Endocrine Functions of the Pancreas & Regulation of Carbohydrate Metabolism

CHAPTER 24

Second Part

OBJECTIVES

After reading this chapter, you should be able to:

- List the hormones that affect the plasma glucose concentration and briefly describe the action of each.
- Describe the structure of the pancreatic islets and name the hormones secreted by each of the cell types in the islets.
- Describe the structure of insulin and outline the steps involved in its biosynthesis and release into the bloodstream.
- List the consequences of insulin deficiency and explain how each of these abnormalities is produced.
- Describe insulin receptors, the way they mediate the effects of insulin, and the way they are regulated.
- Describe the types of glucose transporters found in the body and the function of each.
- List the major factors that affect the secretion of insulin.
- Describe the structure of glucagon and other physiologically active peptides produced from its precursor.
- List the physiologically significant effects of glucagon and the factors that regulate glucagon secretion.
- Describe the physiologic effects of somatostatin in the pancreas.
- Outline the mechanisms by which thyroid hormones, adrenal glucocorticoids, catecholamines, and growth hormone affect carbohydrate metabolism.
- Understand the major differences between type 1 and type 2 diabetes.

Endocrine Functions of the Pancreas & Regulation of Carbohydrate Metabolism	• structure, biosynthesis, & secretion of insulin • fate of secreted insulin • mechanism of action • consequences of insulin deficiency • regulation of insulin secretion • glucagon • other islet cell hormones • hypoglycemia & diabetes mellitus in humans

Role of glucose in insulin secretion:

1. **Glucose** act **directly** on B cells to **increase** insulin **secretion**
2. **Produce biphasic response:**

A- Rapid, short-lived increase in secretion THEN

B- Slow, long-lived (prolonged) increase in secretion

Mechanism of glucose-induced insulin secretion

A: The initial spike of insulin secretion: **Glucose inhibit ATP-sensitive K+ channels**

Explanation - Steps

1. **First** glucose enter B cells vial GLUT2
2. **THEN phosphorylated** by glucokinase and cleave to 2 **pyruvate**
3. **THEN** The pyruvate enter and **metabolize** in the mitochondria ("Citric acid cycle", "Krebs cycle", "tricarboxylic acid cycle") to CO2 and water (**oxidative pathway**) and **ATP** is formed (**phosphorylation pathway**)
4. **THEN** ATP enter the cytoplasm and **inhibits ATP-sensitive K+** channels (**reducing K efflux**) and **depolarizes the B cell**
5. **THEN** **Ca^{+2}** enter the B cell via **voltage gated** Ca^{+2} channels and causes **exocytosis** of already store insulin in secretory granules

B: The prolonged second phase of insulin secretion: **Glucose increase intracellular glutamate**

Explanation: Glutamate **committee** the **second pool** of secretory granules to the **releasable form**

- Glucose produce **+ve feedback** on insulin synthesis (stabilize insulin mRNA) and secretion to produce inulin levels parallel that of glucose

EFFECTS OF THE PLASMA GLUCOSE LEVEL

glucose acts directly on pancreatic B cells to increase insulin secretion. The response to glucose is biphasic; there is a rapid but short-lived increase in secretion followed by a more slowly developing prolonged increase.

Glucose enters the B cells via GLUT-2 transporters and is phosphorylated by glucokinase then metabolized to pyruvate in the cytoplasm (Figure). The pyruvate enters the mitochondria and is metabolized to CO_2 and H_2O via the citric acid cycle with the formation of ATP by oxidative phosphorylation. The ATP enters the cytoplasm, where it inhibits ATP-sensitive K^+ channels, reducing K^+ efflux. This depolarizes the B cell, and Ca^{2+} enters the cell via voltage-gated Ca^{2+} channels. The Ca^{2+} influx causes exocytosis of a readily releasable pool of insulin-containing secretory granules, producing the initial spike of insulin secretion.

Metabolism of pyruvate via the citric acid cycle also causes an increase in intracellular glutamate. The glutamate appears to act on a second pool of secretory granules, committing them to the releasable form release of these granules then produces the prolonged second phase of the insulin response to glucose.

