Paper: Animal Physiology and Endocrinology

TOPIC: Pancreas

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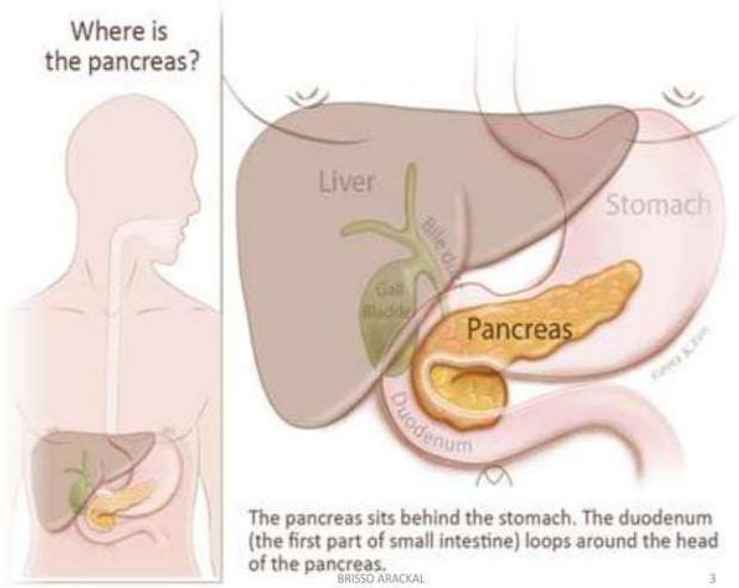
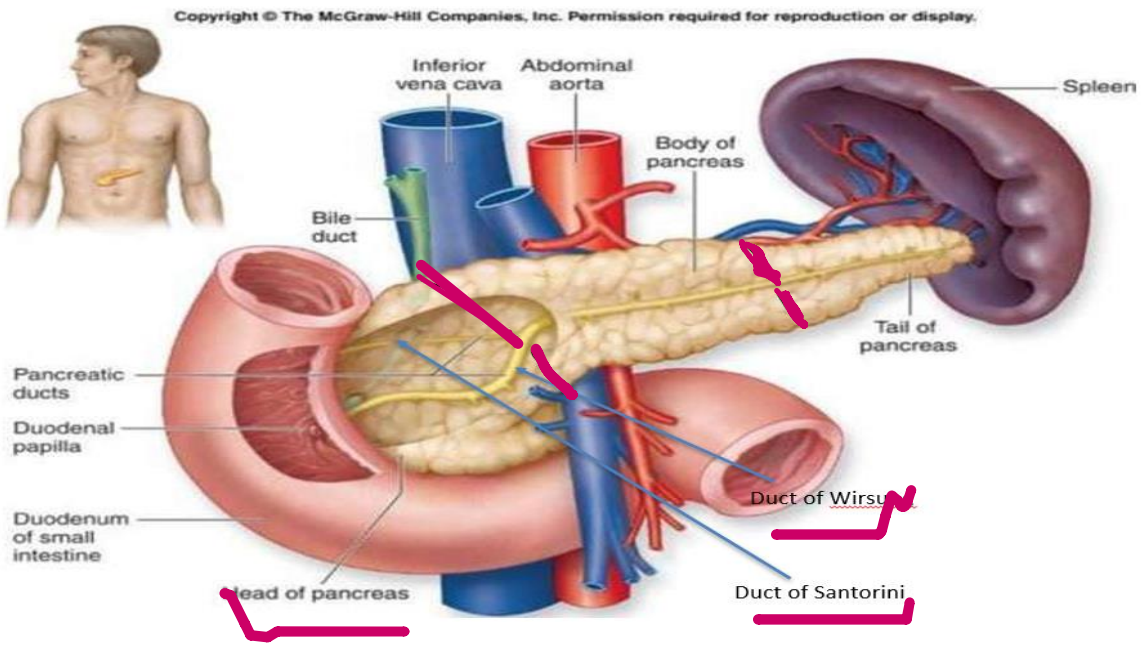
(PANCREAS OF MAMMAL)



- Pancreas is the second biggest gland in the body of mammals
- Found in the junction between stomach and duodenum.
- Originates from endodermal lining of the duodenum

Structure of the Pancreas

ANATOMY



a) Gross Anatomy

The **pancreas** is an elongated leafy structure **which is flat, glandular organ** located in the **abdomen** behind the stomach. The pancreas is approximately 15–20 cm long and weighs around 70–120 grams. Gland is creamy white or pale yellow in color.

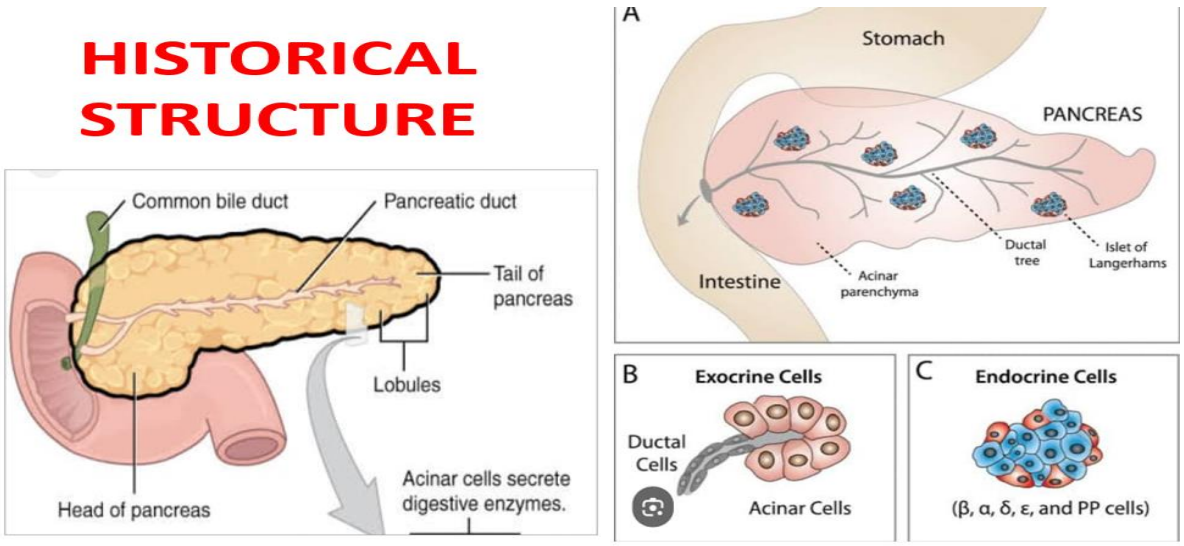
The gland is divided mainly into 3 parts: Head, Body and Tail

