**The Endocrine Pancreas**

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**Abstract**

By the end of this section, you will be able to:

- Describe the location and structure of the pancreas, and the morphology and function of the pancreatic islets
- Compare and contrast the functions of insulin and glucagon

The pancreas is a long, slender organ, most of which is located posterior to the bottom half of the stomach (Figure 1 (Pancreas)). While it is considered a hybrid endocrine gland because it contains cells that carry out both exocrine and endocrine functions, both functions support a common purpose in the organism: supplying the body cells with nutrients and energy.

The exocrine cells secrete a variety of digestive enzymes that are essential to the breakdown and absorption of new nutrients from the digestive tract into the bloodstream. The endocrine cells are found in clusters in the pancreatic tissue that are distinctly visible under a microscope known as the pancreatic islets (formerly called the islets of Langerhans). These endocrine cells manage the uptake, storage, and distribution of the nutrient and energy molecules between the blood and the body cells once they have been absorbed. The major hormones they secrete to accomplish this role are glucagon, insulin, somatostatin, and pancreatic polypeptide (PP).
Figure 1: The pancreatic exocrine function involves the acinar cells secreting digestive enzymes that are transported into the small intestine by the pancreatic duct. Its endocrine function involves the secretion of insulin (produced by beta cells) and glucagon (produced by alpha cells) within the pancreatic islets. These two hormones regulate the rate of glucose metabolism in the body. The micrograph reveals pancreatic islets. LM × 760. (Micrograph provided by the Regents of University of Michigan Medical School ©2012)
1 Cells and Secretions of the Pancreatic Islets

The pancreatic islets each contain four varieties of cells:

- The **alpha cell** produces the hormone glucagon and makes up approximately 20 percent of each islet. Glucagon plays an important role in blood glucose regulation; low blood glucose levels stimulate its release.
- The **beta cell** produces the hormone insulin and makes up approximately 75 percent of each islet. Elevated blood glucose levels stimulate the release of insulin.


http://openstaxcollege.org/l/pancreaticislet

http://cnx.org/content/m47773/1.2/
• The **delta cell** accounts for four percent of the islet cells and secretes the peptide hormone somatostatin. Recall that somatostatin is also released by the hypothalamus (as GHIH), and the stomach and intestines also secrete it. An inhibiting hormone, pancreatic somatostatin inhibits the release of both glucagon and insulin.

• The **PP cell** accounts for about one percent of islet cells and secretes the pancreatic polypeptide hormone. It is thought to play a role in appetite, as well as in the regulation of pancreatic exocrine and endocrine secretions. Pancreatic polypeptide released following a meal may reduce further food consumption; however, it is also released in response to fasting.

## 2 Regulation of Blood Glucose Levels

Glucose is required for cellular respiration. The body derives glucose from the breakdown of the carbohydrate-containing foods and drinks we consume. All body cells can utilize glucose as an energy source, but some body cells, like neurons, can utilize only glucose. Neurons also cannot store glucose, so maintaining adequate levels of glucose within a narrow concentration range is critical for functioning and survival of nervous system cells. Glucose not immediately taken up by cells for fuel can be stored by the liver and muscles as glycogen, or converted to triglycerides and stored in adipose tissue for later release and energy use. Hormones regulate both the storage and the utilization of glucose by body cells and its release from storage when blood glucose levels fall.

Receptors located on or in pancreatic cells sense blood glucose levels and subsequently trigger the secretion of regulatory hormones (messengers) to maintain normal blood glucose concentrations. It should be noted that "normal" glucose levels are transitory. For several hours after a meal blood glucose levels will be "higher than normal" as nutrients are absorbed into the blood and transported to and absorbed by body cells. For several hours after this absorptive stage, blood glucose levels will be "lower than normal" as digestive absorption declines and glucose is removed from the blood for use by body cells. During this postabsorptive phase cells of organs like the liver return glucose to the blood to maintain a "normal" level. In a normal individual concentrations of the hormones insulin and glucagon are continually changing to keep these daily ebbs and tides within a manageable range.

