Endocrine Functions of Pancreas **O B J E C T I V E S**

*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.

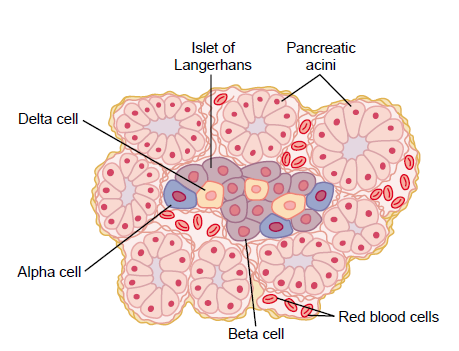
Describe the physiologic effects of somatostatin in the pancreas.

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.

**Physiologic Anatomy of the Pancreas.** The pancreas is composed of two major types of tissues, as shown in Figure: (1) the *acini*, which secrete digestive juices into the duodenum, and (2) the *islets of Langerhans*, which secrete insulin and glucagon directly into the blood. The human pancreas has 1 to 2 million islets of Langerhans( constitute 2% of pancreatic tissues mainly in the tail of pancreas , each only about 0.3 millimeter in diameter and organized around small capillaries into which its cells secrete their hormones.

Islets of Langerhans consist of four types of cells: which are distinguished from one another by their morphological and staining characteristics.



1. A cells or α-cells, which secrete glucagon ( about 25 per cent of the total), secrete *glucagon.*

2. B cells or β-cells, which secrete insulin and *amylin*, a hormone that is often secreted in parallel with insulin, although its function is unclear. (60 per cent of all the cells).

3. D cells or δ-cells, which secrete somatostatins, about 10 percent of the total, secrete *somatostatin.* ***somatostatin,*** *plays a role in the regulation of islet cell secretion*

4. F cells or PP cells, which secrete pancreatic polypeptide. a hormone of uncertain function. is probably concerned primarily with the regulation of HCO–3 secretion to the intestine

The close interrelations among these cell types in the islets of Langerhans allow cell-to-cell communication and direct control of secretion of some of the hormones by the other hormones. For instance, insulin inhibits glucagon secretion, amylin inhibits insulin secretion, and somatostatin inhibits the secretion of both insulin and glucagon.

„ **INSULIN**„ **SOURCE**

**Insulin is secreted by B cells or the β-cells in the islets of Langerhans of pancreas.**

**Insulin Is a Hormone Associated with Energy Abundance .That is, when there is great abundance of energy-giving foods in the diet, especially excess amounts of carbohydrates, insulin is secreted in great quantity. As we will see.**

**CHEMISTRY AND HALF-LIFE**

**Insulin was first isolated from the pancreas in 1922 by Banting and Best,Insulin is a polypeptide with 51 amino acids and a molecular weight of 5,808. It has two amino acid chains called α and β chains, which are linked by disulfide bridges. The α-chain of insulin contains 21 amino acids and β-chain contains 30 amino acids. The biological half-life of insulin is 5 minutes.Basal level of insulin in plasma is 10 μU/mL.**

**Synthesis of insulin occurs in the rough endoplasmic reticulum of β-cells in islets of Langerhans. It is synthesized as preproinsulin, that gives rise to proinsulin. Proinsulin is converted into insulin and C peptide through a series of peptic cleavages.( C peptide is a connecting peptide that connects α and β chains. At the time of secretion, C peptide is detached).**

**Preproinsulin → Proinsulin**

**Peptic cleavage ↓**

**Insulin**

** METABOLISM**

**When insulin is secreted into the blood, it circulates almost entirely in an unbound form; it has a plasma half-life that averages only about 6 minutes, so that it is mainly cleared from the circulation within 10 to 15 minutes. Except for that portion of the insulin that combines with receptors in the target cells, the remainder is degraded by the enzyme *insulinase* mainly in the liver, to a lesser extent in the kidneys and muscles, and slightly in most other tissues.**

**This rapid removal from the plasma is important, because, at times, it is as important to turn off rapidly as to turn on the control functions of insulin.**

**.**

**ACTIONS OF INSULIN**

Insulin is the important hormone that is concerned with the regulation of carbohydrate metabolism and blood glucose level. It is also concerned with the metabolism of proteins and fats.