1. Head:
    - The widest part of the pancreas.
    - Lies within the "C-shaped" curve of the duodenum.
    - Contains the uncinate process, an extension of the head.
2. Body:
    - The central part of the pancreas.
    - Located behind the stomach and in front of major blood vessels like the aorta and the inferior vena cava.
3. Tail:
    - The narrowest part.
    - Located near the spleen, in close proximity to the left kidney.

The main excretory duct of pancreas is called the **Duct of Wirsung** which combines with the common bile duct prior to the opening into the duodenum through the ampulla of vater. The opening of the pancreatic duct is guarded by a ring of smooth muscles fibers called the **sphincter of Oddi**

b) Histological structure

- The pancreas is a mixed gland, being composed of exocrine as well as endocrine tissues. Entire gland is covered by a **thin layer of loose connective tissue** which **forms a capsule** around the pancreas. From this capsule, **septa** extend inwards. These are **thin partitions** made of connective tissue that **divides the gland internally** into smaller sections called **lobules**.
- Inside each lobule, there is a **stroma** (supporting tissue) made of **loose connective tissue** which **surrounds** the functional parts of the pancreas--such as acini in the exocrine portion and islets in the endocrine portion.



- Within and between these lobules, **connective tissue** supports all the vital structures like ducts, blood vessels, and nerves.

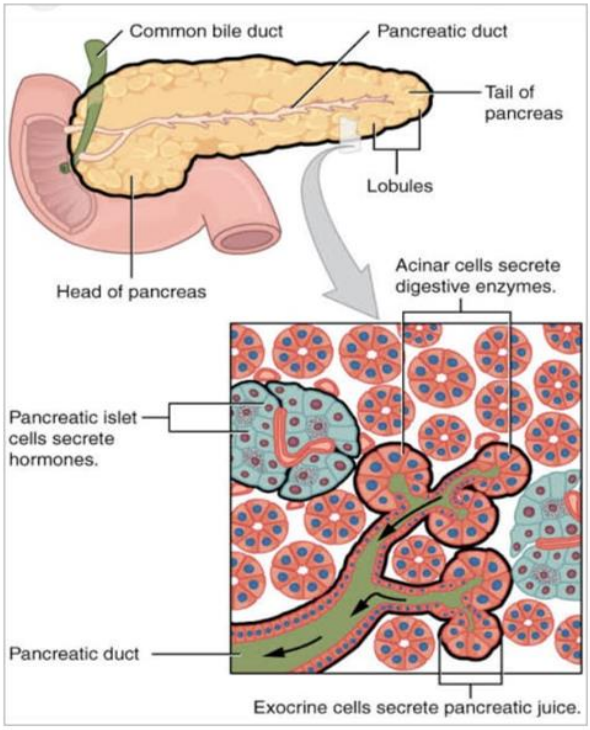
Histologically, it is divided into two main components:

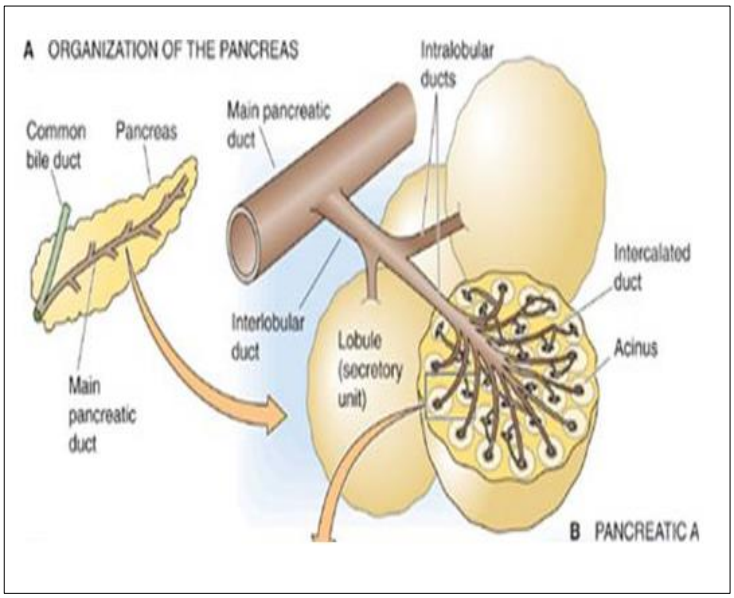
1. **Exocrine Pancreas** **&** **2. Endocrine Pancreas**

The main mass of tissue is the **EXOCRINE PART** of the pancreas within which clusters of **ENDOCRINE CELLS** remain embedded here and there constituting pancreatic islets.

