Al-Mustaqbal University College

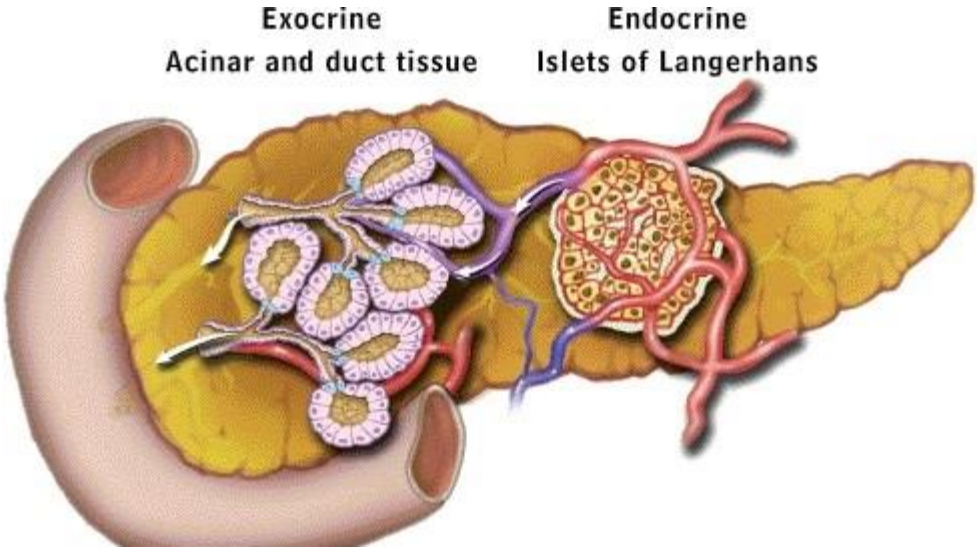
Pathophysiology 3rd stage

Diabetes Mellitus Part I

Dr. Hasanain Owadh

The Pancreas and Diabetes Mellitus (DM)

The pancreas is a large, diffuse abdominal organ that functions as both an exocrine and endocrine gland.



Secretion of Pancreatic Enzymes

The pancreatic enzymes are secreted as inactive proenzymes that are activated when they reach the duodenum.

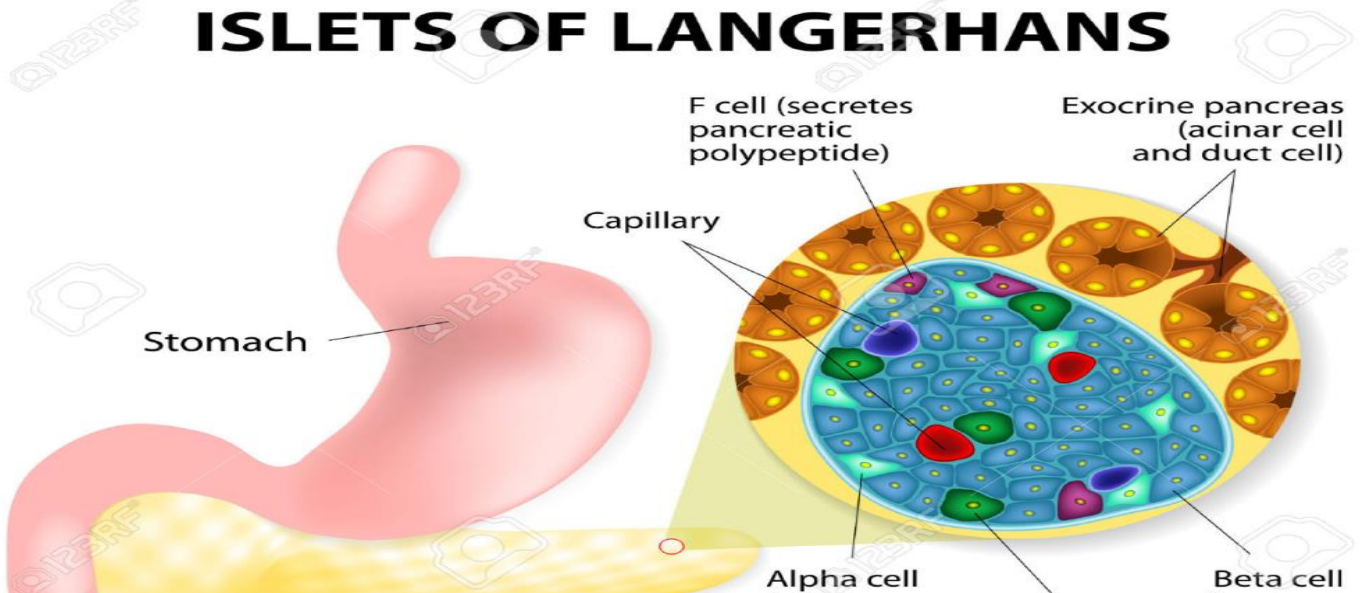
The activated enzymes include trypsin, amylase, and lipase, which are responsible for the digestion of proteins to amino acids, carbohydrates to simple sugars, and fats to free fatty acids and monoglycerides, respectively.