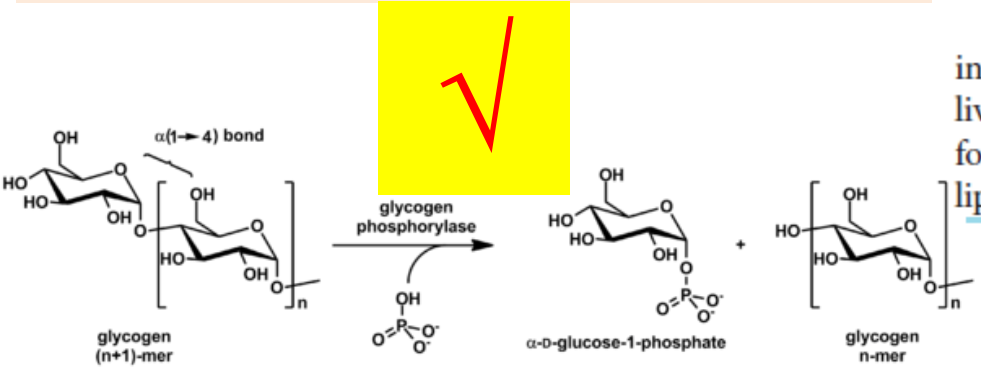
The feedback control of plasma glucose on insulin secretion normally operates with great precision so that plasma glucose and insulin levels parallel each other with remarkable consistency.

Structure: linear polypeptide
Gland: A cells of pancreatic islets of Langerhans and by **upper GIT cells**
Receptors: GPCR
Actions:

1. **Glycogenolysis** (see mechanism below)
2. **Gluconeogenesis** (in liver, this elevate the metabolic rate)
3. **Lipolysis** (stimulate the **hormone-sensitive lipase** in adipose tissue)
4. **Ketogenesis** (from **lipolysis** and by **decreasing malnoyl-CoA** levels in liver)

Mechanism of action of glycogenolysis in liver "**BUT** not in skeletal muscles in which epinephrine is the stimulus for glycogenolysis":

1. Activation of GPCR increase **cAMP** that activate PKA and subsequent **activation** of **phosphorylase** that breakdown glycogen
2. Action on different glucagon receptors in the same hepatocytes activates **PLC-IP3** system with subsequent increase in cytoplasmic **Ca^{+2}** that also stimulate glycogen breakdown



GLUCAGON

CHEMISTRY

Human glucagon, a linear polypeptide produced by the A cells of the pancreatic islets and the upper gastrointestinal tract.

ACTION

Glucagon is glycogenolytic, gluconeogenic, lipolytic, and ketogenic. It acts on G protein–coupled receptors

In the liver, it acts via G_s to activate adenylyl cyclase and increase intracellular cAMP. This leads via protein kinase A to activation of phosphorylase and therefore to increased breakdown of glycogen and an increase in plasma glucose. However, glucagon acts on different glucagon receptors located on the same hepatic cells to activate phospholipase C, and the resulting increase in cytoplasmic Ca^{2+} also stimulates glycogenolysis.

Glucagon does not cause glycogenolysis in muscle. It increases gluconeogenesis from available amino acids in the liver and elevates the metabolic rate. It increases ketone body formation by decreasing malonyl-CoA levels in the liver. Its lipolytic activity, leads in turn to increased ketogenesis.

Conditions cause glucagon secretion:

1. **Hypoglycemia**: **increase**
2. **Hyperglycemia**: **decrease** (GABA is released from B cells "coincide with insulin secretion". GABA act on A cells to inhibit glucagon secretion)
3. **Sympathetic stimulation**: **increase** (via B-adrenergic receptors and cAMP)
4. **Protein meal** or **amino acid infusion**: **increase**
5. **CCK** and **Gastrin** (both increased by protein meal): **increase**
6. **Secretin**: **decrease**
7. **Somatostatin**: **decrease**

TABLE Factors affecting glucagon secretion

Stimulators	Inhibitors
Amino acids (particularly the glucogenic amino acids: alanine, serine, glycine, cysteine, and threonine)	Glucose
CCK, gastrin	Somatostatin
Cortisol	Secretin
Exercise	FFA
Infections	Ketones
Other stresses	Insulin
β-Adrenergic stimulators	Phenytoin
Theophylline	α-Adrenergic stimulators
Acetylcholine	GABA

REGULATION OF SECRETION

The principal factors known to affect glucagon secretion are summarized in Table .

Secretion is increased by hypoglycemia and decreased by a rise in plasma glucose. Pancreatic B cells contain GABA, and evidence suggests that coincident with the increased insulin secretion produced by hyperglycemia, GABA is released and acts on the A cells to inhibit glucagon secretion by activating $GABA_A$ receptors. The $GABA_A$ receptors are Cl^- channels, and the resulting Cl^- influx hyperpolarizes the A cells.