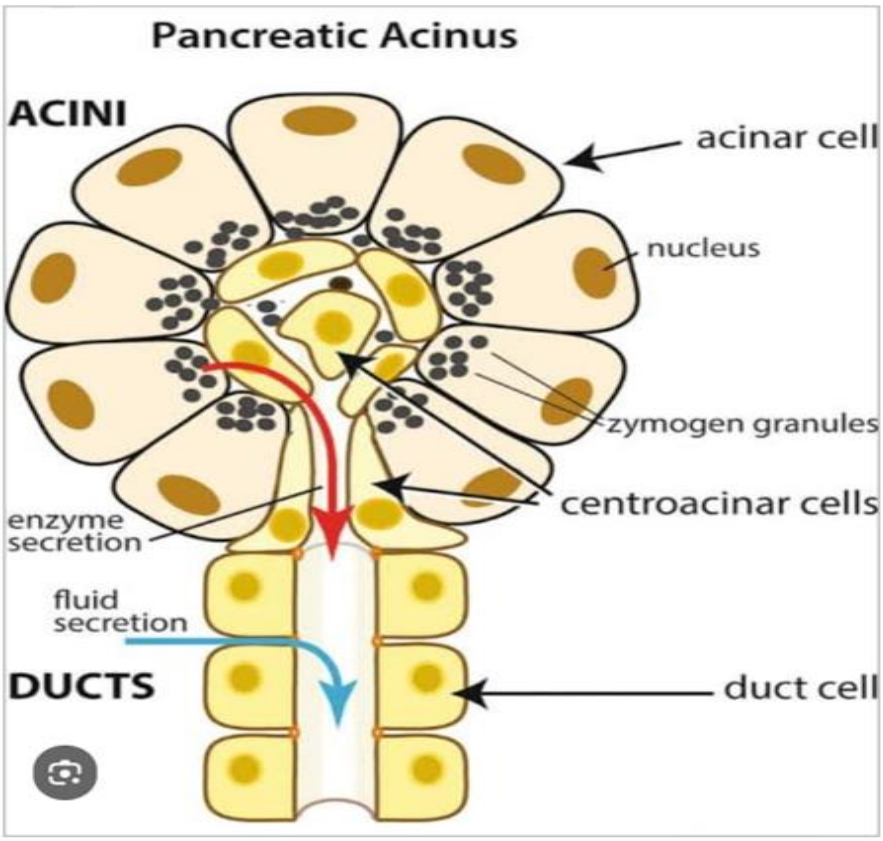
1. Exocrine Part (EXOCRINE PANCREAS)

EXOCRINE PANCREAS





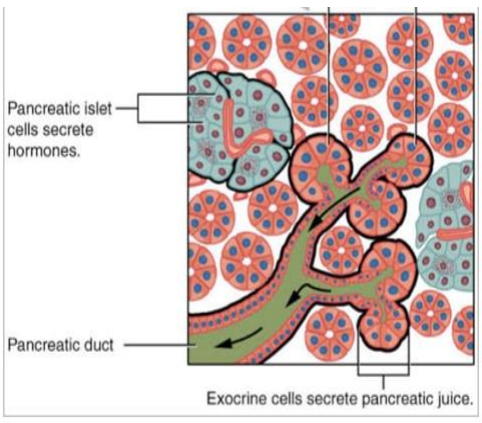
- Exocrine pancreas is made up of acinar cells or acini that produce and secrete digestive enzymes and Duct system and constitutes 98% of total pancrease.
- Acinar cells are organized into lobules, drained by ducts which form the beginning of the duct system-drain into small ducts called **intercalated ducts**.
- Intercalated ducts are short and merge to form larger **intralobular ducts**, which then combine into **interlobular ducts**. Interlobular duct finally drains into main pancreatic duct.
- The main pancreatic duct joins the bile duct and opens into the duodenum at the ampulla of Vater, controlled by the sphincter of Oddi.
- Lobules of acinous gland are bound together by loose connective tissues through which run blood vessels, nerves, lymphatics and endocrine cells.