Before delving into the details about the regulation of blood glucose it may be worth noting that for most of our evolutionary past the main body optimization problem was not removing excess glucose from the blood but keeping glucose (and energy) levels sufficient for proper brain, muscle, growth, and repair functions. It is only in the past 150 years that the human body has been exposed to a consistent excess of high energy foods reversing the regulatory challenge from maintaining sufficient blood glucose levels to reducing excess blood glucose levels.

### 2.1 Alpha-Cell (Glucagon) Effectors Increase Glucose Levels

There is no dispute that glucagon, secreted by the alpha-cells in the pancreatic islets, plays a major role in keeping blood glucose levels from falling too low. However, the factors that directly regulate alpha-cell secretion are currently not completely understood. The scientific literature is full of competing candidates for glucagon inhibitors and modulators, and the experimental results for many of the candidates are contradictory. This section summarizes areas where there appears to be consensus about what stimulates and inhibits glucagon secretion. While the regulated variable (blood glucose), the messenger (glucagon), and to some extent the effectors have consistent support, the receptor, signal, and integration center pathway details have not yet reached consensus.

A number of factors lead to an increase in glucagon release. Some of these may be direct influences (involving alpha-cell receptors), while others may indirectly stimulate the alpha-cell release of glucagon. To complicate the regulation process, glucagon is released not only in response to low glucose levels but also in response to high amino acid levels. These two stimuli can sometimes be at odds.

**Major factors stimulating increased glucagon secretion include:**
• **Hypoglycemia:** It is widely agreed that alpha-cells release glucagon in response to low blood glucose levels, at least in non-diabetic individuals. The proposed mechanisms fall into two camps, those proposing paracrine interaction between pancreatic beta-cells and alpha-cells, and those proposing direct glucose sensing by alpha-cell K\(_{\text{ATP}}\)-channels where glucagon release is mediated by voltage changes in the alpha-cell membrane.

• **Elevated amino-acid levels** also have been shown to increase glucagon levels. This stimulus provides the body with a way to deal with excess amino-acid absorption. The effect is the liver and the effect is stimulation of gluconeogenesis, conversion of amino-acids into glucose, which then can be used or stored for future use. It is important to recognize that gluconeogenesis accomplishes outcomes that simultaneously affect two regulated variables. Reducing high amino acid concentrations in the blood by converting the amino acids to glucose increases the blood glucose levels even if additional blood glucose is not needed.

• **Exercise** also has been shown to increase blood glucagon levels. However, it has not been shown whether this is a direct response to the exercise or an indirect response caused by muscle glucose consumption lowering blood glucose levels.

• **Autonomic stimulation:** both acetylcholine (via muscarinic receptors) and norepinephrine increase glucagon secretion. To some extent these can be viewed as anticipatory stimuli under conditions where the body is either in the absorptive phase (parasympathetic) or will need an energy boost to deal with an emergency or opportunity (sympathetic).

**Major factors inhibiting glucagon secretion include:**

• **Hyperglycemia:** The same mechanisms proposed for directly sensing and responding to low glucose concentrations by alpha-cells cause an inhibiting effect at high glucose concentrations.

• **Insulin:** There seems to be little debate that insulin is a powerful inhibitor of glucagon release. Since insulin levels are a beta-cell response to blood glucose levels, this is an indirect mechanism for alpha-cell sensing of blood glucose levels.

• **Somatostatin:** Alpha-cells have SSTR2 somatostatin receptors that when activated inhibit glucagon release.

• **The Brain:** Increased glucagon levels in the hypothalamus cause an increase in cAMP production. This causes an inhibitory signal to be sent via the vagus nerve to the alpha cells slowing release of glucagon. This pathway has been identified by experiments showing that when the vagus nerve is cut, excess glucagon and cAMP in the hypothalamus no longer inhibit the alpha cells.

