Endocrine Functions of Pancreas

Chapter 69

- ISLETS OF LANGERHANS
- INSULIN
- GLUCAGON
- SOMATOSTATIN
- PANCREATIC POLYPEPTIDE
- REGULATION OF BLOOD GLUCOSE LEVEL
- APPLIED PHYSIOLOGY

ISLETS OF LANGERHANS

Endocrine function of pancreas is performed by the islets of Langerhans. Human pancreas contains about 1 to 2 million islets.

Islets of Langerhans consist of four types of cells:

1. A cells or α-cells, which secrete glucagon
2. B cells or β-cells, which secrete insulin
3. D cells or δ-cells, which secrete somatostatin
4. F cells or PP cells, which secrete pancreatic polypeptide.

INSULIN

SOURCE OF SECRETION

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

CHEMISTRY AND HALF-LIFE

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.

PLASMA LEVEL

Basal level of insulin in plasma is 10 μU/mL.

SYNTHESIS

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

Binding of insulin to insulin receptor is essential for its removal from circulation and degradation. Insulin is degraded in liver and kidney by a cellular enzyme called **insulin protease** or **insulin-degrading enzyme.**

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 antidiabetic hormone secreted in the body, i.e. it is the only hormone in the body that

reduces blood glucose level. Insulin reduces the 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 blood into the cells by increasing the permeability of cell membrane to glucose. Insulin stimulates the rapid uptake of glucose by all the tissues, particularly liver, muscle and adipose tissues. But, it is not required for glucose uptake in some tissues such as brain (except hypothalamus), renal tubules, mucous membrane of intestine and RBCs. Insulin also increases the number of glucose transporters, especially GLUT 4 in the cell membrane.

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*

Insulin promotes the 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.

iii. *Promotes storage of glucose – glycogenesis*

Insulin promotes the rapid conversion of glucose into glycogen (glycogenesis), which is stored in the muscle and liver. Thus, glucose is stored in these two organs in the form of glycogen. Insulin activates the enzymes 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 prevents glycogenolysis, i.e. the breakdown of glycogen into glucose in muscle and liver.

v. *Inhibits gluconeogenesis*

Insulin prevents 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.

Thus, insulin decreases the blood glucose level by:

i. Facilitating transport and uptake of glucose by the cells
ii. Increasing the peripheral utilization of glucose
iii. Increasing the storage of glucose by converting it into glycogen in liver and muscle
iv. Inhibiting glycogenolysis
v. Inhibiting gluconeogenesis.

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
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 conversion of proteins into glucose.

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

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 into cells, particularly the liver cells. This glucose is utilized for the synthesis of fatty acids and triglycerides. Insulin promotes the synthesis of lipids by activating the enzymes which convert:

a. Glucose into fatty acids
b. Fatty acids into triglycerides.

ii. *Transport of fatty acids into adipose tissue*

Insulin facilitates the transport of fatty acids into the adipose tissue.

iii. *Storage of fat*

Insulin promotes the storage of fat in adipose tissue by inhibiting the enzymes which degrade the triglycerides.

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.

Houssay Animal

The importance of insulin and growth hormone in the growth of the body is demonstrated by Houssay animal. Houssay animal is one in which both anterior pituitary and pancreas are removed. Administration of either insulin or growth hormone alone does not induce growth in this animal. However, the administration of both the hormones stimulates the growth. This proves the synergistic actions of these two hormones on growth.

■ MODE OF ACTION OF INSULIN

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.

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.

Subunits of insulin receptor

Insulin receptor is a **tetramer,** formed by four glycoprotein subunits (two α-subunits and two β-subunits). The α-subunits protrude out of the cell and the β-subunits protrude inside the cell (Fig. 69.1). The α and β subunits are linked to each other by disulfide bonds. Intracellular surfaces of α-subunits have the enzyme activity – **protein kinase (tyrosine kinase)** activity.

When insulin binds with α-subunits of the receptor protein, the tyrosine kinase at the β-subunit (that protrudes into the cell) is activated by means of autophosphorylation.

Activated tyrosine kinase acts on many intracellular enzymes by phosphorylating or dephosphorylating them so that some of the enzymes are activated while others are inactivated.

Thus, insulin action is exerted on the target cells by the activation of some intracellular enzymes and by the inactivation of other enzymes.

■ REGULATION OF INSULIN SECRETION

Insulin secretion is mainly regulated by blood glucose level.

