

Pancreas

As chyme floods into the small intestine from the stomach, two things must happen:

- acid must be quickly and efficiently neutralized to prevent damage to the duodenal mucosa
- macromolecular nutrients - proteins, fats and starch - must be broken down much further before their constituents can be absorbed through the mucosa into blood

The pancreas plays a vital role in accomplishing both of these objectives, so vital in fact that insufficient exocrine secretion by the pancreas leads to starvation, even if the animal is consuming adequate quantities of high quality food.

In addition to its role as an exocrine organ, the pancreas is also an endocrine organ and the major hormones it secretes - insulin and glucagon - play a vital role in carbohydrate and lipid metabolism. They are, for example, absolutely necessary for maintaining normal blood concentrations of glucose.

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 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.

Exocrine Secretions of the Pancreas

Pancreatic juice is composed of two secretory products critical to proper digestion: digestive enzymes and bicarbonate. The enzymes are synthesized and secreted from the exocrine acinar cells, whereas bicarbonate is secreted from the epithelial cells lining small pancreatic ducts.

Digestive Enzymes

The pancreas secretes a magnificent battery of enzymes that collectively have the capacity to reduce virtually all digestible macromolecules into forms that are capable of, or nearly capable of being absorbed. Three major groups of enzymes are critical to efficient digestion:

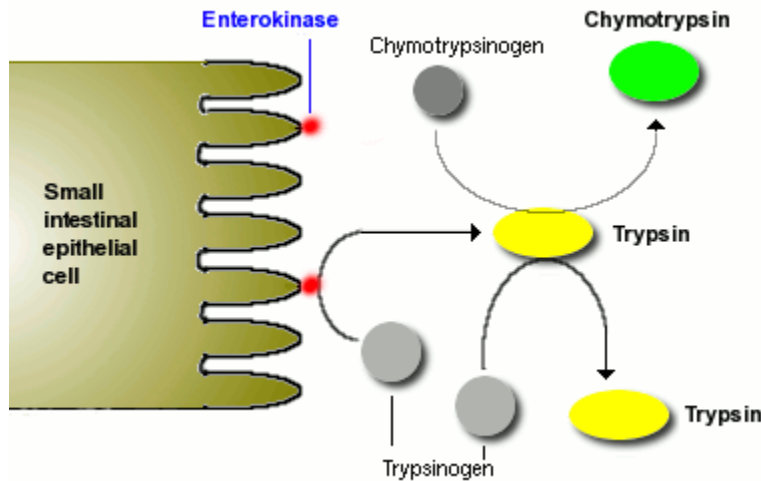
1. Proteases

Digestion of proteins is initiated by pepsin in the stomach, but the bulk of protein digestion is due to the pancreatic proteases. Several proteases are synthesized in the pancreas and secreted into the lumen of the small intestine. The two major pancreatic proteases are *trypsin* and *chymotrypsin*, which are synthesized and packaged into secretory vesicles as the inactive proenzyme trypsinogen and chymotrypsinogen.

As you might anticipate, proteases are rather dangerous enzymes to have in cells, and packaging of an inactive precursor is a way for the cells to safely handle these enzymes. The secretory vesicles also contain a trypsin inhibitor which serves as an additional safeguard should some of the trypsinogen be activated to trypsin; following exocytosis this inhibitor is diluted out and becomes ineffective.

Once trypsinogen and chymotrypsinogen are released into the lumen of the small intestine, they must be converted into their active forms in order to digest proteins. Trypsinogen is activated by the enzyme *enterokinase*, which is embedded in the intestinal mucosa.

Once trypsin is formed it activates chymotrypsinogen, as well as additional molecules of trypsinogen. The net result is a rather explosive appearance of active protease once the pancreatic secretions reach the small intestine.



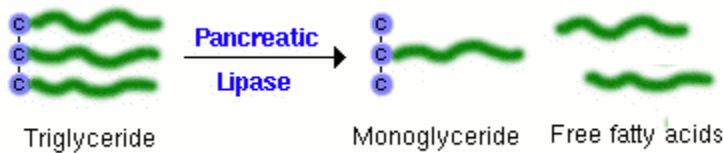
Trypsin and chymotrypsin digest proteins into peptides and peptides into smaller peptides, but they cannot digest proteins and peptides to single amino acids. Some of the other proteases from the pancreas, for instance carboxypeptidase, have that ability, but the final digestion of peptides into amino acids is largely the effect of peptidases on the surface of small intestinal epithelial cells.

