Glucose Metabolism and Regulation: Beyond Insulin and Glucagon

Stephen L. Aronoff, MD, FACP, FACE; Kathy Berkowitz, APRN, BC, FNP, CDE; Barb Shreiner, RN, MN, CDE, BC-ADM; and Laura Want, RN, MS, CDE, CCRC, BC-ADM

Abstract

Insulin and glucagon are potent regulators of glucose metabolism. For decades, we have viewed diabetes from a bi-hormonal perspective of glucose regulation. This perspective is incomplete and inadequate in explaining some of the difficulties that patients and practitioners face when attempting to tightly control blood glucose concentrations. Intensively managing diabetes with insulin is fraught with frustration and risk. Despite our best efforts, glucose fluctuations are unpredictable, and hypoglycemia and weight gain are common. These challenges may be a result of deficiencies or abnormalities in other glucoregulatory hormones. New understanding of the roles of other pancreatic and incretin hormones has led to a multi-hormonal view of glucose homeostasis.

HISTORICAL PERSPECTIVE

Our understanding of diabetes as a metabolic disease has evolved significantly since the discovery of insulin in the 1920s. Insulin was identified as a potent hormonal regulator of both glucose appearance and disappearance in the circulation. Subsequently, diabetes was viewed as a mono-hormonal disorder characterized by absolute or relative insulin deficiency. Since its discovery, insulin has been the only available pharmacological treatment for patients with type 1 diabetes and a mainstay of therapy for patients with insulin-deficient type 2 diabetes.[1–7]

The recent discovery of additional hormones with glucoregulatory actions has expanded our understanding of how a variety of different hormones contribute to glucose homeostasis. In the 1950s, glucagon was characterized as a major stimulus of hepatic glucose production. This discovery led to a better understanding of the interplay between insulin and glucagon, thus leading to a bi-hormonal definition of diabetes. Subsequently, the discovery of a second β-cell hormone, amylin, was first reported in 1987. Amylin was determined to have a role that complemented that of insulin, and, like insulin, was found to be deficient in people with diabetes. This more recent development led to a view of glucose homeostasis involving multiple pancreatic hormones.[8]

In the mid 1970s, several gut hormones were identified. One of these, an incretin hormone, glucagon-like peptide-1 (GLP-1), was recognized as another important contributor to the maintenance of glucose homeostasis.[9,10] Based on current understanding, glucose homeostasis is governed by the interplay of insulin, glucagon, amylin, and incretin hormones.

This enhanced understanding of glucose homeostasis will be central to the design of new pharmacological agents to promote better clinical outcomes and quality of life for people with diabetes. This review will focus on the more recently discovered hormones involved in glucose homeostasis and is not intended to be a comprehensive review of diabetes therapies.

NORMAL PHYSIOLOGY

Plasma glucose concentration is a function of the rate of glucose entering the circulation (glucose appearance) balanced by the rate of glucose removal from the circulation (glucose disappearance). Circulating glucose is derived from three sources:

Address correspondence and requests for reprints to: Barb Schreiner, RN, MN, CDE, BC-ADM, Amylin Pharmaceuticals, Inc., 9360 Towne Centre Drive, San Diego, CA 92121.

intestinal absorption during the fed state, glycogenolysis, and gluconeogenesis. The major determinant of how quickly glucose appears in the circulation during the fed state is the rate of gastric emptying. Other sources of circulating glucose are derived chiefly from hepatic processes: glycogenolysis, the breakdown of glycogen, the polymerized storage form of glucose; and gluconeogenesis, the formation of glucose primarily from lactate and amino acids during the fasting state.

Glycogenolysis and gluconeogenesis are partly under the control of glucagon, a hormone produced in the α-cells of the pancreas. During the first 8–12 hours of fasting, glycogenolysis is the primary mechanism by which glucose is made available (Figure 1A). Glucagon facilitates this process and thus promotes glucose appearance in the circulation. Over longer periods of fasting, glucose, produced by gluconeogenesis, is released from the liver.

Glucoregulatory hormones include insulin, glucagon, amylin, GLP-1, glucose-dependent insulinotropic peptide (GIP), epinephrine, cortisol, and growth hormone. Of these, insulin and amylin are derived from the β-cells, glucagon from the α-cells of the pancreas, and GLP-1 and GIP from the L-cells of the intestine.