**1. *On Carbohydrate Metabolism***

Insulin is the only anti diabetic hormone secreted in the body, i.e. it is the only hormone in the body that 7reduces blood glucose level by its following actions on carbohydrate metabolism:

i. *Increases transport and uptake of glucose by the cells* Insulin facilitates the transport of glucose from bloodinto the cells by increasing the permeability of cell membraneto glucose. Insulin stimulates the rapid uptake ofglucose by all the tissues, particularly liver, muscle andadipose tissues by increases the number of glucosetransporters, especially GLUT 4 in the cell membrane. But, it is not required for glucose uptakein some tissues such as brain (except hypothalamus),renal tubules, mucous membrane of intestine andRBCs

*Glucose transporters:* Usually, glucose is transported into the cells by **sodium-glucose symport pump.** In addition to symport pump, most of the cells have another type of transport proteins called **glucose transporters (GLUT).** So far, seven types of GLUT are identified (GLUT 1–7). Among these, **GLUT4** is insulin sensitive and it is located in cytoplasmic vesicles. It is present in large numbers in muscle fibers and adipose cells.

When insulin-receptor complex is formed in the membrane of such cells, the vesicles containing GLUT4 are attracted towards the membrane and GLUT4 is released into the membrane. Now, GLUT4 starts transporting the glucose molecules from extracellular fluid (ECF) into the cell. The advantage of GLUT4 is that it transports glucose at a faster rate.

ii. *Promotes peripheral utilization of glucose*

In presence of insulin, glucose which enters the cell is oxidized immediately. The rate of utilization depends upon the intake of glucose. *glucokinase*

iii. *Promotes storage of glucose – glycogenesis*

Insulin promotes the rapid conversion of glucose into glycogen (glycogenesis), which is stored in the muscle and liver. Insulin activates the enzymes,*glycogen synthase* which are necessary for glycogenesis. In liver, when glycogen content increases beyond its storing capacity, insulin causes conversion of glucose into fatty acids.

iv. *Inhibits glycogenolysis*. Insulin *inactivates liver phosphorylase*, the principal enzyme that causes liver glycogen to split into glucose.i.e. the breakdown of glycogen into glucose in muscle and liver.

v. *Inhibits gluconeogenesis*

i.e. the formation of glucose from proteins by inhibiting the release of amino acids from muscle and by inhibiting the activities of enzymes involved in gluconeogenesis

**Instead, *the brain cells are permeable to glucose and can use glucose without the intermediation***

***of insulin*.The brain cells are also quite different from most other cells of the body in that they normally use only glucose for energy and can use other energy substrates, such as fats, only with difficulty.Therefore, it is essential that the blood glucose level always be maintained above a critical level, which is one of the most important functions of the blood glucose control system. When the blood glucose falls too low, into the range of 20 to 50 mg/100 ml, symptoms of *hypoglycemic* *shock* develop, characterized by progressive nervous irritability that leads to fainting, seizures, and even coma.**

**2. *On Protein Metabolism***

Insulin facilitates the synthesis and storage of proteins and inhibits the cellular utilization of proteins by the following actions:

i. Facilitating the transport of amino acids into the cell from blood, by increasing the permeability of cell membrane for amino acids Among the amino acids most strongly transported are *valine*, *leucine*, *isoleucine*, *tyrosine*, and *phenylalanine*.

ii. Accelerating protein synthesis by influencing the transcription of DNA and by increasing the translation of mRNA

iii. Preventing protein catabolism by decreasing the activity of cellular enzymes which act on proteins

iv. Preventing gluconeogenesis.. Thus, insulin is responsible for the conservation and storage of proteins in the body.