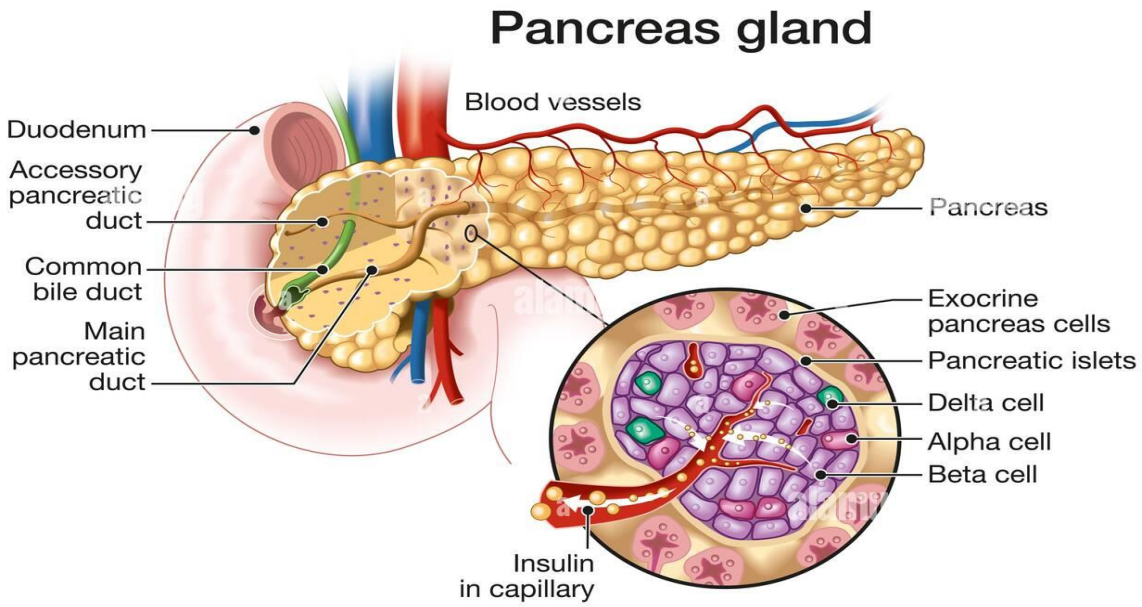
- 

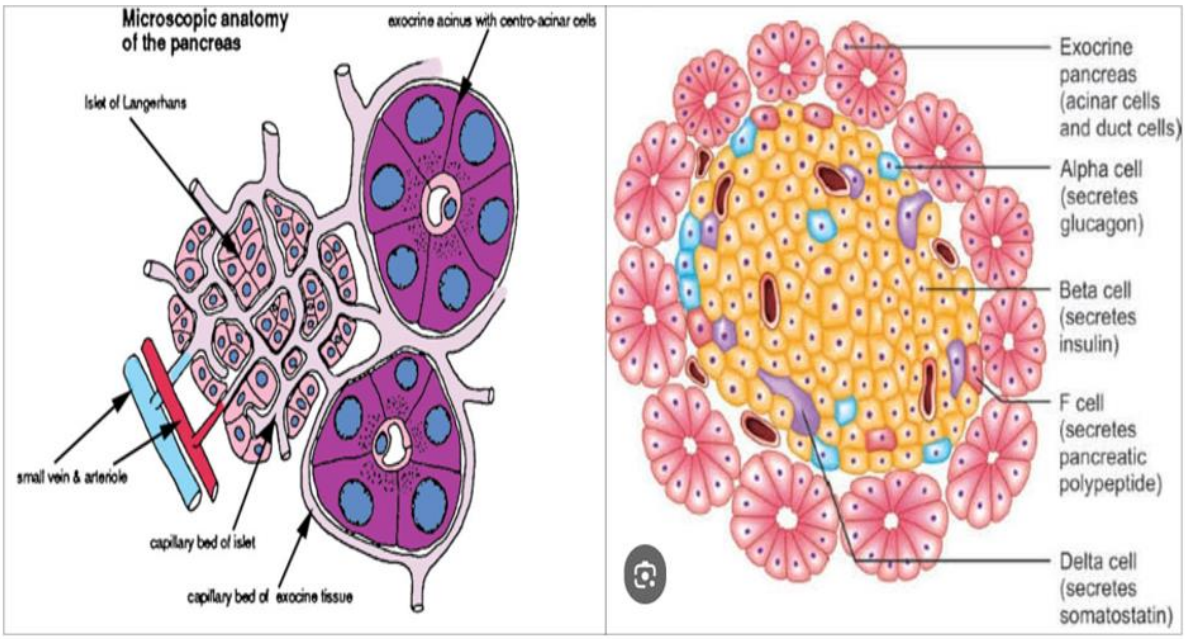
  - The pancreatic acini are composed of secretory zymogenic cells or acinar cells that are of pyramidal shape and are arranged around a central lumen.
  - Cells have a **basophilic basal cytoplasm** due to abundant rough endoplasmic reticulum and a **granular apical cytoplasm** due to zymogen granules (storage of inactive digestive enzymes).
  - The nucleus is round and situated at the broad part of the cell.
  - The acinar cell secretes the pancreatic juice that contains digestive enzymes-amylase, lipase, proteases and bicarbonate-collected by main pancreatic duct and delivers them into the duodenum.

2. <u>Endocrine Part (Islets of Langerhans):</u>

- The endocrine component of the pancreas consists of **specialized cell clusters** called the **Islets of Langerhans**, which are scattered throughout the acinar cells as clusters which are about 1–2% of the pancreatic tissue but are most numerous in the tail portion of pancreas.
- The islets are made up of closely packed mass of cells. These are not connected with duct system but are richly supplied with blood capillaries.







Islet of Langerhans are made up of different Cell Types:

- **Alpha (α) cells:** Constitute ~20% of islet cells; Located mostly at the periphery of the islets, cell are tall and cylindrical--secrete glucagon- **which increases the blood glucose level**
- **Beta (β) cells:** Constitute ~60–70%; Most abundant. Centrally located, cells more or less round or irregular in shape- secrete insulin- **which deceases the blood glucose level**
- **Delta (δ) cells**: Constitute ~5%; Found at the periphery. Cells are large, spindle shaped- secrete somatostatin--**which regulates the release of both insulin and glucagon.**
- **PP (Pancreatic Polypeptide cells)** or F cells: Constitute ~5%; Found at the periphery--Secrete **pancreatic polypeptide**, which regulates exocrine and endocrine pancreatic secretions.

- **Epsilon (ε) cells**: Less than 1%; secrete ghrelin---Secrete **ghrelin**, **which influences appetite.**

Function of Pancreas
&
Hormones released by Pancreas

The pancreas is unique among the glands of our body as it performs both exocrine as well as endocrine functions.

a. Exocrine Functions

The exocrine pancreas aids in digestion by secreting:

1. Digestive Enzymes:
    - Amylase: Breaks down carbohydrates into maltose and dextrins.
    - Lipase: Hydrolyzes triglycerides into glycerol and free fatty acids.
    - Proteases:
        - Trypsin and chymotrypsin: Degrade proteins into smaller peptides.
        - Carboxypeptidase: Breaks peptides into amino acids.
2. Bicarbonate Ions:
    - Neutralize the acidic chyme from the stomach to create an optimal pH for enzyme activity in the small intestine.

b. Endocrine Functions

The endocrine function of the pancreas involves the production and release of hormones that regulate blood sugar levels and other metabolic processes.

a) Insulin (β-cells)

Functions:

- Lowers blood glucose levels by promoting glucose uptake by cells, especially in muscles and adipose tissue.
- Stimulates:
    - Glycogenesis: Conversion of glucose to glycogen (in the liver and muscles).
    - Lipogenesis: Conversion of glucose to fats (in adipose tissue).
- Inhibits gluconeogenesis (glucose production from non-carbohydrate sources).

b. Glucagon (α-cells)

Functions:

- Increases blood glucose levels during fasting by:
  - Glycogenolysis: Breaking down glycogen into glucose in the liver.
  - Gluconeogenesis: Synthesis of glucose from non-carbohydrate precursors.

c. Somatostatin (δ-cells)

Functions:

- Regulates endocrine and exocrine secretions by inhibiting:
  - Insulin and glucagon release.
  - Digestive enzyme and bicarbonate secretion.
- Balances metabolic processes and digestive efficiency.

d. Pancreatic Polypeptide (PP cells)

Functions:

- Modulates exocrine pancreas secretions and gastrointestinal motility.
- Influences appetite regulation.

e. Ghrelin (ε-cells)

Functions:

- Stimulates hunger by acting on the hypothalamus.
- Promotes growth hormone release.
- Regulates energy homeostasis.

Summary Table of Pancreatic Hormones

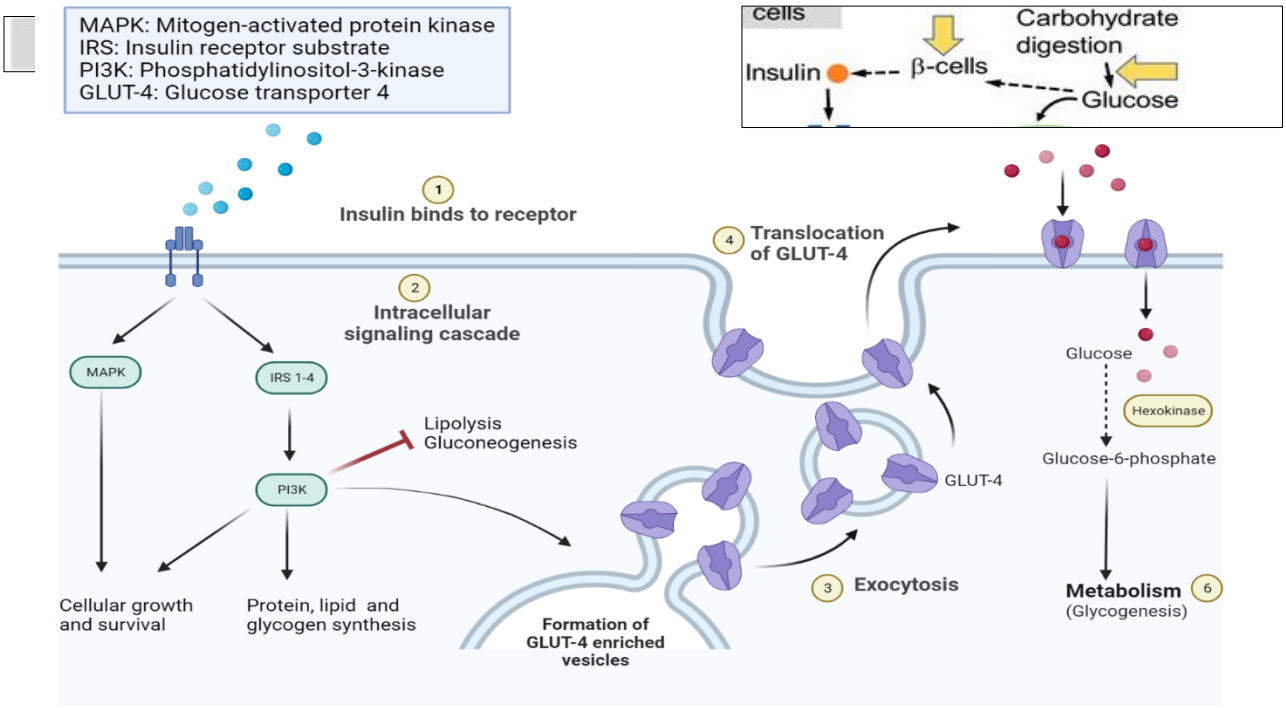
Cell Type	Hormone	Function	Effect on Blood Sugar
α-cells	Glucagon	Increases glucose production	Raises blood sugar
β-cells	Insulin	Increases glucose uptake & storage	Lowers blood sugar
δ-cells	Somatostatin	Inhibits insulin & glucagon	Regulates both
PP-cells	Pancreatic Polypeptide	Regulates exocrine secretions	Neutral
ε-cells	Ghrelin	Stimulates appetite	Indirect effect

Mechanism of Action of Insulin hormone

Target Cells of Insulin:

Muscle Cells (especially skeletal muscle)- GLUT4 transporters
Liver Cells (hepatocytes)- GLUT2 which is always open (membrane)
Fat Cells (adipose tissue)- GLUT4 transporters