The glucoregulatory hormones of the body are designed to maintain circulating glucose concentrations in a relatively narrow range. In the fasting state, glucose leaves the circulation at a constant rate. To keep pace with glucose disappearance, endogenous glucose production is necessary. For all practical purposes, the sole source of endogenous glucose production is the liver. Renal gluconeogenesis contributes substantially to the systemic glucose pool only during periods of extreme starvation. Although most tissues have the ability to hydrolyze glycogen, only the liver and kidneys contain glucose-6-phosphatase, the enzyme necessary for the release of glucose into the circulation. In the bi-hormonal model of glucose homeostasis, insulin is the key regulatory hormone of glucose disappearance, and glucagon is a major regulator of glucose appearance. After reaching a post-meal peak, blood glucose slowly decreases
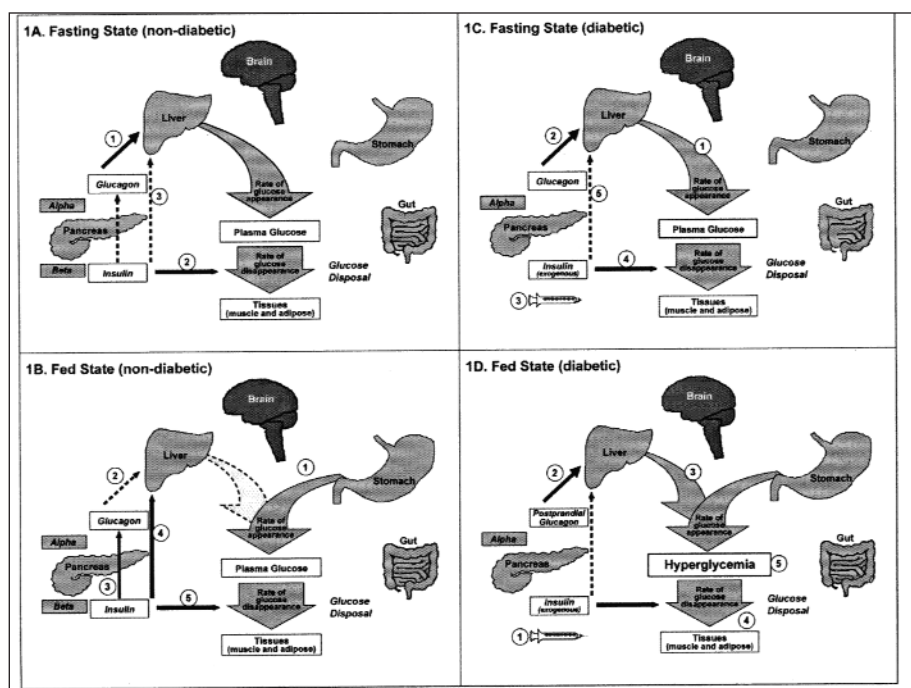
Figure 1. Glucose homeostasis: roles of insulin and glucagon. 1A. For nondiabetic individuals in the fasting state, plasma glucose is derived from glycogenolysis under the direction of glucagon (1). Basal levels of insulin control glucose disposal (2). Insulin's role in suppressing gluconeogenesis and glycogenolysis is minimal due to low insulin secretion in the fasting state (3). 1B. For nondiabetic individuals in the fed state, plasma glucose is derived from ingestion of nutrients (1). In the bi-hormonal model, glucagon secretion is suppressed through the action of endogenous insulin secretion (2). This action is facilitated through the paracrine route (communication within the islet cells) (3). Additionally, in the fed state, insulin suppresses gluconeogenesis and glycogenolysis in the liver (4) and promotes glucose disposal in the periphery (5). 1C. For individuals with diabetes in the fasting state, plasma glucose is derived from glycogenolysis and gluconeogenesis (1) under the direction of glucagon (2). Exogenous insulin (3) influences the rate of peripheral glucose disappearance (4) and, because of its deficiency in the portal circulation, does not properly regulate the degree to which hepatic gluconeogenesis and glycogenolysis occur (5). 1D. For individuals with diabetes in the fed state, exogenous insulin (1) is ineffective in suppressing glucagon secretion through the physiological paracrine route (2), resulting in elevated hepatic glucose production (3). As a result, the appearance of glucose in the circulation exceeds the rate of glucose disappearance (4). The net effect is postprandial hyperglycemia (5).