Secretion of Sodium Bicarbonate

Sodium bicarbonate is secreted from pancreatic ductal cells in response to a second small-intestine hormone, secretin. to neutralizes acidic chyme which come from stomach.

Endocrine Functions of the Pancreas

The endocrine functions of the pancreas involve the synthesis and release of the hormones insulin, glucagon, and somatostatin.



Islets of langerhans

- Clusters of cells between acini of exocrine pancreas
- 150 µm diameter
- Consist of four types of cells:
- A or α cells (20%) secrete glucagon
- B or β cells (75%) secrete insulin
- D or δ cells (3-5%) secrete somatostatin
- F (< 2%) secrete pancreatic polypeptide (PP)

Insulin

Control blood glucose level, storage and utilization of glucose.

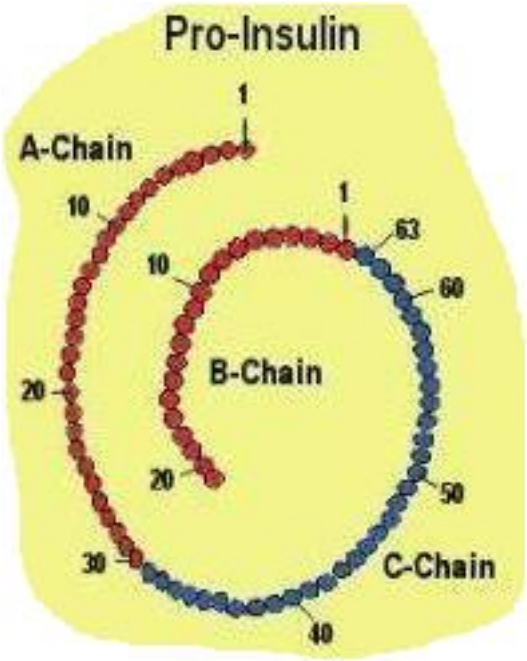
5 min half life.

Is a polypeptide (51 amino acids) consisting of tow chains connecting together by disulphide bridges.

A chain (21 amino acids).

