Pancreas is a tubulo-racemose mixed type of gland, situated within the second part of the duodenum and lies across the vertebral column with a duct to carry the external secretion rich in various enzyme and dealt with in connection with the process of digestion of carbohydrate, protein and fat and assimilation of food. The central part of the pancreas formed by the islet cells of Langerhans which do not contain any acinar or ductular structure and is responsible for the internal secretions of insulin, glucagon and gastrin.

Structure of Islets of Langerhans : These are small irregular collections of epitheloid cells with no ducts and found scattered between the alveoli of the pancreas. The islets are more numerous in the tail of the pancreas than in the head and body. The cells in the islets can be divided into atleast five cell types in human on the basis of their intravitum staining properties with neutral red and morphology. The cytoplasm of all of these cells contains granular endoplasmic reticulum, ribosomes, polysome, mitochondria, Golgi complex, secretion granules, microtubules and cytosol. *Lacy* and *Greider* in 1972 have described the presence of these distinct islet cells types in a large number of mammals which are A, B and D cells. The different types of cells found in the islets of Langerhans are described below :

(1) **α-or A-cells (20%) :** These cells contain oxyphil granules and stain red with the modified Mallory aniline blue stain. The A cells have smaller granules and a more ovoid nucleus which tend

to be deeply indented or lobulated. These cells are situated in peripheral part. The A-cells contain high electron density of secretory granules. The cytoplasm contains a well-developed Golgi complex, a moderate amount of granular endoplasmic reticulum and occassionally free ribosomes. A few small filamentous mitochondria are found in the cytoplasmic matrix. According to *Dragstedt*, this cell is responsible for the formation of a hormone known as *lipocaic* resembling choline in action, preventing fatty changes in the liver. The alpha-cell probably secrete *glucagon*. It is polypeptide in nature which on injection causes hyperglycaemia. According to *Hellerstrom*, it is revealed that α-cell can be classified as α_1 which is argyrophilic and α_2 is non-argyrophilic but rich in protein-bound trypophan.

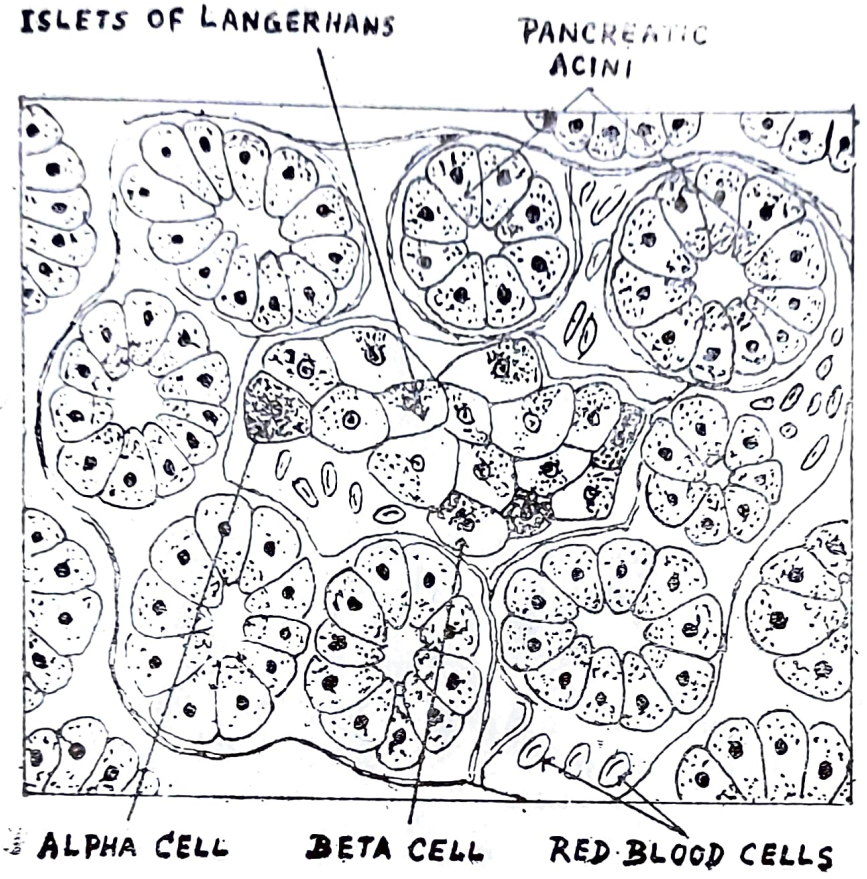

Fig. 81. Histology of the Pancreas showing different types of Islet cell.

