Insulin and Glucagon

The pancreas, in addition to its digestive functions, secretes two important hormones, ***insulin*** and ***glucagon***, that are crucial for normal regulation of glucose, lipid, and protein metabolism.
Although the pancreas secretes other hormones, such as ***amylin***, ***somatostatin***, and ***pancreatic polypeptide***, their functions are not as well established.

Physiologic Anatomy of the Pancreas.

The pancreas is composed of two major types of tissues:(1) the ***acini***, which secrete digestive juices into the duodenum, and (2) the ***islets of Langerhans***, which secrete insulin and glucagon directly into the blood. The PANCREAS is a long, slender organ, most of which is located posterior to the bottom half of the stomach (**Figure 1**). Although it is primarily an **exocrine gland**, secreting a variety of digestive enzymes, the pancreas has an **endocrine** function. Its **PANCREATIC ISLETS**—clusters of cells formerly known as the **ISLETS OF LANGERHANS**—secrete the hormones **glucagon**, **insulin**, **somatostatin**, and **pancreatic polypeptide** (**PP**). Most islets (**islets of Langerhans**) that collectively comprise the endocrine pancreas are too small to be seen by gross examination,Islets vary greatly in size; **~70%** are in the size range of **50-250** µm in diameter in humans with an average in the range of **100-150** µm . Smaller islets are dispersed throughout the **acinar lobules** and most larger **islets** lie along the main and **interlobular ducts** of the pancreas. Most islets are spherical or ellipsoid, but they can be irregular in shape--sometimes reflecting the pressure of an adjacent structure, often a duct, or limitation by a tissue plane. Several reports provide support for the presence of a higher population density of **islets** in the tail of the pancreas than in the head and body although others find no difference. In adult humans the number of

islets is calculated to be 500,000-1 million whereas there are far fewer in smaller animals. Islets comprise 1-2% of the pancreas in adults of most mammalian species. In addition to the islets, isolated islet cells may be found dispersed in the acinar lobules or in association with ducts.

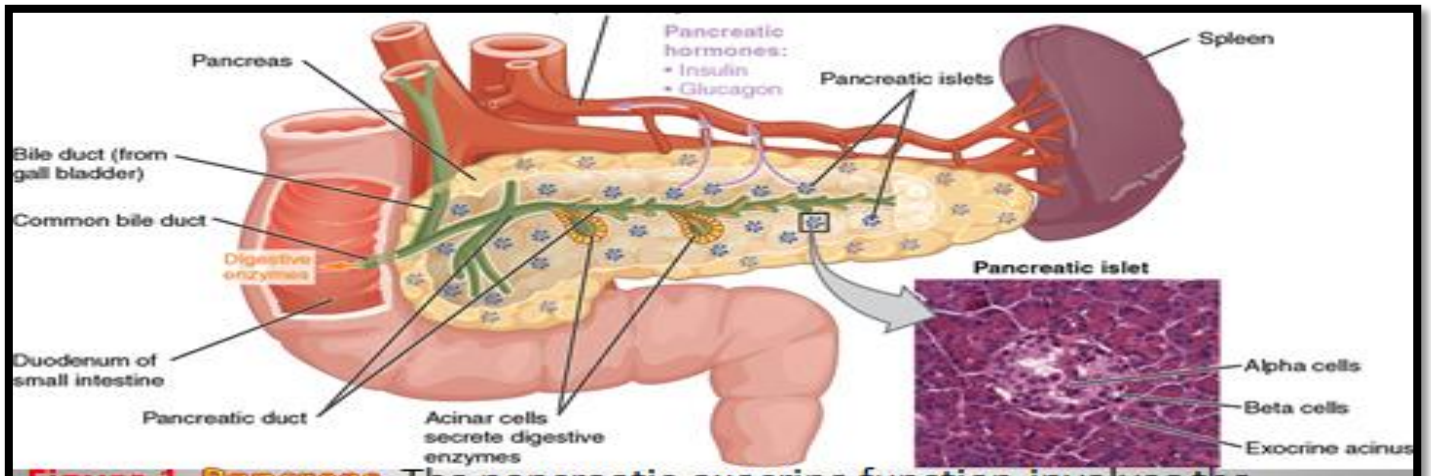


Figure 1. Pancreas. The pancreatic exocrine function involves the **acinar cells** secreting digestive enzymes that are transported into the small intestine by the pancreatic duct. Its endocrine function involves the secretion of insulin (produced by **beta cells**) and glucagon (produced by **alpha cells**) within the pancreatic islets. These two hormones regulate the rate of glucose metabolism in the body. The micrograph reveals pancreatic islets

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.

