The Endocrine Pancreas

Insulin and Glucagon

Donald A. McClain, MD, PhD

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1. The Islets of Langerhans and the Endocrine Function of the Pancreas

The islets were morphologically identified by Paul Langerhans in 1869. Later in the century, Minkowski and von Mering established the endocrine function of the pancreas by showing that pancreatectomy resulted in diabetes. This laid the groundwork for the momentous purification of insulin by Banting and colleagues in the early 1920s. Since then, insulin has played an important role not only in the management of diabetes, but also in the development of the tools of basic science, such as protein sequencing, crystallization, radioimmunoassay, and molecular biology.

From: Endocrinology: Basic and Clinical Principles (P. M. Conn and S. Melmed, eds.), Humana Press Inc., Totowa, NJ.

1.1. Functional Organization of Cells Within the Islet

There are roughly two million islets in the pancreas, each consisting of hundreds to thousands of cells with features typical for their function of peptide secretion. Four cell types can be identified histologically, the α- or A-cells that secrete glucagon, the β- or B-cells that secrete insulin, the δ- or D-cells that secrete somatostatin, and the PP-cells that produce pancreatic polypeptide. The β-cells are most numerous, constituting ~80%, with most of the remainder being α-cells. The cells are intermixed, but β-cells tend to lie more centrally in the islet. The blood flow to the islet is through arterioles that branch into fenestrated capillaries in the central portion of the islet. There is some evidence that blood passes the nonsecretory pole of the β-cell first, then the secretory pole, and then courses more peripher-
ally to pass the α- and δ-cells (Fig. 1). Thus, the non-β-cells are exposed to relatively high concentrations of secreted insulin and have the opportunity to respond to insulin in an endocrine fashion. Indeed, there is evidence that this highly localized endocrine control of glucagon by insulin, and possibly by somatostatin as well, is physiologically important: The loss of the normal inhibitory effect of insulin on glucagon secretion may account for the hyper-glucagonemia of Type I diabetes, for example. The β-cells, on the other hand, probably are exposed to the same concentrations of glucagon and somatostatin that are in peripheral blood. B-cells are stimulated by glucagon and inhibited by somatostatin.

1.2. Modulation of Islet Cell Function by Neuronal and Possibly Paracrine Mechanisms

The most important regulators of insulin and glucagon release are glucose and amino acids, and as described above, the polarized blood supply of the islets also makes possible endocrine regulation of hormone release. In addition to these major regulatory mechanisms, there is opportunity for paracrine activity and direct crosstalk among the cell types by virtue of their shared extracellular space and the presence of gap junctions; current evidence suggest that endocrine control from circulating levels of other islet hormones is, however, the dominant means of hormonal control of islet cell function. Function of the cells of the islet may also be modulated by neuronal mechanisms. Both parasympathetic and sympathetic fibers have nonsynaptic release sites near islet cells, and acetylcholine, norepinephrine, and epinephrine all influence insulin secretion. The sympathetic nervous system has an important role in suppressing insulin and activating glucagon release during exercise, whereas parasympathetic innervation may be important in mediating insulin release during food intake. Finally, a variety of neuropeptides (galanin and vasoactive intestinal peptide (VIP), for example) also modulate insulin secretion.

2. INSULIN, THE CHIEF HORMONE INVOLVED IN CARBOHYDRATE AND LIPID HOMEOSTASIS

Insulin secretion in response to a meal results in the regulation of several enzyme and transport systems leading to the storage of carbohydrate as glycogen in muscle and liver (Table 1). Glucose production through glycogenolysis and gluconeogenesis by the liver, responsible for providing energy to tissues in the fasted state, is inhibited by insulin. Insulin also mediates the conversion of the adipocyte from an energy-releasing cell to an energy-storing cell. Insulin also has general effects on protein synthesis as well as specific transcriptional effects on several key enzymes involved in carbohydrate and lipid metabolism. The mechanism by which insulin exerts these effects has been the subject of intense study since the discovery of insulin earlier in this century.

2.1. Insulin and Its Family of Related Peptides

Insulin-related peptides have been identified in insects and molluscs, and vertebrate insulins are highly conserved; porcine insulin, for example, differs from human insulin at a single amino acid and has full biologic activity when given to humans. The primitive chordate amphioxus has a single gene for an insulin-like peptide homologous both to insulin and the insulin-like growth factor-1 (IGF-1). Successive gene duplications have resulted in three related genes in humans for insulin, IGF-1, and IGF-2 (Fig. 2). In rodents, an additional duplication of the insulin gene has occurred. IGF-1, the main mediator of skeletal growth, is structurally highly homologous to insulin, as is its receptor to the insulin receptor. In fact, each hormone can bind to the other’s receptor with approx 1% of its normal