(2) **β-or B-cell** (60%) : These cells contain basophil granules which occupy the periphery of the islets and are smaller than the other. The granules of the β-cells are alcoholsoluble and stain bluish purple with Mallory aniline staining technique. The β-cells are smaller in size and are believed to produce of an anti-diabetogenic hormone known as *insulin* which produces hypoglycaemia. The granules has fixed in water. The α-cell granules are packets of vesicle. The β-cell has a more prominent Golgi complex. The granules in the β-cell are found between the round or ovoid nucleus and the plasma membrane bordering the capillary. β-cell can be classified into β_1 and β_2. Some β_1-cell granules are hexagonal in shape in case of yellow-tail fish but these granules are cuboidal, needle-like or amorphous in other cases.

(3) **δ-or D-cells** (1 to 8%) : These cells are situated in between A and B cells. According to *Bloom*, δ-cells have been seen only in human pancreas and are not well defined. They are non-granular and stained blue with Mallory-Azan stain. These type of cells are supposed to secrete *somatostatin* or growth hormone inhibitory

factor which was discovered in 1975. Recently, it has been observed that this cell contains *gastrin* hormone.

(4) **Peptide secreting cells** : These are morphologically distinct cells which secrete pancreatic polypeptide. They possess smaller cytoplasmic granules and have got two types :

(a) *PP cells* : These cells are four in number and they are also found in the exocrine portion of the pancreas. These type of cells are supposed to secrete pancreatic polypeptide.

(b) *Pancreatic D_1 cells* : The ultra structure of this type of cell is similar to gastric mucosa cells. The diameter of the granular size becomes 118 nm. These granules do not react with antibovine pancreatic polypeptide serum which may be related to VIP (Vasoactive intestinal peptide). In conditions where there is excessive secretion of VIP, there is excessive diarrhoea resembling cholera.

Endocrine Functions of Pancreas

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.

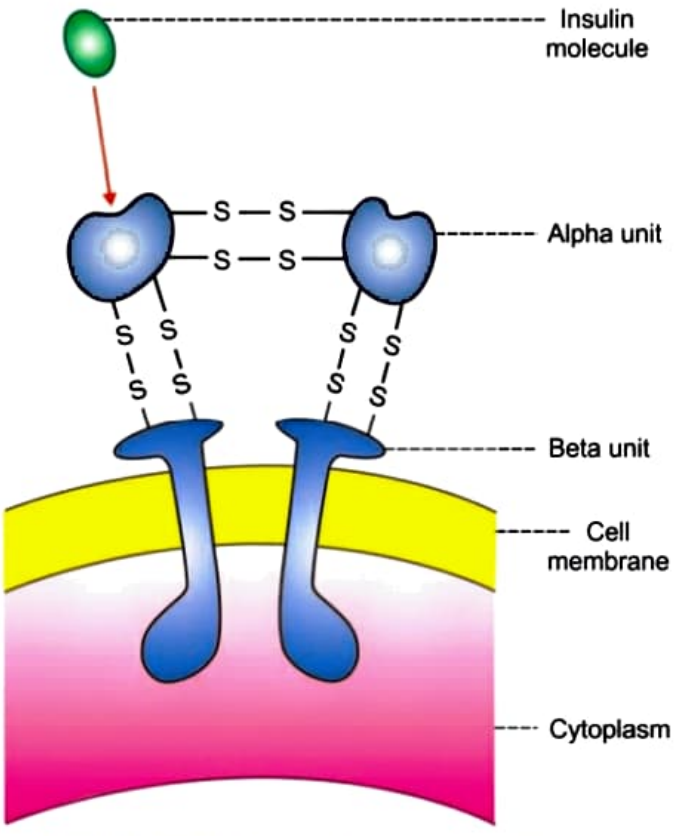

FIGURE 69.1: Diagram showing the structure of insulin receptor. S–S = Disulfide bond.

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.