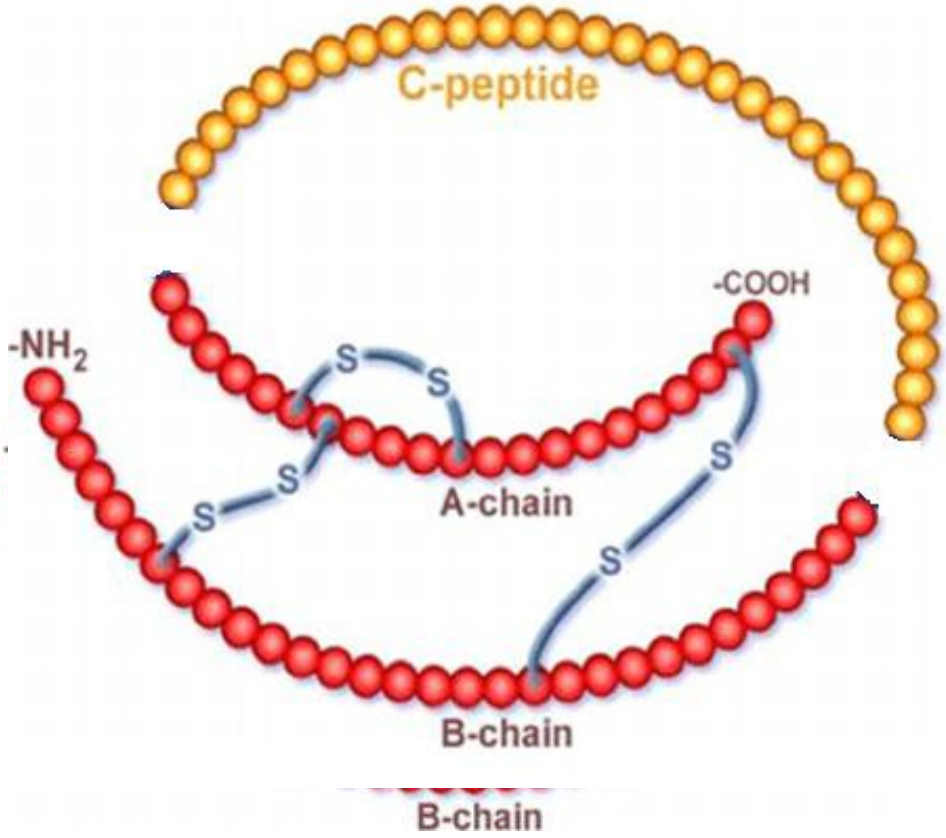
B chain (30 amino acids).

Proinsulin consist of C chain removed before insulin secretion.



Synthesis and Secretion of Insulin

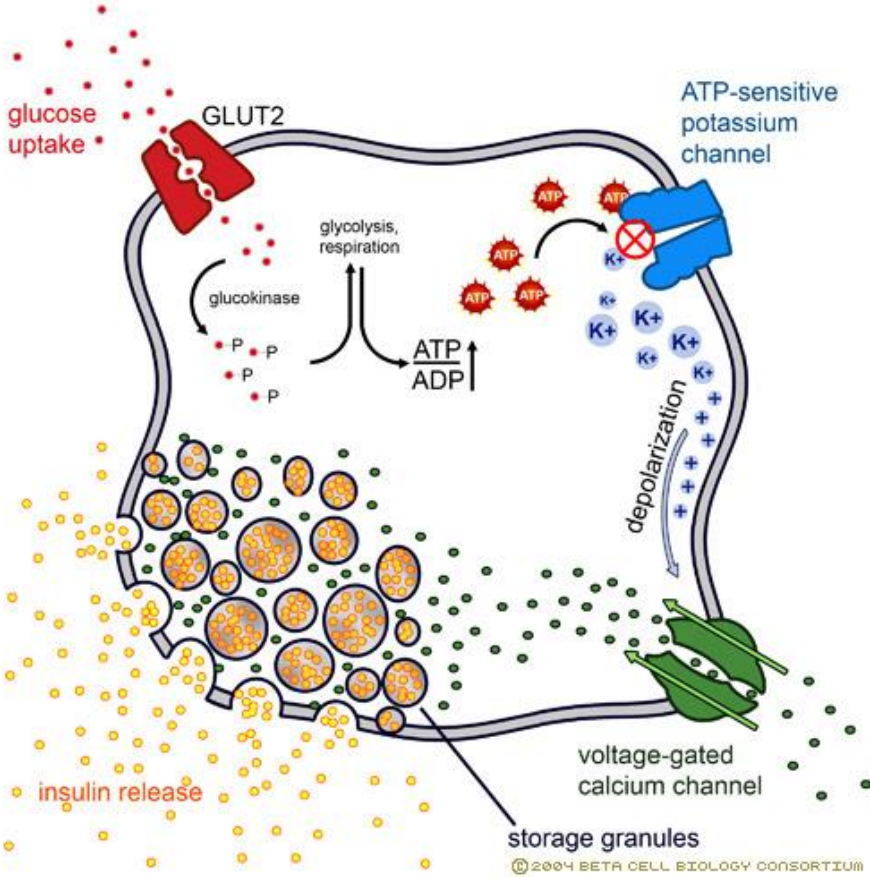
The synthesis of insulin in the pancreas comes from the enzymatic cleavage of the molecule proinsulin.



