University of Jordan - Faculty of Medicine
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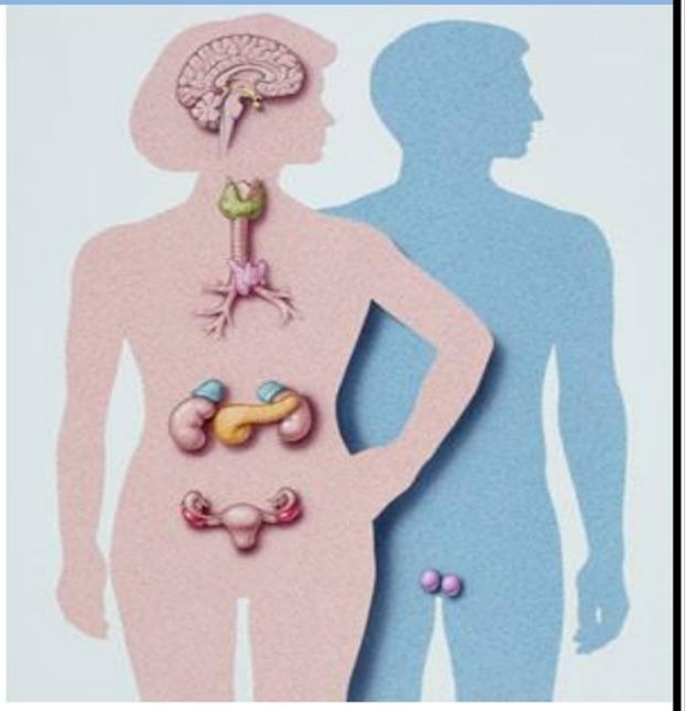
Medical Committee
The University of Jordan

Endocrine System



- ☐ Anatomy/Embryology/Histology
- ☐ Biochemistry
- ■ Physiology
- ☐ Pharmacology
- ☐ Pathology
- ☐ PBL

☐ Slide ■ Sheet ☐ Handout ☐ Other

Lecture #: **7**

Date:

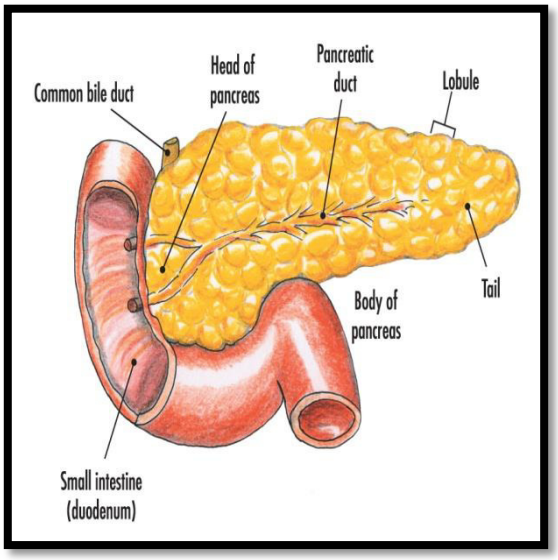
Dr's Name: **Saleem**

Price:

Written by: **نور حماد**

Designed by: Zakaria W. Shkoukani

Pancreas



The pancreas is a dual-function gland, having features of both endocrine and exocrine glands.

- The **exocrine component of the pancreas**, often called simply the **exocrine pancreas**, is the portion of the pancreas that performs exocrine functions (It secretes pancreatic fluid that contains digestive enzymes that pass to the small intestine) while **the endocrine component is made of** four cell type exist in the **islets** and secrets hormones (insulin and glucagon)
- Pancreatic enzymes are the most important and essential enzymes in our bodies because they are the only enzymes in our bodies that work on carbohydrate, proteins and lipids together
- . The enzymes and hormones of pancreas are stimulated by :
- 1. Ingestion of nutrients . 2 . gastrointestinal hormones.