**Insulin Lack Causes Protein Depletion and Increased Plasma Amino Acids.** Virtually all protein storage comes to ahalt when insulin is not available. The catabolism ofproteins increases, protein synthesis stops, and largequantities of amino acids are dumped into the plasma. most of the excess amino acids are usedeither directly for energy or as substrates for gluconeogenesis.

This degradation of the amino acids also leads to enhanced urea excretion in the urine. The

resulting protein wasting is one of the most serious of all the effects of severe diabetes mellitus. It can lead to extreme weakness as well as many deranged functions of the organs.

**Insulin and Growth Hormone Interact Synergistically to Promote Growth.**

**3. *On Fat Metabolism***

Insulin stimulates the synthesis of fat. It also increases the storage of fat in the adipose tissue.

Actions of insulin on fat metabolism are:

i. *Synthesis of fatty acids and triglycerides* Insulin promotes the transport of excess glucose intocells, particularly the liver cells. After the liver glucogen concentration reaches 5 to 6 per cent, this in itself inhibits further glycogen synthesis. Then all the additional glucose entering the liver cells becomes available to form fat

.i. *Transport of fatty acids into adipose tissue*

iii. *Storage of fat*

Insulin promotes the storage of fat in adipose tissue by inhibiting the enzymes which degrade the triglycerides. *Insulin inhibits the action of hormone-sensitive lipase*.

*Most of the fatty acids are then synthesized within the liver itself and used to form triglycerides*, theusual form of storage fat. They are released fromthe liver cells to the blood in the lipoproteins.

Insulin activates *lipoprotein lipase* in the capillary walls of the adipose tissue, which splits the triglycerides again into fatty acids, a requirement for them to be absorbed into the adipose cells, where they are again converted to triglycerides and stored. **Insulin Promotes Conversion of Excess Glucose into Fatty Acids and Inhibits Gluconeogenesis in the Liver.** When the quantityof glucose entering the liver cells is more than canbe stored as glycogen or can be used for local hepatocytemetabolism, *insulin promotes the conversion**of all this excess glucose into fatty acids*. These fattyacids are subsequently packaged as triglycerides in very-low-density lipoproteins and transported in thisform by way of the blood to the adipose tissue anddeposited as fat.

**Insulin Deficiency Causes Lipolysis of Storage Fat and Releaseof Free Fatty Acids.** In the absence of insulin, all theeffects of insulin noted earlier that cause storage offat are reversed. The most important effect is thatthe enzyme *hormone-sensitive lipase* in the fat cellsbecomes strongly activated. This causes hydrolysis of the stored triglycerides, releasing large quantities offatty acids and glycerol into the circulating blood.

Consequently, the plasma concentration of free fatty acids begins to rise within minutes.This free fatty acid then becomes the main energy substrate used by essentially all tissues of the body besides the brain.

**Insulin Deficiency Increases Plasma Cholesterol and Phospholipid Concentrations.** The excess of fatty acids in the plasma associated with insulin deficiency also promotesliver conversion of some of the fatty acids into phospholipids and cholesterol, two of the major productsof fat metabolism. These two substances, along with excess triglycerides formed at the same time in the liver, are then discharged into the blood in the lipoproteins. Occasionally the plasma lipoproteins increase as much as threefold in the absence of insulin, giving a total concentration of plasma lipids of several per cent rather than the normal 0.6 per cent.This high lipid concentration—especially the high concentration of cholesterol—promotes the development of atherosclerosisin people with serious diabetes.