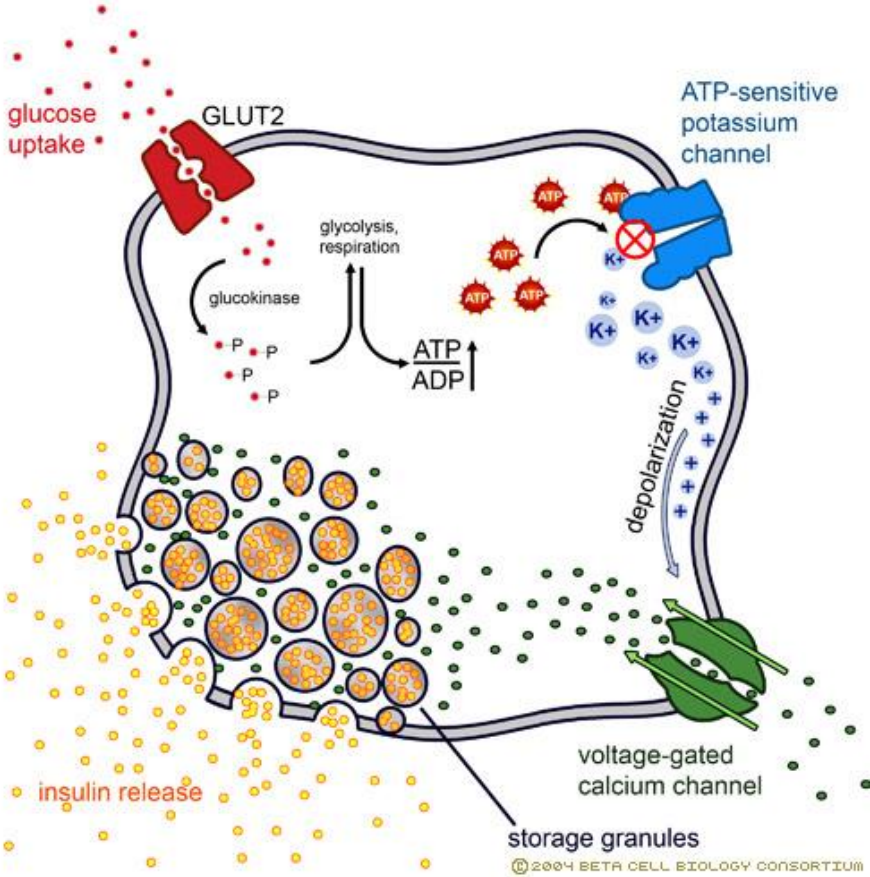
Enzymatic cleavage of the C peptide connections leaves the A and the B peptides connected to each other through only the two disulfide bonds.

Insulin is released at a basal rate by the beta cells of the islets of Langerhans.

