

Chapter 7

The Endocrine Pancreas

The pancreas houses two distinctly different tissues. The bulk of its mass is **exocrine tissue** and associated ducts, which produce an alkaline fluid loaded with digestive enzymes which is delivered to the small intestine to facilitate digestion of foodstuffs. Scattered throughout the exocrine tissue are several hundred thousand clusters of endocrine cells **called the islets of Langerhans** which produce the hormones **insulin** and **glucagon**, plus a few other hormones.

Insulin and glucagon are critical participants in **glucose homeostasis** and serve as acute regulators of **blood glucose concentration**. From a medical perspective, insulin in particular is enormously important - a deficiency in insulin or deficits in insulin responsiveness lead to the disease **diabetes mellitus**.

7.1. Functional Anatomy of the Endocrine Pancreas

The endocrine portion of the pancreas takes the form of many small clusters of cells called **islets of Langerhans**. Humans have roughly one million islets. Pancreatic islets house three major cell types, each of which produces a different endocrine product:

- **Alpha cells** (α cells) secrete the hormone **glucagon**.
- **Beta cells** (β cells) produce **insulin** and are the most abundant of the islet cells.
- **Delta cells** (δ cells) secrete the hormone **somatostatin**, which is also produced by a number of other endocrine cells in the body.

The different cell types within an islet are not randomly distributed - beta cells occupy the central portion of the islet and are surrounded by alpha and delta cells. Islets are richly vascularized, allowing their secreted hormones ready access to the circulation. Although islets comprise only 1-2% of the mass of the pancreas, they receive about 10 to 15% of the pancreatic blood flow. Additionally, they are innervated by parasympathetic and sympathetic neurons, and nervous signals clearly modulate secretion of insulin and glucagon.

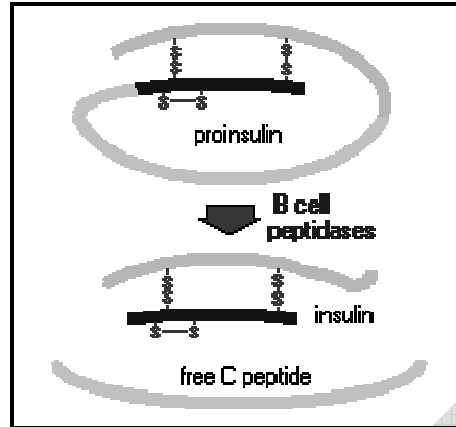
7.3. Insulin Synthesis and Secretion

7.3.1. Structure of Insulin

Insulin is a small protein, with a molecular weight of about 6000 Daltons. It is composed of two chains held together by disulfide bonds. The amino acid sequence is highly conserved among vertebrates, and insulin from one mammal almost certainly is biologically active in another. Even today, many diabetic patients are treated with insulin extracted from pig pancreases.

Biosynthesis of Insulin

Insulin is synthesized in significant quantities only in beta cells in the pancreas. The insulin mRNA is translated as a single chain precursor called preproinsulin, and removal of its signal peptide during insertion into the endoplasmic reticulum generates proinsulin. Proinsulin consists of three domains: an amino-terminal beta chain, a carboxy-terminal alpha chain and a connecting peptide in the middle known as the C peptide. Within the endoplasmic reticulum, proinsulin is exposed to several specific endopeptidases which excise the C peptide, thereby generating the mature form of insulin. Insulin and free C peptide are packaged in the Golgi into secretory granules which accumulate in the cytoplasm.

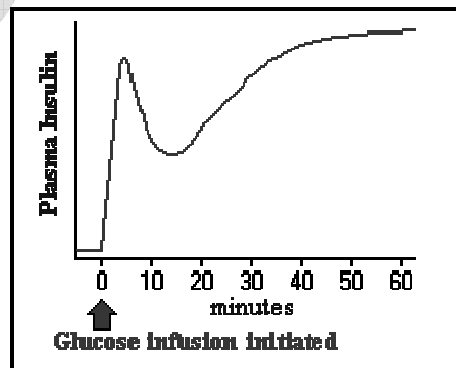


When the beta cell is appropriately stimulated, insulin is secreted from the cell by exocytosis and diffuses into islet capillary blood.

