The Pancreatic Hormones and the blood Glucose regulation

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Lecture Objectives:

1. Describe plasma glucose level in well fed and poor fed state

2. Illustrate plasma pattern of glucose, Insulin and glucagon after a meal and in between meals

3. Explain principal hormones that affect blood glucose concentration in well and poor fed state

4. Explain metabolic effects of presence and absence of insulin

5. Explain the regulation of insulin secretion

6. Explain physiological effects of glucagon

7. Describe the regulation of glucagon secretion

8. Explain metabolic, short- and long-term physiological changes of high level of plasma glucose

Introduction

- 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 with their required energy.

- Therefore, it is important to maintain the blood glucose concentration at a level sufficient to provide this necessary nutrition.

- Throughout the day the human body passes into **two** distinct phases directly related to the ingestion of a meal, namely the **fed state** and the **fasted phase** (i.e. interdigestive period).

introduction (cont.)

1. The **fed state** reflects overall **anabolic metabolism.** Following a meal, in response to the increase in pancreatic insulin release, glucose uptake is increased in muscle, fat, and the hepatosplanchnic bed; hepatic glucose output is suppressed; and glycogen synthesis is increased. In other words, energy is **stored** in the form of energy-rich compounds (adenosine triphosphate [ATP], phosphocreatinine), glycogen, fat, and proteins.

2. The **fasted or catabolic phase** is the period during which endogenous energy sources are utilized. Most of the glucose formed by **gluconeogenesis** during this phase 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.

Introduction (cont.)

- The anabolic and catabolic phases alternate to preserve adequate glucose supply to the brain as well as sufficient energy to maintain body functions and basal metabolic rate.

- The total amount of energy produced per unit of time by a given individual is referred to as the metabolic rate. The basal metabolic rate (**BMR**) is the amount of energy expended by an awake, resting individual, measured 12-14 hours following the last meal.

- The 2 hormones at the core of maintaining this balance are **insulin** and **glucagon**; in particular, their ratio plays a critical role in the dynamic regulation of substrate metabolism

Regulation of metabolic processes by insulin/glucagon ratios

Anabolic ↑ I : G	Metabolic process	Catabolic ↓ I : G
↑	Glycogen synthesis (liver and muscle)	↓
↓	Glycogen breakdown	↑
↓	Gluconeogenesis	↑
↑	Triglyceride synthesis (hepatocytes and adipose tissue)	↓
↑	Muscle protein synthesis	↓
↑	Lipogenesis and triglyceride formation	↓
↓	Lipolysis	↑
↓	Free fatty acid oxidation	↑
↓	Ketone body formation	↑
↓	Muscle proteolysis	↑

G, glucagon; I, insulin.

Introduction (cont.)

- The autonomic nervous system interacts with the endocrine system in the modulation of glucose and fat metabolism. The autonomic nervous system exerts its effects both **directly** and **indirectly**.

- Activation of the sympathetic nervous system through norepinephrine release directly stimulates skeletal muscle glycogenolysis and hepatic glucose output.

- The indirect effects of the autonomic nervous system are exemplified by sympathetic activation of the **adrenal medulla**, stimulating the release of epinephrine. Epinephrine stimulates the pancreatic release of glucagon and suppresses the release of insulin, resulting in an increase in the glucagon to insulin ratio and an overall increase in hepatic glucose production

Glucose

- During fasting, hepatic glucose production is increased and peripheral glucose utilization is inhibited. Initially, hepatic glucose output is derived from breakdown of hepatic glycogen stores (a maximum of **70-100 g** in humans) through glycogenolysis.

- Following an overnight fast, **glycogenolysis** provides approximately 50% of the overall hepatic glucose output. As hepatic glycogen stores are depleted during a period of prolonged fasting (approximately 60 hours), the contribution of glycogenolysis to hepatic glucose output becomes negligible, with hepatic **gluconeogenesis** predominating.

- Glycogenolysis depends on the availability of the principal gluconeogenic precursors, lactate, glycerol, glutamine, and alanine. A smaller, yet significant amount (approximately 25%) of systemic glucose production in the postabsorptive state is derived from **renal gluconeogenesis**.