2. Pancreatic Lipase

A major component of dietary fat is triglyceride, or neutral lipid. A triglyceride molecule cannot be directly absorbed across the intestinal mucosa. Rather, it must first be digested into a 2-monoglyceride and two free fatty acids. The enzyme that performs this hydrolysis is pancreatic lipase, which is delivered into the lumen of the gut as a constituent of pancreatic juice.

Sufficient quantities of bile salts must also be present in the lumen of the intestine in order for lipase to efficiently digest dietary triglyceride and for the resulting fatty acids and monoglyceride to be absorbed.

This means that normal digestion and absorption of dietary fat is critically dependent on secretions from both the pancreas and liver.



Pancreatic lipase has recently been in the limelight as a target for management of obesity. The drug orlistat (Xenical) is a pancreatic lipase inhibitor that interferes with digestion of triglyceride and thereby reduces absorption of dietary fat. Clinical trials support the contention that inhibiting lipase can lead to significant reductions in body weight in some patients.

3. *Amylase*

The major dietary carbohydrate for many species is starch, a storage form of glucose in plants. Amylase (technically alpha-amylase) is the enzyme that hydrolyses starch to maltose (a glucose-glucose disaccharide), as well as the trisaccharide maltotriose and small branch points fragments called limit dextrins. The major source of amylase in all species is pancreatic secretions, although amylase is also present in saliva of some animals, including humans.

Other Pancreatic Enzymes

In addition to the proteases, lipase and amylase, the pancreas produces a host of other digestive enzymes, including ribonuclease, deoxyribonuclease, gelatinase and elastase.

Bicarbonate and Water

Epithelial cells in pancreatic ducts are the source of the bicarbonate and water secreted by the pancreas. Bicarbonate is a base and critical to neutralizing the acid coming into the small intestine from the stomach. The mechanism underlying bicarbonate secretion is

essentially the same as for acid secretion parietal cells and is dependent on the enzyme carbonic anhydrase. In pancreatic duct cells, the bicarbonate is secreted into the lumen of the duct and hence into pancreatic juice.

Control of Pancreatic Exocrine Secretion

As you might expect, secretion from the exocrine pancreas is regulated by both neural and endocrine controls. During interdigestive periods, very little secretion takes place, but as food enters the stomach and, a little later, chyme flows into the small intestine, pancreatic secretion is strongly stimulated.

Like the stomach, the pancreas is innervated by the vagus nerve, which applies a low level stimulus to secretion in response to anticipation of a meal. However, the most important stimuli for pancreatic secretion come from three hormones secreted by the enteric endocrine system:

- *Cholecystokinin*: This hormone is synthesized and secreted by enteric endocrine cells located in the duodenum. Its secretion is strongly stimulated by the presence of partially digested proteins and fats in the small intestine. As chyme floods into the small intestine, cholecystokinin is released into blood and binds to receptors on pancreatic acinar cells, ordering them to secrete large quantities of digestive enzymes.
- *Secretin*: This hormone is also a product of endocrinocytes located in the epithelium of the proximal small intestine. Secretin is secreted in response to acid in the duodenum, which of course occurs when acid-laden chyme from the stomach flows through the pylorus. The predominant effect of secretin on the pancreas is to stimulate duct cells to secrete water and bicarbonate. As soon as this occurs, the enzymes secreted by the acinar cells are flushed out of the pancreas, through the pancreatic duct into the duodenum.

- *Gastrin*: This hormone, which is very similar to cholecystokinin, is secreted in large amounts by the stomach in response to gastric distention and irritation. In addition to stimulating acid secretion by the parietal cell, gastrin stimulates pancreatic acinar cells to secrete digestive enzymes.

Stop and think about this for a minute - control of pancreatic secretion makes perfect sense. Pancreatic secretions contain enzymes which are needed to digest proteins, starch and triglyceride. When these substances enter stomach, and especially the small intestine, they stimulate release of gastrin and cholecystokinin, which in turn stimulate secretion of the enzymes of destruction.

Pancreatic secretions are also the major mechanism for neutralizing gastric acid in the small intestine. When acid enters the small gut, it stimulates secretin to be released, and the effect of this hormone is to stimulate secretion of lots of bicarbonate. As proteins and fats are digested and absorbed, and acid is neutralized, the stimuli for cholecystokinin and secretin secretion disappear and pancreatic secretion falls off.