during the next several hours, eventually returning to fasting levels. In the immediate post-feeding state, glucose removal into skeletal muscle and adipose tissue is driven mainly by insulin. At the same time, endogenous glucose production is suppressed by 1) the direct action of insulin, delivered via the portal vein, on the liver, and 2) the paracrine effect or direct communication within the pancreas between the α- and β-cells, which results in glucagon suppression (Figure 1B).[11–14]

β-CELL HORMONES
Insulin
Until recently, insulin was the only pancreatic β-cell hormone known to lower blood glucose concentrations. Insulin, a small protein composed of two polypeptide chains containing 51 amino acids, is a key anabolic hormone that is secreted in response to increased blood glucose and amino acids following ingestion of a meal. Like many hormones, insulin exerts its actions through binding to specific receptors present on many cells of the

Table 1. Effects of Primary Glucoregulatory Hormones

PANCREAS
α-cells
  Glucagon
  - Stimulates the breakdown of stored liver glycogen
  - Promotes hepatic gluconeogenesis
  - Promotes hepatic ketogenesis

β-cells
  Insulin
  - Affects glucose metabolism and storage of ingested nutrients
  - Promotes glucose uptake by cells
  - Suppresses postprandial glucagon secretion
  - Promotes protein and fat synthesis
  - Promotes use of glucose as an energy source

  Amylin
  - Suppresses postprandial glucagon secretion
  - Slows gastric emptying
  - Reduces food intake and body weight

INTESTINE
L-cells
  GLP-1
  - Enhances glucose-dependent insulin secretion
  - Suppresses postprandial glucagon secretion
  - Slows gastric emptying
  - Reduces food intake and body weight
  - Promotes β-cell health

body, including fat, liver, and muscle cells. The primary action of insulin is to stimulate glucose disappearance.

Insulin helps control postprandial glucose in three ways. Initially, insulin signals the cells of insulin-sensitive peripheral tissues, primarily skeletal muscle, to increase their uptake of glucose.[15] Secondly, insulin acts on the liver to promote glycogenesis. Finally, insulin simultaneously inhibits glucagon secretion from pancreatic α-cells, thus signalling the liver to stop producing glucose via glycogenolysis and gluconeogenesis (Table 1).

All of these actions reduce blood glucose.[13] Other actions of insulin include the stimulation of fat synthesis, promotion of triglyceride storage in fat cells, promotion of protein synthesis in the liver and muscle, and proliferation of cell growth.[13]

Insulin action is carefully regulated in response to circulating glucose concentrations. Insulin is not secreted if the blood glucose concentration is ≤ 3.3 mmol/l, but is secreted in increasing amounts as glucose concentrations increase beyond this threshold.[14] Postprandially, the secretion of insulin occurs in two phases: an initial rapid release of preformed insulin, followed by increased insulin synthesis and release in response to blood glucose. Long-term release of insulin occurs if glucose concentrations remain high.[13,14]

While glucose is the most potent stimulus of insulin, other factors stimulate insulin secretion. These additional stimuli include increased plasma concentrations of some amino acids, especially arginine, leucine, and lysine; GLP-1 and GIP released from the gut following a meal; and parasympathetic stimulation via the vagus nerve.[16,17]

Amylin

Isolated from pancreatic amyloid deposits in the islets of Langerhans, amylin was first reported in the literature in 1987. Amylin, a 37–amino acid peptide, is a neuroendocrine hormone coexpressed and cosecreted with insulin by pancreatic β-cells in response to nutrient stimuli.[8,10,18,19] When secreted by the pancreas, the insulin-to-amylin molar ratio in the portal circulation is approximately 50:1. Because of hepatic extraction of insulin, this ratio falls to ~ 20:1 in the peripheral circulation.[20,21]

Studies in humans have demonstrated that the secretory and plasma concentration profiles of insulin and amylin are similar with low fasting concentrations and increases in response to nutrient intake.[22,23] In healthy adults, fasting plasma amylin concentrations range from 4 to 8 pmol/l rising as high as 25 pmol/l postprandially. In subjects with diabetes, amylin is deficient in type 1 and impaired in type 2 diabetes.[24,25]

Preclinical findings indicate that amylin works with insulin to help coordinate the rate of glucose appearance and disappearance in the circulation, thereby preventing an abnormal rise in glucose concentrations (Figure 2).[26]