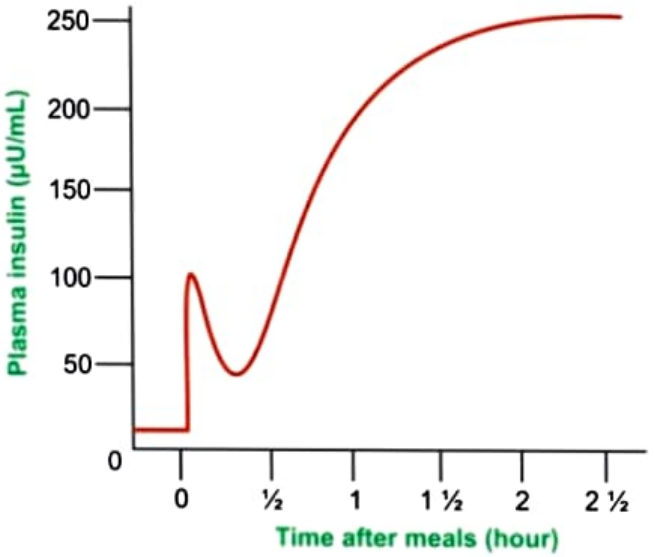

FIGURE 69.2: Changes in plasma level of insulin after meals. Increase in blood glucose level after meals produces biphasic effect on plasma level of insulin.

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*

Glucagon shows lipolytic and ketogenic actions. It increases lipolysis by increasing the release of free fatty acids from adipose tissue and making them available for peripheral utilization. The lipolytic activity of glucagon, in turn promotes ketogenesis (formation of ketone bodies) in liver.

4. *Other Actions*

Glucagon:

i. Inhibits the secretion of gastric juice
ii. Increases the secretion of bile from liver.

■ MODE OF ACTION OF GLUCAGON

On the target cells (mostly liver cells), glucagon combines with receptor and activates adenyl cyclase 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 glucagon is released. Glucagon, in turn increases the blood glucose level. On the other hand, when blood glucose level increases, α-cells are inhibited and the secretion of glucagon decreases.

2. *Role of Amino Acid Level in Blood*

Increase in amino acid level in blood stimulates the secretion of glucagon. Glucagon, in turn converts the amino acids into glucose.

3. *Role of Other Factors*

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.

CHEMISTRY AND HALF-LIFE

Somatostatin is a polypeptide. It is synthesized in two forms, namely somatostatin-14 (with 14 amino acids) and somatostatin-28 (with 28 amino acids). Both the forms have similar actions. Half-life of somatostatin is 2 to 4 minutes.

SYNTHESIS

Somatostatin is synthesized from the precursor prosomatostatin. Prosomatostatin is converted mostly into somatostatin-14 in the D cells of islets in pancreas. However, in the intestine, large amount of somatostatin-28 is produced from prosomatostatin.

METABOLISM

Somatostatin is degraded in liver and kidney.

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).

MODE OF ACTION OF SOMATOSTATIN

Somatostatin brings out its actions through cAMP.

REGULATION OF SECRETION OF SOMATOSTATIN

Pancreatic Somatostatin

Secretion of pancreatic somatostatin is stimulated by glucose, amino acids and CCK. The tumor of D cells of islets of Langerhans causes hypersecretion of somatostatin. It leads to hyperglycemia and other symptoms of diabetes mellitus.

Gastrointestinal Tract Somatostatin

Secretion of somatostatin in GI tract is increased by the presence of chyme-containing glucose and proteins in stomach and small intestine.

PANCREATIC POLYPEPTIDE

SOURCE OF SECRETION

Pancreatic polypeptide is secreted by F cells or PP cells in the islets of Langerhans of pancreas. It is also found in small intestine.

CHEMISTRY AND HALF-LIFE

Pancreatic polypeptide is a polypeptide with 36 amino acids. Its half-life is 5 minutes.

SYNTHESIS

Pancreatic polypeptide is synthesized from pre-prohormone precursor called prepropancreatic polypeptide in the PP cells of islets.

METABOLISM

Pancreatic polypeptide is degraded and removed from circulation mainly in kidney.

ACTIONS OF PANCREATIC POLYPEPTIDE

Exact physiological action of pancreatic polypeptide is not known. It is believed to increase the secretion of glucagon from α-cells in islets of Langerhans.