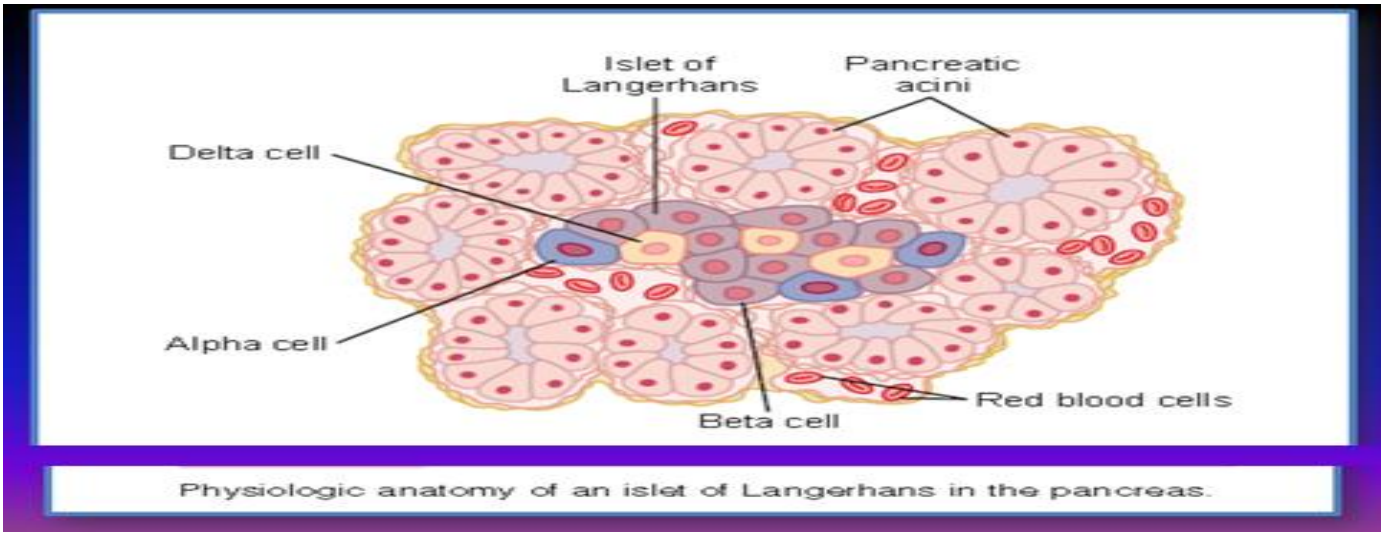
The **beta cell** produces the hormone **insulin** and makes up approximately 75 percent of each islet. Elevated blood glucose levels stimulate the release of insulin. **Amylin**, another hormone

secreted by beta cells it is often secreted in parallel with insulin, although its function is unclear.

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.

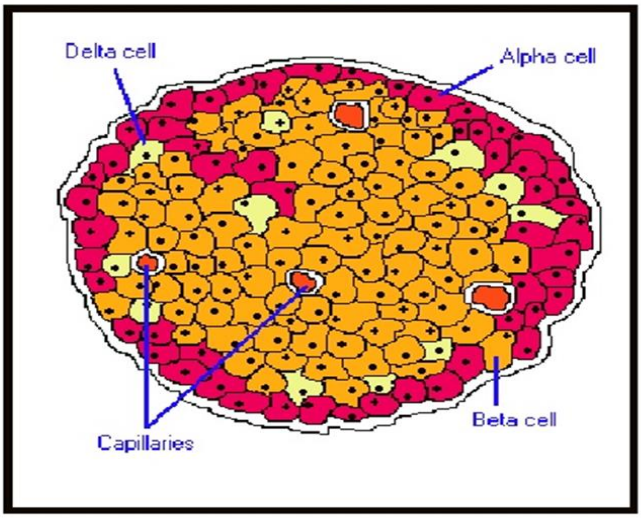
The close interrelations among these cell types in the islets of Langerhans allow cell-to-cell communication and direct control of secretion of some of the hormones by the other hormones. For instance, **insulin** inhibits **glucagon** secretion, **amylin** inhibits **insulin** secretion, and **somatostatin** inhibits the secretion of both **insulin** and **glucagon**.