7.3.2. Control of Insulin Secretion

Insulin is secreted primarily in response to elevated blood concentrations of glucose. Some neural stimuli (e.g. sight and taste of food) and increased blood concentrations of other fuel molecules, including amino acids and fatty acids, also promote insulin secretion. Glucose is transported into the B cell by facilitated diffusion through a glucose transporter; elevated concentrations of glucose in extracellular fluid lead to elevated concentrations of glucose within the beta cell. Elevated concentrations of glucose within the beta cell ultimately leads to membrane depolarization and an influx of extracellular calcium. The resulting increase in intracellular calcium is one of the primary triggers for exocytosis of insulin-containing secretory granules. The mechanisms by which elevated glucose levels within the beta cell cause depolarization is as a result of metabolism of glucose and other fuel molecules within the cell, sensed as an alteration of ATP:ADP ratio and transduced into alterations in membrane conductance. Increased levels of glucose within beta cells also activate calcium-independent pathways that participate in insulin secretion.

Stimulation of insulin release is readily observed in people. The normal fasting blood glucose concentration in humans is 80 to 90 mg per 100 ml, associated with very low levels of insulin secretion. The below depicts the effects on insulin secretion when enough glucose is infused to maintain blood levels two to three times the fasting level for an hour. Almost immediately after the infusion begins, plasma insulin levels increase dramatically. This initial increase is due to secretion of preformed insulin, which is soon significantly depleted. The secondary rise in insulin reflects the considerable amount of newly synthesized insulin that is released immediately. Clearly, elevated glucose not only stimulates insulin secretion, but also transcription of the insulin gene and translation of its mRNA.



7.3.3. Physiologic Effects of Insulin

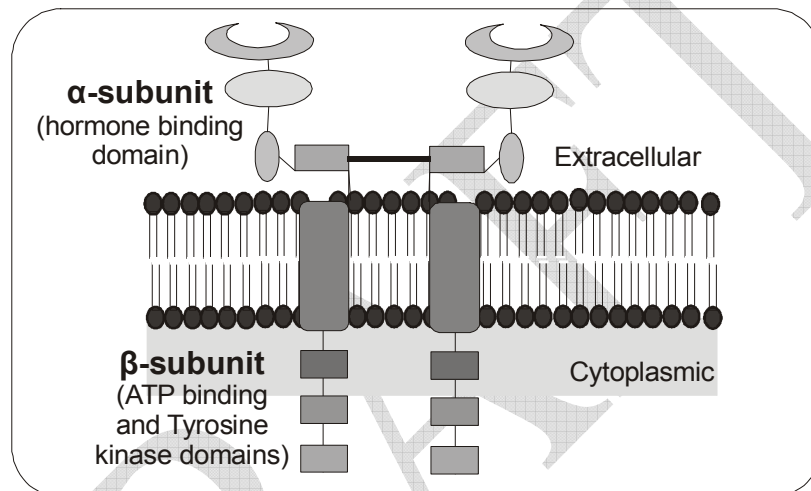
Stand on a streetcorner and ask people if they know what insulin is, and many will reply, "Doesn't it have something to do with blood sugar?" Indeed, that is correct, but such a response is a bit like saying "Mozart? Wasn't he some kind of a musician?"

Insulin is a key player in the control of intermediary metabolism. It has profound effects on both carbohydrate and lipid metabolism, and significant influences on protein and mineral metabolism.

Consequently, derangements in insulin signalling have widespread and devastating effects on many organs and tissues.

(i) The Insulin Receptor and Mechanism of Action

Like the receptors for other protein hormones, the receptor for insulin is embedded in the plasma membrane. The insulin receptor is composed of two alpha subunits and two beta subunits linked by disulfide bonds. The alpha chains are entirely extracellular and house insulin binding domains, while the linked beta chains penetrate through the plasma membrane.



The insulin receptor is a tyrosine kinase. i.e, it functions as an enzyme that transfers phosphate groups from ATP to tyrosine residues on intracellular target proteins. Binding of insulin to the alpha subunits causes the beta subunits to phosphorylate themselves (autophosphorylation), thus activating the catalytic activity of the receptor. The activated receptor then phosphorylates a number of intracellular proteins, which in turn alters their activity, thereby generating a biological response.

