HORMONES OF THE ISLETS OF LANGERHANS

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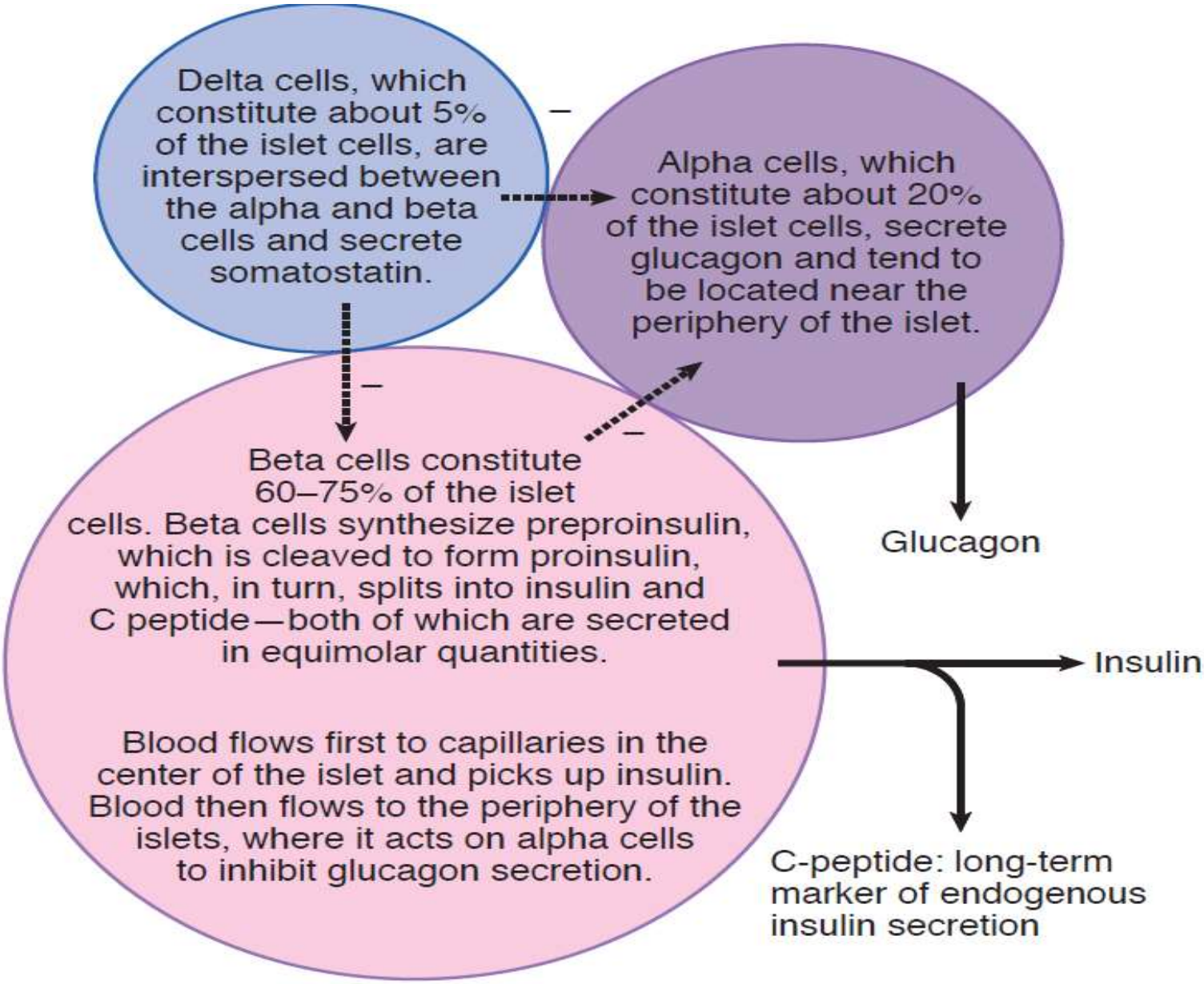
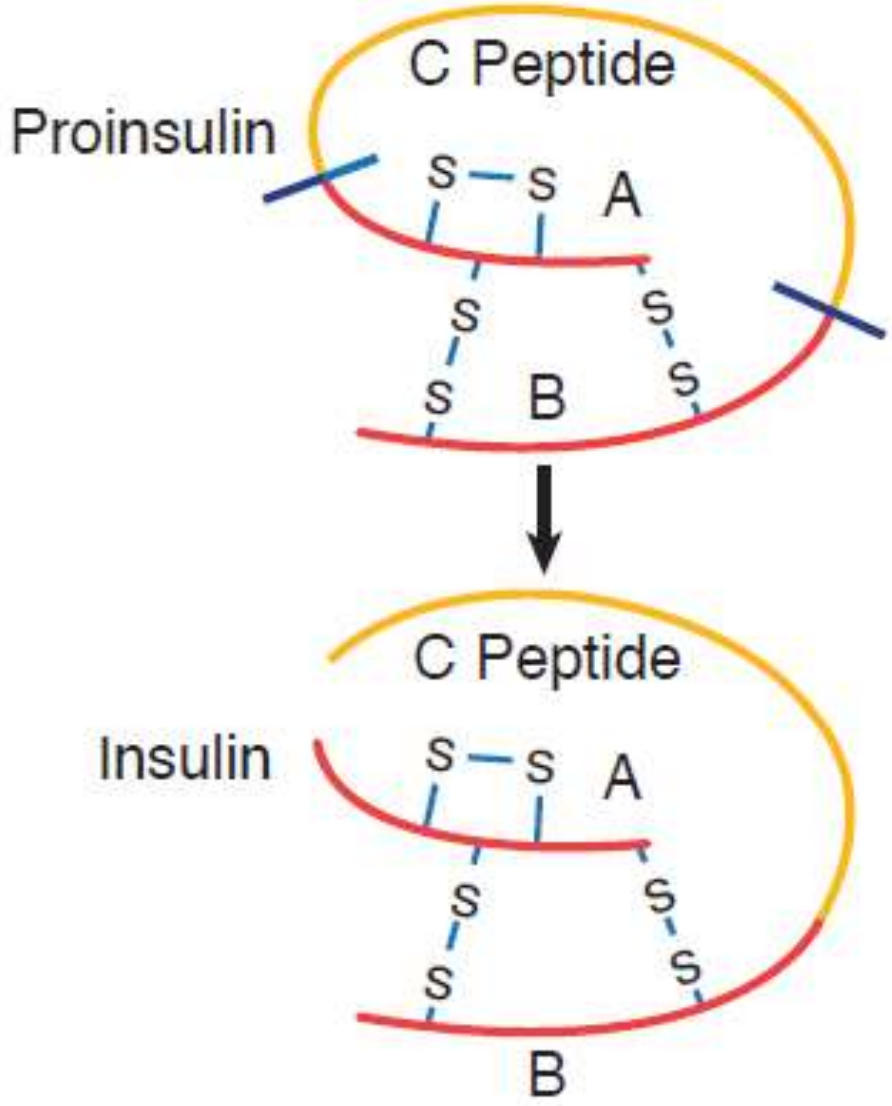
- The location and proportion of each major hormone-secreting cell type of the islets of Langerhans are shown in Figure -1.
- The local inhibitory paracrine action of each islet hormone is shown by dashed arrows. The diameter of each circle
- approximately represents the proportion of that cell type present in the islets.