**The primary effectors that respond to glucagon are:**

**The Liver**

• **Glycogenolysis:** Glucagon activates enzymes that convert stored glycogen back into glucose. The glucose is then released into the circulation for use by body cells.

• **Gluconeogenesis:** Glucagon activates enzymes that convert amino acids from the blood into glucose. The glucose is then released into the circulation for use by body cells. This both reduces blood amino acid concentrations and increases blood glucose concentrations.

**Adipose Cells**

• **Lipolysis:** Glucagon activates enzymes that convert stored triglycerides into free fatty acids and glycerol. Free fatty acids can be used directly by muscle and most other cells to generate ATP by introducing the constituent Acetyl Co-A molecules directly into the Citric Acid Cycle. Additionally, some of the free glycerol released into the bloodstream travels to the liver, which converts it into glucose. This is also a form of gluconeogenesis. **However, it should be noted that some recent experiments indicate that the direct effect of glucagon on lipolysis may be insignificant.**
The diagram below Figure 2 provides a high level summary of the negative feedback processes in glucose and amino acid regulation.

Figure 2

2.2 Beta-Cell (Insulin) Effectors Reduce Glucose Levels

The primary function of insulin is to facilitate the uptake of glucose into body cells. While most body cells have insulin receptors, the primary effectors for regulating blood glucose concentrations are liver cells, skeletal muscle cells, and adipose cells.

The insulin activates a transduction pathway in skeletal muscle and adipose cells that causes vesicles containing GLUT4 transporters to fuse with the cell membrane thus making them active for glucose absorption. In addition to activating glucose absorption from the blood, insulin also activates enzymes that
promote glycogen and triglyceride anabolism and activates transcription factors that stimulate protein synthesis within the cells.

Pancreatic alpha and beta cells, red blood cells, cells of the brain, liver, kidneys, and the lining of the small intestine, do not have insulin receptors on their cell membranes and acquire their glucose directly from blood glucose concentrations through facilitated diffusion.

**Major factors stimulating increased insulin secretion include:**

- **Hyperglycemia:** is the primary stimulus for insulin secretion. Beta-cells react to (sense) glucose levels directly via \( K_{\text{ATP}} \) channels that close when ATP/ADP ratios increase due to increased glucose metabolism. See the note below for a more detailed account of the Beta-Cell glucose sensing and transduction process.
- **Free Fatty Acids and Amino Acids** augment glucose induced insulin secretion.
- **Estrogen:** has been shown to both an increase insulin content in Beta-Cells and insulin release
- **Parasympathetic** release of acetylcholine

**Major factors inhibiting insulin secretion include:**

- **Hypoglycemia:** via opening \( K_{\text{ATP}} \) channels as ATP/ADP ratios decrease due to a decrease in glucose metabolism in the beta cells.
- **Sympathetic** by release of norepinephrine which opens the \( K_{\text{ATP}} \) channels by attaching the alpha-2 adrenergic receptors and by a nonadrenergic cotransmitter that also opens the \( K_{\text{ATP}} \) channels.

**The primary effectors that respond to insulin are:**

**Body Cells**

- **Transposes GLUT4 (glucose) transporters** to cell surface for glucose uptake
- **Stimulates glycolysis:** activates enzymes that catalyze the breakdown of glucose for ATP production
- **Stimulates protein synthesis:** activates transcription factors and mRNA production.

**The Liver**

1. **Stimulates glycogen anabolism:** Liver cells are somewhat unique effectors in this regulatory process as they do not have cell membrane receptors for insulin and do not require insulin to absorb glucose from the blood. However, insulin does activate enzymes inside liver cells that convert the intracellular glucose to glycogen for storage. This maintains a glucose concentration gradient allowing more glucose to continue diffusing from the blood into the cell.
2. **Inhibits glycogenolysis:** insulin slows glycogen catabolism and release of stored glucose by inhibiting required enzymes.
3. **Inhibits gluconeogenesis:** insulin slows formation of new glucose from protein catabolism by inhibiting required enzymes.

