

HOSPITAL PHYSICIAN®

ENDOCRINOLOGY BOARD REVIEW MANUAL

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The *Hospital Physician Endocrinology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in endocrinology. Each manual reviews a topic essential to the current practice of endocrinology.

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New Pathogenic Concepts in Type 2 Diabetes Mellitus

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New Pathogenic Concepts in Type 2 Diabetes Mellitus

Michael Gardner, MD, and John Palmer, DO

INTRODUCTION

Optimal management of type 2 diabetes mellitus (DM) requires an understanding of the pathophysiology of the disease. In the previous manual of this volume, the classic defects of insulin resistance and inadequate insulin secretion were reviewed. This manual reviews the recent findings that the incretin system (gut hormones involved in glucose metabolism) and adipokines (cytokines derived from adipose tissue) play an important role in many of the abnormalities seen in patients with type 2 DM. Adipokines may also be involved in vascular inflammation, endothelial dysfunction, and thrombosis, all of which have been linked to atherosclerosis and vascular events.

INCRETIN INFLUENCES ON GLUCOSE HOMEOSTASIS

Incretin hormones are gut peptides produced by enteroendocrine cells and secreted in response to feeding. Incretins modulate pancreatic hormone secretion in a glucose-dependent fashion to help maintain glucose homeostasis (**Figure 1**). The significant incretin hormones identified to date are glucose-dependent insulinotropic peptide (also known as gastric inhibitory polypeptide; GIP) and glucagon-like peptide-1 (GLP-1).

Initial interest in gut hormones began at the turn of the 20th century, with the discovery of “secretin” by Bayliss and Starling.¹ Interest was rekindled in the 1960s with the development of radioimmunoassays for insulin, which allowed precise quantification of serum insulin levels during different physiologic conditions. An early and important observation was that for the same serum glucose level, insulin levels were 50% to 70% higher when the glucose load was administered orally as opposed to intravenously.^{1,2} It was subsequently discovered that the gut-derived hormones GIP and GLP-1 mediated this augmented response to feeding, which is now

known as the *incretin effect*.^{3,4} Incretin actions that have been documented in humans are shown in the **Table**.

GLUCOSE-DEPENDENT INSULINOTROPIC PEPTIDE Synthesis, Secretion, and Metabolism

GIP was initially discovered in the 1930s as a substance that decreased gastric acid secretion and motility in the denervated dog stomach⁵ and was subsequently shown to be the first substance with incretin activity in humans.³ GIP is a 42-amino acid peptide hormone synthesized in and secreted from the enteroendocrine K cells, which exist throughout the duodenum and jejunum but are found in highest numbers in the proximal duodenum.⁶ GIP is cleaved from a 153-amino acid precursor, preproGIP, by prohormone convertase 1/3⁷ and is secreted in response to the presence of fats and, to a lesser extent, carbohydrate in the gut.⁴ Once released, circulating GIP₁₋₄₂ has a very short half-life of approximately 7 minutes⁸ and is rapidly degraded via N-terminal cleavage by dipeptidyl peptidase-4 (DPP-4). This short half-life may play a role in limiting systemic exposure and makes the therapeutic use of GIP difficult. Both the active hormone and its inactive metabolite, GIP₃₋₄₂, are renally excreted.⁹

Physiologic Actions

The primary action of GIP is to amplify glucose-dependent insulin secretion.^{3,10} This action is mediated by a highly specific GIP receptor on the pancreatic beta cell. The GIP receptor is a type II G protein-coupled receptor belonging to the same superfamily as secretin, glucagon, and vasoactive intestinal peptide.^{11,12} Binding of GIP to its receptor induces production of cyclic adenosine monophosphate (cAMP) by adenylyl cyclase-activating protein kinase. The net effect is membrane depolarization as a result of inhibition (closure) of adenosine triphosphate (ATP)-sensitive potassium channels, increased amplitude of depolarization-evoked calcium ion flow via opening of L-type calcium channels, and potentiation of calcium-mediated exocytosis of insulin via a non-calcium concentration-dependent mechanism.¹³