Physiology for Medical Students

Endocrine 7
Glucose Homeostasis

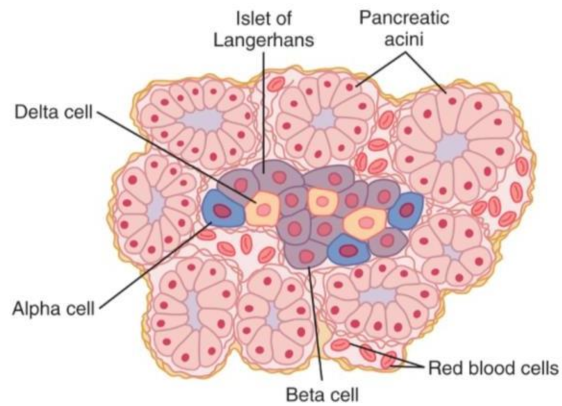
Fatima Daoud. MD. PhD.

Insulin, Glucagon, and Diabetes Mellitus

CHAPTER 78

The Pancreas

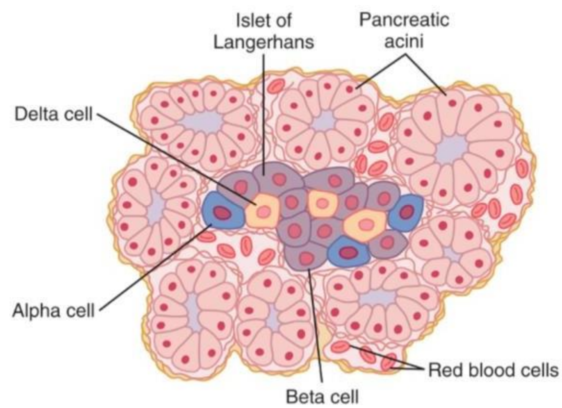
- 1) The acini, which secrete digestive juices into the duodenum
- 2) The islets of Langerhans, which secrete insulin and glucagon directly into the blood.



Scattered among the exocrine acini are 1–2 million tiny clusters of endocrine tissue called pancreatic islet or islets of Langerhans. Abundant capillaries serve both the exocrine and endocrine portions of the pancreas.
The islets make up about 1% to 2% of the total pancreatic mass.

the Pancreas

- Each pancreatic islet includes:
- The beta cells (60%): secrete insulin and amylin
- The alpha cells (25%): secrete glucagon.
- The delta cells (10%) secrete somatostatin.
- The gamma, or F, cells secrete pancreatic polypeptide.



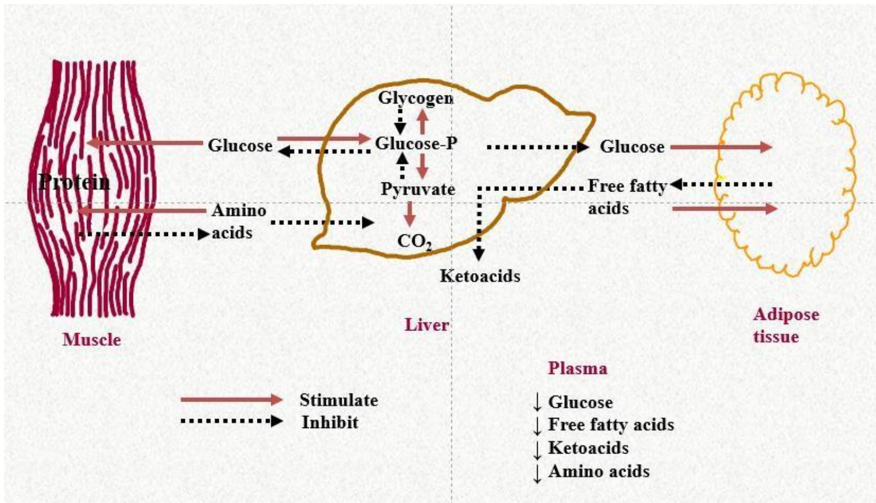
- pancreatic polypeptide. a hormone that plays a possible role in reducing appetite and food intake.

Insulin Is a Hormone Associated with Energy Abundance

- Insulin plays an important role in storing the excess energy.
- Excess carbohydrates → be stored as glycogen mainly in the liver and muscles.
- Excess carbohydrates → converted under the stimulus of insulin into fats and stored in the adipose tissue.
- Promotes amino acid uptake by cells and conversion of these amino acids into protein.
- Inhibits the breakdown of the proteins that are already in the cells.