**Adipose Cells**

- **Stimulates triglyceride formation:** insulin stimulates the anabolism of excess Acetyl Co-A molecules, formed from glycolysis and pyruvate oxidation, into fatty acids for storage and future ATP production.

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http://cnx.org/content/m47773/1.2/
In a resting state the beta-cell $K_{ATP}$ channels are open and the voltage-gated $Ca^{++}$ channels are closed. When the concentrations of blood glucose (regulated variable) exceed the concentrations of beta-cell intracellular glucose, glucose enters the cell by facilitated diffusion through GLUT2 channels. The glucokinase enzyme (receptor) triggers glycolysis, the conversion of intracellular ADP + Phosphate into new ATP molecules. This increases the ATP/ADP ratio (signal) and causes the $K_{ATP}$ channels to close and the beta-cell membrane to depolarize.

A voltage change in the beta-cell membranes to greater than -40mV causes the voltage-gated calcium channels to open. Calcium ions diffuse into the cell, activating a cascade that cause the vesicles containing insulin to fuse with the cell membrane and release their contents (the messenger) via exocytosis.

The increased uptake, use, and conversion of glucose by the effectors reduces the blood glucose concentration. As the glucose concentration gradient drops, less glucose diffuses into the pancreatic beta cells and less ATP is generated lowering the ATP/ADP ratio. As the ratio drops, $K_{ATP}$ channels begin to open repolarizing the cell membrane. This causes the $Ca^{++}$ channels to close and the intracellular calcium levels to drop. Vesicle fusion with the cell membrane slows or stops and with it the release of insulin.

3 Delta-Cell (Somatostatin) Inhibits Glucagon and Insulin

Somatostatin is synthesized and released by cells in several parts of the body, but its general effect is to inhibit hormonal secretion and slow body functions. In the pancreas somatostatin is produced locally by delta cells and inhibits alpha and beta cell hormone secretions as well as acinar cell secretions of digestive enzymes. Its production appears to be stimulated by high levels of insulin and glucagon creating a classic feedback loop to control excess production of these hormones. Somatostatin is found in very small concentrations in general circulation, so the alpha and beta cells of the pancreas are likely influenced primarily by the paracrine action of somatostatin secreted by the pancreatic delta cells.

In other parts of the body the somatostatin function of inhibiting release of other hormones is maintained. In the hypothalamus is released as Growth Hormone Inhibiting Hormone (GHIH) which inhibits the release of both growth hormone and thyroid stimulating hormone slowing growth. In the digestive tract it inhibits the release of gastrointestinal hormones and slows the digestive process.

4 Summary of Pancreatic Hormones

<table>
<thead>
<tr>
<th>Associated hormones</th>
<th>Chemical class</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin (beta cells)</td>
<td>Protein</td>
<td>Reduces blood glucose levels</td>
</tr>
<tr>
<td>Glucagon (alpha cells)</td>
<td>Protein</td>
<td>Increases blood glucose levels</td>
</tr>
<tr>
<td>Somatostatin (delta cells)</td>
<td>Protein</td>
<td>Inhibits insulin and glucagon release</td>
</tr>
<tr>
<td>Pancreatic polypeptide (PP cells)</td>
<td>Protein</td>
<td>Role in appetite</td>
</tr>
</tbody>
</table>

Table 1

http://cnx.org/content/m47773/1.2/
5 Diabetes

Visit this link\(^2\) to view an animation describing the location and function of the pancreas. What goes wrong in the function of insulin in type 2 diabetes?

**Endocrine System: Diabetes Mellitus**

Dysfunction of insulin production and secretion, as well as the target cells’ responsiveness to insulin, can lead to a condition called **diabetes mellitus**. An increasingly common disease, diabetes mellitus has been diagnosed in more than 18 million adults in the United States, and more than 200,000 children. It is estimated that up to 7 million more adults have the condition but have not been diagnosed. In addition, approximately 79 million people in the US are estimated to have pre-diabetes, a condition in which blood glucose levels are abnormally high, but not yet high enough to be classified as diabetes.