Endocrine part

Major cell types in a typical islet of Langerhans

- Pancreatic islets of Langerhans comprise (1-2 %) of the pancreatic mass and they scattered throughout the organ.

Cell type	Approximate % of islet mass	Secretary product
Alpha	20%	glucagon
Beta	75%	insulin and Amylin
Delta	3-5%	somatostatin
F cell(pp cell)	<2%	Pancreatic polypeptide

- Notes:
  - ✓ **Somatostatin**: is a polypeptide hormone, it's a neurohormone (neurotransmitter in the brain and hormone in the pancreas), produced in the hypothalamus and pancreas.
  - ✓ **Ghrelin**:" the hunger hormone "regulates the appetite .it is produced mainly in stomach (fundus) and a little in the intestine and pancreas.

    ** Ghrelin stimulates Insulin secretion indirectly; empty stomach 》 Ghrelin secretion 》 felling hungry 》 eating 》 more carbs 》 insulin secretion
  - ✓ **Amylin**:"islet Myeloid polypeptide". it is co-secreted with insulin from beta cells (complement the action of insulin)

Pro-insulin

Proinsulin is the prohormone precursor to insulin made in the beta cells of the islets of Langerhans

☒ General information about **pro-insulin.**

- ✓ It consists of

  1-A chain (21 amino acids)

  2-B chain (30 amino acids)

  3- C peptide (31 amino acids) which connects between A and B chains

The C-peptide is abstracted from the center of the pro-insulin sequence; the two other ends (the B chain and A chain) remain connected by disulfide bonds to form mature insulin.

- ✓ Pro- insulin is secreted in small amount and it has 10% of insulin activity
- ✓ (50- 60) % of **insulin** is captured by the **liver** (is not released in to circulation),but the remaining **C peptide** is secreted into **circulation**

- ✓ To know how much insulin is secreted (Activity of beta cells),we depend on C peptide level ,since C peptide is secreted in the same amount as insulin.(The C peptide and insulin are packaged in granules and secreted in equimolar amounts)

☒ In diabetic patients, we measure C peptide instead of Insulin level ,because C peptide can assess a person's own insulin secretion even if they receive insulin injections (its level equals just endogenous insulin level NOT both exogenous and endogenous levels).

Normal Regulation of Blood Glucose

The human body wants blood glucose (blood sugar) maintained in a very narrow range. Insulin and glucagon are the main hormones involved in the regulation of blood sugar, butthere are otherhormones that play role in the homeostasis of glucose in the body (Growth hormone, cortisol, catecholamine and thyroid hormones)

☒ The regulators of Glucose concentration either Hypoglycemic agents or hyperglycemic agents

- ✓ Hypoglycemic agents: agents that decrease the level of glucose in the blood
- ✓ Hyperglycemic agents : agents that increase the level of glucose in the blood

- ✓ Insulin is the only natural hypoglycemic hormone in the body
- ✓ Glucagon is the most potent hyperglycemic hormone in the body, followed by cortisol.

❖ Insulin receptor

☒ Insulin's receptor and its second messenger mechanism are unique

The **insulin receptor (IR)** is a transmembrane receptor that is activated by insulin,and belongs to the large class of tyrosine kinase receptors.

Insulin receptor has 4 subunits (2 alpha and 2 beta), the alpha subunits found on the plasma membrane while the beta subunits penetrate the membrane, the alpha subunits are connected to each other and to the beta subunits by **disulfide bonds**. Insulin binds with alpha subunits and immediately beta subunits will be activated .Also, Tyrosine Kinase which is connected with beta subunits will be also activated (The insulin receptor's endogenous ligands include insulin, IGF-I and IGF-II. The binding of ligand to the α-chains induces structural changes within the receptor leading to **autophosphorylation** of various tyrosine residues within the intracellular TK domain of the β-chain.)

☒ Functions of insulin:

Insulin is a hormone which plays a number of roles in the body's metabolism.