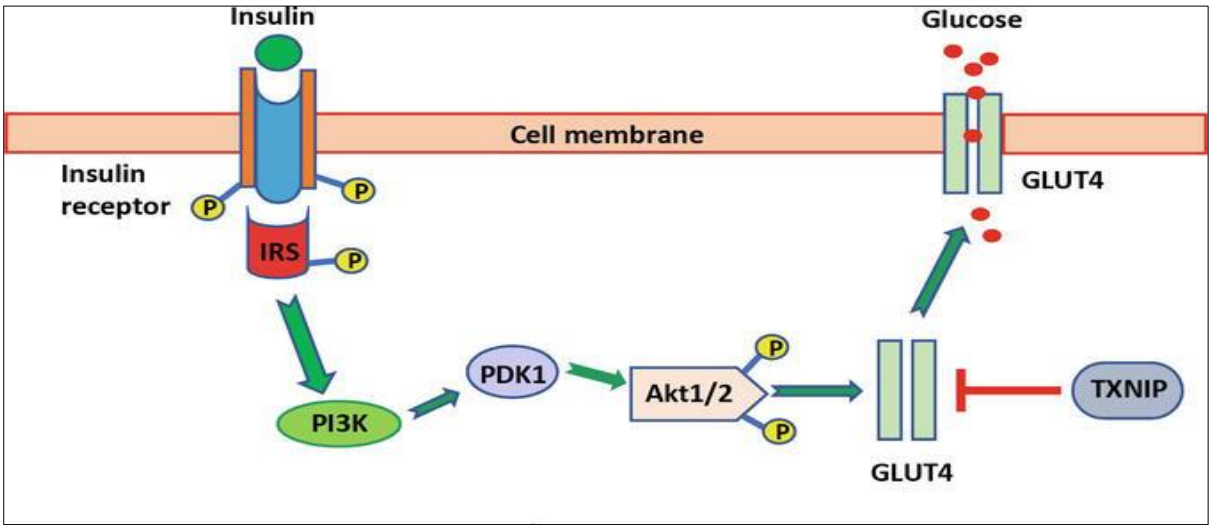
All these cells help in **glucose regulation**



Mechanism of Action (Muscle and fat cells)

- After a meal, **carbohydrates** are digested and converted into **glucose**. This glucose enters the bloodstream, **raising blood sugar levels**. The pancreas detects this increase and releases **insulin** into the blood.

- Released Insulin travels through the blood and reaches **target cells** like:
  - **Muscle cells** (for energy)
  - **Liver cells** (for storage)
  - **Fat (adipose) cells** (for fat production)
- On these cells, insulin binds to **insulin receptors** located on the **cell membrane**. The insulin receptor has **two alpha (α) subunits** and **two beta (β) subunits** (tetramer unit)
- **α-subunits** are **outside** the cell and bind to insulin.
- **β-subunits** span the membrane and contain **tyrosine kinase** enzyme inside the cell.



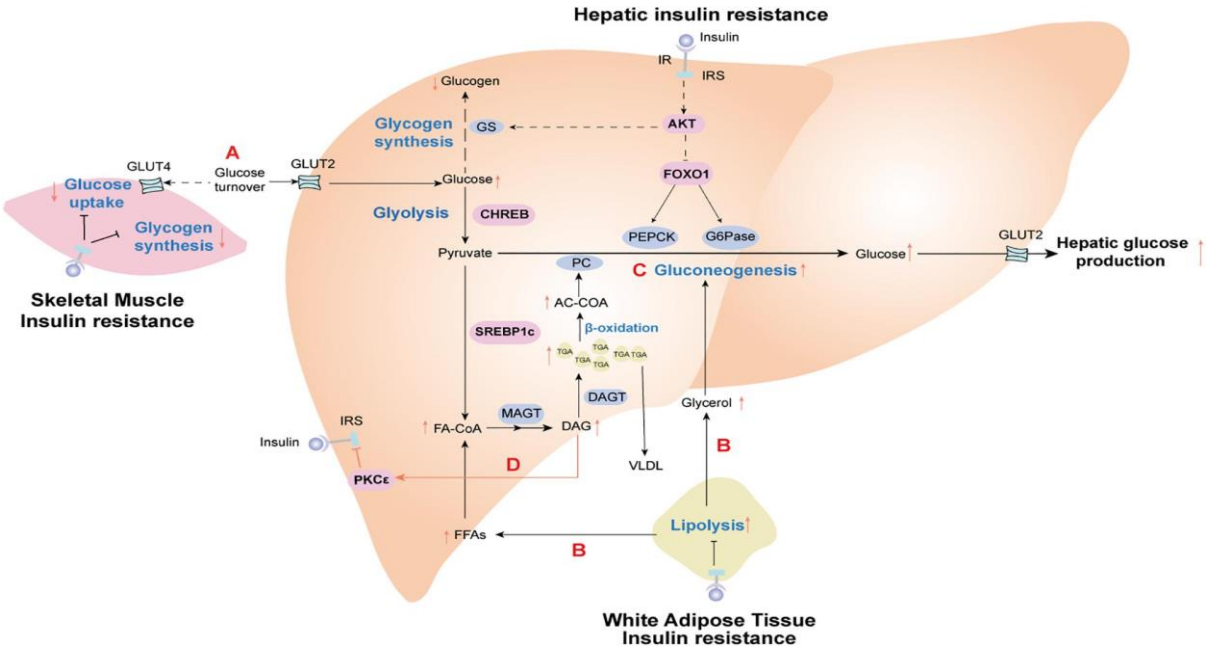
Insulin binds to the α-subunits of the receptor (outside the cell). This causes a change in shape (conformational change). The β-subunits inside the cell become **auto phosphorylated (activated)**. **Autophosphorylation** (adds phosphate groups to itself) of beta subunits of the receptor activates the local tyrosine kinase enzyme attached to it. **Thus, Insulin receptor is an example of ENZYME LINKED RECEPTOR.**

This triggers a chain of signals inside the cell ie., it in turns causes phosphorylation of multiple other intracellular enzymes like:

- IRS (Insulin Receptor Substrate)
- PI3K (Phosphoinositide 3-Kinase)
- Akt (Protein Kinase B)

Akt sends a final message to the vesicles containing GLUT4. These vesicles move toward the cell membrane. The vesicles fuse with the cell membrane, placing GLUT4 transporters on the surface of the cell.