Several intracellular proteins have been identified as phosphorylation substrates for the insulin receptor, the best-studied of which is **insulin receptor substrate 1 or IRS-1**. When IRS-1 is activated by phosphorylation, a lot of things happen. Among other things, IRS-1 serves as a type of docking center for recruitment and activation of other enzymes that ultimately mediate insulin's effects.

(ii) Insulin and Carbohydrate Metabolism

Glucose is liberated from dietary carbohydrate such as starch or sucrose by hydrolysis within the small intestine, and is then absorbed into the blood. Elevated concentrations of glucose in blood stimulate release of insulin, and insulin acts on cells throughout the body to stimulate uptake, utilization and storage of glucose. The effects of insulin on glucose metabolism vary depending on the target tissue. Two important effects are:

- **Insulin facilitates entry of glucose into muscle, adipose and several other tissues.** The only mechanism by which cells can take up glucose is by facilitated diffusion through a family of hexose transporters. In many tissues - muscle being a prime example - the major transporter used for uptake of glucose (called GLUT4) is made available in the plasma membrane through the action of insulin. In the absence of insulin, GLUT4 glucose transporters are present in cytoplasmic vesicles, where they are useless for transporting glucose. Binding of insulin to receptors on such cells leads rapidly to fusion of those vesicles with the plasma membrane and

insertion of the glucose transporters, thereby giving the cell an ability to efficiently take up glucose. When blood levels of insulin decrease and insulin receptors are no longer occupied, the glucose transporters are recycled back into the cytoplasm. It should be noted here that there are some tissues that do not require insulin for efficient uptake of glucose: important examples are brain and the liver. This is because these cells don't use GLUT4 for importing glucose, but rather, another transporter that is not insulin-dependent.

- **Insulin stimulates the liver to store glucose in the form of glycogen.** A large fraction of glucose absorbed from the small intestine is immediately taken up by hepatocytes, which convert it into the storage polymer glycogen.

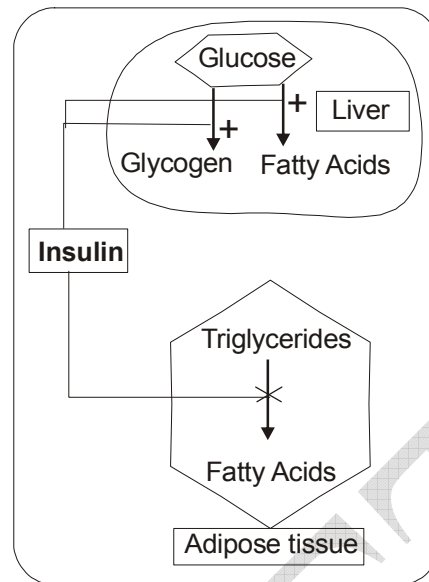
Insulin has several effects in liver which stimulate glycogen synthesis. First, it activates the enzyme hexokinase, which phosphorylates glucose, trapping it within the cell. Coincidentally, insulin acts to inhibit the activity of glucose-6-phosphatase. Insulin also activates several of the enzymes that are directly involved in glycogen synthesis, including phosphofructokinase and glycogen synthase. The net effect is clear: *when the supply of glucose is abundant, insulin "tells" the liver to bank as much of it as possible for use later.*

As blood glucose concentrations fall, insulin secretion ceases. In the absence of insulin, a bulk of the cells in the body become unable to take up glucose, and begin a switch to using alternative fuels like fatty acids for energy. Neurons, however, require a constant supply of glucose, which in the short term, is provided from glycogen reserves. In the absence of insulin, glycogen synthesis in the liver ceases and enzymes responsible for breakdown of glycogen become active. Glycogen breakdown is stimulated not only by the absence of insulin but by the presence of glucagon, which is secreted when blood glucose levels fall below the normal range.