**Excess Usage of Fats During Insulin Lack Causes Ketosis and** **Acidosis.** Insulin lack also causes excessive amounts of *acetoacetic acid* to be formed in the liver cells. This results from the following effect: In the absence of insulin but in the presence of excess fatty acids in the liver cells, the carnitine transport mechanism for transporting fatty acids into the mitochondria becomes increasingly activated. In the mitochondria, beta oxidation of the fatty acids then proceeds very rapidly, releasing extreme amounts of acetyl-CoA.A large part of this excess acetyl-CoA is then condensed to form acetoacetic acid, which in turn is released into the circulating blood. Most of this passes to the peripheral cells, where it is again converted into acetyl-CoA and used for energy in the usual manner.

At the same time, the absence of insulin also depresses the utilization of acetoacetic acid in the peripheral tissues. Thus, so much acetoacetic acid is released from the liver that it cannot all be metabolized by the tissues.Therefore, as shown in Figure 78–5, its concentration rises during the days after cessation of insulin secretion, sometimes reaching concentrations of 10 mEq/L or more, which is a severe state of body fluid acidosis.

some of the acetoacetic acid is also converted into b-hydroxybutyric acid and *acetone*. These two substances, along with the acetoacetic acid, are called *ketone bodies*, and their presence in large quantities in the body fluids is called *ketosis*.

**4. *On Growth***

Along with growth hormone, insulin promotes growth of body by its anabolic action on proteins. It enhances the transport of amino acids into the cell and synthesis of proteins in the cells. It also has the **protein-sparing effect,** i.e. it causes conservation of proteins by increasing the glucose utilization by the tissues.

On the target cells, insulin binds with the receptor protein and forms the insulin-receptor complex. This complex executes the action by activating the intracellular enzyme system. **protein kinase**

**Insulin causes K+ to enter cells, with a resultant lowering of the extracellular K+concentration. Infusions of insulin and glucosesignificantly lower the plasma K+level in normal individualsand are very effective for the temporary relief of hyperkalemiain patients with renal failure.**

**Hypokalemiaoften developswhen patients with diabetic acidosis are treated with insulin.**

**The reason for the intracellular migration of K+is still uncertain.**

**However, insulin increases the activity of Na+–K+ATPasein cell membranes, so that more K+is pumped into cells.**

***Effect on skeletal muscles***

***Insulin Receptor***

Insulin receptor is a glycoprotein with a molecular weight of 340,000. It is present in almost all the cells of the body.

**REGULATION OF INSULIN SECRETION**

**1. *Role of Blood Glucose Level***

When blood glucose level is normal (80 to 100 mg/dL), the rate of insulin secretion is low (up to 10 μU/minute). When blood glucose level increases between 100 and 120 mg/dL, the rate of insulin secretion rises rapidly to 100 μU/minute. When blood glucose level rises above 200 mg/dL, the rate of insulin secretion also rises very rapidly up to 400 μU/minute.

**2. *Role of Proteins***

Excess amino acids in blood also stimulate insulin secretion. Potent amino acids are **arginine** and **lysin.**

Without any increase in blood glucose level, the amino acids alone can cause a slight increase in insulin secretion. However, amino acids potentiate the action of glucose on insulin secretion so that, in the presence of amino acids, elevated blood glucose level increases insulin secretion to a great extent.

**3. *Role of Lipid Derivatives***

The β-ketoacids such as acetoacetate also increase insulin secretion.

**4. *Role of Gastrointestinal Hormones***

Insulin secretion is increased by some of the gastrointestinal hormones such as gastrin, secretin, CCK and GIP.

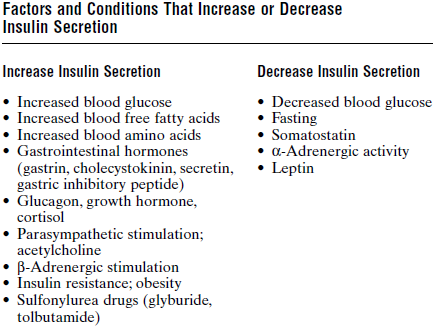
**5. *Role of Endocrine Hormones***

Diabetogenic hormones like glucagon, growth hormone and cortisol also stimulate insulin secretion, indirectly. All these diabetogenic hormones increase the blood glucose level, which stimulates β-cells of islets of Langerhans. So insulin secretion is increased. **Prolonged hypersecretion** of these hormones causes exhaustion of β-cells, resulting in diabetes mellitus.