- Plasma glucose concentrations are maintained within a narrow range throughout the day, usually averaging between **70 and 100 mg/dl** after an overnight fast and before meals and never exceeding 160 mg/dl after meals. The reason for this precise regulation can be explained by the adverse effects of hypoglycemia on the brain and that of hyperglycemia on the cardiovascular system.

- Goal values for Fasting blood sugar (12 hr. fasting):
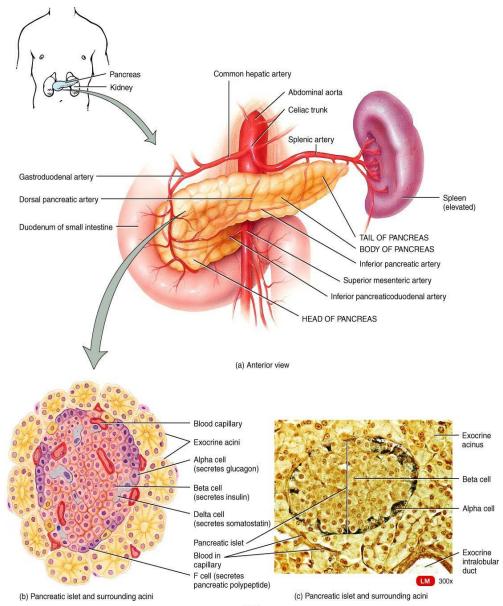
  Less than 100 mg/dl = normal

  Between 110–125 mg/dl = impaired fasting glucose (i.e., prediabetes)

  Greater than 126 mg/dl on two or more samples = diabetes

Note: 1 mmol/l of glucose = 18 mg/dl

The Pancreatic Hormones

- The pancreas is an exocrine and endocrine gland. Its endocrine portion secretes:
    1. **Insulin** (from β cells, 60% of cells of Islet of **Langerhans**)
    2. **Glucagon** (from α cells, 25% of cells of Islet of Langerhans)
    3. **Amylin** (from β cells)
    4. **Somatostatin** (from delta cells (δ), 10% of cells of Islet of Langerhans)
    5. **Pancreatic Polypeptide** (from PP or F cells, 5% of cells located in the periphery of Islet of Langerhans)

- Insulin, when secreted, inhibits its neighbor α cells from releasing glucagon. Amylin inhibits insulin secretion, somatostatin inhibits both insulin and glucagon secretion

- Insulin is a hormone that **stores** the excess energy. It is secreted in great quantities when there is great abundance of energy-giving foods in the diet. Insulin is a protein of a half-life of 6 minutes. The enzyme **insulinase** (from the liver) degrades insulin and clear it from circulation

- Pancreatic polypeptide is released into the circulation after a meal, exercise, and vagal stimulation. Inhibits gall bladder contraction and Inhibits secretion of pancreatic digestive enzymes (i.e. **pancreatic exocrine secretion**). Also it modulate gastric acid secretion, and gastrointestinal motility.

Pancreas
Kidney

Common hepatic artery

Abdominal aorta

Celiac trunk

Splenic artery

Gastroduodenal artery

Dorsal pancreatic artery

Duodenum of small intestine

Spleen (elevated)

TAIL OF PANCREAS
BODY OF PANCREAS

Inferior pancreatic artery

Superior mesenteric artery

Inferior pancreaticoduodenal artery

HEAD OF PANCREAS

(a) Anterior view

Blood capillary

Exocrine acini

Alpha cell (secretes glucagon)

Beta cell (secretes insulin)

Delta cell (secretes somatostatin)

Pancreatic islet

Blood in capillary

F cell (secretes pancreatic polypeptide)

(b) Pancreatic islet and surrounding acini

Exocrine acinus

Beta cell

Alpha cell

Exocrine intralobular duct

LM 300x

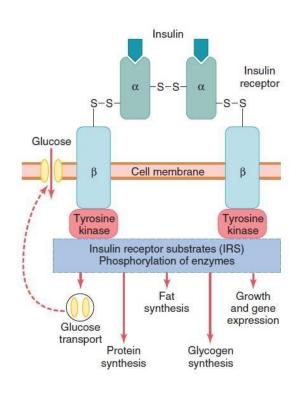(c) Pancreatic islet and surrounding acini

18.18

The Pancreatic Hormones (cont.)