MODE OF ACTION OF PANCREATIC POLYPEPTIDE

Pancreatic polypeptide brings out its actions through cAMP.

REGULATION OF SECRETION

Secretion of pancreatic polypeptide is stimulated by the presence of chyme containing more proteins in the small intestine.

REGULATION OF BLOOD GLUCOSE 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, the excess glucose is converted into glycogen and stored in liver. Afterwards, when blood glucose level falls, the glycogen in liver is converted into glucose and released into 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 Chapter).

ROLE OF OTHER HORMONES IN THE MAINTENANCE OF BLOOD GLUCOSE LEVEL

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.

APPLIED PHYSIOLOGY

HYPOACTIVITY – DIABETES MELLITUS

Diabetes mellitus is a metabolic disorder characterized by high blood glucose level, associated with other manifestations. 'Diabetes' means 'polyuria' and 'mellitus' means 'honey'. The name 'diabetes mellitus' was coined by Thomas Willis, who discovered sweetness of urine from diabetics in 1675.

In most of the cases, diabetes mellitus develops due to deficiency of insulin.

Classification of Diabetes Mellitus

There are several forms of diabetes mellitus, which occur due to different causes. Diabetes may be primary or secondary. Primary diabetes is unrelated to another disease. Secondary diabetes occurs due to damage or disease of pancreas by another disease or factor.

Recent classification divides primary diabetes mellitus into two types, Type I and Type II. Differences between the two types are given in Table 69.2.

Type I Diabetes Mellitus

Type I diabetes mellitus is due to deficiency of insulin because of destruction of β-cells in islets of Langerhans. This type of diabetes mellitus may occur at any age of life. But, it usually occurs before 40 years of age and the persons affected by this require insulin injection. So it is also called insulin-dependent diabetes mellitus (IDDM). When it develops at infancy or childhood, it is called juvenile diabetes.

Type I diabetes mellitus develops rapidly and progresses at a rapid phase. It is not associated with obesity, but may be associated with acidosis or ketosis.

Causes of type I diabetes mellitus

1. Degeneration of β-cells in the islets of Langerhans of pancreas
2. Destruction of β-cells by viral infection
3. Congenital disorder of β-cells
4. Destruction of β-cells during autoimmune diseases. It is due to the development of antibodies against β-cells (Refer Chapter 17 for details).

Other forms of type 1 diabetes mellitus

1. Latent autoimmune diabetes in adults (LADA): LADA or slow onset diabetes has slow onset and slow progress than IDDM and it occurs in later life after 35 years. It may be difficult to distinguish LADA from type II diabetes mellitus, since pancreas takes longer period to stop secreting insulin.
2. Maturity onset diabetes in young individuals (MODY): It is a rare inherited form of diabetes mellitus that occurs before 25 years. It is due to hereditary defects in insulin secretion.

Type II Diabetes Mellitus

Type II diabetes mellitus is due to insulin resistance (failure of insulin receptors to give response to insulin). So, the body is unable to use insulin. About 90% of diabetic patients have type II diabetes mellitus. It usually occurs after 40 years. Only some forms of Type II diabetes require insulin. In most cases, it can be controlled by oral hypoglycemic drugs. So it is also called noninsulin-dependent diabetes mellitus (NIDDM).

Type II diabetes mellitus may or may not be associated with ketosis, but often it is associated with obesity.

Causes for type II diabetes mellitus

In this type of diabetes, the structure and function of β-cells and blood level of insulin are normal. But insulin receptors may be less, absent or abnormal, resulting in insulin resistance.

Common causes of insulin resistance are:

1. Genetic disorders (significant factors causing type II diabetes mellitus)
2. Lifestyle changes such as bad eating habits and physical inactivity, leading to obesity
3. Stress.

Other forms of type II diabetes mellitus

1. Gestational diabetes: It occurs during pregnancy. It is due to many factors such as hormones secreted during pregnancy, obesity and lifestyle before and during pregnancy. Usually, diabetes disappears after delivery of the child. However, the woman has high risk of development of type II diabetes later.
2. Pre-diabetes: It is also called chemical, subclinical, latent or borderline diabetes. It is the stage between normal condition and diabetes. The person does not show overt (observable) symptoms of diabetes but there is an increase in blood glucose level. Though pre-diabetes is reversible, the affected persons are at a high risk of developing type II diabetes mellitus.