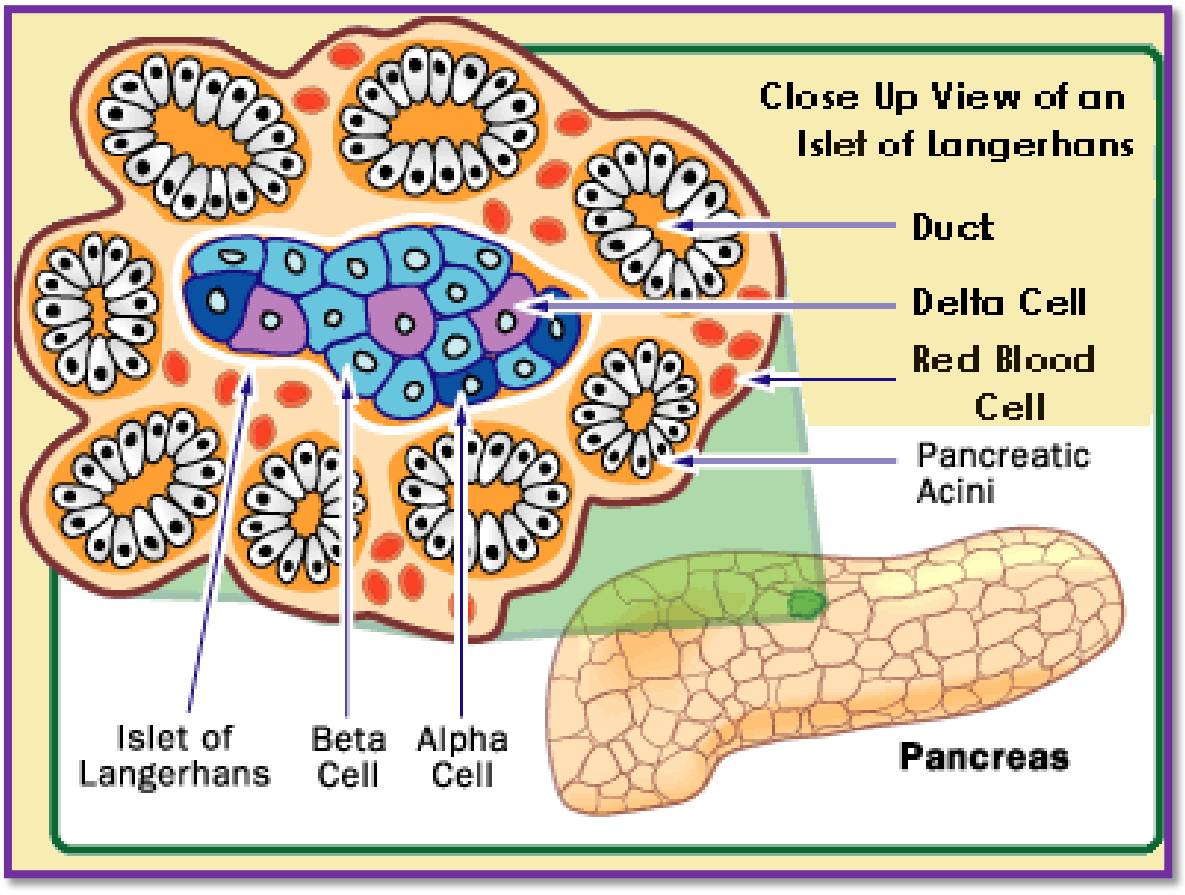


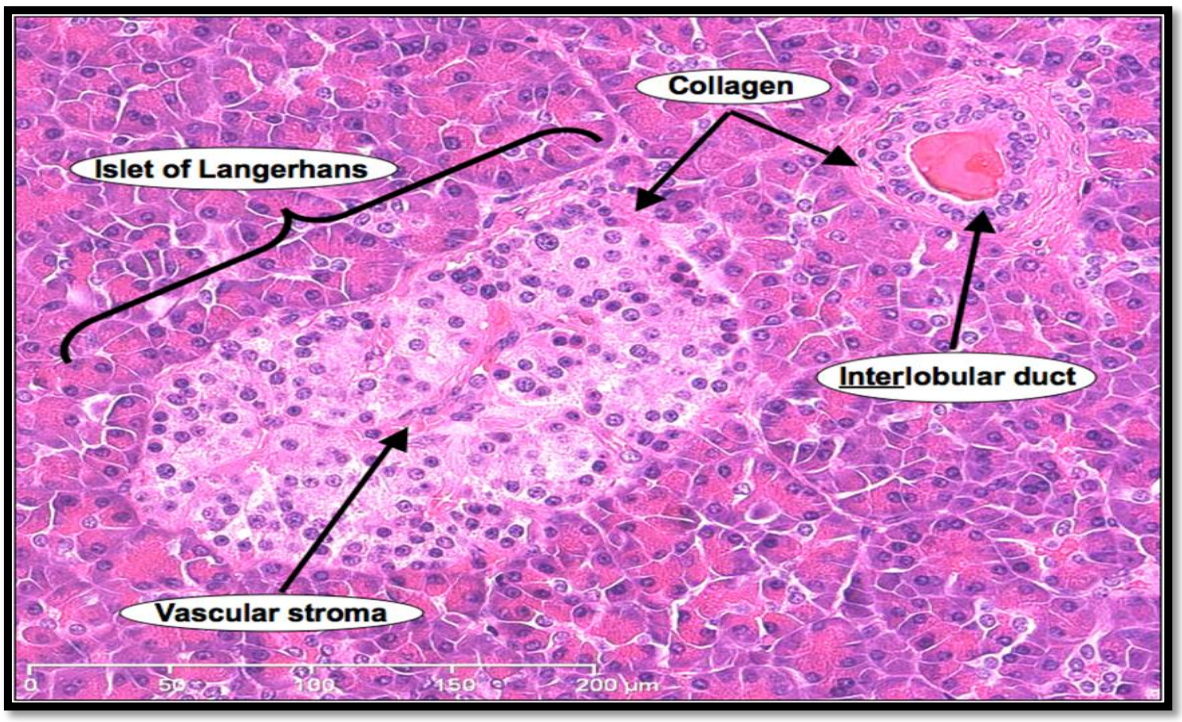
Physiologic anatomy of an islet of Langerhans in the pancreas.

Histology- **Islets of Langerhans**

- Contain the cells that secrete:
- Glucagon - alpha cells, 20% of cells
- Insulin - beta cells, 70% of cells
- Somatostatin - delta cells, 5% of cells

