The Pathophysiologic Role of Incretins

Jeffrey S. Freeman, DO

Many patients with type 2 diabetes mellitus (T2DM) are unable to achieve adequate glycemic control. Of the approximately 19 million individuals with T2DM in the United States, only about a third achieve the hemoglobin A1c (HbA1c) goal set forth by the American Diabetes Association (HbA1c <7% [6% if it can be achieved safely]). The incretin mimetics are a new class of medications available for treating patients with T2DM. They mimic the action of incretins, which are peptide hormones that originate in the gastrointestinal tract. The two major incretins in humans are glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). These hormones are released during nutrient absorption, augmenting insulin secretion. However, incretins are susceptible to degradation by dipeptidyl peptidase IV (DPP-IV). Dipeptidyl peptidase IV inhibitors suppress the degradation of incretins, thus extending the activity of GLP-1 and GIP. The glycemic profiles of patients after administration of incretin mimetics and DPP-IV inhibitors show improvement in postprandial glucose levels and ultimately in HbA1c. Therefore, incretin mimetics and DPP-IV inhibitors may play a clinically significant role in the treatment of patients with T2DM.

J Am Osteopath Assoc. 2007;107(suppl 3):S6-S9

Despite lifestyle changes and pharmacologic interventions, many individuals with type 2 diabetes mellitus (T2DM) fail to achieve adequate glycemic control. This failure is noticed most often among patients undergoing long-term management. Of the approximately 19 million individuals affected with T2DM in the United States, only about a third achieve the hemoglobin A1c (HbA1c) goal previously set forth by the American Diabetes Association (HbA1c <7% [6% if it can be safely achieved]).

The pathophysiologic development of T2DM includes a progressive decline of β-cell function. This decline results in deficient insulin secretion by the β cells, as well as excessive glucagon production by the α cells of the pancreas. Pharmacologic intervention to both increase insulin secretion and decrease glucagon secretion may alter the natural progression of T2DM and improve the glycemic profile of patients.

The “Incretin Effect”

The incretin mimetics are a new class of medications available for treating patients with T2DM. Incretin mimetics mimic the action of incretins, which are peptide hormones that originate in the gastrointestinal tract. Incretins are released during nutrient absorption, augmenting insulin secretion. The effects of incretins on both insulin levels and glucagon levels are glucose dependent. Unlike sulfonylureas, which may produce insulin-stimulating effects during periods of hypoglycemia, the effect of incretins on insulin stimulation and glucagon suppression can be suppressed in a hypoglycemic environment. This suppression, in turn, may reduce hypoglycemic incidents in patients with T2DM.

A number of important considerations exist regarding the use of incretin mimetics in treating patients with T2DM. These considerations include the following:

- the physiologic role of incretins in both healthy individuals and patients with T2DM
- the physiologic role of the incretins glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) in glucose homeostasis
- the physiologic roles of dipeptidyl peptidase IV (DPP-IV) and DPP-IV inhibitors, including their roles in glycemic control

The β-cell secretion of insulin is greater after the oral administration of glucose than after the intravenous administration of glucose, expressed as C-peptide levels, in subjects without T2DM.
This difference in insulin secretion is referred to as the “incretin effect.”9,14

An impaired incretin effect, expressed as C-peptide levels, occurs in patients with T2DM in response to both oral and intravenous administration of glucose.10,14 Regardless of the method of glucose administration, the insulin response is delayed, blunted, and prolonged in patients with T2DM, compared with that response in healthy subjects. The incretin effect may have important implications in reducing mealtime hyperglycemia in individuals with T2DM.10,14

**Two Major Incretins**

The two major incretins in humans are GLP-1 and GIP. These incretins share a considerable amino acid identity.10 They both increase insulin secretion; however, only GLP-1 suppresses glucagon secretion. Both GLP-1 and GIP are rapidly inactivated by the enzyme DPP-IV.11-13

Endogenous GIP is a 42-chain amino acid peptide secreted by the lymphocyte K cells, which are located within the intestinal epithelium of the proximal duodenum and regulated predominantly with fat consumption.10,15,16 Glucose-dependent insulinotropic peptide is reduced during the fasting state and increased after food ingestion. The primary action of GIP is to stimulate glucose-dependent insulin secretion. Thus, enhancement of GIP signaling may have beneficial effects in patients with T2DM, but these benefits remain to be determined in clinical practice.10,15,16

Both GIP and GLP-1 are ubiquitous hormones. Their receptor distribution is located within several organs, including the brain, duodenum, kidneys, liver, lungs, pancreas, and stomach.17 The receptors for these hormones are mediated through a G-protein-coupled adenylate cyclase, resulting in an increase of cyclic adenosine monophosphate and activation of protein kinase A.17 These actions lead to increased insulin secretion. Other signaling mechanisms involving GIP and GLP-1 receptors have been described in β cells.12,13,17 Figure 1 illustrates the progression of events involving GIP and GLP-1 leading to insulin secretion within β cells. Also noted in Figure 1 is the tissue receptor distribution of both GIP and GLP-1.17