- Insulin has important effects on carbohydrate, fat, and protein metabolism. It lowers the blood levels of glucose, fatty acids, and amino acids and promotes their storage.
- As these nutrient molecules enter the blood during the absorptive state, insulin promotes their cellular uptake and conversion into glycogen, triglycerides, and protein, respectively.
- Insulin exerts its many effects by altering either transport of specific blood-borne nutrients into cells or activity of the enzymes involved in specific metabolic pathways.
- To accomplish its effects, in some instances insulin increases the activity of an enzyme, for example glycogen synthase, the enzyme that synthesizes glycogen from glucose molecules. In other cases, however, insulin decreases the activity of an enzyme, for example by inhibiting hormone-sensitive lipase, the enzyme that catalyzes the breakdown of stored triglycerides back to free fatty acids and glycerol.

Metabolic effect of Insulin



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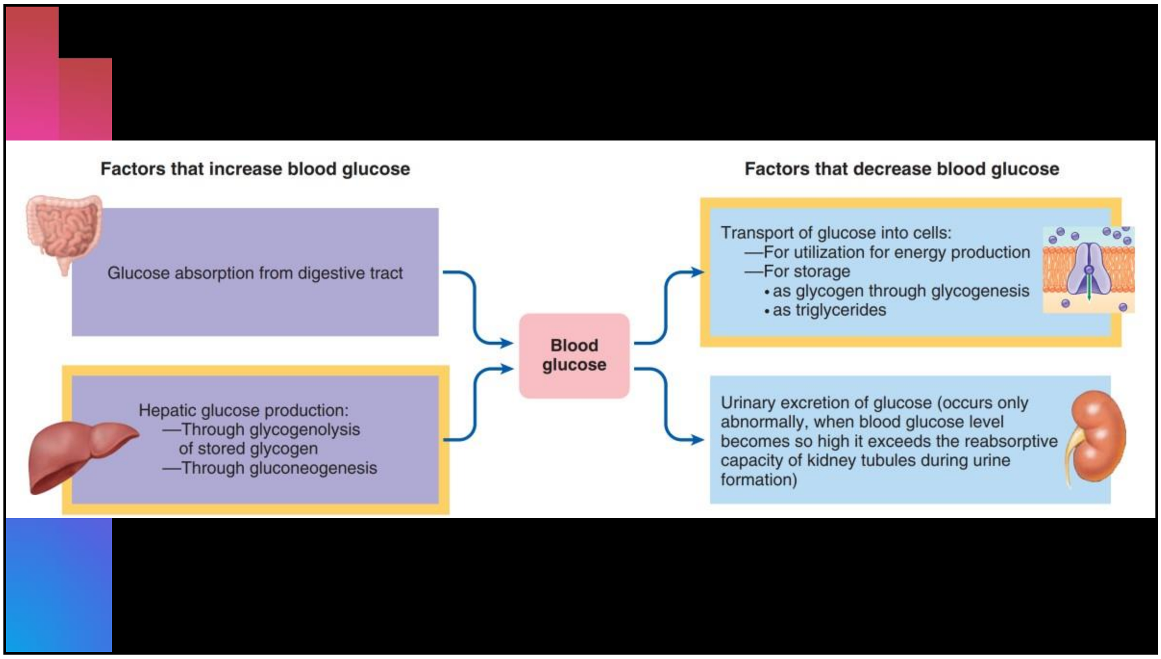
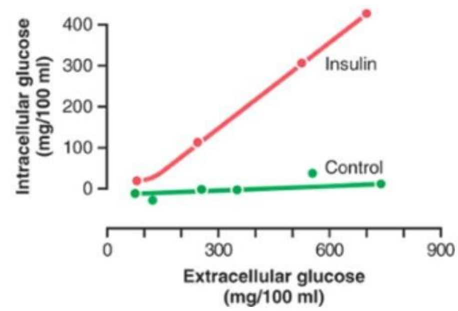


Factors that increase blood glucose
Glucose absorption from digestive tract
Hepatic glucose production:
—Through glycogenolysis of stored glycogen
—Through gluconeogenesis
Blood glucose
Factors that decrease blood glucose
Transport of glucose into cells:
—For utilization for energy production
—For storage
• as glycogen through glycogenesis
• as triglycerides
Urinary excretion of glucose (occurs only abnormally, when blood glucose level becomes so high it exceeds the reabsorptive capacity of kidney tubules during urine formation)