\(^2\)http://openstaxcollege.org/l/pancreas1

http://cnx.org/content/m47773/1.2/
The term diabetes means "high urine output" describing the early manifestations of the disease, excessive urination and as a result excessive thirst. Not all types of diabetes are caused by excess glucose. For example, diabetes insipidus is caused by a lack of antidiuretic hormone (ADH) and a consequent lack of active aquaporins in the renal collecting ducts for water reabsorption. Temporary diabetes insipidus can be induced by heavy alcohol or caffeine consumption, both of which inhibit ADH.

Diabetes mellitus demonstrates how the out-of-control levels of glucose in the blood affect kidney function. Excessive blood glucose is not able to be reabsorbed from the renal filtrate and remains in the urine, increasing its concentration. This causes a lower osmotic gradient between the kidney medulla and the urine so less water is reabsorbed from the urine in the collecting ducts. As a result the person eliminates an abnormally large quantity of sweet urine (mellitus means "honey sweet"). The inability to reabsorb enough water leaves the body dehydrated, and so the person is unusually and continually thirsty. The person may also experience persistent hunger because the body cells are unable to access the glucose in the bloodstream.

There are two main forms of diabetes mellitus. Type 1 diabetes is an autoimmune disease affecting the beta cells of the pancreas. Certain genes are recognized to increase susceptibility. The beta cells of people with type 1 diabetes do not produce insulin; thus, synthetic insulin must be administered by injection or infusion. This form of diabetes accounts for less than five percent of all diabetes cases.

Type 2 diabetes accounts for approximately 95 percent of all cases. It is acquired, and lifestyle factors such as poor diet, inactivity, and the presence of pre-diabetes greatly increase a person's risk. About 80 to 90 percent of people with type 2 diabetes are overweight or obese. In type 2 diabetes, cells become resistant to the effects of insulin. In response, the pancreas increases its insulin secretion, but over time, the beta cells become exhausted. In many cases, type 2 diabetes can be reversed by moderate weight loss, regular physical activity, and consumption of a healthy diet; however, if blood glucose levels cannot be controlled, the diabetic will eventually require insulin.

Over time, persistently high levels of glucose in the blood injure tissues throughout the body, especially those of the blood vessels and nerves. Inflammation and injury of the lining of arteries lead to atherosclerosis and an increased risk of heart attack and stroke. Damage to the microscopic blood vessels of the kidney impairs kidney function and can lead to kidney failure. Damage to blood vessels that serve the eyes can lead to blindness. Blood vessel damage also reduces circulation to the limbs, whereas nerve damage leads to a loss of sensation, called neuropathy, particularly in the hands and feet. Together, these changes increase the risk of injury, infection, and tissue death (necrosis), contributing to a high rate of toe, foot, and lower leg amputations in people with diabetes. Uncontrolled diabetes can also lead to a dangerous form of metabolic acidosis called ketosis. Deprived of glucose, cells increasingly rely on fat stores for fuel. However, in a glucose-deficient state, the liver is forced to use an alternative lipid metabolism pathway that results in the increased production of ketone bodies (or ketones), which are acidic. The build-up of ketones in the blood causes ketosis, which—if left untreated—may lead to a life-threatening "diabetic coma." Together, these complications make diabetes the seventh leading cause of death in the United States.

Diabetes is diagnosed when lab tests reveal that blood glucose levels are higher than normal, a condition called hyperglycemia. The treatment of diabetes depends on the type, the severity of the condition, and the ability of the patient to make lifestyle changes. As noted earlier, moderate weight loss, regular physical activity, and consumption of a healthful diet can reduce blood glucose levels. Some patients with type 2 diabetes may be unable to control their disease with these lifestyle changes, and will require medication. Historically, the first-line treatment of type 2 diabetes was insulin. Research advances have resulted in alternative options, including medications that enhance pancreatic function and more recently medications that block glucose transporters in the kidney.

http://cnx.org/content/m47773/1.2/
tubules so excess glucose is eliminated in the urine, reducing the blood glucose levels by increasing the diabetic symptoms.