TABLE 69.2: Differences between type I and type II diabetes mellitus

Features	Type I (IDDM)	Type II (NIDDM)
Age of onset	Usually before 40 year	Usually after 40 year
Major cause	Lack of insulin	Lack of insulin receptor
Insulin deficiency	Yes	Partial deficiency
Immune destruction of β-cells	Yes	No
Involvement of other endocrine disorders	No	Yes
Hereditary cause	Yes	May or may not be
Need for insulin	Always	Not in initial stage May require in later stage
Insulin resistance	No	Yes
Control by oral hypoglycemic agents	No	Yes
Symptoms appear	Rapidly	Slowly
Body weight	Usually thin	Usually overweight
Stress-induced obesity	No	Yes
Ketosis	Yes	May or may not be

Secondary Diabetes Mellitus

Secondary diabetes mellitus is rare and only about 2% of diabetic patients have secondary diabetes. It may be temporary or may become permanent due to the underlying cause.

Causes of secondary diabetes mellitus

1. Endocrine disorders such as gigantism, acromegaly and Cushing's syndrome.
   Hyperglycemia in these conditions causes excess stimulation of β-cells. Constant and excess stimulation, in turn causes burning out and degeneration of β-cells. The β-cell exhaustion leads to permanent diabetes mellitus.
2. Damage of pancreas due to disorders such as chronic pancreatitis, cystic fibrosis and hemochromatosis (high iron content in body causing damage of organs)
3. Pancreatectomy (surgical removal)
4. Liver diseases such as hepatitis C and fatty liver
5. Autoimmune diseases such as celiac disease
6. Excessive use of drugs like antihypertensive drugs (beta blockers and diuretics), steroids, oral contraceptives, chemotherapy drugs, etc.
7. Excessive intake of alcohol and opiates.

Signs and Symptoms of Diabetes Mellitus

Various manifestations of diabetes mellitus develop because of three major setbacks of insulin deficiency.

1. Increased blood glucose level (300 to 400 mg/dL) due to reduced utilization by tissue
2. Mobilization of fats from adipose tissue for energy purpose, leading to elevated fatty acid content in blood. This causes deposition of fat on the wall of arteries and development of atherosclerosis
3. Depletion of proteins from the tissues.

Following are the signs and symptoms of diabetes mellitus:

1. *Glucosuria*

Glucosuria is the loss of glucose in urine. Normally, glucose does not appear in urine. When glucose level rises above 180 mg/dL in blood, glucose appears in urine. It is the renal threshold level for glucose.

2. *Osmotic diuresis*

Osmotic diuresis is the diuresis caused by osmotic effects. Excess glucose in the renal tubules develops osmotic effect. Osmotic effect decreases the reabsorption of water from renal tubules, resulting in diuresis. It leads to polyuria and polydipsia.

3. *Polyuria*

Excess urine formation with increase in the frequency of voiding urine is called polyuria. It is due to the osmotic diuresis caused by increase in blood glucose level.

4. *Polydipsia*

Increase in water intake is called polydipsia. Excess loss of water decreases the water content and increases the salt content in the body. This stimulates the thirst center in hypothalamus. Thirst center, in turn increases the intake of water.

5. *Polyphagia*

Polyphagia means the intake of excess food. It is very common in diabetes mellitus.

6. *Asthenia*

Loss of strength is called asthenia. Body becomes very weak because of this. Asthenia occurs due to protein depletion, which is caused by lack of insulin. Lack of insulin causes decrease in protein synthesis and increase in protein breakdown, resulting in protein depletion. Protein depletion also occurs due to the utilization of proteins for energy in the absence of glucose utilization.

7. *Acidosis*

During insulin deficiency, glucose cannot be utilized by the peripheral tissues for energy. So, a large amount of fat is broken down to release energy. It causes the formation of excess ketoacids, leading to acidosis.

One more reason for acidosis is that the ketoacids are excreted in combination with sodium ions through urine (ketonuria). Sodium is exchanged for hydrogen ions, which diffuse from the renal tubules into ECF adding to acidosis.

