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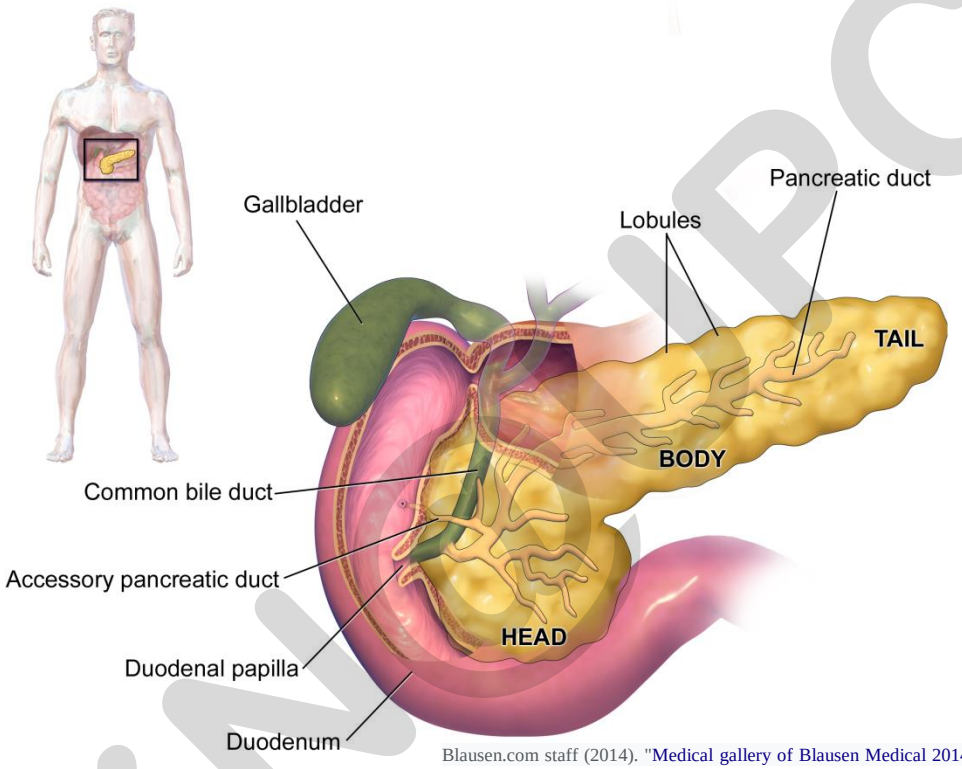
Contents

1. Pancreas: brief introduction

Pancreas is an important organ of vertebrates including mammals. It is an elongated leaf-like tapered organ situated across the back of abdomen, just behind stomach. It has three arbitrary regions – *head, body and tail* (**Fig. 1**). Head is the widest part of the pancreas and lies in the curves of duodenum. Body of the pancreas tapers left from the head and extends up to spleen as tail. There is also less prominent *neck region* connecting *body* with *head*.



Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". *WikiJournal of Medicine* **1** (2). DOI:10.15347/wjm/2014.010. ISSN 2002-4436.

Figure 1. Pancreas: location and gross structure

Pancreas is a type of mixed gland consisting of both endocrine as well as exocrine portions. Exocrine pancreas is composed of acini, network of ducts and main pancreatic duc, and assists in the digestion of food components (proteins, carbohydrates and fats) by pouring alkaline juice and enzymes in the duodenum. Endocrine pancreas is consisting of ***Islets of Langerhans***, cells of which secrete important hormones (insulin, glucagon, somatostatin) to regulate the metabolism of macronutrients especially for carbohydrates. A very common disease – diabetes mellitus is associated with the dysfunction of pancreas. It is of *endodermal* in embryonic origin.

2. Histological organisation

Pancreas is a compound or mixed or composite gland, made up of exocrine as well as endocrine parts (**Fig. 2**). It is externally invested by a thin sheath of connective tissue.

Exocrine part is divided into many lobes and lobules bound together by connective tissues containing pancreatic ducts, blood vessels, lymphatics and nerves. Each lobule consists of several branching tubules, called acini, embedded in connective tissue. Each acini is composed of pyramidal or wedge shaped glandular pancreatic cells surrounding a lumen. The pancreatic digestive enzymes are secreted by acini and sodium bicarbonate by small ductules and larger ducts.