- In the pancreas the islets of Langerhans represent only 1%–2% of the mass of the pancreas, however, they receive approximately 10%–15% of the pancreatic blood flow.
- Venous blood from the pancreas drains into the hepatic portal vein. Therefore, the liver, a principal target organ for the physiologic effects of pancreatic hormones, is exposed to the highest concentrations of pancreatic hormones. More than 50% of insulin is degraded during its first pass through the liver.
- Parasympathetic, sympathetic, and sensory nerves richly innervate the pancreatic islets.
- Acetylcholine, vasoactive intestinal polypeptide (VIP), pituitary adenylate cyclase-activating polypeptide, and gastrin-releasing peptide are released from the parasympathetic nerve terminals.
- Norepinephrine, galanin, and neuropeptide Y are released from sympathetic nerve terminals.
- Vagal nerve activation stimulates the secretion of insulin, glucagon, somatostatin, and pancreatic polypeptide.
- Sympathetic nerve stimulation inhibits basal and glucose-stimulated insulin secretion (through α_2-adrenergic mechanism) and somatostatin release and stimulates glucagon and pancreatic polypeptide secretion.

Insulin

Effect of Insulin on cells

1. Insulin (an anabolic polypeptide hormone with a half-life of **3-8 minutes**) increases the glucose uptake of 80% of body cells. This is especially true of **muscle** cells and **adipose** cells. Insulin is degraded predominantly by the liver, with more than 50% of insulin degraded during its first pass.

2. The insulin induced glucose uptake is not true of most <u>brain neurons, renal epithelium, intestinal epithelium, erythrocytes, and liver.</u>

3. To initiate its effects on target cells, insulin first binds with and activates a membrane receptor protein. The insulin receptor is a combination of four subunits held together by disulfide linkages: **two alpha** subunits that lie entirely outside the cell membrane and **two beta** subunits that penetrate through the membrane, protruding into the cell cytoplasm.

Effect of Insulin on cells (cont.)

4. Activated insulin receptor causes glucose transport proteins to bind with the cell membrane and thus facilitate glucose uptake into the cells.

5. When insulin is no longer available, these glucose transporters separate from the cell membrane within about **3 to 5 minutes** and move back to the cell interior to be used again and again as needed.

6. Insulin also makes cell membrane more permeable for many amino acids, K^+, and phosphate ions to move internally.

7. Insulin remolds many cellular enzymatic machinery to achieve its metabolic goals.

Note: The number of available insulin receptors is modulated by exercise, diet, insulin, and other hormones. Chronic exposure to high insulin levels, obesity, and excess growth hormone all lead to a **downregulation** of insulin receptors. In contrast, exercise and fasting **upregulate** the number of receptors, improving insulin responsiveness.
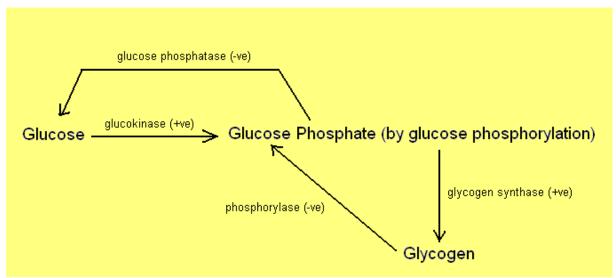
Table   Main features of glucose transporters (GLUTs)