Insulin Synthesis and Secretion

Insulin is a rather 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 pancreas. Insulin is synthesized in significant quantities only in beta cells in the pancreas. The insulin mRNA is translated as a single chain precursor called proinsulin, and removal of its signal peptide during insertion into the endoplasmic reticulum generates proinsulin.

Proinsulin consists of three domains: an amino-terminal B chain, a carboxy-terminal A 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. C peptide is also secreted into blood, but has no known biological activity.

Control of Insulin Secretion

Insulin is secreted primarily in response to elevated blood concentrations of glucose. This makes sense because insulin is “in charge” of facilitating glucose entry into cells. 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.

Our understanding of the mechanisms behind insulin secretion remains somewhat fragmentary. Nonetheless, certain features of this process have been clearly and repeatedly demonstrated, yielding the following model:

Biosynthesis of Insulin

- Glucose is transported into the beta 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 lead to membrane depolarization and an influx of extracellular calcium. The resulting increase in intracellular calcium is thought to be 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 not clearly established, but seems to result from metabolism of glucose and other fuel molecules

- within the cell, perhaps sensed as an alteration of ATP:ADP ratio and transduced into alterations in membrane conductance.
- Increased levels of glucose within beta cells also appear to activate calcium-independent pathways that participate in insulin secretion.
 - Stimulation of insulin release is readily observed in whole animals or people. The normal fasting blood glucose concentration in humans and most mammals is 80 to 90 mg per 100 ml, associated with very low levels of insulin secretion.

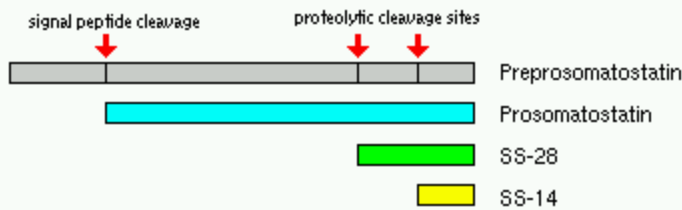
Almost immediately after the infusion begins, plasma insulin levels increase dramatically. This initial increase is due to secretion of preformed insulin, which is soon significantly depleted. The secondary rise in insulin reflects the considerable amount of newly synthesized insulin that is released immediately. Clearly, elevated glucose not only stimulates insulin secretion, but also transcription of the insulin gene and translation of its mRNA.

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.

Structure and Synthesis

Two forms of somatostatin are synthesized. They are referred to as SS-14 and SS-28, reflecting their amino acid chain length. Both forms of somatostatin are generated by proteolytic cleavage of prosomatostatin, which itself is derived from preprosomatostatin. Two cysteine residuals in SS-14 allow the peptide to form an internal disulfide bond.



The relative amounts of SS-14 versus SS-28 secreted depend upon the tissue. For example, SS-14 is the predominant form produced in the nervous system and apparently the sole form secreted from pancreas, whereas the intestine secretes mostly SS-28. In addition to tissue-specific differences in secretion of SS-14 and SS-28, the two forms of this hormone can have different biological potencies. SS-28 is roughly ten-fold more potent in inhibition of growth hormone secretion, but less potent than SS-14 in inhibiting glucagon release.

Receptors and Mechanism of Action

Five somatostatin receptors have been identified and characterized, all of which are members of the G protein-coupled receptor superfamily. Each of the receptors activates distinct signaling mechanisms within cells, although all inhibit adenylyl cyclase. Four of the five receptors do not differentiate SS-14 from SS-28.

Physiologic Effects

Somatostatin acts by both endocrine and paracrine pathways to affect its target cells. A majority of the circulating somatostatin appears to come from the pancreas and gastrointestinal tract. If one had to summarize the effects of somatostatin in one phrase, it would be: “*somatostatin inhibits the secretion of many other hormones*”.

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. Additionally, animals treated with antisera to somatostatin show elevated blood concentrations of growth hormone, as do animals that are genetically engineered to disrupt their somatostatin gene.

Ultimately, growth hormone secretion is controlled by the interaction of somatostatin and growth hormone releasing hormone, both of which are secreted by hypothalamic neurons.

Effects on the Pancreas

Cells within pancreatic islets secrete insulin, glucagon and somatostatin. Somatostatin appears to 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.