Endocrine part of pancreas is composed of *Islets of Langerhans*. These islets are ovoid, 76x175 µm collection of cells scattered throughout the pancreas among large exocrine tissues. This fact of endocrine portion as *islets* dispersed among the exocrine pancreas was first demonstrated by Langerhans, that's why the name *Islets of Langerhans*. Human pancreas contains about 1-2 millions of such islets constituting only 2% of total pancreatic volume. Each islet has copious blood supply which drains into the hepatic portal vein. The cells in the islets are divided into following four principal types on the basis of their staining properties and morphology:

a) Alpha (α or A) cells – constituting ~ 15-20% and secret glucagon

b) Beta (β or B) cells – constituting ~ 60-75% and secret insulin

c) Delta (δ or D) cells – constituting ~ 08% and secret somatostatin

d) F cells – constituting ~ small portion and secret pancreatic polypeptide (PP)

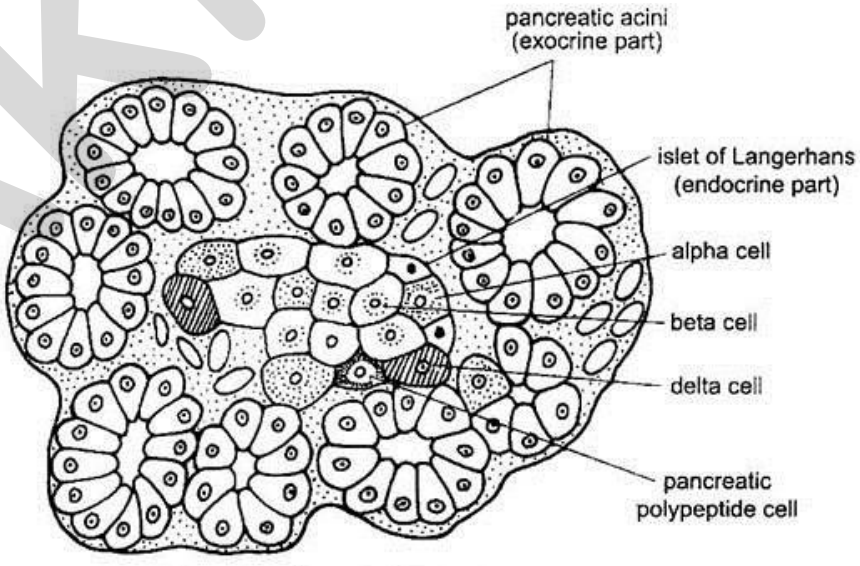


Figure 2. T.S. of pancreas showing exocrine acini and endocrine *Islets of Langerhans*
(https://www.notesonzoology.com/vertebrates/endocrine-glands-of-vertebrates-with-diagram-chordata-zoology/9009)

3. Hormones from Endocrine Pancreas or Islets of Langerhans

Following hormones and factors are synthesised and secreted from different cell types of *islets of Langerhans*:

S/N	Hormone/factor	Source cell type	Major function
Major Pancreatic Hormones			
1.	Glucagon	Alpha (α) cells	Insulin and glucagon reciprocally regulate the blood glucose level and overall carbohydrate metabolism along with protein and fat.
2.	Insulin	Beta (β) cells	
3.	Somatostatin	Delta (δ/D) cells	Both act locally in paracrine fashion to regulate other pancreatic hormones
4.	Pancreatic polypeptide (PP)	F cells	

4. Physiological roles of pancreatic hormones

4.1. Glucagon

Glucagon was discovered by Kimball and Murlin in 1923. They, for the first time, demonstrated its hyperglycemic activity, and hence named as *glucagon* i.e. mobilization of glucose. This hormone is synthesised and secreted from alpha (α) cell of pancreatic islets of Langerhans, is also known as hyperglycemic - glycogenolytic factor (HGF).

Glucagon is a single chain polypeptide of 29 amino acid residues with a molecular mass of 3.45 kDa (**Fig. 3**). It has no cysteine residue and hence lacks any disulphide bond.

Figure 3. Primary structure of glucagon.

4.1.1. Physiological roles/functions of glucagon

- Glucagon plays catabolic role in carbohydrate metabolism.
- Its major target sites of action are hepatocytes (liver cells) and adipocytes.