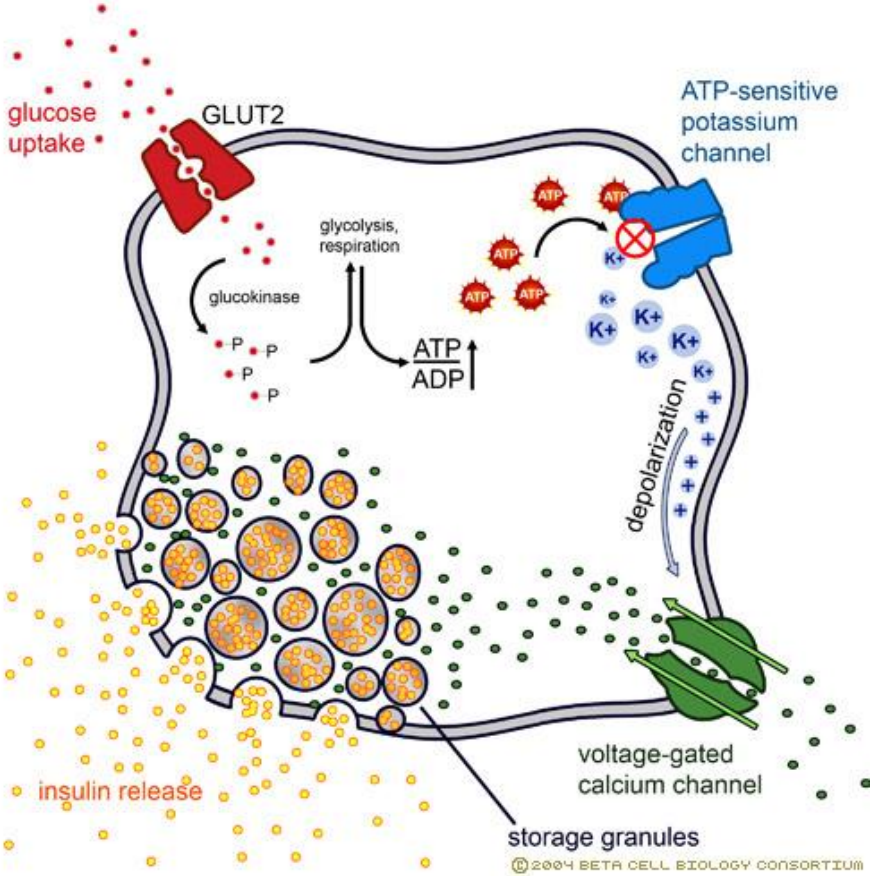
A rise in blood glucose is the **primary stimulus** to increase insulin release above baseline.



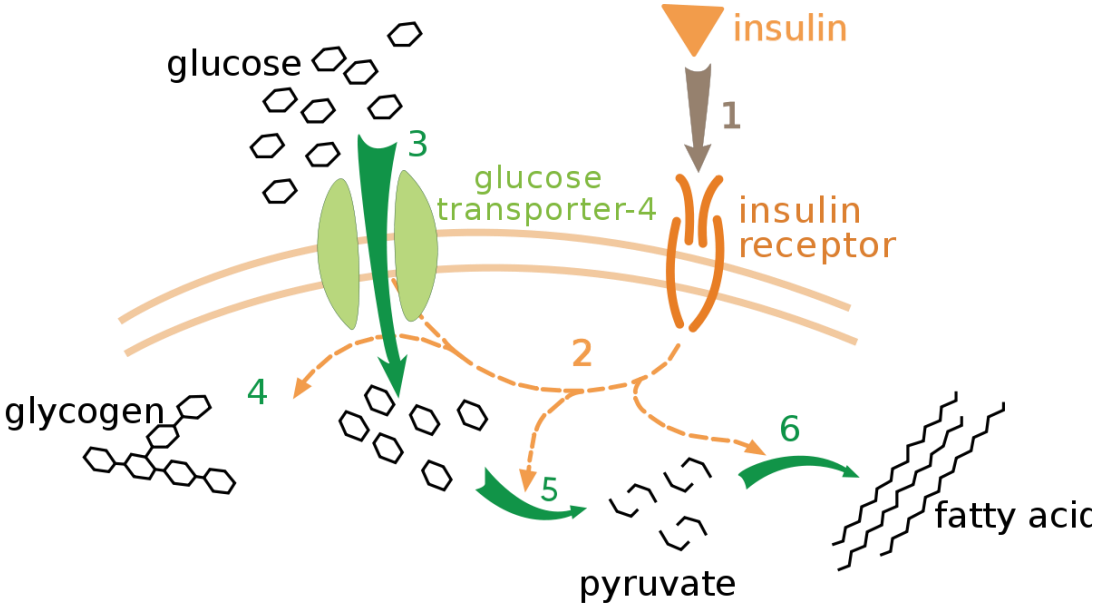
Fasting blood glucose level is normally 80 to 90 mg/100 mL of blood.