Delta cells, which constitute about 5% of the islet cells, are interspersed between the alpha and beta cells and secrete somatostatin.
Alpha cells, which constitute about 20% of the islet cells, secrete glucagon and tend to be located near the periphery of the islet.
Beta cells constitute 60–75% of the islet cells. Beta cells synthesize preproinsulin, which is cleaved to form proinsulin, which, in turn, splits into insulin and C peptide—both of which are secreted in equimolar quantities.
Blood flows first to capillaries in the center of the islet and picks up insulin. Blood then flows to the periphery of the islets, where it acts on alpha cells to inhibit glucagon secretion.
Glucagon
Insulin
C-peptide: long-term marker of endogenous insulin secretion

- C-peptide was considered to have no biological function, but more recently Studies suggest that
- C-peptide receptors exist on cells,
- C-peptide may serve a protective role, helping to prevent the renal, neural, and microvascular pathologies seen when it is absent, i.e., type I diabetes mellitus.


Proinsulin
C Peptide
S
S
A
S
S
S
S
B
Insulin
C Peptide
S
S
A
S
S
S
S
B

Insulin Receptor

- The portion of the insulin receptor that faces externally has the hormone-binding domain.
- The portion of the insulin receptor that faces the cytosol has tyrosine kinase activity.
- When occupied by insulin, the receptor phosphorylates itself and other proteins.

Peripheral Uptake of Glucose

- Glucose is taken up by peripheral tissues by facilitated diffusion. Insulin facilitates this uptake in some tissues.
- insulin increases glucose transporters in the cell membranes of
  - Adipose tissue
  - Resting skeletal muscle (working muscle without the aid of insulin)
  - Liver because of glucokinase stimulation

Insulin independed tissues

- Tissues in which glucose uptake is not affected by insulin are:
- Nervous tissue
- Kidney tubules
- Intestinal mucosa
- Red blood cells
- β-cells of pancreas

Metabolic Actions of Insulin

- Insulin is a major anabolic hormone, and it secreted in response to a carbohydrate- and/or protein-containing meal.
- Anabolic hormones tend to promote protein synthesis (increase lean body mass).
- Other anabolic hormones include:
- Thyroid hormones
- Growth hormone/IGF I
- l Sex steroids (androgens)

Effects of insulin on carbohydrate metabolism

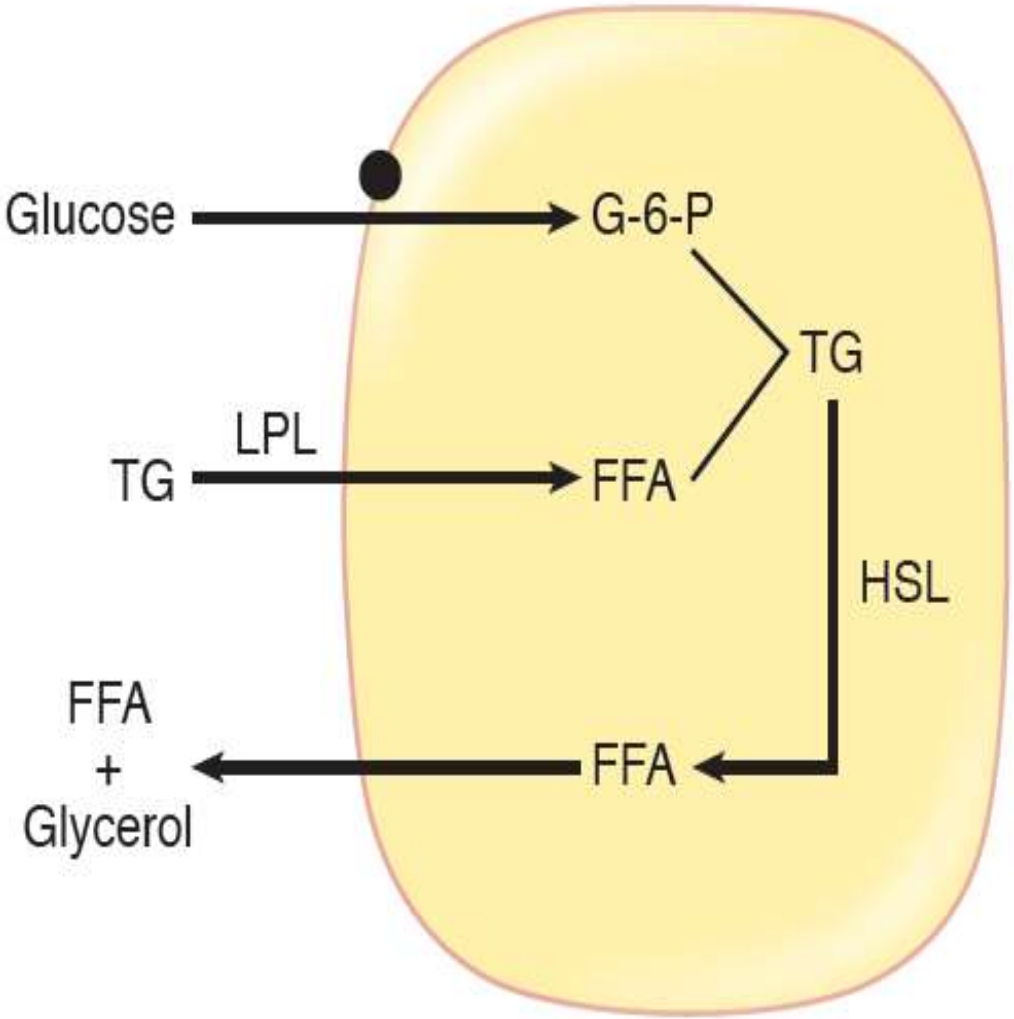
- Insulin increases the uptake of glucose and its metabolism in muscle and fat. By increasing glucose uptake in muscle, its metabolism increases, i.e., its conversion to carbon dioxide and water is increased.
- Insulin increases glycogen synthesis in liver and muscle. The activity of enzymes that promote glycogen synthesis (glucokinase and glycogen synthetase) is increased.
- The activity of those enzymes that promote glycogen breakdown (phosphorylase and glucose-6-phosphatase) is decreased.
- Glucokinase and glucose-6-phosphatase are expressed by the liver but not by muscle