**6. *Role of Autonomic Nerves***

Stimulation of parasympathetic nerve to the pancreas (right vagus) increases insulin secretion. Chemical neurotransmitter involved is acetylcholine. Stimulation of sympathetic nerves inhibits the secretion of insulin and the neurotransmitter is noradrenaline. However, the role of these nerves on the regulation of insulin secretion under physiological conditions is not clear.

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**EFFECTS OF HYPERGLYCEMIA**

Hyperglycemia by itself can cause symptoms resulting from the hyperosmolality of the blood. In addition, there is glycosuria because the renal capacity for glucose reabsorption is exceeded.

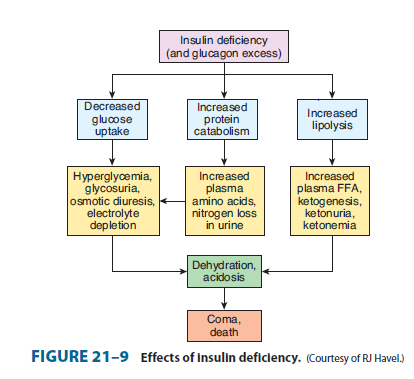
Excretion of the osmotically active glucose molecules entails the loss of large amounts of water (osmotic diuresis; see Chapter 38). The resultant dehydration activates the mechanisms regulating water intake, leading to polydipsia. There is an appreciable urinary loss of Na+and K+as well. For every gram of glucose excreted, 4.1 kcal is lost from the body. Increasing the oral caloric intake to cover this loss simply raises the plasma glucose further and increases the glycosuria, so mobilization of endogenous protein and fat stores and weight loss are not prevented. When plasma glucose is episodically elevated over time, small amounts of hemoglobin A are nonenzymatically glycated to form**HbA**Ic

(see Chapter 32). Careful control of the diabetes with insulin reduces the amount formed and consequently HbA Ic concentration is measured clinically as an integrated index of diabetic control for the 4- to 6-wk period before the measurement.

The role of chronic hyperglycemia in production of the long-term complications of diabetes is discussed below.

Deficient glucose utilization and deficient hormone sensing (insulin, leptin, CCK) in the cells of the hypothalamus that regulate satiety are the probable causes of hyperphagia in diabetes.

The feeding area of the hypothalamus is not inhibited and thus satiety is not sensed so food intake is increased. Glycogen depletion is a common consequence of intracellular glucose deficit, and the glycogen content of liver and skeletal muscle in diabetic animals is usually reduced.



**GLUCAGON**

Glucagon is secreted from **A cells** or **α-cells** in the islets of Langerhans of pancreas. It is also secreted from **A** **cells** of stomach and **L cells** of intestine.

 **CHEMISTRY AND HALF-LIFE**

Glucagon is a polypeptide with a molecular weight of 3,485. It contains 29 amino acids. Half-life of glucagon is 3 to 6 minutes.

 **SYNTHESIS**

Glucagon is synthesized from the preprohormone precursor called **preproglucagon** in the α-cells of islets. Preproglucagon is converted into **proglucagon,** which gives rise to glucagon.

„ **METABOLISM**

About 30% of glucagon is degraded in liver and 20% in kidney. The cleaved glucagon fragments are excreted through urine. 50% of the circulating glucagon is degraded in blood itself by enzymes such as **serine** and **cysteine proteases.**

„ **ACTIONS OF GLUCAGON**

Actions of glucagon are antagonistic to those of insulin (Table 69.1). It increases the blood glucose level, peripheral utilization of lipids and the conversion of proteins into glucose.. Glycogenolysis, gluconeogenesis, Glucagon shows lipolytic and ketogenic actions.