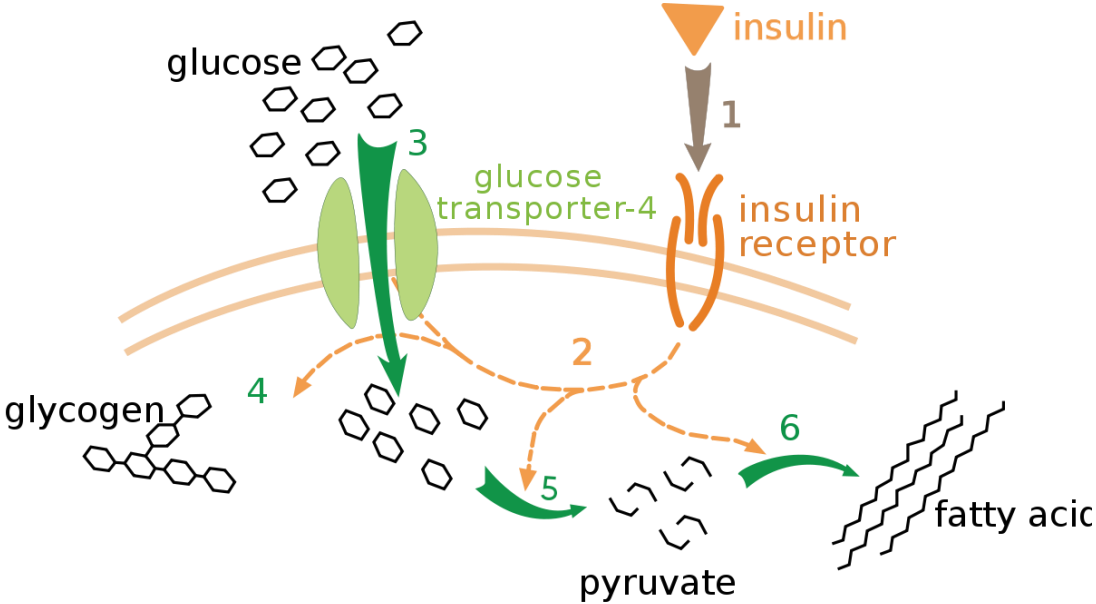
When blood glucose increases to more than 100 mg/100 mL of blood, insulin secretion from the pancreas increases rapidly and then returns to baseline in 2 to 3 hours.



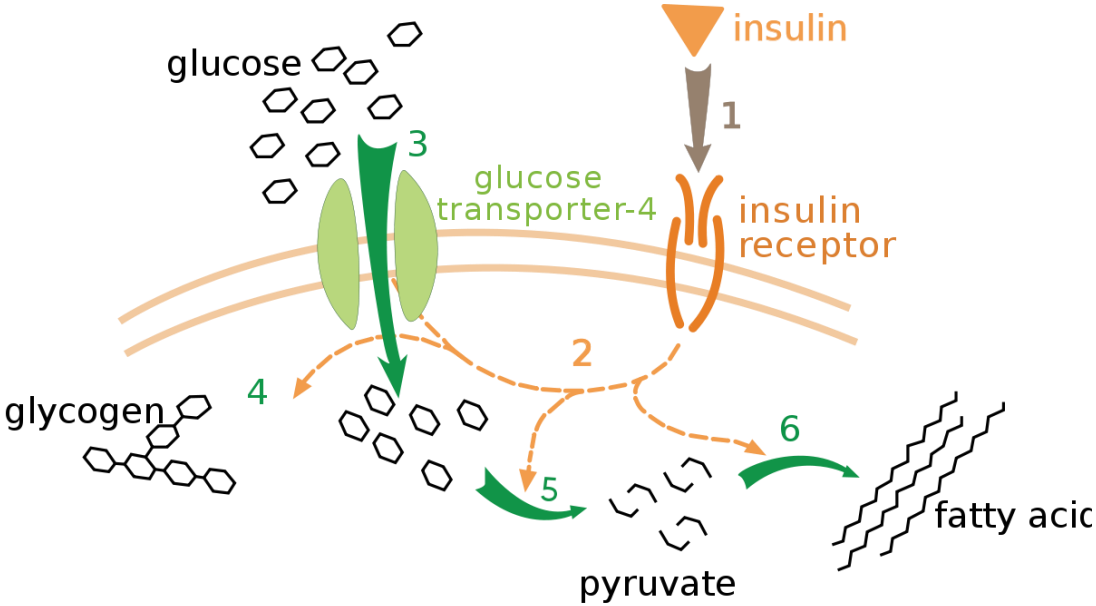
Insulin activates glucose-transporter molecules, called glut-4 glucose transporters, which necessary for the facilitated diffusion of glucose into most cells.



inside the cells, glucose can be used for immediate energy production through the Krebs cycle or it can be stored in the cell as glycogen.