(iii) Insulin and Lipid Metabolism

The metabolic pathways for utilization of fats and carbohydrates are deeply and intricately intertwined. Considering insulin's profound effects on carbohydrate metabolism, it stands to reason that insulin also has important effects on lipid metabolism. Notable effects of insulin on lipid metabolism include the following:

- **Insulin promotes synthesis of fatty acids in the liver.** Insulin is stimulatory to synthesis of glycogen in the liver. However, as glycogen accumulates to high levels (roughly 5% of liver mass), further synthesis is strongly suppressed. When the liver is saturated with glycogen, any additional glucose taken up by hepatocytes is shunted into pathways leading to synthesis of fatty acids, which are exported from the liver as lipoproteins. The lipoproteins are ripped apart in the circulation, providing free fatty acids for use in other tissues, including adipocytes, which use them to synthesize triglyceride.
- **Insulin inhibits breakdown of fat in adipose tissue** by inhibiting the intracellular lipase that hydrolyzes triglycerides to release fatty acids. Insulin facilitates entry of glucose into adipocytes, and within those cells, glucose can be used to synthesize glycerol. This glycerol, along with the fatty acids delivered from the liver, are used to synthesize triglyceride within the adipocyte. By these mechanisms, insulin is involved in further accumulation of triglyceride in fat cells.



From a whole body perspective, insulin has a fat-sparing effect. Not only does it drive most cells to preferentially oxidize carbohydrates instead of fatty acids for energy, insulin indirectly stimulates accumulation of fat in adipose tissue.

(iv) Other Notable Effects of Insulin

In addition to insulin's effect on entry of glucose into cells, it also stimulates the uptake of amino acids, again contributing to its overall anabolic effect. When insulin levels are low, as in the fasting state, the balance is pushed toward intracellular protein degradation.

Insulin also increases the permeability of many cells to potassium, magnesium and phosphate ions. The effect on potassium is clinically important. Insulin activates sodium-potassium ATPases in many cells, causing a flux of potassium into cells. Under certain circumstances, injection of insulin can kill patients because of its ability to acutely suppress plasma potassium concentrations.

7.3.4. Insulin Deficiency and Excess Diseases

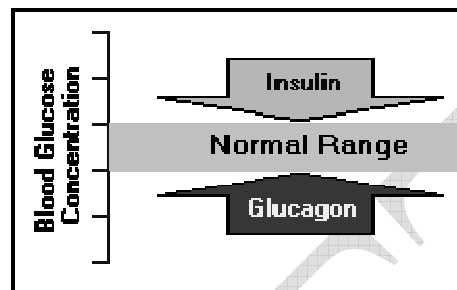
Diabetes mellitus, arguably the most important metabolic disease of man, is an insulin deficiency state. It also is a significant cause of disease in dogs and cats. Two principal forms of this disease are recognized:

- **Type I or insulin-dependent diabetes mellitus** is the result of a deficiency of insulin. The onset of this disease typically is in childhood. It is due to destruction pancreatic beta cells, most likely the result of autoimmunity to one or more components of those cells. Many of the acute effects of this disease can be controlled by **insulin replacement therapy**. Maintaining tight control of blood glucose concentrations by monitoring, **treatment with insulin** and **dietary management** will minimize the long-term adverse effects of this disorder on blood vessels, nerves and other organ systems, allowing a healthy life.
- **Type II or non-insulin-dependent diabetes mellitus** begins as a syndrome of insulin resistance. That is, target tissues fail to respond appropriately to insulin. Typically, the onset of this disease is in adulthood. In some patients, the insulin receptor is abnormal, in others, one or more aspects of insulin signalling is defective, and in others, no defect has been identified. Because there is not, at least initially, an inability to secrete adequate amounts of insulin, insulin injections are not useful for therapy. Rather the disease is controlled through **dietary therapy** and **hypoglycemic agents**.

Hyperinsulinemia or excessive insulin secretion is usually the result of an insulin-secreting tumour. This condition is much less common than diabetes mellitus. The high levels of insulin resulting from this condition or from an overdose of insulin causes a precipitous drop in blood glucose concentrations. The brain becomes starved for energy, leading to the syndrome of **insulin shock**, which is acutely life-threatening.

7.4. Glucagon

Glucagon has a major role in maintaining normal concentrations of glucose in blood, and is often described as having the opposite effect of insulin, i.e. glucagon has the effect of increasing blood glucose levels.



Glucagon is a linear peptide of 29 amino acids. Its primary sequence is almost perfectly conserved among vertebrates, and it is structurally related to the secretin family of peptide hormones. Glucagon is synthesized as proglucagon and proteolytically processed to yield glucagon within alpha cells of the pancreatic islets. Proglucagon is also expressed within the intestinal tract, where it is processed not into glucagon, but to a family of glucagon-like peptides (enteroglucagon).