Amylin complements the effects of insulin on circulating glucose concen-
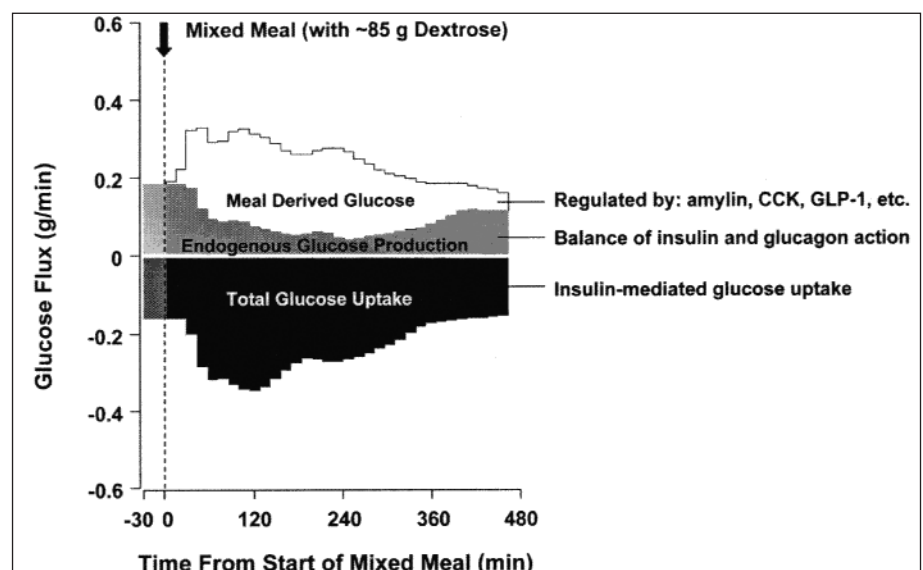
Figure 2. Postprandial glucose flux in nondiabetic controls. Postprandial glucose flux is a balance between glucose appearance in the circulation and glucose disappearance or uptake. Glucose appearance is a function of hepatic (endogenous) glucose production and meal-derived sources and is regulated by pancreatic and gut hormones. Glucose disappearance is insulin mediated. Calculated from data in the study by Pehling et al.[26]
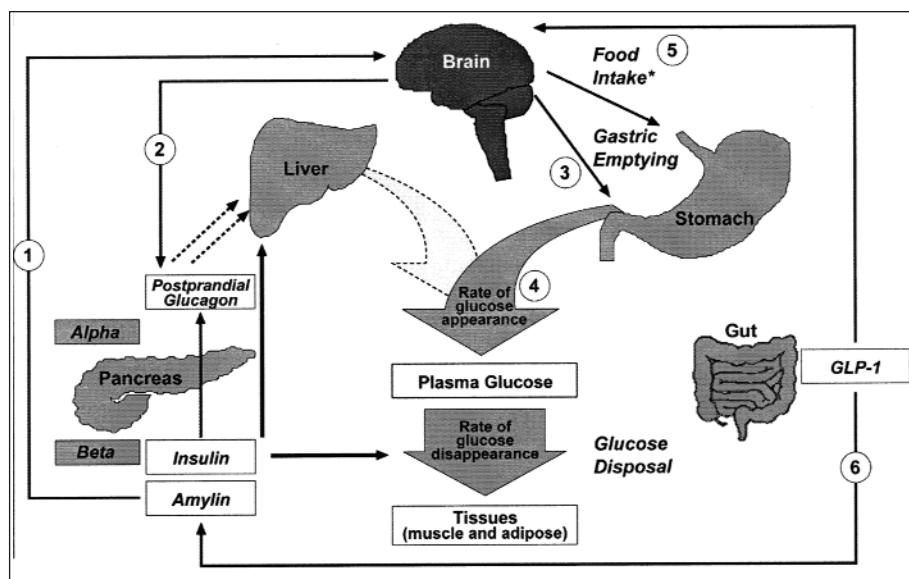
*Figure 3. Glucose homeostasis: roles of insulin, glucagon, amylin, and GLP-1. The multi-hormonal model of glucose homeostasis (nondiabetic individuals): in the fed state, amylin communicates through neural pathways (1) to suppress postprandial glucagon secretion (2) while helping to slow the rate of gastric emptying (3). These actions regulate the rate of glucose appearance in the circulation (4). *In animal models, amylin has been shown to dose-dependently reduced food intake and body weight (5). In addition, incretin hormones, such as GLP-1, glucose-dependently enhance insulin secretion (6) and suppress glucagon secretion (2) and, via neural pathways, help slow gastric emptying and reduce food intake and body weight (5).*