When glucose is carried into the cell, it results in decreased blood levels of glucose, reducing further stimulation of insulin release.



Insulin release is also regulated by:

2- Amino acids and the hormones of digestion cholecystokinin (CCK), secretin, and glucose-dependent insulinotropic polypeptide [GIP].

3- Parasympathetic nerves to the pancreas.

Both the release of GIP and the activation of the autonomic nervous system occur when one starts eating, resulting in a release of insulin at the beginning of a meal, even before glucose is absorbed.

While Sympathetic stimulation to the pancreas decreases insulin release via α receptors.

Insulin release is also regulated by:

4- High level of ketoacids stimulate insulin secretion.

5- Somatostatin inhibit secretion of insulin.

6- Thiazide diuretics inhibit it secretion.

Insulin action:

1- Stimulating glucose uptake by cells and maintain plasma glucose levels.

2- Increases amino acid transport into cells and stimulates protein synthesis.

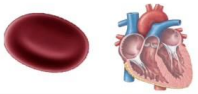
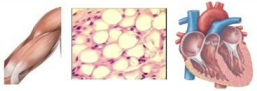
3- Inhibits the breakdown of fat, protein, and glycogen stores.

4- Inhibits gluconeogenesis.

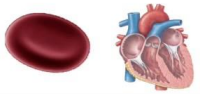
5- Increase K^+ up take by increasing Na^+-K^+ pump.

The Brain, Glucose, and Insulin

Unlike most other cells, brain cells do not require insulin for glucose entry.

GLUT1	• Blood • Blood-Brain Barrier • Heart (lesser extent) 	• Insulin-Independent
GLUT2	• Liver • Pancreas • Small Intestine 	• Insulin-Independent • High K_m • Low Affinity
GLUT3	• Brain • Neurons • Sperm 	• Insulin-Independent • Low K_m • High Affinity
GLUT4	• Skeletal Muscle • Adipose Tissue • Heart 	
GLUT5		

Also, unlike other cells that may use free fatty acids or amino acids for energy, brain cells must use only glucose or glycogen to meet their energy demands and drive their cellular functions.

GLUT1	• Blood • Blood-Brain Barrier • Heart (lesser extent) 	• Insulin-Independent
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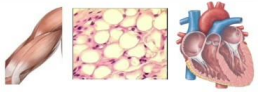
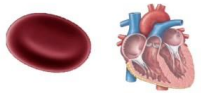
GLUT4	• Skeletal Muscle • Adipose Tissue • Heart 	
GLUT5		

In other words, brain cells are obligate users of glucose and glycogen. This means that gluconeogenesis by the liver is important;

GLUT1	• Blood • Blood-Brain Barrier • Heart (lesser extent) 	• Insulin-Independent
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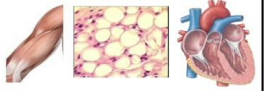
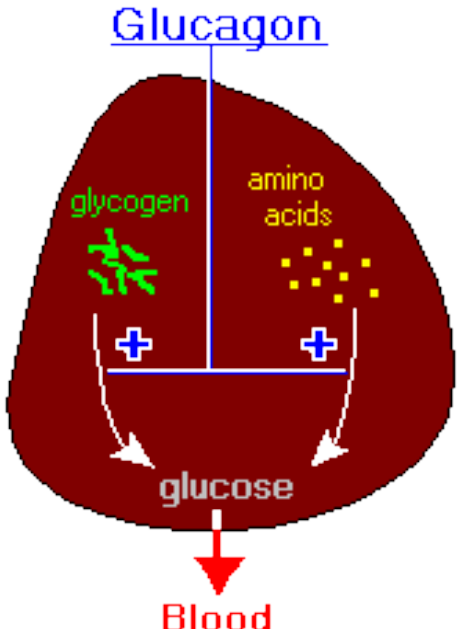
GLUT4	• Skeletal Muscle • Adipose Tissue • Heart 	
GLUT5		