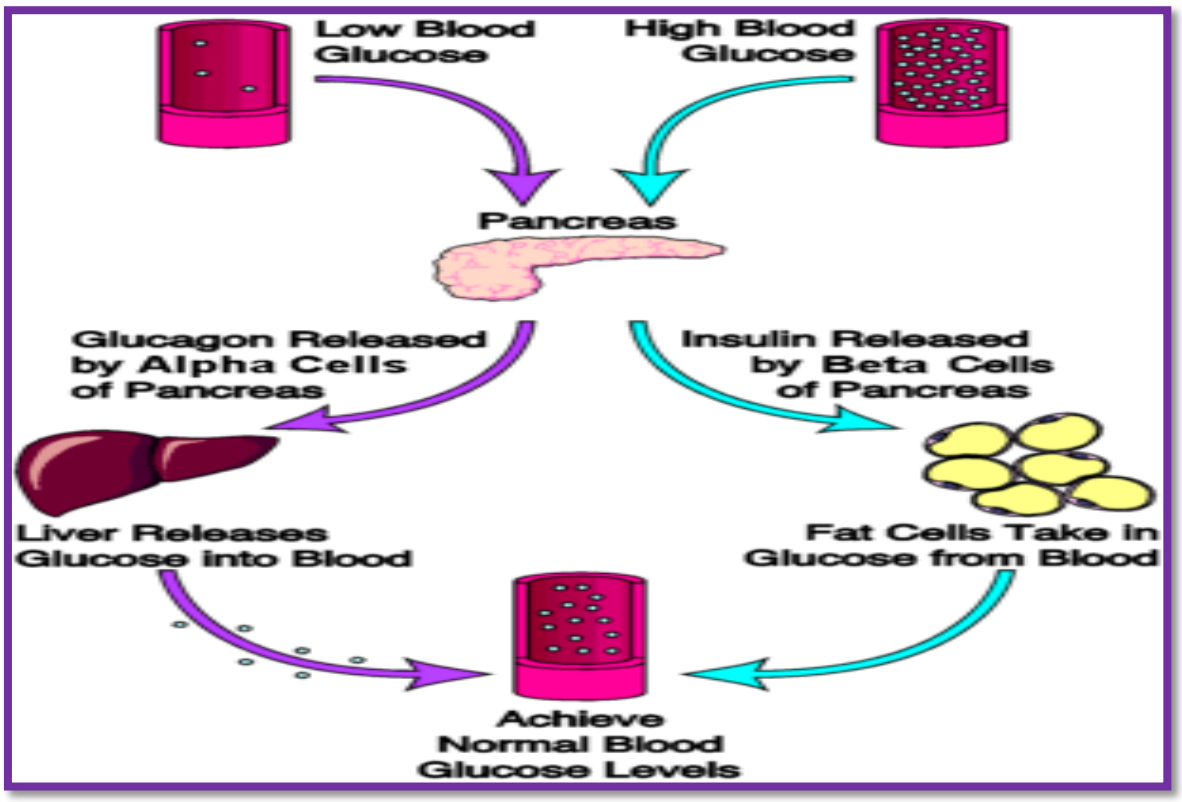






Insulin and Its Metabolic Effects

Insulin was first isolated from the **pancreas** in **1922** by Banting and Best, and almost overnight the outlook for the severely diabetic patient changed from one of rapid decline and death to that of a nearly normal person. Historically, **insulin** has been associated with "**blood sugar**," and true enough, **insulin** has profound effects on **carbohydrate metabolism**. Yet it is abnormalities of **fat metabolism**, causing such conditions as **acidosis** and **arteriosclerosis**, that are the usual causes of death in diabetic patients. Also, in patients with prolonged diabetes, diminished ability to synthesize proteins leads to wasting of the tissues as well as many cellular functional disorders. Therefore, it is clear that **insulin** affects **fat** and **protein** metabolism almost as much as it does **carbohydrate metabolism**.



Regulation of Blood Glucose Levels by Insulin and Glucagon

Glucose is required for **cellular respiration** and is the preferred **fuel** for all body cells. The body derives glucose from the breakdown of the **carbohydrate-containing foods** and **drinks** we consume. **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 the adipose tissue. Hormones regulate both the **storage** and the **utilization** of glucose as required. **Receptors** located in the pancreas sense blood glucose levels, and subsequently the pancreatic cells secrete glucagon or insulin to maintain normal levels.

Glucagon

Receptors in the pancreas can sense the decline in blood glucose levels, such as during periods of fasting or during prolonged labor or exercise (**Figure 2**). In response, the **alpha cells** of the pancreas secrete the hormone **glucagon**, which has several effects:

- It stimulates the **liver** to convert its stores of **glycogen** back into **glucose**. This response is known as **glycogenolysis**. The glucose is then released into the circulation for use by body cells.
- It stimulates the **liver** to take up **amino acid**s from the blood and convert them into **glucose**. This response is known as **gluconeogenesis.**
- It stimulates **lipolysis**, the breakdown of stored **triglycerides** into free **fatty acids** and **glycerol**. 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**.

Taken together, these actions increase blood glucose levels. The activity of glucagon is regulated through a negative feedback mechanism; rising blood glucose levels inhibit further glucagon production and secretion.

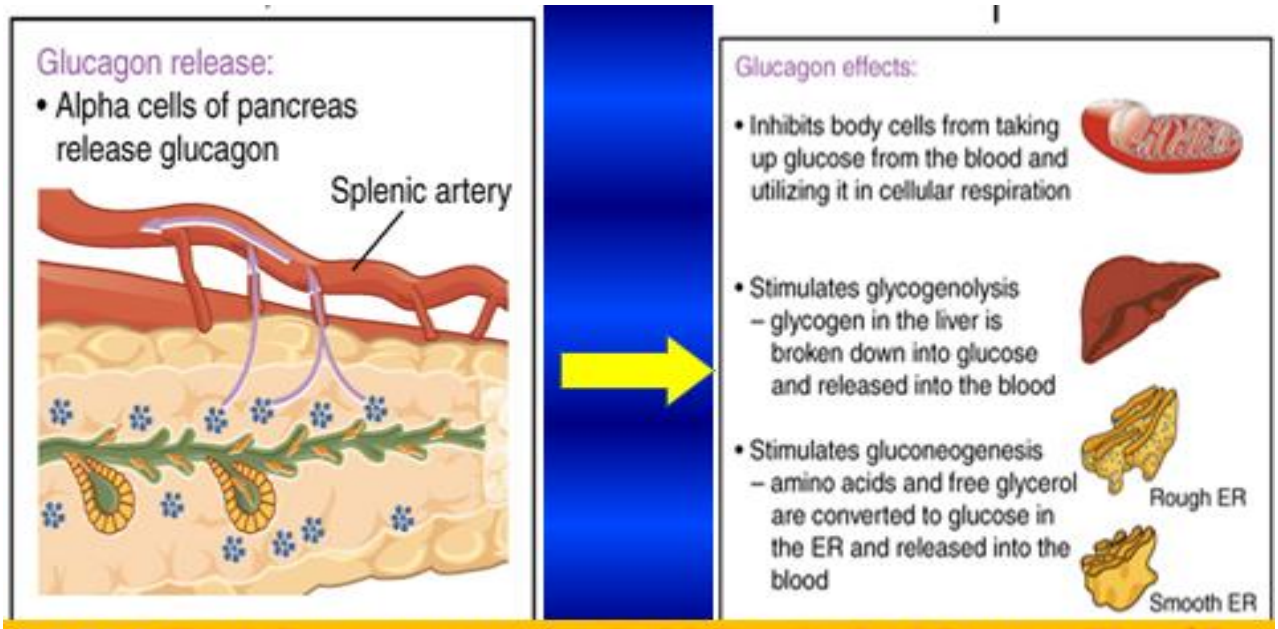
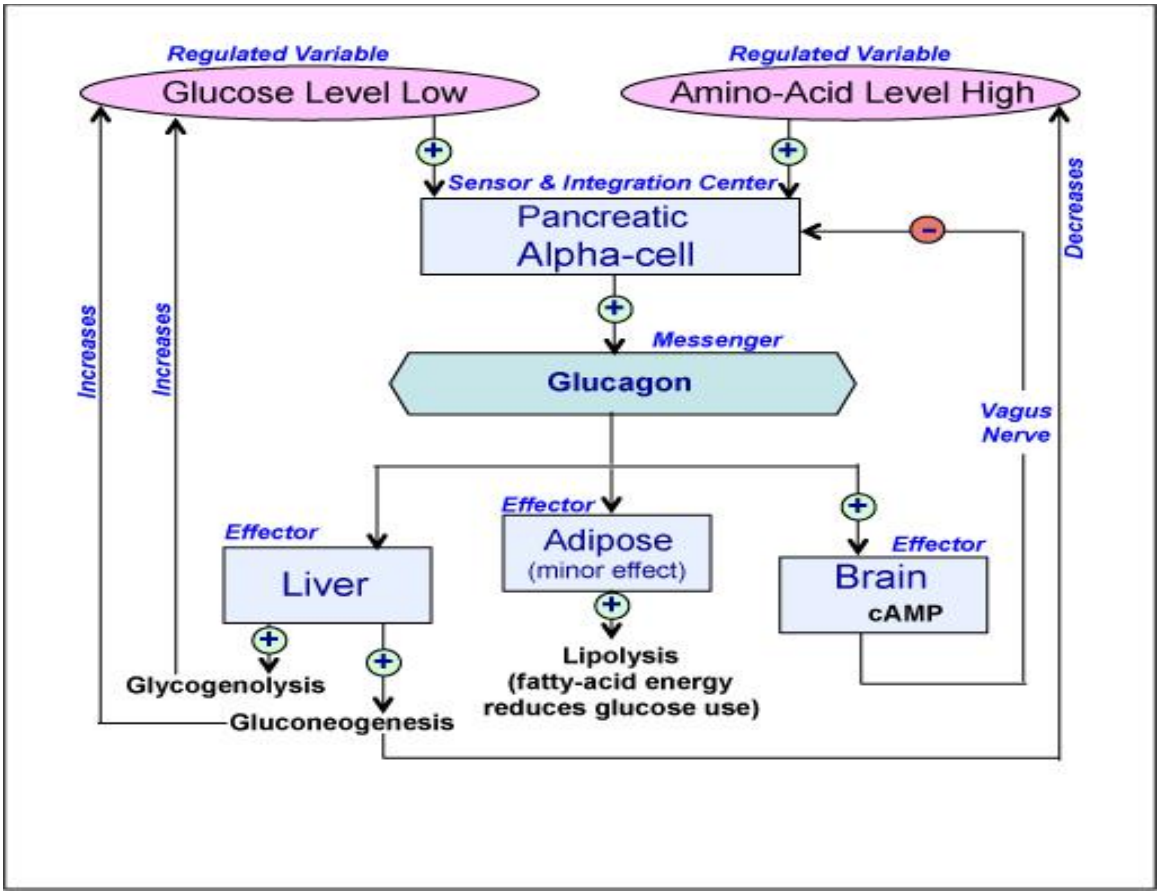