Insulin regulates how the body uses and stores glucose and fat

- ✓ Activation of glucose transporters especially glucose **transporter 4**. So it **stimulates** glycogen formation and **decreases** glycogenolysis and gluconeogenesis.
- ✓ Plays role in protein synthesis (by stimulating amino acids uptake).
- ✓ Plays role in **Fat synthesis** (by increased esterification of fatty acids). –
- ✓ Growth and gene expression. –

- ✓ Increase potassium, phosphate and magnesium uptake into the cells.
- ✓ Activates phospholipase C that produces IP3 and DAG as second messengers.
- ☒ Similar to other hormones, insulin may activate phospholipase C which stimulates amino acid uptake for protein synthesis and ions (k+, Mg+2, PO4 -3) uptake.

Factors and Conditions That Increase or Decrease Insulin Secretion.

- . Increase insulin Secretion

- ✓ Increased blood glucose
- ✓ Increased blood free fatty acids
- ✓ Increased blood amino acids
- ✓ Gastrointestinal hormones (gastrin, cholecystokinin, secretin, gastric inhibitory peptide)
- ✓ Glucagon, growth hormone, cortisol
- ✓ Parasympathetic stimulation; acetylcholine
- ✓ ~-Adrenergic stimulation
- ✓ Insulin resistance; Obesity
- ✓ Sulfonylurea drugs (glyburide, tolbutamide) ..
- ✓ ghrelin-

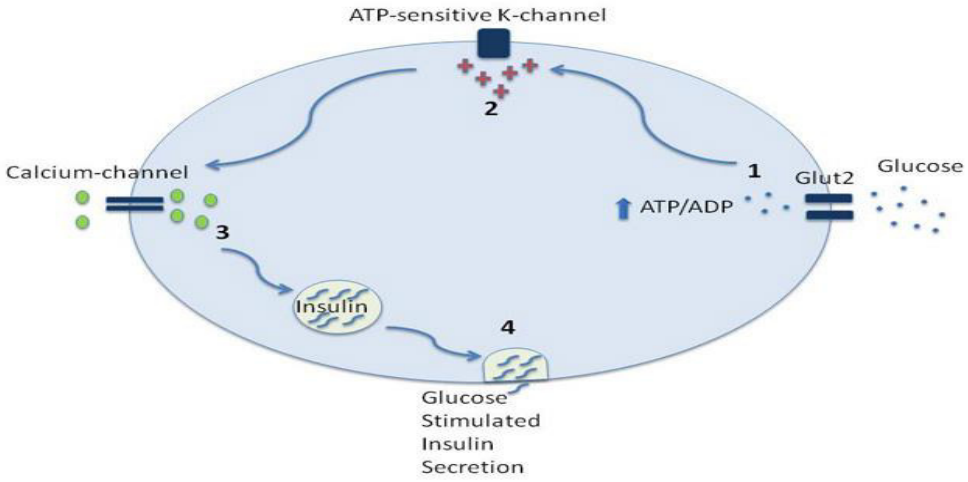
Decrease Insulin Secretion

- ✓ Decreased blood glucose
- ✓ Fasting ·
- ✓ Somatostatin -
- ✓ Alpha Adrenergic activity
- ✓ Leptin from adipose tissue

❖ The key steps leading to glucose-stimulated insulin secretion

- Increased levels of glucose in the circulation lead to increased glucose uptake into pancreatic beta cells through GLUT2, a glucose transporter.
- Increased intracellular glucose then leads to increased production of ATP, and an increase in the ATP/ADP ratio (1); the increased ATP/ADP ratio leads to closing of the potassium channel and depolarization of the cell (2); and cell depolarization opens a calcium channel (3) which leads to insulin secretion (4).

Look at the figure below:



☒ Insulin secretion stops when glucose concentration equal or less than 50 mg/100ml. - The maximum level of insulin secretion appears when glucose concentration is about (300 – 400) mg/100ml.