8. *Acetone breathing*

In cases of severe ketoacidosis, acetone is expired in the expiratory air, giving the characteristic acetone or fruity breath odor. It is a life-threatening condition of severe diabetes.

9. *Kussmaul breathing*

Kussmaul breathing is the increase in rate and depth of respiration caused by severe acidosis.

10. *Circulatory shock*

Osmotic diuresis leads to dehydration, which causes circulatory shock. It occurs only in severe diabetes.

11. *Coma*

Due to Kussmaul breathing, large amount of carbon dioxide is lost during expiration. It leads to drastic

reduction in the concentration of bicarbonate ions causing severe acidosis and coma. It occurs in severe cases of diabetes mellitus.

Increase in the blood glucose level develops hyperosmolarity of plasma which also leads to coma. It is called hyperosmolar coma.

Complications of Diabetes Mellitus

Prolonged hyperglycemia in diabetes mellitus causes dysfunction and injury of many tissues, resulting in some complications. Development of these complications is directly proportional to the degree and duration of hyperglycemia. However, the patients with well-controlled diabetes can postpone the onset or reduce the rate of progression of these complications.

Initially, the untreated chronic hyperglycemia affects the blood vessels, resulting in vascular complications like atherosclerosis. Vascular complications are responsible for the development of most of the complications of diabetes such as:

1. Cardiovascular complications like:
   i. Hypertension
   ii. Myocardial infarction
2. Degenerative changes in retina called diabetic retinopathy
3. Degenerative changes in kidney known as diabetic nephropathy
4. Degeneration of autonomic and peripheral nerves called diabetic neuropathy.

Diagnostic Tests for Diabetes Mellitus

Diagnosis of diabetes mellitus includes the determination of:

1. Fasting blood glucose
2. Postprandial blood glucose
3. Glucose tolerance test (GTT)
4. Glycosylated (glycated) hemoglobin.

Determination of glycosylated hemoglobin is commonly done to monitor the glycemic control of the persons already diagnosed with diabetes mellitus.

Abnormal response in diagnostic tests

Abnormal response in diagnostic tests occurs in conditions like pre-diabetes (see above). There is an increased fasting blood glucose level or impaired (decreased) glucose tolerance.

Treatment for Diabetes Mellitus

Type I diabetes mellitus

Type I diabetes mellitus is treated by exogenous insulin. Since insulin is a polypeptide, it is degraded in GI tract if taken orally. So, it is generally administered by subcutaneous injection.

Type II diabetes mellitus

Type II diabetes mellitus is treated by oral hypoglycemic drugs. Patients with longstanding severe diabetes mellitus may require a combination of oral hypoglycemic drugs with insulin to control the hyperglycemia.

Oral hypoglycemic drugs are classified into three types.

1. *Insulin secretagogues:* These drugs decrease the blood glucose level by stimulating insulin secretion from β-cells. Sulfonylureas (tolbutamide, gluburide, glipizide, etc.) are the commonly available insulin secretagogues
2. *Insulin sensitizers:* These drugs decrease the blood glucose level by facilitating the insulin action in the target tissues. Examples are biguanides (metformin) and thiazolidinediones (pioglitazone and rosiglitazone)
3. *Alpha glucosidase inhibitors:* These drugs control blood glucose level by inhibiting α-glucosidase. This intestinal enzyme is responsible for the conversion of dietary and other complex carbohydrates into glucose and other monosaccharides, which can be absorbed from intestine. Examples of α-glucosidase inhibitors are acarbose and meglitol.

■ HYPERACTIVITY – HYPERINSULINISM

Hyperinsulinism is the hypersecretion of insulin.

Cause of Hyperinsulinism

Hyperinsulinism occurs due to the tumor of β-cells in the islets of Langerhans.

Signs and Symptoms of Hyperinsulinism

1. *Hypoglycemia*

Blood glucose level falls below 50 mg/dL.

2. *Manifestations of central nervous system*

Manifestations of central nervous system occur when the blood glucose level decreases. All the manifestations are together called neuroglycopenic symptoms.

Initially, the activity of neurons increases, resulting in nervousness, tremor all over the body and sweating. If not treated immediately, it leads to clonic convulsions and unconsciousness. Slowly, the convulsions cease and coma occurs due to the damage of neurons.