Effects of insulin on protein metabolism

- Insulin increases amino acid uptake by muscle cells.
- Insulin increases protein synthesis.
- Insulin decreases protein breakdown (deficiency of insulin results in a breakdown of protein).

Effects of insulin on fat metabolism

- insulin stimulates the conversion of carbohydrate into fat by Insulin increasing:-
- Glucose uptake by fat cells (increases membrane transporters). By increasing glucose uptake, insulin also makes triose phosphates available for triglyceride synthesis in adipose tissue.
- Triglyceride uptake by fat cells. It increases the activity of lipoprotein lipase. Lipoprotein lipase is located on the endothelium of capillaries, and it catalyzes the release of free fatty acids from triglycerides.
- Triglyceride synthesis (lipogenesis) in adipose tissue and liver by stimulating the rate-limiting step, namely the carboxylation of acetyl CoA to malonyl CoA.


Glucose
G-6-P
TG
LPL
TG
FFA
HSL
FFA
+
Glycerol
FFA

Effects of insulin on fat metabolism

- Insulin decreases:
- Triglyceride breakdown (lipolysis) in adipose tissue by decreasing the activity of hormone-sensitive lipase HSL.
- HSL is activated by stress hormones (i.e., cortisol, growth hormone, epinephrine [glucagon]).
- Formation of ketone bodies by the liver.

Insulin Effects on Potassium

- Insulin promotes K+ movement into cells. By increasing the activity of Na/K-ATPase in most body tissues.
- This K+-lowering action of insulin is used to treat acute, life-threatening hyperkalemia. For example, sometimes the hyperkalemia of renal failure is successfully lowered by the simultaneous administration of insulin and glucose.

CONTROL OF INSULIN SECRETION

- plasma glucose. Above a threshold of 100 mg%, insulin secretion is directly proportional to plasma glucose.
- Glucose enters the cell, causing a rise in intracellular ATP, which then secrete insulin and C-peptide into the blood through rising intracellular Ca.