- It mobilises glucose and fatty acids from their stores into blood. Therefore, It has hyperglycemic effect i.e. glucagon increases blood glucose level.
- Glucagon is glycogenolytic, gluconeogenic and lipolytic hormone. It stimulates and enhances the processes of:
  - glycogenolysis (breakdown of glycogen into glucose) in liver,
  - gluconeogenesis (formation of glucose from non-carbohydrate precursors like amino acids, glycerol etc.) in liver, and
  - lipolysis (breakdown of lipids into free fatty acids and glycerol) in adipose tissues. Glycerol released in this way goes into liver and converted into glucose through gluconeogenesis under the effect of glucagon.

  Glucose formed in these processes in liver is released into blood. Altogether, effects of glucagon greatly enhance the availability of glucose to other organs of the body by raising blood glucose level.
- It also increases amino acid uptake by liver cells (hepatocytes) to increase the rate of gluconeogenesis.
- Thus, under the glucose demanding conditions like prolonged fasting or exercise, and also during neonatal life, gluconeogenic action of glucagon that raises the blood glucose level which is important for the maintenance of glucose homeostasis.
- Under the prolonged effect of high glucagon level, excessive lipolysis leads to increased blood free fatty acids (FFAs). Beyond the physiological need of energy, FFAs are converted into ketone bodies causing ketosis in body. Therefore, glucagon is also considered as ketogenic in action.
- All these physiological effects of glucagon are opposite to those of insulin. Therefore, glucagon is said to have antagonistic action of insulin.

4.2. Insulin

Insulin is anabolic hormone. It is synthesized and secreted by beta (β) cells of pancreatic islets of Langerhans. It has antagonistic effect of glucagon. It increases storage of glucose, fatty acids and amino acids, and thereby reduces blood glucose level.

4.2.1. Structure and chemistry of insulin

Insulin is a small polypeptide hormone containing 51 amino acid residues with molecular mass of 5.808 kDa. Mature and biologically active form of insulin is composed of two polypeptide chains – A chain and B chain with following characteristics:

- A chain or acidic chain: having 21 amino acid residues
- B chain or basic chain: having 30 amino acid residues

These chains are linked together by two interchain disulphide (-S-S-) bonds due the presence of cysteine residues in both the chains. An intrachain disulphide bond is also present between 6th and 11th cysteine residues within the A chain (**Fig. 4**).

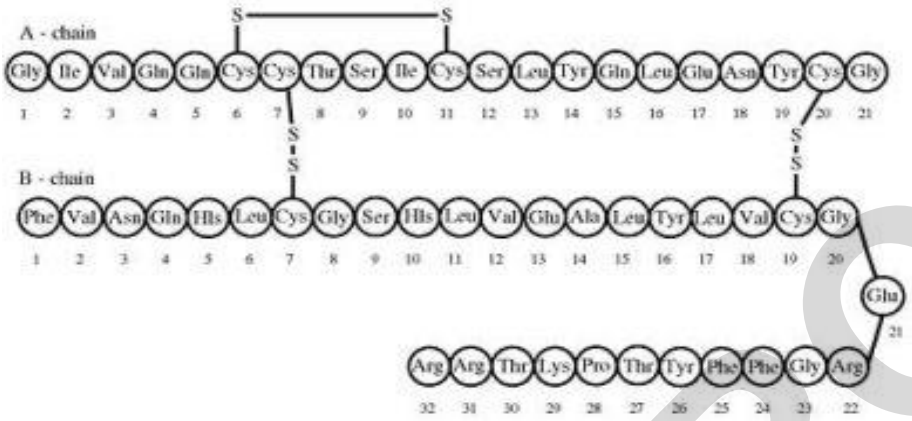


Figure 4. Diagrammatic representation of primary structure of insulin
(https://teachmephysiology.com/endocrine-system/pancreas/insulin/)

Insulin is the cleavage product of a *proinsulin* molecule where both the chains A & B are united by a connecting *C-peptide* (C-terminal peptide) of 31 amino acid residues. During the processing of *proinsulin* molecule before secretion of final hormone, C-peptide is enzymatically cleaved out to from physiologically active insulin.