Transporter	Expression	Function
GLUT 1	Ubiquitous, with particularly high levels in human erythrocytes and in the endothelial cells lining the blood vessels of the brain. Expressed in skeletal muscle and fat.	Glucose uptake by skeletal muscle and fat under basal conditions
GLUT 2	Low-affinity glucose transporter present in pancreatic β-cells, liver, intestine, and kidney	Functions in the glucose sensor system and ensures that glucose uptake by pancreatic β-cells and hepatocytes occurs only when circulating glucose levels are high
GLUT 3	Primarily in neurons	Together, GLUT 1 and GLUT 3 are crucial in allowing glucose to cross the blood-brain barrier and enter neurons
GLUT 4	Predominantly in striated muscle and adipose tissue. In contrast to the other GLUT isoforms, which are primarily localized on the cell membrane, GLUT 4 transporter proteins are sequestered in specialized storage vesicles that remain within the cell's interior under basal conditions.	The major insulin-responsive transporter
GLUT 5	Spermatozoa and small intestine	Predominantly a fructose transporter

In human, there are **three** classes of glucose transporters (GLUT proteins): the **facilitative glucose transporters**, the **sodium-glucose cotransporters**, and **SWEETs** or sugar efflux transporters. SWEET is a glucose uniporter. SWEET is expressed in enterocytes, hepatocytes, and β cells. One or more GLUT proteins are expressed in every cell type of the human body.

Effect of Insulin on carbohydrate metabolism

A. Insulin promotes glucose uptake by all tissues and glycogen synthesis by muscles and liver. The storage of glycogen in the liver is almost 100 g. During exercise the skeletal muscle become permeable to glucose <u>even in the absence of insulin</u>, this is because muscle contraction increases translocation of glucose transporter 4 (GLUT 4) from intracellular storage depots to the cell membrane. In addition to glucose, exercising muscles consume fatty acids as well. The effect of insulin on glucose metabolism in the liver can be summarized in this diagram:

Note: Unlike the liver, the muscle cannot convert glycogen back to glucose and release it to blood as it lacks the enzyme glucose phosphatase. Therefore, the liver is the organ that is responsible for the maintenance of stable serum glucose level (i.e. responsible for homeostasis).

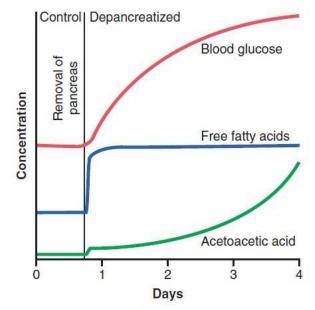# Effect of Insulin on carbohydrate *metabolism (Cont.)*

B. Insulin promotes the conversion of excess glucose into **fatty acids** by the liver, whereas gluconeogenesis is inhibited. Fatty acids are packaged as triglycerides in **very low density lipoproteins**, transported in this form to the adipose tissue, and deposited as **fat**.

C. Insulin has little effect on brain uptake or use of glucose. Brain cells are already permeable to glucose and cannot use fatty acids only with difficulty. Hypoglycemia down to 20-50 mg/dl → hypoglycemic shock (irritability, fainting, seizures, and even coma).

Effect of insulin on fat metabolism

A. Insulin promotes fat synthesis and storage in adipose tissue. This function is achieved by (1) sparing the use of fat since it increases glucose utilization and (2) converting extra glucose to acetyl-CoA then → fatty acids → triglycerides in the liver. Triglycerides will be transported by blood lipoproteins to adipose cells. It should be noted:

   1. Insulin activates capillary **lipoprotein lipase** in the adipose tissue. This enzyme converts triglycerides into fatty acids to be absorbed into the adipose cells, and then triglycerides will be reconstructed and stored inside the fat cells.

   2. Insulin inhibits the enzyme **lipase** stored in fat cells. Therefore, release of fatty acids from the adipose tissue into the circulating blood is inhibited. Insulin antagonizes catecholamine-induced lipolysis.

   3. Insulin promotes glucose transport through the cell membrane into fat cells. Some of this glucose is then used to synthesize **glycerol** that combines with fatty acids to form triglycerides, which are the storage form of fat in adipose cells.

Effect of insulin on fat metabolism (cont.)

B. Insulin deficiency causes:

1. Lipolysis of stored fat and release of free fatty acids and glycerol due to activation of lipase in fat cells. This enhancement occurs normally between meals when secretion of insulin is minimal. However, this enhancement becomes extreme and evident in diabetes and after removal of pancreas.