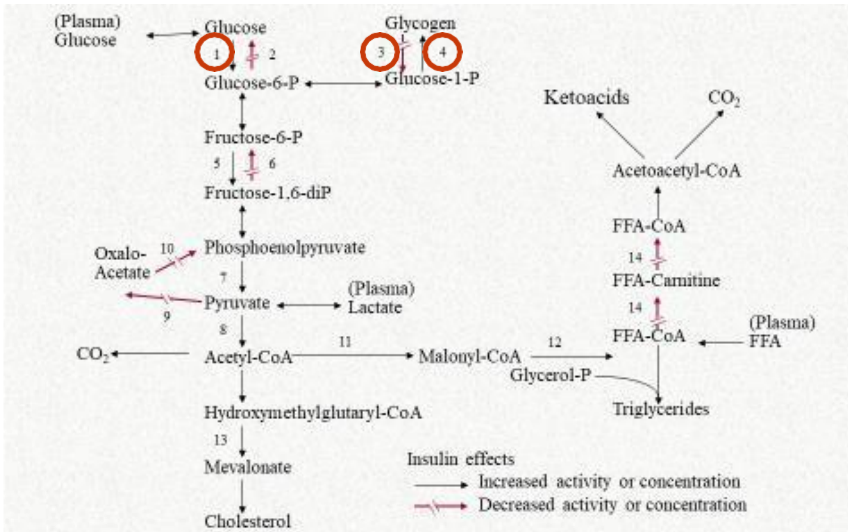
Effect of Insulin on Carbohydrate Metabolism

- Insulin promotes glucose uptake and metabolism.
- Increases glycogen storage in skeletal muscle and liver.
- Insulin inhibits glycogenolysis and gluconeogenesis.



*The transporter responsible for glucose uptake by most body cells is GLUT-4, which operates only at the binding of insulin. Glucose molecules cannot readily penetrate most cell membranes in the absence of insulin, making most tissues highly dependent on insulin for uptake of glucose from the blood and for its subsequent use.
* GLUT-4 is especially abundant in the tissues that account for the bulk of glucose uptake from the blood during the absorptive state, namely, resting skeletal muscle and adipose tissue cells.
*GLUT-4 is the only type of transporter that responds to insulin. Unlike the other types of GLUT molecules, which are always present in the plasma membranes at the sites where they perform their functions, GLUT-4 is not present in the plasma membrane in the absence of insulin. Insulin promotes glucose uptake by transporter recruitment.

Effect of Insulin on Carbohydrate (Liver)



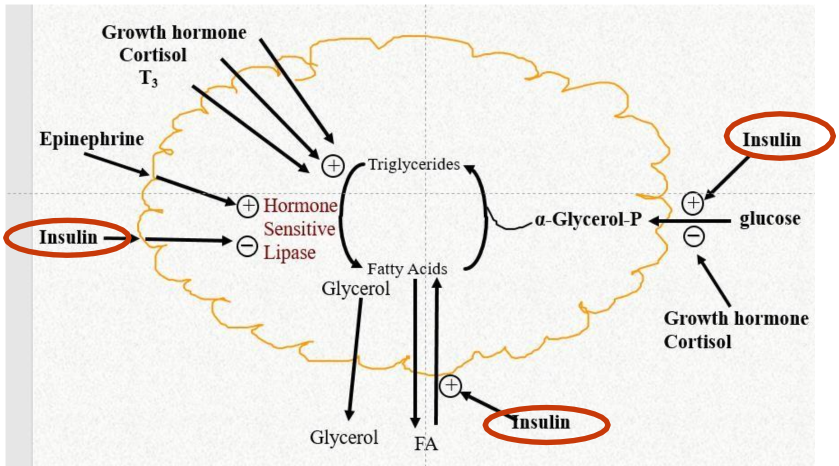
- Insulin exerts its many effects by altering either transport of specific blood-borne nutrients into cells or activity of the enzymes involved in specific metabolic pathways.

1. Insulin causes *enhanced uptake of glucose* from the blood by the liver cells. It does this by *increasing the activity of the enzyme glucokinase,* which is one of the enzymes that causes the initial phosphorylation of glucose after it diffuses into the liver cells. Once phosphorylated, the glucose is *temporarily* trapped inside the liver cells because phosphorylated glucose cannot diffuse back through the cell membrane.

4. Insulin also increases the activities of the enzymes that promote glycogen synthesis, including especially *glycogen synthase,* which is responsible for polymerization of the monosaccharide units to form the glycogen molecules.

3. Insulin *inactivates liver phosphorylase,* the principal enzyme that causes liver glycogen to split into glucose. This prevents breakdown of the glycogen that has been stored in the liver cells.

