly produced in enteroendocrine L cells of the gut and is secreted into the blood stream when food containing fat, protein hydrolysate, and/or glucose enters the duodenum. Its particular effects on insulin and glucagon secretion have generated a flurry of research activity over the past 20 years culminating in a naturally occurring GLP-1 receptor (GLP-1R) agonist, exendin 4 (Ex-4), now being used to treat type 2 diabetes mellitus (T2DM). GLP-1 engages a specific guanine nucleotide-binding protein (G-protein) coupled receptor (GPCR) that is present in tissues other than the pancreas (brain, kidney, lung, heart, and major blood vessels). The most widely studied cell activated by GLP-1 is the insulin-secreting  $\beta$  cell where its defining action is augmentation of glucose-induced insulin secretion. Upon GLP-1R activation, adenylyl cyclase (AC) is activated and cAMP is generated, leading, in turn, to cAMP-dependent activation of second messenger pathways, such as the protein kinase A (PKA) and Epac pathways. As well as short-term effects of enhancing glucose-induced insulin secretion, continuous GLP-1R activation also increases insulin synthesis,  $\beta$  cell proliferation, and neogenesis. Although these latter effects cannot be currently monitored in humans, there are substantial improvements in glucose tolerance and increases in both first phase and plateau phase insulin secretory responses in T2DM patients treated with Ex-4. This review will focus on the effects resulting from GLP-1R activation in the pancreas.

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<sup>\*</sup> Corresponding author. Diabetes Section, Box 23, 5600 Nathan Shock Drive, Baltimore, MD 21224, USA. Tel.: 410 558 8414; fax: 410 558 8381. E-mail address: eganj@grc.nia.nih.gov (J.M. Egan).

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#### 1. Introduction

The incretin effect refers to the augmented insulin secretory response to a glucose load delivered to the gut relative to that achieved by intravenous glucose when the plasma levels of glucose, under both conditions, are comparable. This effect accounts for up to 60% of the insulin secretory response following an oral glucose load (Nauck et al., 1986) and is due to the insulinotropic effects of incretin hormones that are released from enteroendocrine cells of the gut. Glucose-dependent insulinotropic peptide (GIP, also referred to as gastric inhibitory polypeptide) and glucagon-like peptide 1 (GLP-1) are the main incretin hormones (Mojsov et al., 1987; Meier et al., 2002; see Table 1 for their amino acid sequences). GLP-1 results from a posttranslational cleavage of the product of the glucagon gene by the prohormone convertase PC1/3 (Dhanvantari et al., 2001). The majority of circulating biologically active GLP-1 in man is the GLP-1 (7-36) amide form, with lesser amounts of the bioactive GLP-1 (7-37) form also detectable (Orskov et al., 1994). The actions of GLP-1 have been extensively studied over the last 2 decades because its acute intravenous infusion or subcutaneous administration lowers blood glucose and increases insulin secretion. Most importantly, it does so in humans suffering from diabetes. Therefore therapeutic strategies based on activating the GLP-1 receptors (GLP-1R) on β cells and enhancing GLP-1 actions have been developed. One of the major drawbacks to the use of the native peptide in the clinic is its rapid degradation in serum due to the presence of a dipeptidyl peptidase IV (DPP-IV, also known as CD26) recognition site in the N-terminus (Hansen et al., 1999). This enzyme, which is present in the blood stream and on cell membranes, cleaves GLP-1 (7-36) peptide to yield the inactive GLP-1 (9-36) form. Therefore, many modifications have been made to GLP-1 to increase its biological half-life and consequently its efficacy in vivo. Exendin 4 (Ex-4, also called exenatide), a GLP-1R agonist is now available for treating type 2 diabetes mellitus (T2DM). This compound is synthesized in the salivary glands of the *Heloderma suspectum* or Gila monster lizard, native to Gila county in southern Arizona. Ex-4 does not possess the DPP-IV

Table 1
Amino acid sequences for the human gut peptides, GLP-1 and GIP, and Ex-4, the compound originally isolated from the salivary glands of the *H. suspectum* 

GLP-1 numbering	7	11	16	21	26	31			
GLP-1	HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR								
GIP numbering	1	5	10	15	20	25	30	35	
GIP	YAE	GTFIS	SDYSL	AMDKI	HQQDF	VNWLL.	AQKGK	KND	
	WKHNITQ								
Ex-4 numbering	1	5	10	15	20	25	30	35	
Ex-4	HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGA								
	PPPS	5							

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