Secretion is also increased by stimulation of the sympathetic nerves to the pancreas, and this sympathetic effect is mediated via β-adrenergic receptors and cAMP.

A protein meal and infusion of various amino acids increase glucagon secretion.

CCK and gastrin increase glucagon secretion, whereas secretin inhibits it. Because CCK and gastrin secretion are both increased by a protein meal, either hormone could be the gastrointestinal mediator of the glucagon response. The inhibition produced by somatostatin is discussed below.

MCQ: Glucose act directly on pancreatic B cells to increase insulin secretion. Which of the followings is not involved in the mechanism of glucose-induced insulin secretion?

A. Glucokinase-induced phosphorylation of glucose
B. Inhibition of ATP-sensitive K^+ channels
C. **Hyperpolarization of B cells**
D. Increase in intracellular glutamate
E. Prolonging the life span of insulin mRNA

MCQ: A meal rich in proteins containing the amino acids that stimulate insulin secretion but low in carbohydrates does not cause hypoglycemia because

A. The meal causes a compensatory increase in T4 secretion
B. Cortisol in the circulation prevents glucose from entering muscle
C. Glucagon secretion is also stimulated by the meal
D. The amino acids in the meal are promptly converted to glucose
E. Insulin does not bind to insulin receptors if the plasma concentration of amino acids is elevated

MCQ: Many hormones affect carbohydrates, proteins and lipids metabolism. Which of the following is incorrectly paired?

A. Epinephrine: increased glycogenolysis in skeletal muscle
B. Insulin: increased protein synthesis
C. Glucagon: increased gluconeogenesis
D. Progesterone: increased plasma glucose level
E. Growth hormone: increased plasma glucose level

MCQ: Human glucagon is a linear polypeptide. Which of the followings is not related to glucagon?

A. It induces glycogenolysis
B. It induces glycogenesis
C. t induces gluconeogenesis
D. It induces lipolysis
E. It induces ketogenesis

MCQ: A rat has been injected with a drug that kill all of its pancreatic B cells. Which of the following would be least likely to be seen 14 days after injection of this drug?

A. A rise in the plasma H^+ concentration
B. A rise in the plasma glucagon concentration
C. A fall in the plasma HCO_3^- concentration
D. A fall in the plasma amino acid concentration
E. A rise in plasma osmolality

MCQ: Many factors are known to affect glucagon secretion. Which of the followings does not enhance glucagon secretion?

A. Acetylcholine
B. Epinephrine
C. Cortisol
D. Gastrin
E. Secretin

√

Types of somatostatin:
1. **Somatostatin 14 (SS 14):** Less active
2. **Somatostatin 28 (SS 28):** More active

Gland: D cells of pancreatic islets of Langerhans
Action: both somatostatins **inhibit insulin**, **glucagon** and **pancreatic polypeptide** secretion
Stimulus for secretion:
1. Insulinogogues agents: **glucose**, **arginine** and **leucine**)
2. **CCK**

Structure linear polypeptide closely related to the GI polypeptide YY and the neuropeptide Y in brain and autonomic nervous system
Gland: F cells of pancreatic islets of Langerhans
Function: **Slows** the **absorption** of food in humans to **smooth out** the **peaks** and **valleys** of **absorption**
Stimulus for secretion:
1. **Protein** meal
2. **Fasting**
3. **Exercise**
4. Acute **hypoglycemia**

Inhibitor for secretion
1. **Somatostatin**
2. i.v. glucose (acute **hyperglycemia**)

OTHER ISLET CELL HORMONES

SOMATOSTATIN

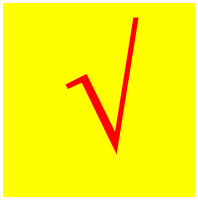
Somatostatin 14 (SS 14) and its amino terminal-extended form somatostatin 28 (SS 28) are found in the D cells of pancreatic islets. Both forms inhibit the secretion of insulin, glucagon, and pancreatic polypeptide and act locally within the pancreatic islets in a paracrine fashion. SS 28 is more active than SS 14 in inhibiting insulin secretion,

The secretion of pancreatic somatostatin is increased by several of the same stimuli that increase insulin secretion, that is, glucose and amino acids, particularly arginine and leucine. It is also increased by CCK.