Effects on the Gastrointestinal Tract

Somatostatin is secreted by scattered cells in the GI epithelium, and by neurons in the enteric nervous system. It has been shown to inhibit 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, somatostatin has a variety of other inhibitory effects on the GI tract, which may reflect its effects on other hormones, plus some additional direct effects. Somatostatin suppresses secretion of gastric acid and pepsin, lowers the rate of gastric emptying, and reduces smooth muscle contractions and blood flow within the intestine. Collectively, these activities seem to have the overall effect of decreasing the rate of nutrient absorption.

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.

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.

Other Endocrine Tissues and Hormones

In terms of name recognition, the pituitary, thyroid and the adrenal glands get a lion's share of the glory. These organs have no significant function other than to produce hormones, and were relatively easy to study years ago using "remove it and see what happens" type of experiments. There are however a number of other endocrine tissues and hormones that, while less well known, are just as important in controlling vital bodily functions. In fact, there is probably no tissue that is not, in some way, an endocrine tissue.

Several of the 'other' endocrine cells and tissues discussed here are sometimes referred to as the *diffuse endocrine system* to reflect that concept that many organs house clusters of cells that secrete hormones. The kidney, for example, contains scattered cells that secrete erythropoietin, a hormone essential for production of red blood cells. Even the heart contains cells that produce atrial naturetic hormone, which is important in sodium and water balance.

Core information on other hormones and endocrine tissues are presented as the following topics:

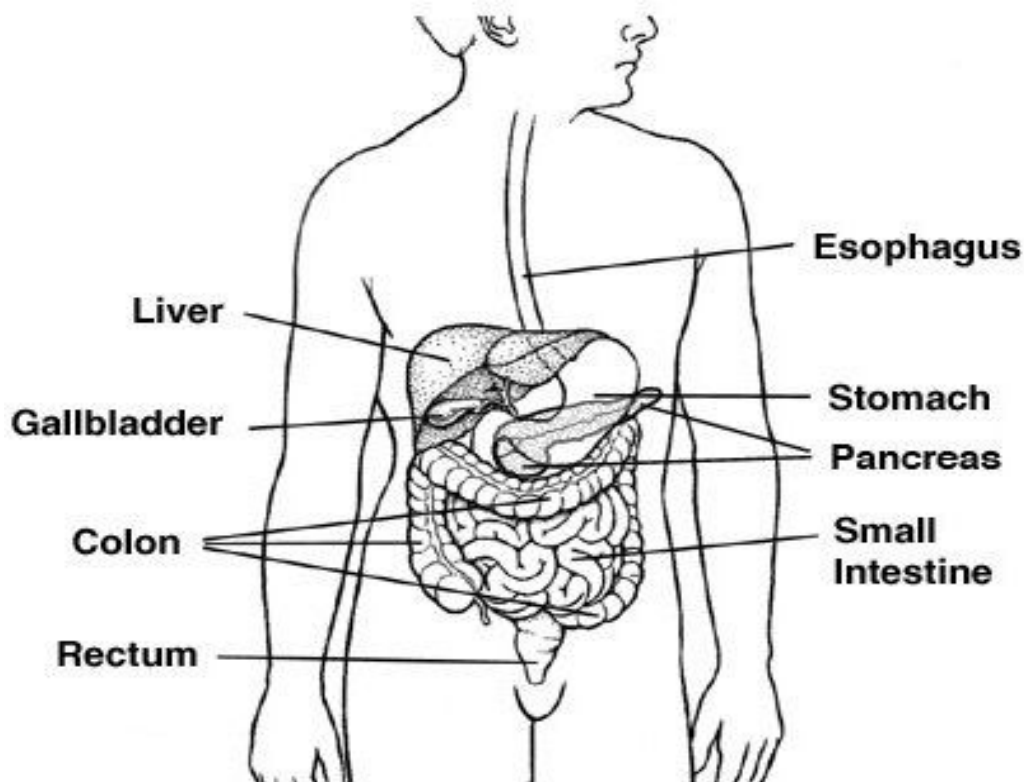
- *Atrial Naturetic Hormone*
- *Erythropoietin*
- *Histamine*

- *Insulin-like Growth Factors*
- *Pineal Gland and Melatonin*
- *Renin-Angiotensin System*
- *Somatostatin*
- *Vitamin D (Calcitriol)*

What Is Cancer of the Pancreas?

The normal pancreas

The pancreas is an organ located behind the stomach. It is shaped a little bit like a fish with a wide head, a tapering body, and a narrow, pointed tail. It is about 6 inches long but less than 2 inches wide and extends horizontally across the abdomen. The head of the pancreas is on the right side of the abdomen, behind the place where the stomach meets the duodenum (the first part of the small intestine). The body of the pancreas is located behind the stomach and the tail of the pancreas is on the left side of the abdomen next to the spleen.