trations via two main mechanisms (Figure 3). Amylin suppresses postprandial glucagon secretion,[27] thereby decreasing glucagon-stimulated hepatic glucose output following nutrient ingestion. This suppression of postprandial glucagon secretion is postulated to be centrally mediated via efferent vagal signals. Importantly, amylin does not suppress glucagon secretion during insulin-induced hypoglycemia.[21,28] Amylin also slows the rate of gastric emptying and, thus, the rate at which nutrients are delivered from the stomach to the small intestine for absorption.[29] In addition to its effects on glucagon secretion and the rate of gastric emptying, amylin dose-dependently reduces food intake and body weight in animal models (Table 1).[30–32]

Amylin exerts its actions primarily through the central nervous system. Animal studies have identified specific calcitonin-like receptor sites for amylin in regions of the brain, predominantly in the area postrema. The area postrema is a part of the dorsal vagal complex of the brain stem. A notable feature of the area postrema is that it lacks a blood-brain barrier, allowing exposure to rapid changes in

plasma glucose concentrations as well as circulating peptides, including amylin.[33–36]

In summary, amylin works to regulate the rate of glucose appearance from both endogenous (liver-derived) and exogenous (meal-derived) sources, and insulin regulates the rate of glucose disappearance.[37]

α-CELL HORMONE: GLUCAGON

Glucagon is a key catabolic hormone consisting of 29 amino acids. It is secreted from pancreatic α-cells. Described by Roger Unger in the 1950s, glucagon was characterized as opposing the effects of insulin.[38] Glucagon plays a major role in sustaining plasma glucose during fasting conditions by stimulating hepatic glucose production.

Unger was the first to describe the diabetic state as a "bi-hormonal" disease characterized by insulin deficiency and glucagon excess. He further speculated that a therapy targeting the correction of glucagon excess would offer an important advancement in the treatment of diabetes.[38]

Hepatic glucose production, which is primarily regulated by glucagon,

maintains basal blood glucose concentrations within a normal range during the fasting state. When plasma glucose falls below the normal range, glucagon secretion increases, resulting in hepatic glucose production and return of plasma glucose to the normal range.[39,40] This endogenous source of glucose is not needed during and immediately following a meal, and glucagon secretion is suppressed. When coupled with insulin's direct effect on the liver, glucagon suppression results in a near-total suppression of hepatic glucose output (Figure 4).

In the diabetic state, there is inadequate suppression of postprandial glucagon secretion (hyperglucagonemia)[41,42] resulting in elevated hepatic glucose production (Figure 4). Importantly, exogenously administered insulin is unable both to restore normal postprandial insulin concentrations in the portal vein and to suppress glucagon secretion through a paracrine effect. This results in an abnormally high glucagon-to-insulin ratio that favors the release of hepatic glucose.[43] These limits of exogenously administered insulin therapy are well documented in individuals with type 1 or type 2 diabetes and are considered to be important contributors to the postprandial hyperglycemic state characteristic of diabetes.

INCRETIN HORMONES GLP-1 AND GIP

The intricacies of glucose homeostasis become clearer when considering the role of gut peptides. By the late 1960s, Perley and Kipnis[44] and others demonstrated that ingested food caused a more potent release of insulin than glucose infused intravenously. This effect, termed the "incretin effect," suggested that signals from the gut are important in the hormonal regulation of glucose disappearance. Additionally, these hormonal signals from the proximal gut seemed to help regulate gastric emptying and gut motility.