2. ↑ in plasma cholesterol and phospholipids concentrations due to liver conversion of some fatty acids into these products and discharging them in blood in the **lipoproteins** → severe atherosclerosis (commonly seen in diabetics)

3. Ketosis and acidosis due to formation of **acetoacetic acid** by the liver due to excess acetyl-CoA formation. Acetoacetic acid and substances that can be derived from it (hydroxyl-butyric acid and acetone) are called **Ketone bodies**. Severe acidosis can lead to coma, which may lead to death.
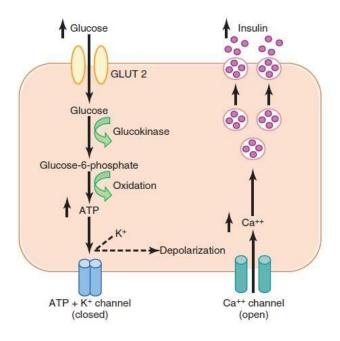

The effect of removing the pancreas on the approximate concentrations of blood glucose, plasma free fatty acids, and acetoacetic acid.

Effect of insulin on protein metabolism *and growth*

1. Insulin promotes protein synthesis and storage by increasing the cellular uptake of amino acids (i.e. like growth hormone) and turns on the **ribosomal machinery** by increasing the translation of messenger RNA.

2. Insulin inhibits protein catabolism especially in muscle cells

3. Insulin inhibits hepatic gluconeogenesis. This conserves amino acids in body protein. Therefore, insulin lack → ↑ amino acids in circulation → ↑ **urea** excretion.

4. Combination of insulin and growth hormone are essential for growth. The two hormones function **synergistically** to promote growth.

Control of insulin secretion

1. The pancreatic β-cell functions as a neuroendocrine integrator that responds to changes in plasma levels of energy substrates (**glucose and amino acids**), hormones (insulin, glucagon-like peptide I, somatostatin, and epinephrine), and neurotransmitters (norepinephrine and acetylcholine) by increasing or decreasing insulin release.

2. Glucose is the principal stimulus for insulin release from the pancreatic β-cells.

3. Glucose enters the β-cell through a membrane-bound glucose transporter 2 (GLUT 2) → ATP formation → closure of ATP-sensitive K^+ channels → depolarization of cell membrane → opening of voltage-dependent Ca^{2+} channels → exocytosis of insulin into the extracellular space.

4. **Sulfonylurea drugs** stimulate insulin secretion by binding to the ATP-sensitive K^+ channels and blocking their activity. This mechanism results in a depolarizing effect that triggers insulin secretion, making these drugs useful in stimulating insulin secretion in patients with type 2 diabetes.

Control of insulin secretion (cont.)

5. Some amino acids, such as arginine and lysine, cause a *small* rise in insulin secretion if glucose remains stable. However, secretion is enhanced with hyperglycemia even more than if glucose rises alone, i.e. amino acids potentiate the glucose stimulus for insulin secretion.

6. Gastro-intestinal hormones; such as gastrin, secretin, CCK, glucagonlike peptide-1 (GLP-1), and gastric inhibitory peptide(GIP); cause moderate secretion of insulin. GLP-1 is produced in the intestinal cells in response to a high concentration of glucose in the intestinal lumen.

7. GLP-1 and GIP, appear to be the most potent and are often called **incretins** because they enhance the rate of insulin release from the pancreatic beta cells in response to an increase in plasma glucose.

   These hormones are released in the gastrointestinal tract after a person eats a meal. They then cause an "**anticipatory increase in blood insulin** in preparation for the glucose and amino acids to be absorbed from the meal.