With GLUT4 on the surface, glucose flows **from the blood into the cells**.
As glucose leaves the blood, the **blood sugar level decreases** — returning to normal range.



In Muscle Cells:

- Glucose is used to make **energy (ATP)** for muscle activity.
- Extra glucose is stored as **glycogen** (a storage form of glucose) for later use.

In Liver Cells:

- Insulin promotes **glycogenesis** – the process of forming **glycogen from glucose**.
- It also **stops gluconeogenesis**, the creation of new glucose from proteins or fats.

In Fat (Adipose) Cells:

- Glucose is converted into **fatty acids** and stored as **triglycerides** (fats).
- This process is called **lipogenesis**.

This is how insulin **controls and maintains normal blood glucose levels**.

Mechanism of Action of Glucagon Hormone

- When blood glucose falls (usually below 70 mg/dL), the **α-cells in the Islets of Langerhans** in the pancreas detect this and causes the release of glucagon into the bloodstream.
- Glucagon travels through the blood and mainly targets the **liver cells**. Liver cells have specific **Glucagon Receptors (GCGR)** on their surface. These receptors are part of the **G-protein-coupled receptor (GPCR)** family.
- When glucagon binds to its receptor:
    - It **activates a G-protein** inside the liver cell.
    - The G-protein **stimulates an enzyme called adenylyl cyclase**.
- **Adenylyl cyclase converts ATP into cAMP (cyclic adenosine monophosphate)**. **cAMP acts as a "second messenger"** -The increase in cAMP **activates Protein Kinase A (PKA)**. PKA then **phosphorylates (activates or deactivates)** several enzymes that control **glucose metabolism**.

Metabolic Effects of Glucagon

1. **Glycogenolysis (Breakdown of Glycogen):** PKA activates the enzyme **glycogen phosphorylase**. This enzyme **breaks down glycogen** (stored glucose in the liver) into **glucose-1-phosphate**, then into **glucose**. This **free glucose** is released into the blood which causes rapid increase in blood sugar from **stored glycogen**.

2. **Gluconeogenesis (Making New Glucose):** Glucagon also activates enzymes that **create glucose from non-carbohydrate sources**, such as: Amino acids, Lactic acid & Glycerol (from fat breakdown). Important enzymes like **PEPCK**, **Fructose-1,6-bisphosphatase**, and **glucose-6-phosphatase** are involved.

   This process ensures a **long-term supply of glucose**, especially during **prolonged fasting** or starvation.

The glucose produced from glycogenolysis and gluconeogenesis is sent into the bloodstream. This **raises the blood glucose level back to normal**.

Difference between insulin and Glucagon

Feature	Glucagon	Insulin
Secreted by	α-cells (pancreas)	β-cells (pancreas)
Triggered by	Low blood sugar	High blood sugar
Target organ	**Liver (main)**	Liver, muscle, fat
Main actions	Increases glucose	Decreases glucose

Dysfunction and Related Diseases of Pancreatic Hormones

1. Insulin Dysfunction and Related Diseases

Insulin's Normal Role

- Insulin is secreted by **β-cells** of the pancreas.
- Its main function is to **lower blood glucose** by:
  - Helping cells take in glucose
  - Storing glucose as glycogen
  - Converting glucose to fat
  - Inhibiting glucose production in the liver

When Insulin Doesn't Work Properly- it causes a disease called DIABETES MELLITUS which can be due to two major types of insulin-related dysfunctions:

1) Insulin Deficiency (Not Enough Insulin Production):

This gives rise to a **condition called**

- **Type 1 Diabetes Mellitus (T1DM) or Insulin-Dependent Diabetes Mellitus (IDDM): It is** an **autoimmune disease** where the body's immune system attacks the **β-cells** of the pancreas as a result **Very little or no insulin is produced**. Usually appears in **childhood or adolescence**, but can occur at any age.

Diabetes Mellitus

- Diabetes mellitus is a syndrome of impaired carbohydrate, fat, and protein metabolism caused by either lack of insulin secretion or decreased sensitivity of the tissues to insulin
- Two forms of diabetes mellitus
- Type I diabetes mellitus, also called insulin-dependent diabetes mellitus (IDDM), is caused by impaired secretion of insulin.
- Type II diabetes mellitus, also called non–insulin-dependent diabetes mellitus (NIDDM), is caused by resistance to the metabolic effects of insulin in target tissues.

Type I Diabetes

- Caused by Impaired Secretion of Insulin by the Beta Cells of the Pancreas
- Often, type I diabetes is a result of autoimmune destruction of beta cells, but it can also arise from the loss of beta cells resulting from viral infections.
- Because the usual onset of type I diabetes occurs during childhood, it is referred to as **juvenile diabetes**.
- Pathophysiological features:
- Hyperglycemia as a result of impaired glucose uptake into tissues and increased glucose production by the liver (increased gluconeogenesis)

- Depletion of proteins resulting from decreased synthesis and increased catabolism
- Depletion of fat stores and increased ketosis
- As a result of these fundamental derangements:

- Glucosuria, osmotic diuresis, hypovolemia
- Hyperosmolality of the blood, dehydration, polydipsia
- Hyperphagia but weight loss; lack of energy
- Acidosis progressing to diabetic coma; rapid and deep breathing
- Hypercholesterolemia and atherosclerotic vascular disease

This leads to effects like:

- Glucose **cannot enter cells** → stays in the bloodstream
- **High blood sugar (hyperglycemia)** occurs
- Body starts breaking down fat and muscle for energy
- **Ketones** are produced → leads to **diabetic ketoacidosis (DKA)**

- **Chronic High Glucose Concentration Causes Tissue Injury**
- When blood glucose is poorly controlled over long periods, blood vessels in multiple tissues throughout the body begin to function abnormally and undergo structural changes that result in inadequate blood supply to the tissues.
- This in turn leads to increased risk for heart attack, stroke, end-stage kidney disease, retinopathy and blindness, and ischemia and gangrene of the limbs.
- Chronic high glucose concentration also causes damage to many other tissues. For example, peripheral neuropathy and autonomic nervous system dysfunction

Symptoms observed in such T1DM patients

- Excessive urination (polyuria)
- Excessive thirst (polydipsia)
- Weight loss
- Fatigue
- Sweet-smelling breath (due to ketones)

Management:

- Patients **must take insulin injections** daily to survive.
- **Without insulin**, blood sugar remains dangerously high.