Effect of Insulin on Fat Metabolism



Actions on Fat Insulin exerts multiple effects to lower blood fatty acids and promote triglyceride storage:

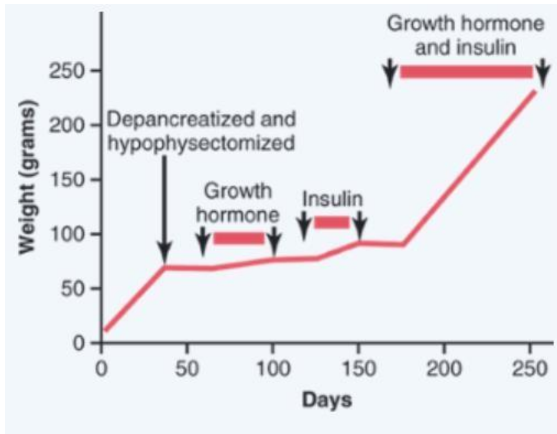
1. It enhances entry of fatty acids from the blood into adipose tissue cells.
2. It increases transport of glucose into adipose tissue cells by means of GLUT-4 recruitment. Glucose serves as a precursor for formation of fatty acids and glycerol, which are the raw materials for triglyceride synthesis.
3. It inhibits lipolysis

Effect of Insulin on Protein Metabolism and on Growth

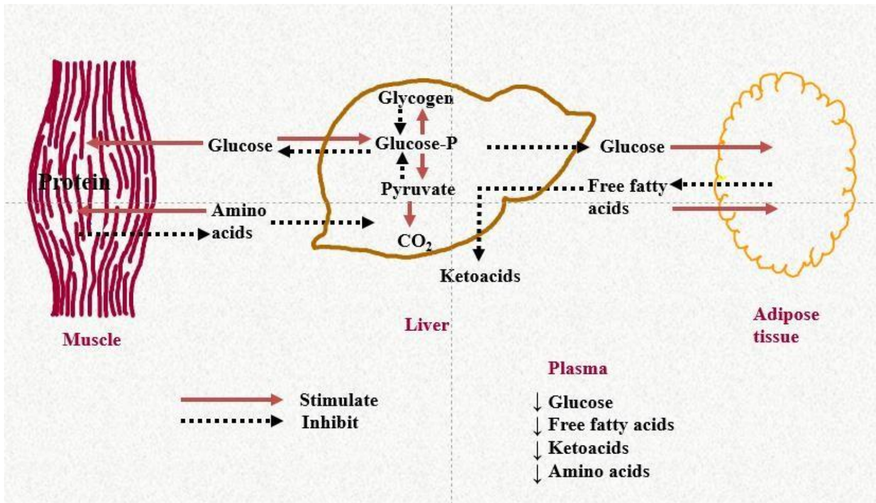
- insulin promotes protein synthesis and storage.
- 1. insulin stimulates transport of many of the amino acids into the cells.
- 2. insulin increases the translation of messenger RNA, thus forming new proteins.
- 3. insulin also increases the rate of transcription of selected DNA genetic sequences.
- 4. insulin inhibits the catabolism of proteins.
- 5. in the liver, insulin depresses the rate of gluconeogenesis

Insulin lowers blood amino acid levels and enhances protein synthesis.
The collective result of these actions is a protein anabolic effect. For this reason, insulin is essential for normal growth.

Insulin and Growth Hormone Interact Synergistically to Promote Growth

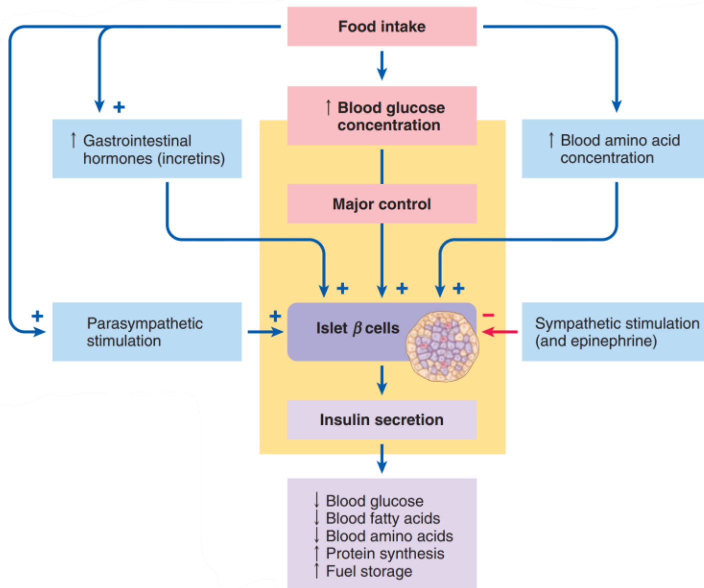


Metabolic effect of Insulin



In short, insulin primarily exerts its effects by acting on the liver, adipose tissue, and nonworking skeletal muscle. It stimulates biosynthetic pathways that lead to increased glucose use, increased carbohydrate and fat storage, and increased protein synthesis. In so doing, this hormone lowers the blood glucose, fatty acid, and amino acid levels. This metabolic pattern is characteristic of the absorptive state. Indeed, insulin secretion rises during this state and shifts metabolic pathways to net anabolism