PANCREATIC POLYPEPTIDE

Human pancreatic polypeptide is a linear polypeptide that is produced by F cells in the islets. It is closely related to two other polypeptides, **polypeptide YY**, a gastrointestinal peptide , and **neuropeptide Y**, which is found in the brain and the autonomic nervous system.

Its secretion is increased by a meal containing protein and by fasting, exercise, and acute hypoglycemia. Secretion is decreased by somatostatin and intravenous glucose. Pancreatic polypeptide slows the absorption of food in humans, and it may smooth out the peaks and valleys of absorption.



Hypoglycemia : is a common insulin reaction in type 1 DM

Chronic mild hypoglycemia: cause incoordination and slurred speech (mistaken for drunkenness)

In individuals in whom **diabetes develop later**, **functional hypoglycemia** is tested by giving a test dose of glucose. The plasma glucose rise normally but later on falls overshoot to hypoglycemic levels (<50mg/dL)

Sever acute hypoglycemia is **fatal**

HYPOGLYCEMIA & DIABETES MELLITUS IN HUMANS

HYPOGLYCEMIA

"Insulin reactions" are common in type 1 diabetics and occasional hypoglycemic episodes are the price of good diabetic control in most diabetics.

Chronic mild hypoglycemia can cause incoordination and slurred speech, and the condition can be mistaken for drunkenness.

In **functional hypoglycemia,** the plasma glucose rise is normal after a test dose of glucose, but the subsequent fall overshoots to hypoglycemic levels, producing symptoms 3–4 h after meals. This pattern is sometimes seen in individuals in whom diabetes develops later.

DIABETES MELLITUS

The constellation of abnormalities caused by insulin deficiency is called diabetes mellitus.

Diabetes is characterized by polyuria (passage of large volumes of urine), polydipsia (excessive drinking), weight loss in spite of polyphagia (increased appetite), hyperglycemia, glycosuria, ketosis, acidosis, and coma.

The fundamental defects to which most of the abnormalities can be traced are:

(1) reduced entry of glucose into various "peripheral" tissues and

(2) increased liberation of glucose into the circulation from the liver. Therefore, there is an extracellular glucose excess and, in many cells, an intracellular glucose deficiency—a situation that has been called "starvation in the midst of plenty.".

Types of DM:

1. Insulin deficiency due to destruction of B cells (**type 1, IDDM**)
2. Decrease in peripheral action of insulin (**type 2, NIDDM**)

Signs and symptoms:

1. Polyuria (due to osmotic diuresis)
2. Polydipsia (due to dehydration)
3. Polyphagia
4. Hyperglycemia
5. Glycosuria
6. Ketoacidosis
7. Coma

These abnormalities are due to

A: Reduced glucose entry into cells (**cell starvation**)

B: **Gluconeogenesis**

CLINICAL BOX 24–1

Diabetes Mellitus

The constellation of abnormalities caused by insulin deficiency is called **diabetes mellitus.** Greek and Roman physicians used the term "diabetes" to refer to conditions in which the cardinal finding was a large urine volume, and two types were distinguished: "diabetes mellitus," in which the urine tasted sweet; and "diabetes insipidus," in which the urine had little taste. Today, the term "diabetes insipidus" is reserved for conditions in which there is a deficiency of the production or action of vasopressin (see Chapter 38), and the unmodified word "diabetes" is generally used as a synonym for diabetes mellitus.

The cause of clinical diabetes is always a deficiency of the effects of insulin at the tissue level. **Type 1 diabetes,** or **insulin-dependent diabetes mellitus (IDDM),** is due to insulin deficiency caused by autoimmune destruction of the B cells in the pancreatic islets, and it accounts for 3–5% of cases and usually presents in children. **Type 2 diabetes, or non–insulin-dependent diabetes mellitus (NIDDM),** is characterized by the dysregulation of insulin release from the B cells, along with insulin resistance in peripheral tissues such as skeletal muscle, brain, and liver. Type 2 diabetes historically presented in overweight or obese adults, although it is increasingly being diagnosed in children as childhood obesity increases.

THERAPEUTIC HIGHLIGHTS

In type 1 diabetes, the mainstay of therapy is provision of exogenous insulin, carefully titrated to dietary intake of glucose. In type 2 diabetes, lifestyle changes such as alterations in the diet or increased exercise can often delay symptoms in early disease, but these are difficult to secure. Insulin-sensitizing drugs represent second-line agents (see Chapter 16).