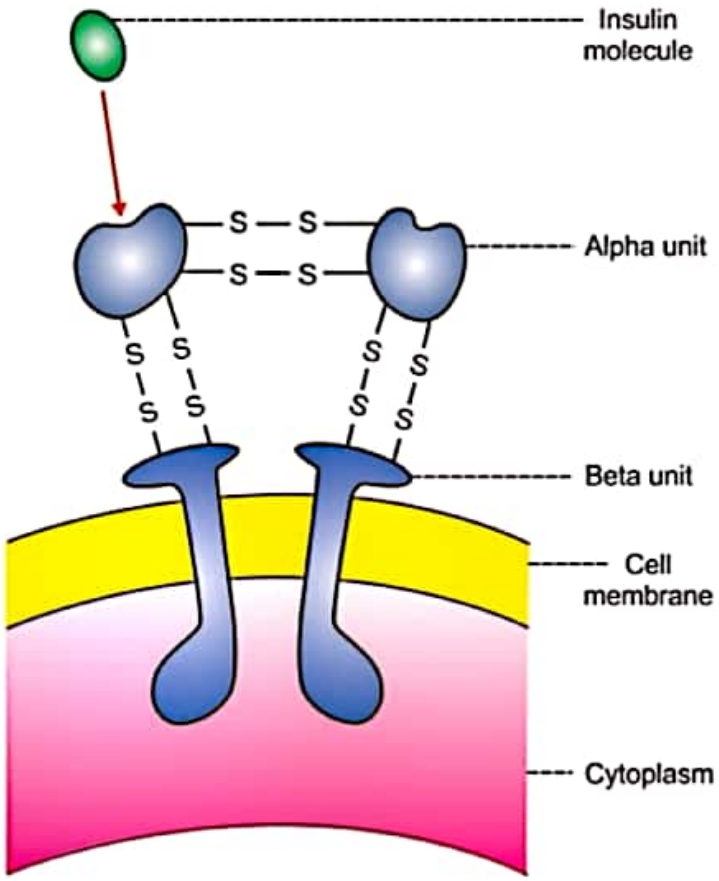

FIGURE 69.1: Diagram showing the structure of insulin receptor. S–S = Disulfide bond.

In addition, other factors like amino acids, lipid derivatives, gastrointestinal and endocrine hormones and autonomic nerve fibers also stimulate 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.

Biphasic effect of glucose

Action of blood glucose on insulin secretion is biphasic.

I. Initially, when blood glucose level increases after a meal, the release of insulin into blood increases rapidly. Within few minutes, concentration of insulin in plasma increases up to 100 µU/mL from the basal level of 10 µU/mL. It is because of release of insulin that is stored in pancreas. Later, within 10 to 15 minutes, the insulin concentration in the blood reduces to half the value, i.e. up to 40 to 50 µU/mL of plasma.

ii. After 15 to 20 minutes, the insulin secretion rises once again. This time it rises slowly but steadily. It reaches the maximum between 2 and 2½ hours. The prolonged increase in insulin release is due to the formation of new insulin molecules continuously from pancreas (Fig. 69.2).

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.

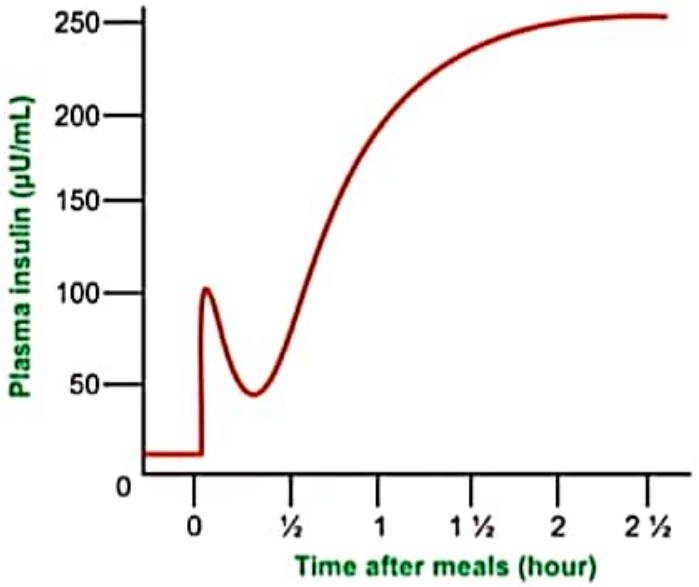

FIGURE 69.2: Changes in plasma level of insulin after meals. Increase in blood glucose level after meals produces biphasic effect on plasma level of insulin.

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.

■ GLUCAGON

■ SOURCE OF SECRETION

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.

1. *On Carbohydrate Metabolism*

Glucagon increases the blood glucose level by:

i. Increasing glycogenolysis in liver and releasing glucose from the liver cells into the blood.