4.2.2. Physiological roles/functions of insulin

Physiological effects of insulin are diverse and complex and are as follows:

- Insulin secretion after stimulus from increased blood glucose level enhances the uptake of glucose by hepatic, muscle and adipose tissue cells. Insulin interacts with specific cell surface receptors to increases the permeability of plasma membrane for glucose. Insulin activates GLUT-4 (glucose transporters) transporter proteins in cells for glucose uptake. It is the only hormone that can directly lower the blood glucose level.
- Insulin has following effects:
  - ***Hypoglycemic effect***: Insulin rapidly lowers the blood glucose level due to increased transport into insulin sensitive hepatocytes, adipocytes and muscle cells.
  - ***Glycogenic effect***: Insulin stimulates glycogenesis (glycogen synthesis – conversion of glucose into glycogen) by activating glycogen synthase enzyme in liver and muscles.
  - ***Glycolytic effect:*** It promotes glycolysis in liver cells.
  - ***Antigluconeogenic and antiglycogenolytic effects:*** Insulin inhibits gluconeogenic and glycogenolytic pathways to down regulate the carbohydrate catabolism and to lower blood glucose level towards normal range.

  In this way, insulin and glucagon has antagonistic effects to each other.

- Insulin stimulates the storage of energy in the form of glycogen, triglycerides and proteins by increasing their synthesis. It also increases in m-RNA synthesis for lipogenic and other anabolic enzymes and factors.
- It promotes hepatic fatty acid synthesis. From there, fatty acids are transported into adipose tissues to be stored as fats.
- It also reduces the rate of release of fatty acids from adipose tissues.
- Insulin stimulates uptake of **K^+ ions** into insulin sensitive cells (especially *hepatocytes*, *adipocytes* and *skeletal muscles*).

4.3. Somatostatin

4.3.1. Sources and structure

Somatostatin (SS) is released from delta (δ or D) cells of pancreatic islets of Langerhans. Apart from this source, this hormone is also released from gastrointestinal tract (GIT) and hypothalamus. Hypothalamic somatostatin is also known as somatotropin release-inhibitory factor (SRIF) for its inhibitory effect on somatotropin (pituitary growth hormone).

Somatostatin has two forms – SS14 (having 14 amino acid residues) and SS28 (with 28 amino acid residues). Human pancreatic somatostatin is a tetradecapeptide (SS14 from) having one disulphide bond.

4.3.2. Physiological roles

- Pancreatic somatostatin acts locally in paracrine fashion (acting on nearby/adjacent cells or targets) within islets of Langerhans.
- It inhibits the syntheses and secretions of glucagon, insulin and pancreatic polypeptide from α, β and F cells respectively.
- Gastric and pancreatic somatostatin also regulates the absorption of nutrients throughout GIT.

4.4. Pancreatic polypeptide (PP)

4.4.1. Sources and structure

Pancreatic polypeptide is secreted by F-cells of pancreatic islets of Langerhans. It is a linear polypeptide that contains 36 amino acid residues.

4.4.2. Physiological roles

Precise physiological function of pancreatic polypeptide is not well understood. However, scientific researches revealed following proposed functions:

- In birds, PP inhibits liver glycogen synthesis and increases lipogenesis. It also reduces plasma glycerol and free fatty acid levels by inhibiting lipolysis.

- In human, PP inhibits somatostatin secretion from pancreatic islets of Langerhans and gut.
- It inhibits gall bladder contraction and reduces secretion of pancreatic enzymes.
- It also slows down nutrient absorption from gut.

5. Pathophysiology of endocrine pancreas

5.1. Pathophysiology associated with glucagon

Abnormally high secretion (hypersecretion) of glucagon results in increased blood glucose level (hyperglycemia). During diabetes mellitus, this glucagon hypersecretion makes hyperglycemic condition worse.

Deficiency or decreased secretion of glucagon leads to hypoglycemic condition and may be dangerous during prolonged fasting or extraneous exercise.

5.2. Pathophysiology associated with insulin

5.2.1. Insulin deficiency

Insulin deficiency is the result of its decreased secretion from beta cells of islets of Langerhans (malfunctioning of beta cells). Pathological condition associated with insulin deficiency is known as ***diabetes mellitus***.

"Diabetes mellitus is a clinical or pathological condition, characterised by hyperglycemia (high blood glucose level), polyuria (increased urine volume with frequent urination) and glucosuria or glycosuria (excretion of glucose in urine)." In this condition, uptake of glucose from blood into body cells becomes reduced due to insulin deficiency. Blood glucose is not properly taken up and utilised by body cells and leads to increase in blood glucose level (hyperglycemia).