FIGURE 2. Blood glucose concentration is tightly maintained between 70 mg/dL and 110 mg/dL. If blood glucose concentration drops below this range, glucagon is released, which stimulates body cells to release glucose into the blood.



Insulin

The primary function of **insulin** is to facilitate the uptake of **glucose** into body cells. Red blood cells, as well as cells of the brain, liver, kidneys, and the lining of the small intestine, **do not have insulin receptors** on their cell membranes and **do not require insulin for glucose uptake**. Although all other body cells do require insulin if they are to take glucose from the bloodstream, skeletal muscle cells and adipose cells are the primary targets of insulin. (**Figure 3**)

The presence of food in the intestine triggers the release of gastrointestinal tract hormones such as glucose-dependent insulinotropic peptide (previously known as gastric inhibitory peptide). This is in turn the initial trigger for **insulin** production and secretion by the **beta** cells of the **pancreas**. Once nutrient absorption occurs, the resulting surge in blood glucose levels further stimulates insulin secretion.

Precisely how **insulin** facilitates **glucose** uptake is not entirely clear. However, **insulin** appears to activate a **tyrosine kinase receptor**, triggering the phosphorylation of many substrates within the cell. These multiple biochemical reactions converge to support the movement of intracellular vesicles containing facilitative **glucose** transporters to the cell membrane. In the absence of **insulin**, these transport proteins are normally recycled slowly between the cell

membrane and cell interior. **Insulin** triggers the rapid movement of a pool of **glucose** transporter vesicles to the cell membrane, where they fuse and expose the **glucose** transporters to the extracellular fluid. The transporters then move **glucose** by facilitated diffusion into the cell interior.

