Glucose Metabolism and Regulation: Beyond Insulin and Glucagon

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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:
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 insulino tropic 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 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

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**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).
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. 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. 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.

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. 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.

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.

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. 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.

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. 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.

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). Amylin complements the effects of insulin on circulating glucose concent-

### Table 1. Effects of Primary Glucregulatory Hormones

<table>
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| Glucagon | • Stimulates the breakdown of stored liver glycogen  
|          | • Promotes hepatic gluconeogenesis  
|          | • Promotes hepatic ketogenesis  |
| β-cells  | • 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  |

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

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**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.
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 reduce 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).

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 secretion increases, resulting in hepatic glucose production and return of plasma glucose to the normal range.29,40 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 Kipnis44 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
GLP-1 has many glucoregulatory effects and plays a crucial role in 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 diabetes. Insulin therapy has included not only improved sources and purity of the hormone, but also developing more physiological means of delivery.
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.64–71

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.72 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 A1c 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-
malties 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.

References


Diabetes Care 18:715–730, 1995