Insulin deficiency hampers most of the insulin dependent physiological processes leading to following conditions:

- Reduced or no glucose uptake by hepatocytes, adipocytes, muscle cells
- Hampered glycogen synthesis by blood glucose
- Reduced utilisation of hepatic glucose by glycolysis
- Unavailability of glucose for lipogenesis (lipid synthesis)
- Increased glycogenolysis, lipolysis, proteolysis and gluconeogenesis

Thus, insulin deficiency causes deceased blood glucose utilisation, and increases mobilisation of glucose from energy stores, leading to detrimental hyperglycemia.

Diabetes mellitus is characterised by following symptoms:

- Polyuria with frequent urination – increased urine volume (highly diluted urine) with frequent urination

- Polydipsia – increased thirst
- Weight loss in spite of polyphagia (increased appetite – frequent urge of eating something)
- Hyperglycemia – high blood glucose level
- Glucosuria – excretion of glucose in urine
- Ketosis – high levels of ketone bodies (ketones, acetoacetate and β-hydroxybutyrate) in blood
- Acidosis – increased acidity (decreased pH) of blood and body fluids (diabetic ketosis sometimes results into fatal metabolic acidosis)
- Coma and death (if not treated and managed properly)

Types of Diabetes Mellitus

There are two types of diabetes mellitus:

1) Primary Diabetes Mellitus

Further, it is of two types:

i. Type-I Diabetes Mellitus or Insulin-dependent diabetes mellitus (IDDM)

In IDDM, insulin deficiency is caused by destruction of insulin secreting beta (β) cells in pancreatic islets of Langerhans. The destruction may be due to autoimmune disorders resulting from the development of antibodies against beta cells. This condition is also known as "*juvenile-onset diabetes*" as it often predominates in youth under the age of 40 years. Certain viral infections also lead to this type of diabetes.

ii. Type-II Diabetes Mellitus or Noninsulin-dependent diabetes mellitus (NIDDM)

NIDDM is also known as "*maturity or adult-onset diabetes*" as it is prevalent in the people over the ages of 35-40 years. In this condition, patients have normal or higher levels of blood insulin level but their cells do not respond to the hormone. Such a condition is known as ***insulin resistance***. Insulin resistance in NIDDM may also be of two types:

a) **Type A insulin resistance:** It is due a decrease in number of insulin receptors on target cells.

b) **Type B insulin resistance:** It is caused by the presence of circulating antibodies against insulin receptors that interfere with binding of insulin with its receptors on target cell surfaces.

2) Secondary Diabetes Mellitus

Secondary DM may be a result of pancreatectomy, pancreatitis or due to accidental intake of beta cell poisons e.g. alloxan, streptozocin etc.

5.2.2. Insulin excess (hypersecretion of insulin)

Due to over secretion of insulin from beta cells of pancreatic islets of Langerhans, blood insulin level becomes abnormally high. Due to high insulin level, there is rapid rush of blood glucose to insulin sensitive hepatic, adipose and muscle cells. This rapid removal of glucose from blood causes decreased glucose level (hypoglycemia) creating "*glucose debt*" or glucose deficiency for nerve cells and also for brain. This condition is known as "*neuroglycopenia.*"

Neuroglycopenia is characterised by malfunction of nerves, brain, including symptoms of palpitation (noticeable rapid, strong and irregular heart beat), hunger, excessive sweating and nervousness (due to irregular autonomic discharges), confusion and cognitive abnormalities. If not treated, this condition may be fatal leading to coma and sudden collapse/death. Best quick treatment is giving glucose rich fluid or fruit juices to the patient.

Suggested readings

- Hadley: Endocrinology
- Norris: Vertebrate Endocrinology, 2nd Ed.
- Ganong: Review of Medical Physiology, 22nd Ed.
- Guyton and Hall: Text Book of Medical Physiology, 11th, Ed.
- Pandey and Shukla: Regulatory Mechanism in Vertebrates
- Singh and Kumar: Animal Physiology and Biochemistry

Practice questions/problems

Short answer type questions:

1. Draw a well labelled diagram showing cross section of pancreas.

2. Enumerate hormones secreted from pancreatic islets of Langerhans.

3. What are the physiological functions of glucagon?

4. Write in brief about functions of insulin in controlling carbohydrate metabolism.

5. Write a short note on somatostatin and its physiological functions.

6. Comment upon the source and physiological roles of pancreatic polypeptide.

7. Explain in brief about pathophysiology related to glucagon.

8. Explain in brief about pathophysiology related to insulin.

9. What is diabetes mellitus? Comment on its symptoms.

10. What is insulin resistance?

11. What is neuroglycopenia? What are its symptoms?