7.4.1. Physiologic Effects of Glucagon

The major effect of glucagon is to stimulate an increase in blood concentration of glucose. The brain in particular has an absolute dependence on glucose as a fuel, because neurons cannot utilize alternative energy sources like fatty acids to any significant extent. When blood levels of glucose begin to fall below the normal range, it is imperative to find and pump additional glucose into blood. Glucagon exerts control over two pivotal metabolic pathways within the liver, leading that organ to dispense glucose to the rest of the body:

- **Glucagon stimulates breakdown of glycogen stored in the liver.** When blood glucose levels are high, large amounts of glucose are taken up by the liver. Under the influence of insulin, much of this glucose is stored in the form of glycogen. Later, when blood glucose levels begin to fall, glucagon is secreted and acts on hepatocytes to activate the enzymes that depolymerize glycogen and release glucose.
- **Glucagon activates hepatic gluconeogenesis.** Gluconeogenesis is the pathway by which non-hexose substrates such as amino acids are converted to glucose. As such, it provides another source of glucose for blood.
- Glucagon also has a minor effect of enhancing **lipolysis** of triglyceride in adipose tissue, which could be viewed as an additional means of conserving blood glucose by providing fatty acid fuel to most cells.

7.4. 2. Control of Glucagon Secretion

Two other conditions trigger glucagon secretion:

- Elevated blood levels of amino acids, as would be observed after consumption of a protein-rich meal: In this situation, glucagon would foster conversion of excess amino acids to glucose by enhancing gluconeogenesis. Since high blood levels of amino acids also stimulate insulin release, this would be a situation in which both insulin and glucagon are active.

- **Exercise:** In this case, it is not clear whether the actual stimulus is exercise per se, or the accompanying exercise-induced depletion of glucose.

In terms of negative control, **glucagon secretion is inhibited by high levels of blood glucose**. Another hormone well known to inhibit glucagon secretion is **somatostatin**.

7.4.3. Disease States

Diseases associated with excessively high or low secretion of glucagon are rare. Cancers of alpha cells (glucagonomas) are one situation known to cause excessive glucagon secretion. These tumours typically lead to a wasting syndrome and, interestingly, rash and other skin lesions. Although insulin deficiency is clearly the major defect in type 1 diabetes mellitus, there is considerable evidence that aberrant secretion of glucagon contributes to the metabolic derangements observed in this disease. For example, many diabetic patients with hyperglycemia also have elevated blood concentrations of glucagon, but glucagon secretion is normally suppressed by elevated levels of blood glucose.

7.5. Somatostatin

Somatostatin was first discovered in hypothalamic extracts and identified as a hormone that inhibited secretion of growth hormone. Subsequently, somatostatin was found to be secreted by a broad range of tissues, including pancreas, intestinal tract and regions of the central nervous system outside the hypothalamus.

7.5.1. Physiologic Effects

Somatostatin acts by both endocrine and paracrine pathways to affect its target cells. It inhibits the effects of other hormones.

(i) Effects on the Pituitary Gland

Somatostatin was named for its effect of inhibiting secretion of growth hormone from the pituitary gland. Experimentally, all known stimuli for growth hormone secretion are suppressed by somatostatin administration. Ultimately, growth hormone secretion is controlled by the interaction of somatostatin and growth hormone releasing hormone, both of which are secreted by hypothalamic neurons.

(ii) Effects on the Pancreas

Cells within pancreatic islets secrete insulin, glucagon and somatostatin. Somatostatin act primarily in a paracrine manner to inhibit the secretion of both insulin and glucagon. It also has the effect in suppressing pancreatic exocrine secretions, by inhibiting cholecystokinin-stimulated enzyme secretion and secretin-stimulated bicarbonate secretion.

(iii) Effects on the Gastrointestinal Tract

Somatostatin is secreted by scattered cells in the GI epithelium, and by neurons in the enteric nervous system. Secretion of many of the other GI hormones, including gastrin, cholecystokinin, secretin and vasoactive intestinal peptide. In addition to the direct effects of inhibiting secretion of other GI hormones.

(iv) Effects on the Nervous System

Somatostatin is often referred to as having neuromodulatory activity within the central nervous system, and appears to have a variety of complex effects on neural transmission. Injection of somatostatin into the brain of rodents leads to such things as increased arousal and decreased sleep, and impairment of some motor responses.