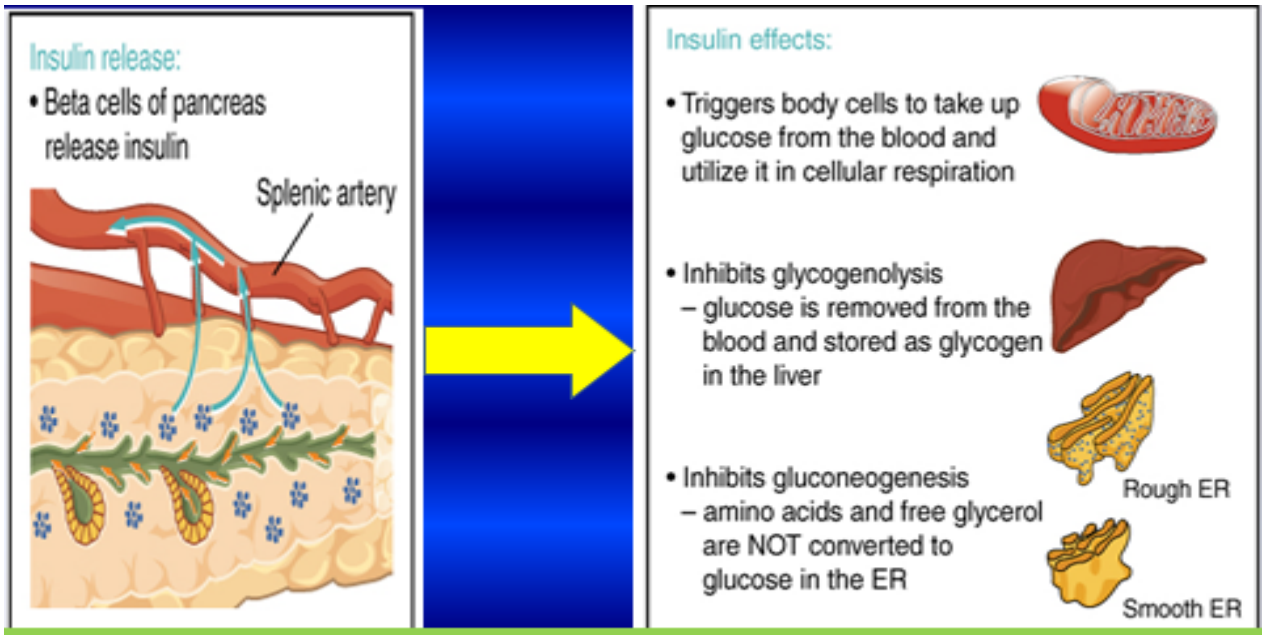
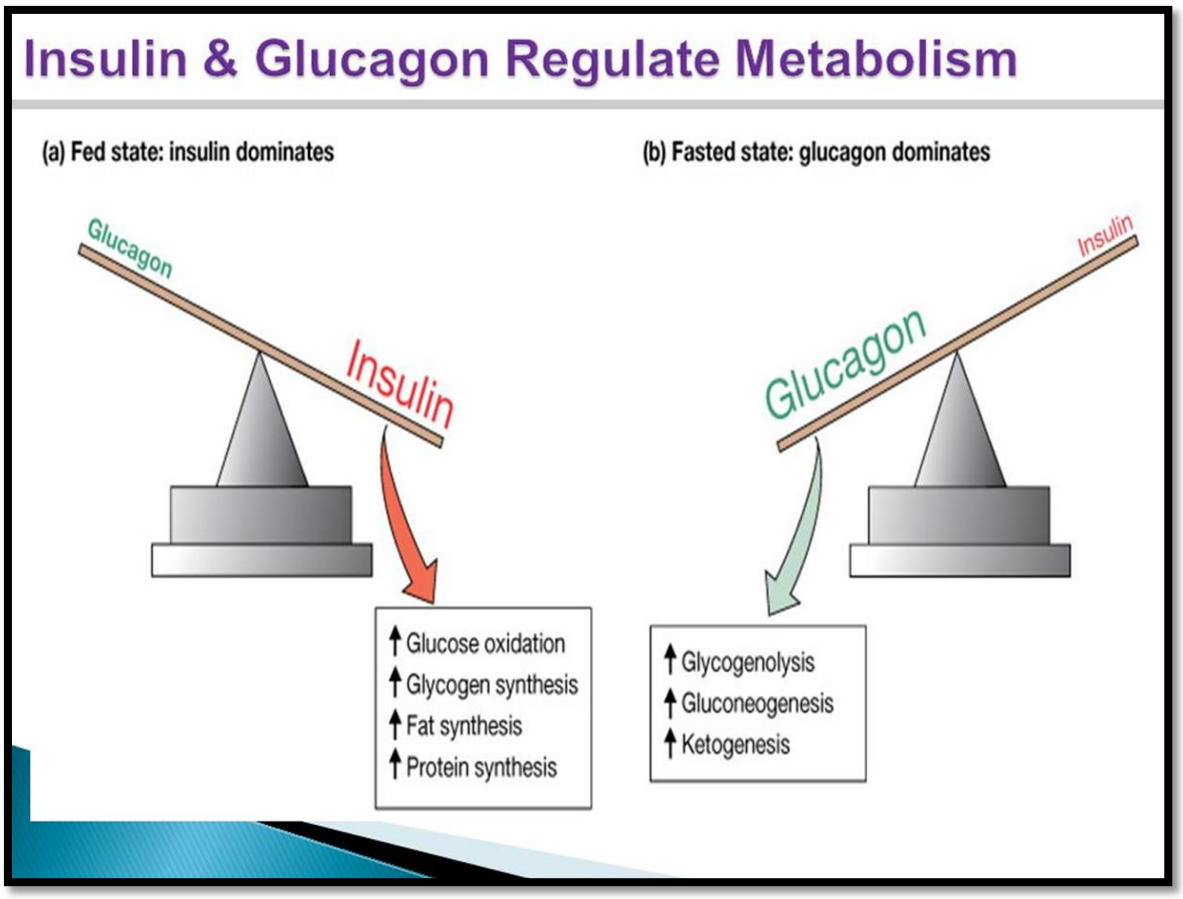
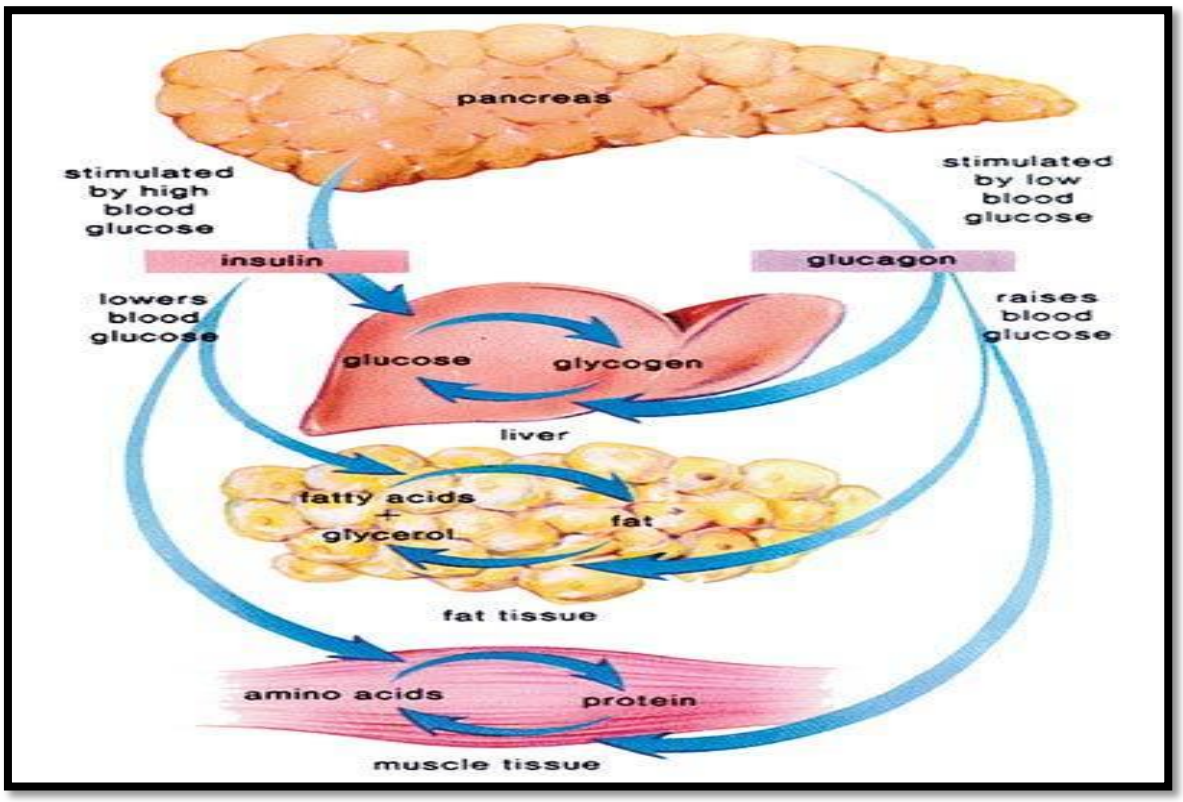