☒ Down regulation of insulin receptors

The number or the affinity, or both, of insulin receptors is affected by insulin and other hormones exercise ,food and other factors .Exposure to increased amounts of insulin decreases the receptor concentration ,and exposure to low amounts of insulin increases the affinity of the receptors. The number of receptors per cell is increased in starvation

and decreased in obesity. The affinity of receptors is increased in adrenal insufficiency and decreased in excess glucocorticoid

☒ **Diabetes mellitus** (**DM**), commonly referred to as **diabetes**, is a group of metabolic diseases in which there are **high blood sugar levels** over a prolonged period

☒ Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced. There are three main types of diabetes mellitus:

- **Type 1 DM** results from the pancreas' failure to produce enough insulin. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The cause is unknown

Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses a lack of insulin may also develop. This form was previously referred to as "non insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The primary cause is excessive body weight and not enough exercise (DM2 occurs in obese and old individuals, but sometimes it can also occur in old people (with normal weight) but this is rare.)

- **Diabetes associated with other conditions :**examples diabetes due to pancreateoctomy

Releasing of Insulin

After having a meal (glucose intake), beta cells release insulin in two phases (increase then decrease):

1. First phase (a sudden increase) is rapidly triggered in response to increased blood glucose levels (in this phase the insulin blood concentration is very high because beta cells release the stored pre synthesized insulin)

2. Second phase (the decrease) is a sustained, slow release of newly formed vesicles (in the beginning of this phase we will notice sharp decline in insulin concentration).

❖ Effect of insulin on glucose uptake in tissues which it has been investigated

✓ Some organs take glucose continuously and spontaneously- without the need of insulin-; because those are vital organs, while other organs need insulin to take glucose.

☒ 1) Tissues In which Insulin facilitates glucose uptake

- Skeletal muscle
- Cardiac muscle
- Smooth muscle
- Adipose tissue
- Leukocytes
- · Crystalline lens of the eye Pituitary
- Fibroblasts Mammary gland
- Aorta. A cells of pancreatic islets

☒ 2)Tissues in which insulin does not facilitates glucose uptake :

- Brain (except probably part of hypothalamus)
- Kidney tubules
- Red blood cells
- Intestinal mucosa

☒Homeostasis of glucose

- The normal blood glucose level (tested while fasting) for non-diabetics, should be between 90 and 100 milligrams per deciliter (mg/dL) . - Fasting glucose level above 110mg/dl have considered abnormal (pre-diabetic or diabetic). So its normal range between (70-100)
- (The homeostasis of glucose: 90% of population have glucose concentration in blood ranging between 90-100 mg/dL, rare below that up to 70 mg/dL, very rare above 100 till 110 mg/dL (there is something wrong in the metabolism of glucose))

- 5% percent of glucose concentration alternates between circulation and liver (liver uptakes 5% of glucose and it also supplies the circulation with 5% of its glucose concentration).
- Glucose normally **is not** excreted in the urine (this is not absolute, there might be a little glucose) but When blood glucose levels **exceed 180mg/dl** (the renal threshold), glucose will be excreted in urine (Glycosuria), and it increases with the increasing blood concentration.

Insulin deficiency

- Deficiency of insulin lead to abnormality or disorder in metabolism of carbohydrates, lipids and proteins, the combination of the disorders of carbohydrate, fat and protein metabolism at diabetic leads to specific micro vascular lesion in the retina, renal glomerulus and peripheral nerves.

- ### The relationship between obesity and diabetes

  Diabetes and obesity are closely linked. As we said before, obesity is one the factors that increase the secretion of the insulin hormone, and this leads to decrease the number of its receptors due to down regulation.

  - National health and nutrition organization survey: 2/3 of the adults (men and women) in USA with diagnosis of diabetes have Body Mass Index (BMI) more than 27 (high percentage in obese or individuals).

☒ • Symptoms of diabetic patients (used for diagnosis of diabetes) :

- 1.frequent Urination.
- 2. Increased food consumption.
- 3. Weight loss

Note: The vast majority of obese old individuals have diabetes type 2 and this does not mean that normal people cannot be diabetic patients.

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