TABLE 69.1: Differences between insulin and glucagon

Features	Insulin	Glucagon
Source of secretion	β-cells of islets of langerhans	α-cells of islets of langerhans
Action on carbohydrate metabolism	*Decreases blood glucose level by:* 1. Facilitating transport and uptake of glucose by all cells except liver cells 2. Increasing peripheral utilization of glucose 3. Increasing glycogenesis in liver and muscle 4. Preventing glycogenolysis 5. Preventing gluconeogenesis	*Increases blood glucose level by:* 1. Facilitating glucose transport into liver cells 2. Increasing glycogenolysis 3. Increasing gluconeogenesis
Action on protein metabolism	1. Facilitates amino acid transport 2. Accelerates protein synthesis 3. Prevents protein catabolism 4. Prevents conversion of proteins into glucose	1. Increases transport of amino acids into liver cells 2. Increases utilization of amino acids for gluconeogenesis
Action on fat metabolism	1. Increases synthesis and storage of fat 2. No ketogenic effect	1. Increases lipolysis 2. Promotes ketogenesis
Blood fatty acids	Decreases	Increases
Hypersecretion leads to	Hypoglycemia	Hyperglycemia
Hyposecretion leads to	Diabetes mellitus	Hypoglycemia

Glucagon does not induce glycogenolysis in muscle

ii. Increasing gluconeogenesis in liver by:
   a. Activating the enzymes, which convert pyruvate into phosphoenol pyruvate
   b. Increasing the transport of amino acids into the liver cells. The amino acids are utilized for glucose formation.

2. *On Protein Metabolism*

Glucagon increases the transport of amino acids into liver cells. The amino acids are utilized for gluconeogenesis.

3. *On Fat Metabolism*

via G protein. Adenyl cyclase causes the formation of cyclic adenosine monophosphate (AMP) which brings out the actions of glucagon. Glucagon receptor is a peptide with a molecular weight of 62,000.

■ REGULATION OF GLUCAGON SECRETION

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

1. *Role of Blood Glucose Level*

Important factor that regulates the secretion of glucagon is the decrease in blood glucose level. When blood glucose level decreases below 80 mg/dL of blood, α-cells of islets of Langerhans are stimulated and more

■ ANTIDIURETIC HORMONE

Source of Secretion

Antidiuretic hormone (ADH) is secreted mainly by **supraoptic nucleus** of hypothalamus. It is also secreted by **paraventricular nucleus** in small quantity. From here, this hormone is transported to posterior pituitary through the nerve fibers of hypothalamo-hypophyseal tract, by means of axonic flow.

Chemistry and Half-life

Antidiuretic hormone is a polypeptide containing 9 amino acids. Its half-life is 18 to 20 minutes.

Actions

Antidiuretic hormone has two actions:
1.Retention of water
2.Vasopressor action.

1. *Retention of water*

Major function of ADH is retention of water by acting on kidneys. It increases the **facultative reabsorption** of water from distal convoluted tubule and collecting duct in the kidneys (Chapter 52).

In the absence of ADH, the distal convoluted tubule and collecting duct are totally impermeable to water. So, reabsorption of water does not occur in the renal tubules and dilute urine is excreted. This leads to loss of large amount of water through urine. This condition is called **diabetes insipidus** and the excretion of large amount of

Potent stimulants for ADH secretion are:
1. Decrease in the extracellular fluid (ECF) volume
2. Increase in osmolar concentration in the ECF.

Role of osmoreceptors

Osmoreceptors are the receptors which give response to change in the osmolar concentration of the blood. These receptors are situated in the hypothalamus near supraoptic and paraventricular nuclei. When osmolar concentration of blood increases, the osmoreceptors are activated. In turn, the osmoreceptors stimulate the supraoptic and paraventricular nuclei which send motor impulses to posterior pituitary through the nerve fibers and cause release of ADH. ADH causes reabsorption of water from the renal tubules. This increases ECF volume and restores the normal osmolarity.

■ OXYTOCIN

Source of Secretion

Oxytocin is secreted mainly by **paraventricular nucleus** of hypothalamus. It is also secreted by **supraoptic nucleus** in small quantity and it is transported from hypothalamus to posterior pituitary through the nerve fibers of hypothalamo-hypophyseal tract.

In the posterior pituitary, the oxytocin is stored in the nerve endings of hypothalamo-hypophyseal tract. When suitable stimuli reach the posterior pituitary from hypothalamus, oxytocin is released into the blood. Oxytocin is secreted in both males and females.

Chemistry and Half-life