The pancreas contains 2 different types of glands: exocrine and endocrine.

The *exocrine* glands make pancreatic ‘juice,’ which is released into the intestines. This juice contains enzymes that help you digest fats, proteins, and carbohydrates in the food you eat. Without these, some of the food you eat would just pass through your intestines without being absorbed. The enzymes are released into tiny tubes called *ducts*. These tiny ducts merge together to form larger ducts that carry the pancreatic juice to the small intestine. More than 95% of the cells in the pancreas are exocrine glands and ducts.

A small percentage of the cells in the pancreas are *endocrine* cells. These cells are arranged in small clusters called islets (or *islets of Langerhans*). The islets release important hormones, such as insulin and glucagon, directly into the blood. Insulin reduces the amount of sugar in the blood, while glucagon increases it. Diabetes results from a defect in insulin production.

Types of pancreatic tumors

The exocrine cells and endocrine cells of the pancreas form completely different types of tumors.

Exocrine tumors

These are by far the most common type of pancreas cancer. When someone says that they have pancreatic cancer, they usually mean an exocrine pancreatic cancer. Benign (non-cancerous) cysts and benign tumors called cystadenomas can occur, but most pancreatic exocrine tumors are malignant (cancerous).

An adenocarcinoma is a cancer that starts in gland cells. About 95% of cancers of the exocrine pancreas are adenocarcinomas. These cancers usually begin in the ducts of the pancreas, but they sometimes develop from the cells that make the pancreatic enzymes (Acinar cell carcinomas).

Less common types of ductal cancers of the exocrine pancreas include adenosquamous carcinomas, squamous cell carcinomas, and giant cell carcinomas. These types are distinguished from one another based on how they look under the microscope.

The treatment of an exocrine pancreatic cancer is mostly based on the stage of the cancer, not its exact type. The stage of the cancer describes how large the tumor is and how far it has spread.

A special type of cancer, called *ampullary cancer* (or carcinoma of the ampulla of Vater) deserves mention here. The place where the bile duct and pancreatic duct come together and empty into the duodenum is called the *ampulla of Vater*. Cancers that start here are called ampullary cancers. These cancers often block the bile duct while they are still small and have not spread far. This blockage causes bile to build up in the body, which leads to a yellowing of the skin and eyes (jaundice) and can turn the urine dark. This easily recognized sign alerts people that something is wrong. Because of this, ampullary cancers are usually found at an earlier stage than most pancreatic cancers, which means they usually have a better outlook than typical pancreatic cancers.

Endocrine tumors

Tumors of the endocrine pancreas are uncommon. As a group, they are known as pancreatic neuroendocrine tumors (NETs), or sometimes as islet cell tumors. There are several subtypes of islet cell tumors. Each is named according to the type of hormone-making cell it starts in:

- *insulinomas* come from cells that make insulin
- *glucagonomas* come from cells that make glucagon
- *gastrinomas* come from cells that make gastrin
- *somatostatinomas* come from cells that make somatostatin
- *VIPomas* come from cells that make vasoactive intestinal peptide (VIP)
- *PPomas* come from cells that make pancreatic polypeptide

About half of pancreatic NETs are “functioning,” meaning they make hormones that are released into the blood. Tumors that do not make hormones are called “non-functioning.”

Islet cell tumors can be benign or malignant. Benign tumors are called pancreatic neuroendocrine tumors, while malignant tumors are called pancreatic neuroendocrine cancers or carcinomas. The malignant and benign tumors can look very similar under the microscope, so it is not always clear at the time of diagnosis whether or not a NET is cancer. Sometimes the diagnosis only becomes clear when the tumor has spread outside of the pancreas.

Pancreatic neuroendocrine cancers make up only 1% of all pancreatic cancers diagnosed. Treatment and prognosis (outlook) depends on the specific tumor type and the stage (extent) of the tumor but is generally better than that of pancreatic exocrine cancers. The most common types of pancreatic endocrine tumors are gastrinomas and insulinomas. The other types occur very rarely.

It is very important to distinguish between exocrine and endocrine cancers of the pancreas. They have distinct risk factors and causes, have different signs and symptoms, are diagnosed using different tests, are treated in different ways, and have different prognoses (outlooks). In this document, the term pancreatic neuroendocrine tumor is used to mean both benign and malignant endocrine pancreatic tumors.