Control of Insulin Secretion



** The primary control of insulin secretion is a direct negative feedback system between the pancreatic b cells and the concentration of glucose in the blood
** An elevated blood amino acid level, such as after a high protein meal, directly stimulates the b cells to increase insulin secretion. In negative-feedback fashion

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Glucagon

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Glucagon affects many of the same metabolic processes that insulin influences, but in most cases glucagon's actions are opposite to those of insulin. The major site of action of glucagon is the liver, where it exerts a variety of effects on carbohydrate, fat, and protein metabolism.

Glucagon Effects on carbohydrates Metabolism

(1) Enhances glycogenolysis (within minutes).

(2) Increased gluconeogenesis in the liver.

- Increase the rate of amino acid uptake by the liver.
- Activating multiple enzymes that are required for amino acid transport and gluconeogenesis (converting pyruvate to phosphoenolpyruvate, a rate-limiting step in gluconeogenesis).

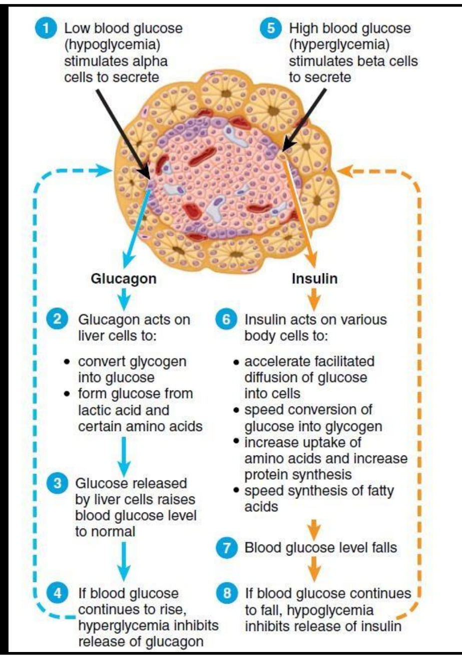
→enhance the availability of glucose to the other organs of the body.

Glucagon Effects on Fat Metabolism

- Glucagon also antagonizes the actions of insulin with regard to fat metabolism by:
- promoting lipolysis and inhibiting triglyceride synthesis, thus increasing blood levels of fatty acids

Glucagon Effects on Protein Metabolism

- Glucagon inhibits hepatic protein synthesis and promotes degradation of hepatic protein.
- Stimulation of gluconeogenesis further contributes to glucagon's catabolic effect on hepatic protein metabolism.
- Glucagon promotes protein catabolism in the liver, but it does not have any significant effect on blood amino acid levels because it does not affect muscle protein, the major protein store in the body.



The opposite effects exerted by blood concentrations of glucose and fatty acids on the pancreatic a and b cells are appropriate for regulating the circulating levels of these nutrient molecules because the actions of insulin and glucagon on carbohydrate and fat metabolism oppose one another.
** The effect of blood amino acid concentration on the secretion of these two hormones is a different story. A rise in blood amino acid concentration stimulates both insulin and glucagon secretion. Why this seeming paradox because glucagon does not exert any effect on blood amino acid concentration? The identical effect of high blood amino acid levels on both insulin and glucagon secretion makes sense if you consider the concomitant effects these two hormones have on blood glucose levels. If, during absorption of a protein-rich meal, the rise in blood amino acids stimulated only insulin secretion, hypoglycemia might result. Because little carbohydrate is available for absorption following consumption of a high-protein meal, the amino acid–induced increase in insulin secretion would drive too much glucose into the cells, causing a sudden, inappropriate drop in blood glucose. However, the simultaneous increase in glucagon secretion elicited by elevated blood amino acid levels increases hepatic glucose production. Because the hyperglycemic effects of glucagon counteract the hypoglycemic actions of insulin, the net result is maintenance of normal blood glucose levels.

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- pancreatic polypeptide. a hormone that plays a possible role in reducing appetite and food intake.