„ **REGULATION OF GLUCAGON SECRETION**

Secretion of glucagon is controlled mainly by glucose and amino acid levels in the blood.

*Factors which increase glucagon secretion:*

i. Exercise

ii. Stress

iii. Gastrin

iv. Cholecystokinin (CCK)

v. Cortisol.

*Factors which inhibit glucagon secretion:*

i. Somatostatin

ii. Insulin

iii. Free fatty acids

iv. Ketones.

„ **SOMATOSTATIN**

„ **SOURCE OF SECRETION**

Somatostatin is secreted from:

1. Hypothalamus

2. D cells (δ-cells) in islets of Langerhans of pancreas

3. D cells in stomach and upper part of small

intestine.

 **ACTIONS OF SOMATOSTATIN**

1. Somatostatin acts within islets of Langerhans and, inhibits β and α cells, i.e. it inhibits the secretion of

both glucagon and insulin

2. It decreases the motility of stomach, duodenum and gallbladder

3. It reduces the secretion of gastrointestinal hormones gastrin, CCK, GIP and VIP

4. Hypothalamic somatostatin inhibits the secretion of GH and TSH from anterior pituitary. That is why, it is also called **growth hormone-inhibitory hormone** (GHIH).

**REGULATION OF BLOOD GLUCOS LEVEL (BLOOD GLUCOSE LEVEL)**

**NORMAL BLOOD GLUCOSE LEVEL** In normal persons, blood glucose level is controlled

within a narrow range. In the early morning after overnight **fasting,** the blood glucose level is low ranging between 70 and 110 mg/dL of blood. Between first and second hour after meals **(postprandial),** the blood glucose level rises to 100 to 140 mg/dL. Glucose level in blood is brought back to normal at the end of second hour after the meals. Blood glucose regulating mechanism is operated through liver and muscle by the influence of the pancreatic hormones – insulin and glucagon. Many other hormones are also involved in the regulation of blood glucose level. Among all the hormones, insulin is the only hormone that reduces the blood glucose level and it is called the **antidiabetogenic hormone.** The hormones which increase blood glucose level are called **diabetogenic hormones** or **anti-insulin hormones.**

***Necessity of Regulation of Blood Glucose Level***

Regulation of blood glucose (sugar) level is very essential because, glucose is the only nutrient that is utilized for energy by many tissues such as brain tissues, retina and germinal epithelium of the gonads.

„ **ROLE OF LIVER IN THE MAINTENANCE OF BLOOD GLUCOSE LEVEL**

Liver serves as an important **glucose buffer system.** When blood glucose level increases after a meal, theexcess glucose is converted into glycogen and storedin liver. Afterwards, when blood glucose level falls, theglycogen in liver is converted into glucose and releasedinto the blood. The storage of glycogen and release of glucose from liver are mainly regulated by insulin and glucagon.

„ **ROLE OF INSULIN IN THE MAINTENANCE**

**OF BLOOD GLUCOSE LEVEL**

Insulin decreases the blood glucose level and it is the only antidiabetic hormone available in the body (Refer the actions of insulin on carbohydrate metabolism in this

Chapter).

„ **ROLE OF GLUCAGON IN THE MAINTENANCE OF BLOOD GLUCOSE LEVEL** Glucagon increases the blood glucose level (Refer

actions of glucagon on carbohydrate metabolism in this Other hormones which increase the blood glucose level are:

1. Growth hormone (Chapter 66)

2. Thyroxine (Chapter 67)

3. Cortisol (Chapter 70)

4. Adrenaline (Chapter 71).

Thus, liver helps to maintain the blood glucose level by storing glycogen when blood glucose level is high after meals; and by releasing glucose, when blood glucose level is low after 2 to 3 hours of food

intake. Insulin helps to control the blood glucose level, especially after meals, when it increases. Glucagon and other hormones help to maintain the blood glucose level by raising it in between the meals.