Microvascular abnormalities:
Diabetic retinopathy: proliferative scarring of retina
Diabetic nephropathy: glomerulosclerosis (glycation of matrix proteins) leading to chronic kidney diseases

Macrovascular abnormalities:
Cause by accelerated atherosclerosis secondary to increase plasma LDL-cholesterol (this increase the risk of stroke and MI)

Neuropathic abnormalities:
Diabetic neuropathy: decrease in functions of autonomic and peripheral nerves

Diabetes is sometimes complicated by acidosis and coma, and in long-standing diabetes, additional complications occur. These include microvascular, macrovascular, and neuropathic disease.

The microvascular abnormalities are proliferative scarring of the retina (**diabetic retinopathy**) leading to blindness and renal disease (**diabetic nephropathy**) leading to chronic kidney disease.

The macrovascular abnormalities are due to accelerated atherosclerosis, which is secondary to increased plasma LDL. The result is an increased incidence of stroke and myocardial infarction.

The neuropathic abnormalities (**diabetic neuropathy**) involve the autonomic nervous system and peripheral nerves.

The neuropathy plus the atherosclerotic circulatory insufficiency in the extremities and reduced resistance to infection can lead to chronic ulceration and gangrene, particularly in the feet.

In addition, intracellular glucose can be converted to so-called Amadori products, and these in turn can form **advanced glycosylation end products** (AGEs), which cross-link matrix proteins. This damages blood vessels. The AGEs also interfere with leukocyte responses to infection.

As body weight increase:
Insulin resistance increases and accompany by:

1. **Decrease movement of insulin into fat and muscle**
2. **Inability to inhibit gluconeogesis**

Weight reduction: will decreases insulin resistance

Insulin resistance (Metabolic syndrome) **characterized by**:

1. **Obesity** (increased body weight)
2. **Hyperinsulinemia**
3. **Dyslipidemia** (low HDL)
4. Accelerated **atherosclerosis**

OBESITY, THE METABOLIC SYNDROME, & TYPE 2 DIABETES

Obesity is increasing in incidence, and relates to the regulation of food intake and energy balance and overall nutrition. As body weight increases, insulin resistance increases, that is, there is a decreased ability of insulin to move glucose into fat and muscle and to shut off glucose release from the liver. Weight reduction decreases insulin resistance. Associated with obesity there is hyperinsulinemia, dyslipidemia (characterized by high circulating triglycerides and low high-density lipoprotein [HDL]), and accelerated development of atherosclerosis. This combination of findings is commonly called the **metabolic syndrome** .

MCQ: Somatostatin is a polypeptide secreted by pancreas and other tissues. Which of the followings is not correct about pancreatic somatostatin?

A. It is secreted from D cells of islets of Langerhans
B. The SS28 isoform is the most active form
C. Mainly it is a stimulatory hormone
D. Its secretion is induced by glucose and arginine
E. Its secretion is enhanced by cholecystokinin

MCQ: Pancreatic polypeptide is a linear polypeptide hormone secreted by F cells of islets of Langerhans. Which of the followings is not correct about pancreatic polypeptide?

A. It is closely related to YY polypeptide
B. It is closely related to Y polypeptide
C. It function mainly to smooth out the fluctuations in food absorption
D. Its secretion is inhibited by somatotropin
E. Its secretion is induced by protein meal, fasting and hypoglycemia

MCQ: The constellation of abnormalities caused by insulin deficiency is called diabetes mellitus (DM). Which of the followings is not correct about DM?

A. The fundamental defects in type 1 DM are related to cell starvation
B. Type 2 DM is related to decrease sensitivity of insulin receptors to insulin
C. The mainstay of therapy in type 1 DM is provision of exogenous insulin
D. Diabetic ketoacidosis is more common in typ2 DM
E. Hypoglycemic coma is more common in type 1 DM

MCQ: The cause of clinical diabetes is always a deficiency of the effects of insulin at tissue level. Which of the followings is incorrect about type 2 DM?

A. It is characterized by autoimmune destruction of B cells
B. It is accompany by insulin resistance in peripheral tissues
C. It is presented in overweight or obese adults and children
D. It is managed by changing lifestyle and or insulin-sensitizing drugs
E. None of the above is incorrect

MCQ: Insulin resistance also called metabolic syndrome is characterized by the followings EXCEPT:

A. Increase in body weight
B. Hyperinsulinemia
C. Hyperglucagonemia
D. Dyslipidemia (low HDL)
E. Accelerated atherosclerosis