ACTIONS OF GLUCAGON

- Glucagon is a peptide hormone. It is secreted by the α-cells of the pancreatic islets.
- The primary target for glucagon action is the liver hepatocyte, where its action is mediated by an increase in the concentration of cAMP.
- The cAMP activates protein kinase A, which, by catalyzing phosphorylation, alters the activity of enzymes.

Specific Actions of Glucagon on the Liver

1. Increases liver glycogenolysis.
2. Increases liver gluconeogenesis.

Glucagon inhibits phosphofructokinase-2 (PFK-2), thereby reducing 2,6 bisphosphate, which in turn inhibits PFK-1 (an important enzyme driving glycolysis). Inhibition of PFK-1 aids gluconeogenesis.

glucagon, along with cortisol, enhances phosphoenolpyruvate carboxykinase, a key enzyme in the gluconeogenic pathway. Finally, glucagon stimulates glucose-6-phosphatase, thereby releasing glucose into the blood

3. Increases liver ketogenesis and decreases lipogenesis.

   Glucagon inhibits the activity of acetyl CoA carboxylase, decreasing the formation of malonyl CoA. When the concentration of malonyl CoA is low, ketogenesis is favored over lipogenesis.

4. Increases ureagenesis.

   It stimulates N-acetylglutamate synthesis, which stimulates the production of urea

5. Increases insulin secretion.
   - The amino acid sequence of glucagon is similar to that of the duodenal hormone, secretin. Like secretin (and most other gut hormones), glucagon stimulates insulin secretion.
6. Increases lipolysis in the liver.
   - Glucagon activates hormone-sensitive lipase in the liver, but because the action is on the liver and not the adipocyte, glucagon is not considered a major fat-mobilizing hormone.

Insulin : Glucagon Ratio

- Insulin and glucagon: move substrates in opposite directions. The direction of substrate fluxes is very sensitive to this ratio.
- Normal postabsorptive ratio: 2.0
- States requiring mobilization of substrates ratio: 0.5 or less
- Carbohydrate meal, ratio 10 or more
- Protein meal or fat meal produces little change in the ratio.

Insulinomas

- Most common islet cell tumor
- Found almost exclusively within the pancreas and hypersecrete insulin
- Most common symptoms due to the hypoglycemia (confusion, disorientation, headache)
- Association with MEN 1
- Insulin measured to determine insulin-mediated versus noninsulin mediated hypoglycemia
- Insulin-secreting tumor: insulin and C-peptide both elevated
- Factitious hypoglycemia: C-peptide below normal
- Treat with removal

Glucagonoma

- Alpha cell over secretion
- Hyperglycemia/diabetes
- Localize with CT scan
- Surgically remove

Leptin

- Leptin is produced in adipose tissue and is thought to be a “long-term” regulator of appetite and energy balance.
- Secretion is circadian, with the highest levels occurring at night and the nadir in the morning. Individual meals do not stimulate the release of leptin.
- Leptin decreases hypothalamic neuropeptide Y (NPY), which is a potent activator of feeding (orexigenic). By inhibiting NPY synthesis, leptin promotes satiety (anorexigenic).
- Leptin increases energy expenditure, in part by increasing fatty acid oxidation, and it decreases fat stores. Lack of and/or resistance to leptin causes obesity.

Adiponectin

- Adiponectin is produced in adipose tissue, and it increases insulin sensitivity and tissue fat oxidation.
- Dysregulation of adiponectin, may play a role in obesity, insulin resistance
- Plasma levels of adiponectin are low in Type II diabetics, and infusion of this hormone decreases plasma glucose in experimental animal models of diabetes mellitus.

Ghrelin

- Ghrelin is produced by cells of the stomach.
- Circulating levels of ghrelin are reduced in response to a meal and highest in the fasting state.
- Ghrelin activates hypothalamic NYP neurons and is thus a potent orexigenic hormone. It also stimulates the release of growth hormone (GH)
- Ghrelin levels are decreased in obese individuals and elevated by low calorie diets, strenuous exercise, and patients.
- Ghrelin is a peptide hormone that works via Gq and Gs. Its mechanism of action