7.5.2. Pharmacologic Uses

Somatostatin and its synthetic analogs are used clinically to treat a variety of neoplasms. It is also used in to treat gigantism and acromegaly, due to its ability to inhibit growth hormone secretion.

Revision Questions

- (1) Protein hormones bind to specific receptors that are located _____ of target cells (a) free in the cytoplasm (b) in the plasma membrane (c) in either the cytoplasm or nucleus (d) attached to DNA (e) in the nucleus
- (2) A hormone that is secreted by one cell, diffuses and acts on neighboring cells is said to act through a _____ route. (a) autocrine (b) apocrine (c) exocrine (d) paracrine (e) endocrine
- (3) Elevated concentrations of cyclic AMP within a cell are often associated with an increase in protein phosphorylation, because cyclic AMP activates _____. (a) ATPase (b) adenylate cyclase (c) phosphodiesterase (d) protein kinase C (e) protein kinase A
- (4) Cretinism is a syndrome of growth and mental retardation caused by: (a) an excess of thyroid hormones early in life (b) a deficiency in parathyroid hormone originating in teenagers (c) a deficiency in thyroid hormones originating in teenagers (d) a deficiency in thyroid hormones early in life (e) an excess of thyroid hormones originating in teenagers (f) an excess of parathyroid hormone originating in teenagers
- (5) Which of the following is the best description of the chemical nature of the thyroid hormones thyroxine and triiodothyronine? (a) derivatives of fatty acids (b) large peptides (c) proteins (d) a type of carbohydrate (e) modified tyrosines (f) modified nucleotides
- (6) Which of the following is the best description of the distribution of thyroid hormone receptors within the body: (a) occur in almost all cells except liver (b) occur almost exclusively in liver cells (c) present in most if not all cells (d) present only in reproductive organs and brain (e) An uncorrected deficiency in which of the following hormones would lead to lethal imbalances in sodium and potassium: (a) norepinephrine (b) epinephrine (c) cortisol (d) aldosterone
- (7) Adrenocorticotropic hormone, or ACTH, was named because it stimulates the cortex of the adrenal gland. Which adrenal hormone causes negative feedback to shut off ACTH secretion? (a) epinephrine (b) cortisol and aldosterone (c) cortisol (d) epinephrine and cortisol (e) aldosterone (f) aldosterone and epinephrine
- (8) What is the major mechanism by which glucocorticoids and mineralocorticoids affect their target cells? (a) causing increased oxygen uptake (b) alteration of transcription of specific genes within the cell (c) enhancing or suppressing translation of cellular mRNAs (d) stimulating generation of cyclic AMP (e) causing assembly of ribosomes
- (9) Cortisol, and its synthetic derivatives, are commonly used as drugs because they: (a) stimulate muscle growth (b) eliminate bacterial infections (c) suppress inflammation (d) enhance cognitive function (e) stimulate an increase in blood levels of calcium
- (10) The receptor for epinephrine is: (a) an intracellular protein found in the cytoplasm that is moved to the nucleus after epinephrine binds (b) a membrane-bound receptor in the inner mitochondrial membrane (c) a transmembrane protein found in the plasma membrane of target cells (d) a receptor present in the nuclei of target cells (e) a type of steroid
- (11) Which of the following is the best description of the structure of insulin? (a) a large glycoprotein (b) a fatty acid derivative (c) a two-chain peptide hormone (d) a type of modified amino acid (e) a steroid
- (12) Which of the following best summarizes the role of insulin and glucagon in controlling glucose metabolisms? (a) insulin stimulates glycogenesis, but glucagon has little effect on glycogen metabolism (b) glucagon stimulates glycogenesis; insulin stimulates glycogenolysis (c) both glucagon and insulin strongly stimulate glycogenolysis (d)

both glucagon and insulin strongly stimulate glycogenesis (e) insulin stimulates glycogenesis; glucagon stimulates glycogenolysis (f) glucagon stimulates glycogenolysis, but insulin has little effect on glycogen metabolism.

Main Textbooks

Berne & Levy Principles of Physiology: by Matthew N. Levy, Bruce M. Koeppen, Bruce A. Stanton
Textbook of Medical Physiology by Arthur C. Guyton, John E. Hall

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