Visit this link³ to view an animation describing the role of insulin and the pancreas in diabetes.

6 Section Review

The pancreas has both exocrine and endocrine functions. The pancreatic islet cell types include alpha cells, which produce glucagon; beta cells, which produce insulin; delta cells, which produce somatostatin; and PP cells, which produce pancreatic polypeptide. Insulin and glucagon are involved in the regulation of glucose metabolism. Insulin is produced by the beta cells in response to high blood glucose levels. It enhances glucose uptake and utilization by target cells, as well as the storage of excess glucose for later use. Dysfunction of

³http://opencollege.org/l/insulin
the production of insulin or target cell resistance to the effects of insulin causes diabetes mellitus, a disorder characterized by high blood glucose levels. The hormone glucagon is produced and secreted by the alpha cells of the pancreas in response to low blood glucose levels. Glucagon stimulates mechanisms that increase blood glucose levels, such as the catabolism of glycogen into glucose.

7 Interactive Link Questions

Exercise 1  
(Solution on p. 13.)
Visit this link[^4] to view an animation describing the location and function of the pancreas. What goes wrong in the function of insulin in type 2 diabetes?

8 Review Questions

Exercise 2  
(Solution on p. 13.)
If an autoimmune disorder targets the alpha cells, production of which hormone would be directly affected?

a. somatostatin  
b. pancreatic polypeptide  
c. insulin  
d. glucagon

Exercise 3  
(Solution on p. 13.)
Which of the following statements about insulin is true?

a. Insulin acts as a transport protein, carrying glucose across the cell membrane.  
b. Insulin facilitates the movement of intracellular glucose transporters to the cell membrane.  
c. Insulin stimulates the breakdown of stored glycogen into glucose.  
d. Insulin stimulates the kidneys to reabsorb glucose into the bloodstream.

9 Critical Thinking Questions

Exercise 4  
(Solution on p. 13.)
What would be the physiological consequence of a disease that destroyed the beta cells of the pancreas?
Solutions to Exercises in this Module

**to Exercise (p. 12)**
Insulin is overproduced.

**to Exercise (p. 12)**
D

**Solution to Exercise (p. 12)**
B

**to Exercise (p. 12)**
The beta cells produce the hormone insulin, which is important in the regulation of blood glucose levels. All insulin-dependent cells of the body require insulin in order to take up glucose from the bloodstream. Destruction of the beta cells would result in an inability to produce and secrete insulin, leading to abnormally high blood glucose levels and the disease called type 1 diabetes mellitus.

Glossary

**Definition 2: alpha cell**
pancreatic islet cell type that produces the hormone glucagon

**Definition 2: beta cell**
pancreatic islet cell type that produces the hormone insulin

**Definition 2: delta cell**
minor cell type in the pancreas that secretes the hormone somatostatin

**Definition 2: diabetes mellitus**
condition caused by destruction or dysfunction of the beta cells of the pancreas or cellular resistance to insulin that results in abnormally high blood glucose levels

**Definition 2: glucagon**
pancreatic hormone that stimulates the catabolism of glycogen to glucose, thereby increasing blood glucose levels

**Definition 2: hyperglycemia**
abnormally high blood glucose levels

**Definition 2: insulin**
pancreatic hormone that enhances the cellular uptake and utilization of glucose, thereby decreasing blood glucose levels

**Definition 2: pancreas**
organ with both exocrine and endocrine functions located posterior to the stomach that is important for digestion and the regulation of blood glucose

**Definition 2: pancreatic islets**
specialized clusters of pancreatic cells that have endocrine functions; also called islets of Langerhans

**Definition 2: PP cell**
minor cell type in the pancreas that secretes the hormone pancreatic polypeptide