Several incretin hormones have been characterized, and the dominant ones for glucose homeostasis are GIP and GLP-1. GIP stimulates insulin secretion and regulates fat metabolism, but does not inhibit glucagon secretion or gastric emptying.[45] GIP levels are normal or slightly elevated in people with type 2 diabetes.[46]
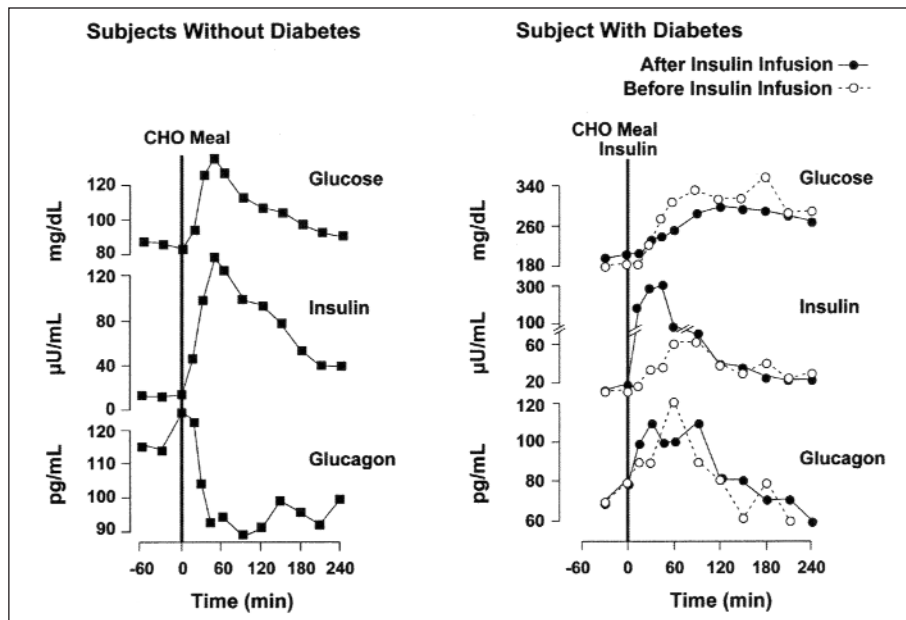
Figure 4. Insulin and glucagon secretion: nondiabetic and diabetic subjects. In nondiabetic subjects (left panel), glucose-stimulated insulin and amylin release from the β-cells results in suppression of postprandial glucagon secretion. In a subject with type 1 diabetes, infused insulin does not suppress α-cell production of glucagon. Adapted from Ref. 38.

While GIP is a more potent incretin hormone, GLP-1 is secreted in greater concentrations and is more physiologically relevant in humans.[47]

GLP-1 also stimulates glucose-dependent insulin secretion but is significantly reduced postprandially in people with type 2 diabetes or impaired glucose tolerance.[46,48] GLP-1 stimulates insulin secretion when plasma glucose concentrations are high but not when plasma glucose concentrations approach or fall below the normal range. Derived from the proglucagon molecule in the intestine, GLP-1 is synthesized and secreted by the L-cells found mainly in the ileum and colon. Circulating GLP-1 concentrations are low in the fasting state. However, both GIP and GLP-1 are effectively stimulated by ingestion of a mixed meal or meals enriched with fats and carbohydrates.[49,50] In contrast to GIP, GLP-1 inhibits glucagon secretion and slows gastric emptying.[51]

GLP-1 has many glucoregulatory effects (Table 1 and Figure 3). In the pancreas, GLP-1 stimulates insulin secretion in a glucose-dependent manner while inhibiting glucagon secretion.[52,53] Animal studies have demonstrated that the action of GLP-1 occurs directly through activation of GLP-1 receptors on the pancreatic β-cells and indirectly through sensory nerves.[54] GLP-1 has a plasma half-life of about 2 minutes, and its disappearance is regulated primarily by the enzyme dipeptidyl peptidase-IV (DPP-IV), which rapidly cleaves and inactivates GLP-1.

Infusion of GLP-1 lowers postprandial glucose as well as overnight fasting blood glucose concentrations.[55] The postprandial effect of GLP-1 is partly due to inhibition of glucagon secretion. Yet while GLP-1 inhibits glucagon secretion in the fed state, it does not appear to blunt glucagon's response to hypoglycemia.[56] GLP-1 helps regulate gastric emptying and gastric acid secretion,[17] perhaps by signalling GLP-1 receptors in the brain and thereby stimulating efferent tracts of the vagus nerve.[56] As gastric emptying slows, the postprandial glucose excursion is reduced. Administration of GLP-1 has been associated with the regulation of feeding behavior and body weight.[57,58] In addition, there have been reported observations of GLP-1 improving insulin sensitivity and enhancing glucose disposal.[58]

Of significant and increasing interest is the role GLP-1 may have in preservation of β-cell function and β-cell proliferation.[59] In animal studies, GLP-1 has been shown to enhance functional β-cell mass.[59]