Endogenous GLP-1 is a gastrointestinal hormone secreted from the L cells of the distal aspect of the small intestine. It is derived from a large proglucagon (ie, glucagon precursor) that also encodes for glucagon.10,16 Like GIP, GLP-1 is reduced in the fasting state and increases rapidly after a meal. It has potent effects on the β-cell secretion of insulin and on gastrointestinal motility.18 The increase in insulin secretion after a meal is only partially influenced by GLP-1 local activity. Most likely, influences that are hormonally and neurally mediated also exist.18,19

The release of GLP-1 is attenuated in patients with T2DM after ingestion of a mixed meal. This attenuation has been demonstrated in patients with T2DM (N = 54), with a significant reduction of the GLP-1 area under the curve during a period of 240 minutes after a meal, compared with individuals with normal glucose levels (P < .05).19 In addition, patients with impaired glucose tolerance in the study had a reduced GLP-1 response to a mixed meal. After a mixed meal, a reduction of GIP was also observed in patients with T2DM, but this reduction did not reach statistical significance.19

The effect of GLP-1 action protects β-cell function.20 The outcome of events of GLP-1 stimulation results in increased insulin secretion, as well as decreased glucagon secretion, gastric emptying, and food consumption.20 These changes lead to improved glycemic control and a reduction of free fatty acids, which, in turn, may result in attenuation of both glucotoxicity and lipotoxicity in patients.20 In addition, GLP-1 stimulation produces direct effects on β cells, resulting in proliferation of β cells, increased cell regeneration, and reduced cell apoptosis. These effects have been demonstrated only in animal studies. They remain to be demonstrated in human subjects.20

**Figure 1.** Target tissues of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) receptors: The progression of events involving GLP-1 and GIP leads to insulin secretion in β cells. Also shown is the tissue-receptor distribution of GLP-1 (left) and GIP (right). Abbreviations: Ac, adenylate cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; Gc, guanylate cyclase; PKA, protein kinase A. (Source: Fehmann HC, Goke R, Goke B. Cell and molecular biology of the incretin hormones glucagon-like peptide-1 and glucose-dependent insulin releasing polypeptide. Endocr Rev. 1995;16:390-410.)
Besides GLP-1 and GIP, there are several other substrates for DPP-IV inhibition. These substrates include glucagon, the clinical significance of which is not known. Many of the biologic effects of DPP-IV inhibition are currently under investigation.

In a crossover study, GLP-1 reduced hunger and increased early satiety in patients with T2DM (N = 12) who received a GLP-1 infusion while consuming a mixed meal.21 Hunger scores and satiety scores associated with GLP-1 infusion were compared with those associated with saline infusion. After the start of the meal, hunger and satiety were improved significantly (hunger P = .026; satiety P = .028) and, as a result, food consumption was less in patients who received GLP-1.21

Peptidases

Both GLP-1 and GIP are proteins that are rapidly degraded by dipeptidyl peptidase IV (DPP-IV).22 These peptidases are ubiquitous serine proteases that are widely distributed in numerous tissues. By cleaving N-terminal amino acids, they cause inactivation of both GLP-1 and GIP. This inactivation process is not exclusive to GLP-1 and GIP, though the substrate “preferences” of DPP-IV are GLP-1 and GIP. The DPP-IV inactivation process results in greater than 50% inactivation of GLP-1 within 1 to 2 minutes, and greater than 50% inactivation of GIP within 7 minutes.22-24

Exenetide is an exogenous incretin mimetic that is not susceptible to degradation by DPP-IV. Therefore, the action of exenetide lasts longer than that of the endogenous incretins GLP-1 and GIP. However, inhibiting the DPP-IV enzyme will prolong the actions of GLP-1 and GIP. Dipeptidyl peptidase IV inhibitors suppress the degradation of incretins, thus extending the activity of GLP-1 and GIP.22 Several DPP-IV inhibitors are either available or in development for patient treatment, including sitagliptin phosphate and vildagliptin.22-24

Comment

Incretins play an integral role in glucose homeostasis. The ubiquitous nature of these peptide hormones, as well as the use of incretin mimetics in the treatment of patients with T2DM, is currently under investigation. The most widely investigated endogenous incretins are GLP-1 and GIP. These incretins are inactivated by DPP-IV. The glycemic profiles of patients after administration of incretin mimetics and DPP-IV inhibitors show improvement in postprandial glucose levels and ultimately in HbA1c, with a low incidence of hypoglycemia resulting from glucose-dependent mechanisms. Therefore, incretin mimetics and DPP-IV inhibitors may play a clinically significant role in the treatment of patients with T2DM.

References