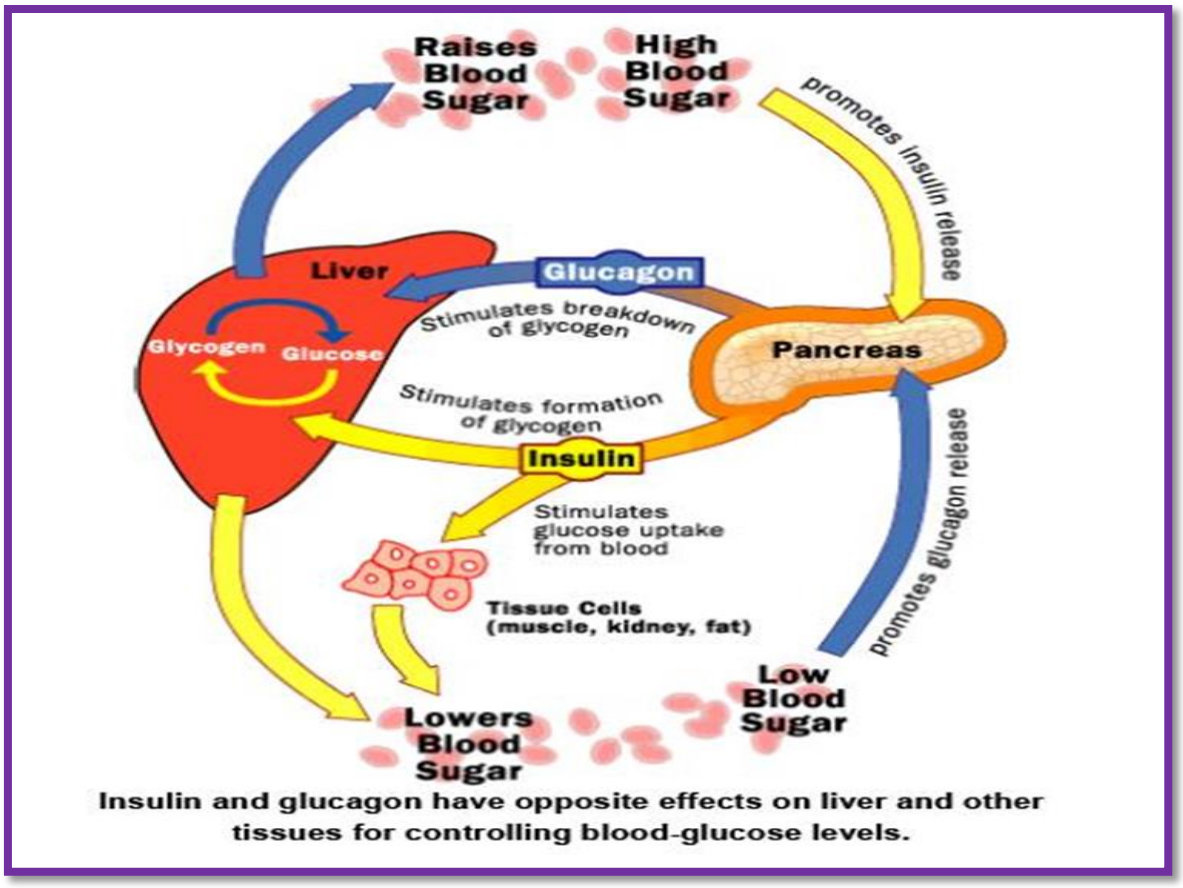
Figure 3. Homeostatic Regulation of Blood Glucose Levels. Blood glucose concentration is tightly maintained between 70 mg/dL and 110 mg/dL. If blood glucose concentration rises above this range, insulin is released, which stimulates body cells to remove glucose from the

Insulin also reduces blood **glucose** levels by stimulating **glycolysis**, the metabolism of **glucose** for generation of **ATP**. Moreover, it stimulates the liver to convert excess **glucose** into glycogen for storage, and it inhibits enzymes involved in **glycogenolysis** and **gluconeogenesis**. Finally, **insulin** promotes triglyceride and protein synthesis. The secretion of **insulin** is regulated through a **negative feedback** mechanism. As blood glucose levels decrease, further insulin release is inhibited.