DIABETES PATHOPHYSIOLOGY
Our understanding of the pathophysiology of diabetes is evolving. Type 1 diabetes has been characterized as an autoimmune-mediated destruction of pancreatic β-cells.[60] The resulting deficiency in insulin also means a deficiency in the other cosecreted and colocated β-cell hormone, amylin.[25] As a result, postprandial glucose concentrations rise due to lack of insulin-stimulated glucose disappearance, poorly regulated hepatic glucose production, and increased or abnormal gastric emptying following a meal.[61]

Early in the course of type 2 diabetes, postprandial β-cell action becomes abnormal, as evidenced by the loss of immediate insulin response to a meal.[62] Peripheral insulin resistance coupled with progressive β-cell failure and decreased availability of insulin, amylin, and GLP-1[63] contribute to the clinical picture of hyperglycemia in diabetes.

Abnormal gastric emptying is common to both type 1 and type 2 diabetes. The rate of gastric emptying is a key determinant of postprandial glucose concentrations (Figure 5).[64] If gastric emptying is accelerated, then the presentation of meal-derived glucose to the circulation is poorly timed with insulin delivery. In individuals with diabetes, the absent or delayed secretion of insulin further exacerbates postprandial hyperglycemia. Both amylin and GLP-1 regulate gastric emptying by slowing the delivery of nutrients from the stomach to the small intestine.

REPLACEMENT OF INSULIN
For the past 80 years, insulin has been the only pharmacological alternative, but it has replaced only one of the hormonal compounds required for glucose homeostasis. Newer formulations of insulin and insulin secretagogues, such as sulfonylureas and meglitinides, have facilitated improvements in glycemic control. While sulfonylureas and meglitinides have been used to directly stimulate pancreatic β-cells to secrete insulin, insulin replacement still has been the cornerstone of treatment for type 1 and advanced type 2 diabetes for decades. Advances in insulin therapy have included not only improving the source and purity of the hormone, but also developing more physiological means of delivery.
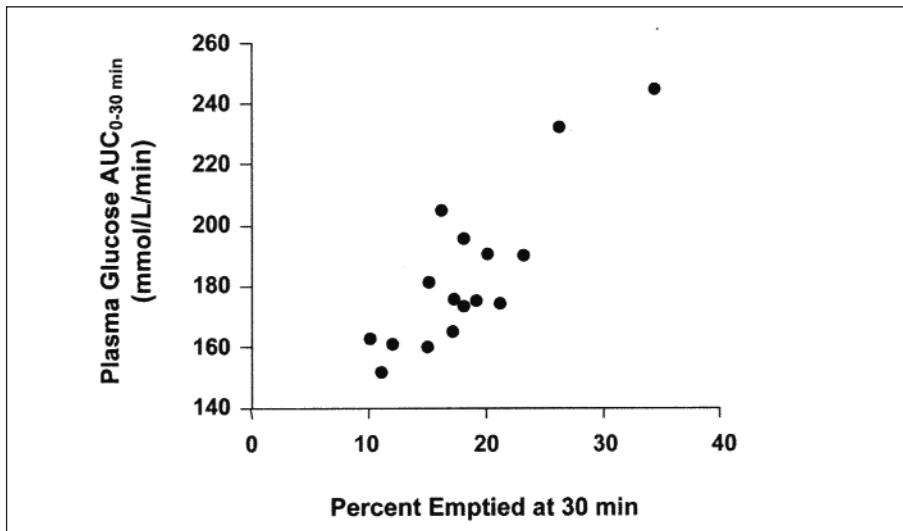
*Figure 5. Gastric emptying rate is an important determinant of postprandial glycemia. In nondiabetic subjects (*n = 16), plasma glucose concentration increases as the rate of gastric emptying increases (*r = 0.58,* P < 0.05). Adapted from Ref. 64.*