8. The pancreas islets are richly innervated with sympathetic and parasympathetic nerves.

   Parasympathetic nerve stimulation → ↑ insulin secretion during hyperglycemic conditions

   Sympathetic nerve stimulation → ↑ glucagon secretion and ↓ insulin secretion during hypoglycemia
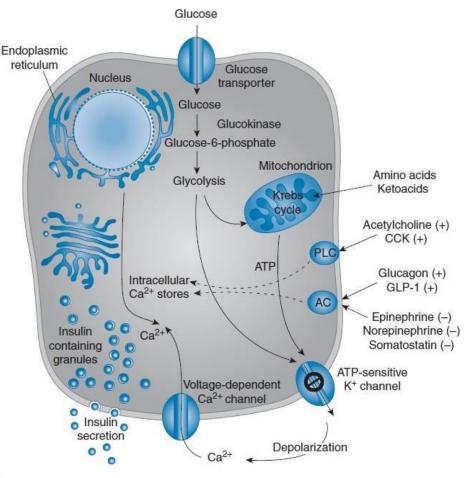
Figure Regulation of insulin release. Glucose is the principal stimulus for insulin release from the pancreatic β-cell. Glucose enters the β-cell cell by a specific glucose transporter protein (GLUT 2) undergoes glycolysis leading to generation of ATP. The increased ATP/ADP ratio leads to inhibition and closure of the ATP-sensitive K^+ channels (the target of sulfonylurea drugs), resulting in plasma membrane depolarization and opening of the voltage-dependent Ca^{2+} channels. The increased Ca^{2+} influx coupled with mobilization of Ca^{2+} from intracellular stores leading to the fusion of insulin-containing secretory granules with the plasma membrane and the release of insulin (and C-peptide) into the circulation. Addition factors can also stimulate insulin release from the β-cell, including hormones (glucagon-like peptide 1) and neurotransmitters (acetylcholine). Glucose synergizes with these mediators and enhances the secretory response of the β-cell to these factors. AC, adenylate cyclase; ADP, adenosine diphosphate; ATP, adenosine triphosphate; CCK, cholecystokinin; GLP 1, glucagon-like peptide-1; PLC, phospholipase C.

Agents that Affect Insulin Secretion

Primary Stimuli	Secondary Stimuli	Inhibitors
Physiologic		
↑ Glucose	↑ Glucagon	Somatostatin
↑ Mannose	↑ Growth hormone	Epinephrine (α_2)
↑ Leucine	↑ Secretin	Norepinephrine (α_2)
↑ Arginine	↑ Cholecystokinin	Leptin
↑ Lysine	↑ Gastrin	Starvation
↑ Short chain fatty acids	↑ Gastric inhibitory peptide	Exercise
↑ Long chain fatty acids	↑ Acetylcholine	
Acetoacetate (Ketoacid)	↑ Prostaglandin E1 and E2	
β-Hydroxybutyrate	Obesity	
Pharmacological		
N-Acetylglucosamine	Theophylline	Diazoxide
Glyceraldehyde	Caffeine	Mannoheptulose
Dihydroxyacetone	Isobutyl-methylxanthine	2-Deoxyglucose
Glucosamine	Sulfonylureas	Iodoacetate
Inosine	β-adrenergic agonists	α-adrenergic agonists

Glucagon

- Glucagon, is a 29-amino acid polypeptide hormone secreted by the α-cells of the islets of Langerhans. It is structurally related to the secretin family of peptide hormones.

- Glucagon has a short half-life (5-10 minutes) and is degraded mostly in the liver.

- The principal target tissue for glucagon is the **liver**. However, glucagon receptor is expressed in liver, pancreatic β-cells, kidney, adipose tissue, heart, and vascular tissues, as well as in some regions of the brain, stomach, and adrenal glands. The role of glucagon receptors in many tissues other than the liver is still unclear.

- In general, the function of this hormone is opposite to that of insulin; i.e. it is glycogenolytic; gluconeogenic; lipolytic; ketogenic; and stimulates secretion of GH, insulin, and pancreatic somatostatin.

Mechanism of secretion

1. Blood glucose is the principal control factor in exactly the opposite direction for the effect of glucose on insulin secretion.

    Hypoglycemia → ↑ plasma concentration of glucagon

    Hyperglycemia → ↓ plasma concentration of glucagon

2. Increased levels of amino acids, especially **alanine** and **arginine**, in blood (after protein intake mainly by mouth) → stimulation of glucagon secretion. This is a similar effect to insulin secretion. This response aids gluconeogenesis. CCK and gastrin assists further to glucagon secretion by this mechanism.