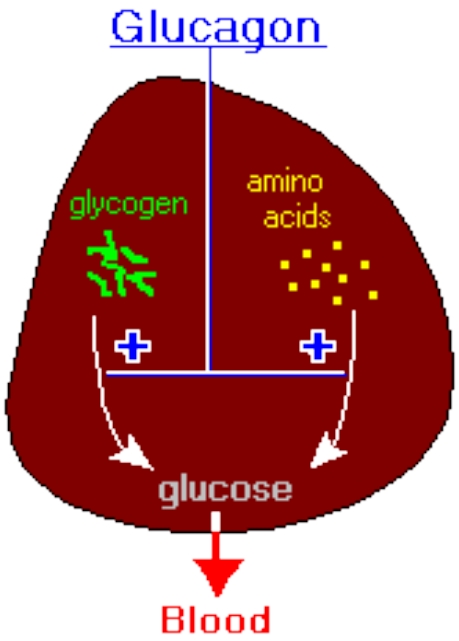
Secretion of Glucagon

Glucagon is a protein hormone released from the alpha cells of the islets of Langerhans in response to low blood glucose levels and increased plasma amino acids.



Glucagon is primarily a hormone of the postabsorptive stage of digestion that occurs during fasting periods in between meals.

Its functions are mainly catabolic (breaking down).



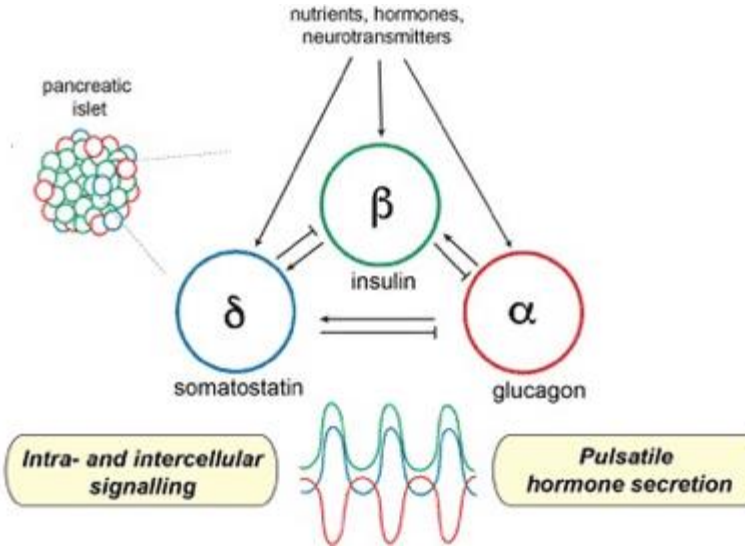
Secretion of Somatostatin

Secreted by **delta** cells.

Called **“growth hormone inhibiting hormone”** and is released as well by the hypothalamus.

Somatostatin from the hypothalamus inhibits the release of growth hormone from the anterior pituitary.

Somatostatin releasing from the pancreas to control metabolism by inhibiting the secretion of **insulin and glucagon**.



Diabetes mellitus (DM)

DM is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.

Diabetes mellitus is derived from the Greek word **diabetes** meaning siphon - to pass through and the Latin word **mellitus** meaning honeyed or sweet.

Hyperglycemia

Hyperglycemia is defined as plasma glucose higher than the normal, fasting range of 126 mg/100 mL of blood.

Hyperglycemia is caused by:

1- Insulin deficiency, as seen in type 1 diabetes.

2- Decreased cellular responsiveness to insulin, as seen in type 2 diabetes.

3- Cushing's syndrome can cause hyperglycemia by stimulation of liver gluconeogenesis.

4- Prolonged high levels of thyroid hormone, prolactin, and growth hormone overstimulate insulin release by beta cells of the pancreas, leading to an eventual decrease in the cellular response to insulin.

5- The catecholamines epinephrine and norepinephrine inhibit insulin secretion, increase the breakdown of stored fats, and promote the use of glycogen for energy.

The American Diabetes Association (ADA) classifies four categories of diabetes mellitus, as follows:

1. Type 1 (beta-cell destruction, usually leading to absolute insulin deficiency).

2. Type 2 (ranging from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance).

3. Other specific types.

4. Gestational diabetes.


Thank You