Clearly, there are limitations that hinder normalizing blood glucose using insulin alone. First, exogenously administered insulin does not mimic endogenous insulin secretion. In normal physiology, the liver is exposed to a two- to fourfold increase in insulin concentration compared to the peripheral circulation.[65] Peripherally injected insulin does not approach this ratio, thus resulting in inadequate hepatic glucose suppression.[66–68] Second, insulin's paracrine suppression of glucagon is limited in diabetes and inadequately compensated for by peripherally delivered insulin (Figures 1C, 1D). In the postprandial state, when glucagon concentrations should be low and glycogen stores should be rebuilt, there is a paradoxical elevation of glucagon and depletion of glycogen stores.[69] And finally, therapeutically increasing insulin doses results in further peripheral hyperinsulinemia, which may predispose the individual to hypoglycemia and weight gain. As demonstrated in the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study, intensified care is not without risk. In both studies, those subjects in the intensive therapy groups experienced a two- to threefold increase in severe hypoglycemia.[4,6] Additionally, intensification of diabetes management was associated with weight gain.[70]

REGULATION OF GLUCAGON ACTION

Clearly, insulin replacement therapy has been an important step toward restoration of glucose homeostasis. But it is only part of the ultimate solution. The vital relationship between insulin and glucagon has suggested additional areas for treatment. With inadequate concentrations of insulin and elevated concentrations of glucagon in the portal vein, glucagon's actions are excessive, contributing to an endogenous and unnecessary supply of glucose in the fed state. To date, no pharmacological means of regulating glucagon exist and the need to decrease postprandial glucagon secretion remains a clinical target for future therapies.

AMYLIN ACTIONS

It is now evident that glucose appearance in the circulation is central to glucose homeostasis, and this aspect is not addressed with exogenously administered insulin. Amylin works with insulin and suppresses glucagon secretion. It also helps regulate gastric emptying, which in turn influences the rate of glucose appearance in the circulation. A synthetic analog of human amylin that binds to the amylin receptor, an amylinomimetic agent, is in development.

GLP-1 ACTIONS

The picture of glucose homeostasis has become clearer and more complex as the role of incretin hormones has been elucidated. Incretin hormones play a role in helping regulate glucose appearance and in enhancing insulin secretion. Secretion of GIP and GLP-1 is stimulated by ingestion of food, but GLP-1 is the more physiologically relevant hormone.[71,72]

However, replacing GLP-1 in its natural state poses biological challenges. In clinical trials, continuous subcutaneous or intravenous infusion was superior to single or repeated injections of GLP-1 because of the rapid degradation of GLP-1 by DPP-IV.

To circumvent this intensive and expensive mode of treatment, clinical development of compounds that elicit similar glucoregulatory effects to those of GLP-1 are being investigated. These compounds, termed incretin mimetics, have a longer duration of action than native GLP-1. In addition to incretin mimetics, research indicates that DPP-IV inhibitors may improve glucose control by increasing the action of native GLP-1. These new classes of investigational compounds have the potential to enhance insulin secretion and suppress prandial glucagon secretion in a glucose-dependent manner, regulate gastric emptying, and reduce food intake.[73] Lastly, incretin mimetics may also play a role in preservation of β-cell function and β-cell proliferation.

SUMMARY

Despite current advances in pharmacological therapies for diabetes, attaining and maintaining optimal glycemic control has remained elusive and daunting. Intensified management clearly has been associated with decreased risk of complications.[6,74] Yet, despite this scientific understanding, the average hemoglobin A_{1c} in patients with diabetes in the United States is > 9%.[75]

Glucose regulation is an exquisite orchestration of many hormones, both pancreatic and gut, that exert effect on multiple target tissues, such as muscle, brain, liver, and adipocyte. While health care practitioners and patients have had multiple therapeutic options for the past 10 years, both continue to struggle to achieve and maintain good glycemic control. Currently available therapies do not perfectly address many of the abnor-

malities and/or deficiencies of type 1 or type 2 diabetes.

There remains a need for new interventions that complement our current therapeutic armamentarium without some of their clinical shortcomings such as the risk of hypoglycemia and weight gain. These evolving therapies offer the potential for more effective management of diabetes from a multi-hormonal perspective (Figure 3) and are now under clinical development.

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Stephen L. Aronoff, MD, FACP, FACE, is a partner and clinical endocrinologist at Endocrine Associates of Dallas and director at the Research Institute of Dallas in Dallas, Tex. Kathy Berkowitz, APRN, BC, FNP, CDE, and Barb Schreiner, RN, MN, CDE, BC-ADM, are diabetes clinical liaisons with the Medical Affairs Department at Amylin Pharmaceuticals, Inc., in San Diego, Calif. Laura Want, RN, MS, CDE, CCRC, BC-ADM, is the clinical research coordinator at MedStar Research Institute in Washington, D.C.