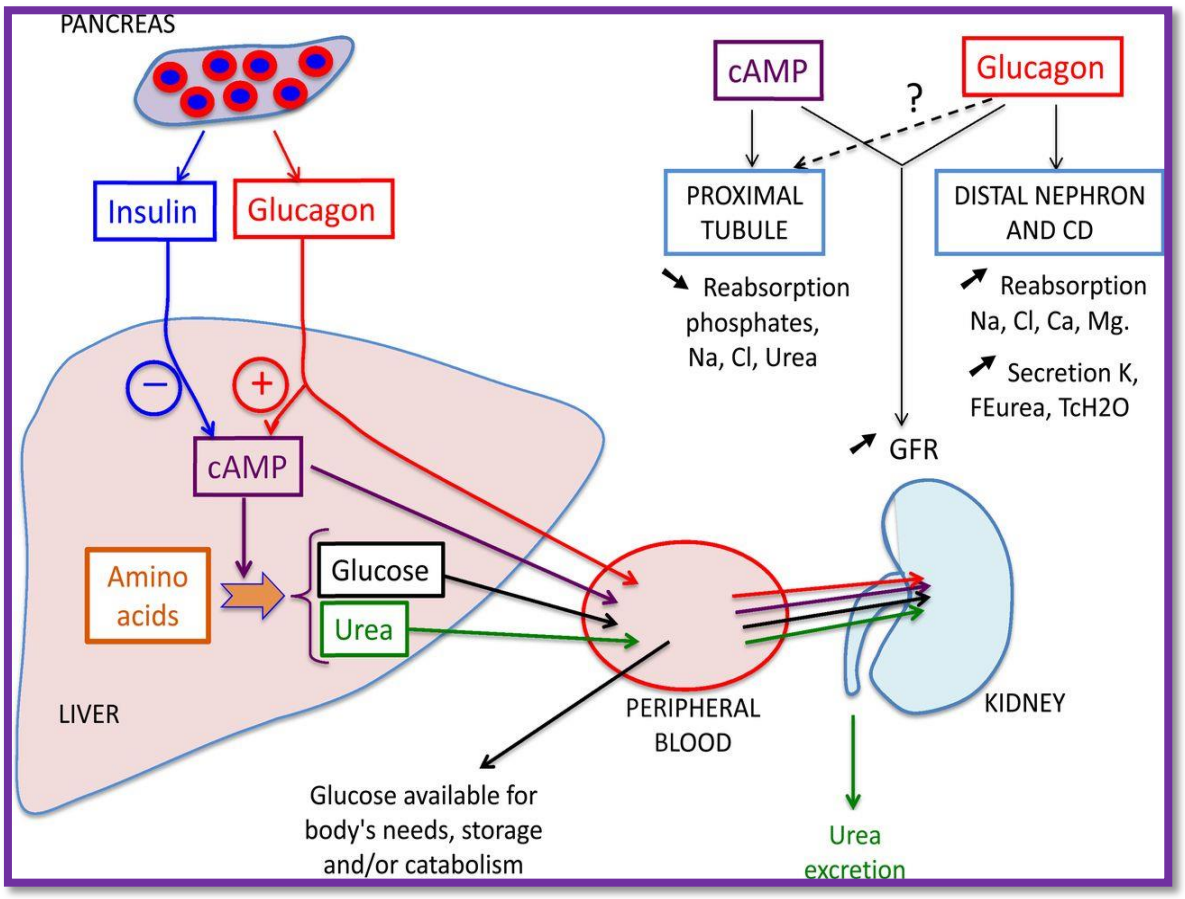
Insulin	Glucagon
Shifts metabolism into storage mode	Shifts metabolism into burning mode
Converts glucose & protein to fat	Converts protein and fat to glucose
Converts dietary fat to storage	Converts dietary fats to ketones and sends them to the tissues for energy
Removes fat from blood and transports it into fat cells	Releases fat from fat cells into the blood for use by tissues as energy
Increases body's production of cholesterol	Decreases the body's production of cholesterol
Makes kidney retain excess fluid	Makes the kidneys release excess fluid
Stimulates the use of glucose for energy	Stimulates the use of fat for energy







Insulin and glucagon have opposite effects on liver and other tissues for controlling blood-glucose levels.



Importance of Blood Glucose Regulation.

One might ask, "Why is it so important to maintain a constant blood glucose concentration, particularly because most tissues can shift to utilization of fats and proteins for energy in the absence of glucose?" The answer is that glucose is the only nutrient that normally can be used by the *brain, retina,* and *germinal epithelium of the gonads* in sufficient quantities to supply them optimally with their required energy. Therefore, it is important to maintain the blood glucose concentration at a level sufficient to provide this necessary nutrition. Most of the glucose formed by gluconeogenesis during the interdigestive period is used for metabolism in the brain. Indeed, it is important that the pancreas not secrete insulin during this time; otherwise, the scant supplies of glucose that are available would

all go into the muscles and other peripheral tissues, leaving the brain without a nutritive source. It is also important that blood glucose concentration not rise too high for several reasons:

1. Glucose can exert a large amount of osmotic pressure in the extracellular fluid, and a rise in glucose concentration to excessive values can cause considerable cellular dehydration.
2. An excessively high level of blood glucose concentration causes loss of glucose in the urine.
3. Loss of glucose in the urine also causes osmotic diuresis by the kidneys, which can deplete the body of its fluids and electrolytes.
4. Long-term increases in blood glucose may cause damage to many tissues, especially to blood vessels. Vascular injury associated with uncontrolled diabetes mellitus leads to increased risk for heart attack, stroke, end-stage renal disease, and blindness.