3. Exercise induces glucagon secretion. The mechanism is unknown. A beneficial effect of the glucagon secretion is that it prevents a decrease in blood glucose.

    It could be due to sympathetic stimulation of the islets of Langerhans (via β_2 receptors), while stimulation of α receptors inhibits glucagon secretion. It should be noted that sympathetic β receptors predominate in the pancreas.

4. Vagal (parasympathetic) stimulation increases glucagon release.

Factors that Regulate Glucagon Secretion

Stimuli

Hypoglycemia

Low fatty acid levels

Most amino acids

Epinephrine (β_2)

Norepinephrine (β_2)

Acetylcholine (vagus)

Dopamine

Gastrin

Cholecystokinin

Gastric inhibitory polypeptide

Vasoactive intestinal polypeptide

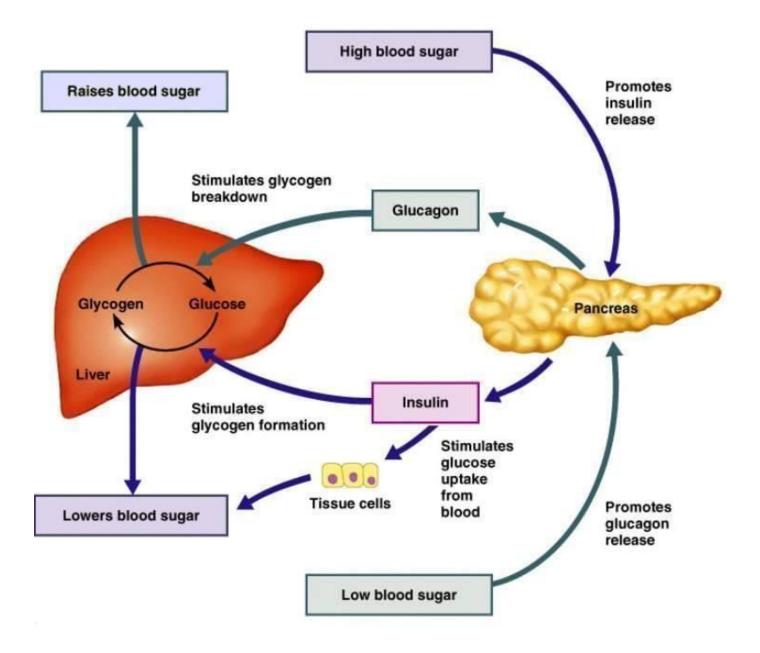Exercise

Starvation

Inhibitors

Hyperglycemia

High fatty acid levels

Ketone bobies

Secretin

Somatostatin

Serotonin

The pancreatic Somatostatin

- Pancreatic somatostatin _acts locally_ within the islets of Langerhans and inhibits glucagon and insulin secretion.

- Somatostatin release is inhibited by insulin.

- It is released in response to factors related to food ingestion:
    1. ↑ serum glucose level
    2. ↑ serum amino acids
    3. ↑ serum fatty acids
    4. ↑ level of many GI hormones

Functions of pancreatic somatostatin

1. ↓ secretion of both insulin and glucagon.
2. ↓ stomach, duodenal, and gallbladder contractions.
3. ↓ secretion and absorption in the GIT.

   These effects will extend the period over which the food nutrients are assimilated into the blood and prevent the rapid exhaustion of the food by insulin and glucagon.

4. ↓ the tone of mesenteric arteries and portal-systemic collateral veins (the mechanism is unknown). Therefore, somatostatin analogues are used in the treatment of portal hypertension.
5. Somatostatin is used in the clinical setting for the management of insulin or glucagon producing tumors.
6. It *may* have a protective role against liver fibrosis.

Test Question:

Q. Insulin regulates glucose transport into muscle and fat cells via which glucose transporter?

   A. GLUT-1.

   B. GLUT-2.

   C. GLUT-3.

   D. GLUT-4.

   E. GLUT-5.