2. Insulin Resistance (Cells Don't Respond to Insulin)

Condition: Type 2 Diabetes Mellitus (T2DM) or Insulin-Independent Diabetes Mellitus (IDDM)

In such dysfunction, Insulin is **produced**, but body **cells become resistant** to its action. Common in **adults**, especially with **obesity, sedentary lifestyle**, and **genetic factors**.

Early stages can often be managed with **diet, exercise**, and **oral medication**. In later stages, **insulin may be required** if beta cells become exhausted.

Type II Diabetes Mellitus

- Insulin Resistance Is the Hallmark of Type II Diabetes Mellitus
- Type II diabetes is far more common than type I diabetes (accounting for approximately 90% of all cases of diabetes)
- Usually associated with obesity.
- This form of diabetes is characterized by impaired ability of target tissues to respond to the metabolic effects of insulin, which is referred to as insulin resistance.
- In contrast to type I diabetes, pancreatic beta cell morphology is normal throughout much of the disease, and there is an elevated rate of insulin secretion.

Metabolic syndrome

- Metabolic syndrome include:

(1) obesity, especially accumulation of abdominal fat;
(2) Insulin resistance
(3) fasting hyperglycemia
(4) lipid abnormalities such as increased blood triglycerides
(5) hypertension.

- Type II diabetes usually develops in adults and therefore is also called **adult-onset diabetes**.
- Caloric restriction and weight reduction usually improve insulin resistance in target tissues
- Drugs that increase insulin sensitivity, such as thiazolidinediones and metformin, or drugs that cause additional release of insulin by the pancreas, such as sulfonylureas, may also be used.
- In the late stages of the disease when insulin secretion is impaired, insulin administration is required.

Effects:

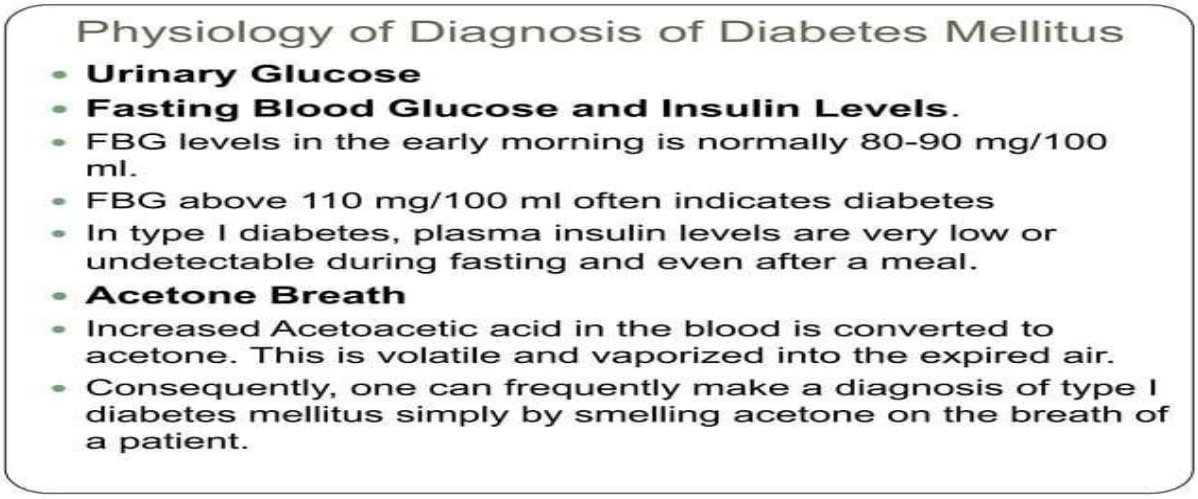
- Glucose uptake by cells is reduced
- Blood sugar remains high (chronic hyperglycemia)
- Over time, the pancreas may **wear out**, reducing insulin production

Symptoms:

- Similar to Type 1 but often milder and slower in onset. This Can be managed with **diet, exercise, oral medications**, and sometimes **insulin in severe case.**

C. Other Conditions from Insulin Dysfunction

- **Hypoglycemia** (Low blood sugar):
  - Occurs if too much insulin is given or too little food is consumed
  - Symptoms: shaking, sweating, confusion, fainting



Difference between

Feature	Type 1 Diabetes	Type 2 Diabetes
Onset	Sudden	Gradual
Cause	Autoimmune destruction of β-cells	Insulin resistance
Insulin	**Absent** → Must be injected	**Present** (early), may decline later
Severity	**Life-threatening without insulin**	**Can be managed** early on
Long-term Complications	Common if poorly controlled	Common, especially if undiagnosed for long
Ketoacidosis risk	High	Low (but possible)

- **Type 1** is **more immediately harmful** because **insulin is absolutely required** for survival.
- **Type 2** may be **more common** and **dangerous long-term** due to being **undiagnosed or untreated** for years, leading to:
  - Heart disease
  - Kidney failure
  - Nerve damage
  - Vision problems

So, both are serious, but **Type 1 is more acutely dangerous**, while **Type 2 is more dangerous in the long run** if ignored.