SAWA UNIVERSITY

Clinical Endocrinology

Pancreas Gland

Sawa University

College of health and medical techniques

Department of Medical Laboratories

جامعـــــة ســـــاوة الاهلية

كليـــة التقنيـــات الصحيـة والطبيـة

قسم تقنيات المختبرات الطبية

المرحلـــــــــــة الثالـثة

الجانب النظري

محاضرة رقم 9

Theoretical

Lecture No. 9

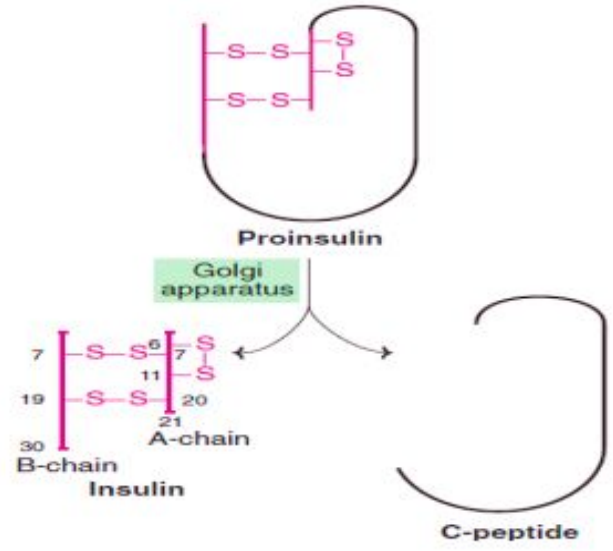
.Third . Stage

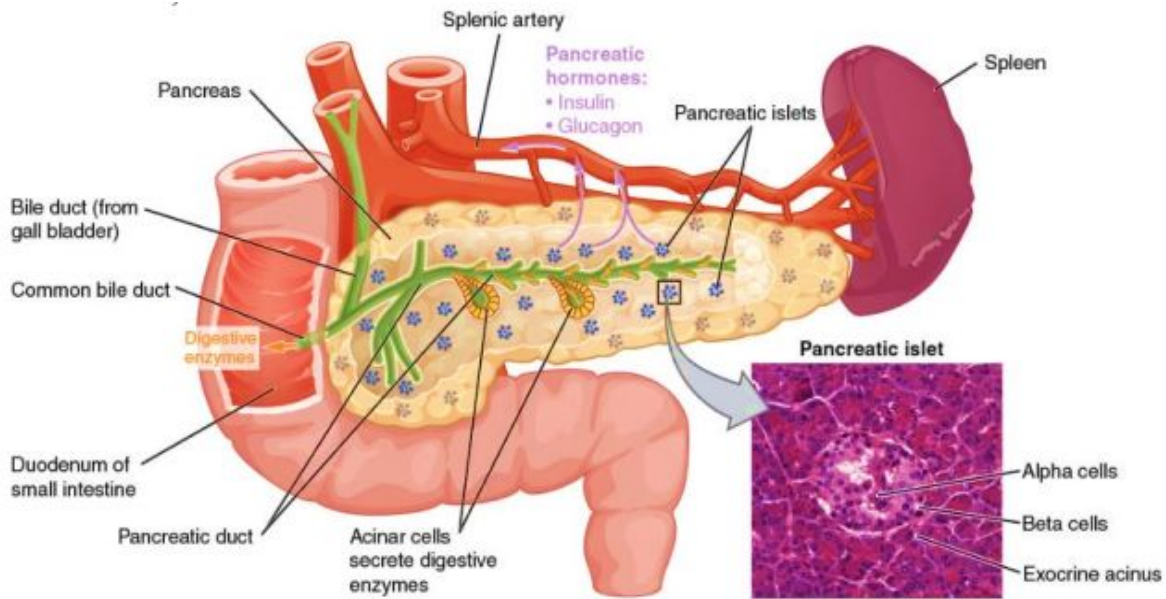
تدريسي المادة : م.م عقيل محمد رسول

Pancreatic Hormones

The hormone-secreting, endocrine portion of pancreas is the **islet of Langerhans**, which contains α, β, □, and F cells. Insulin and glucagon are perhaps the most influential intermediary metabolism regulating hormones;

insulin is **released from** the **β-cells** in response **to high blood glucose levels** (e.g. after a meal) and **glucagon** from **α-cells** in response **to low blood glucose levels**. The ***□-cells produce somatostatin*** and ***F cells secrete pancreatic polypeptide***. All these pancreatic hormones are peptides **and not under any major pituitary**, hypothalamic, or neural control.





1) Insulin

Insulin is **a protein** hormone*, secreted by β-cells of islets of Langerhans of pancreas*. It plays an important role in metabolism ***causing increased carbohydrate metabolism***, *glycogenesis and glycogen storage; FA synthesis/TG storage and amino acid uptake/protein synthesis*. Thus, **insulin** is an **important anabolic hormone** which *act on variety of tissues*. Major target tissues of insulin are the muscles, liver, adipose tissue and heart.

Chemistry: **Insulin** is a **heterodimer protein**; has been isolated from pancreas and prepared in crystalline form. **For crystallization**, it requires **Zn++. Zinc** is also a *constituent of stored insulin and normal pancreatic tissue* is relatively rich in Zn**.** **Insulin** molecule is composed of **two polypeptide chains**, called '**A'-chain and 'B'-chain**, containing total of **51 amino acids**. *A-chain contains 21 amino acids and B-chain contains 30 amino acids*. Both the chains are **held** by **two S–S linkages**.

- **Importance of S–S bridges**: **Breaking of the disulfide bonds** with alkali or reducing agents **inactivate insulin**. **Digestion of insulin protein with proteolytic enzymes** also **inactivates the hormone**.

Regulation of insulin secretion

About 40-50 units of insulin is secreted daily by human pancreas. The normal insulin concentration in **plasma is 20-30 µU/ml**. The **important factors that influence the release** of insulin from **the β-cells** of pancreas.

1. **Factors stimulating insulin secretion**: These include glucose, amino acids and gastrointestinal hormones.
2. **Factors inhibiting insulin secretion**: **Epinephrine** is the most potent **inhibitor of insulin release**. **In emergency situations** *like stress, extreme exercise and trauma*, **the nervous system stimulates adrenal medulla to release epinephrine**. **Epinephrine suppresses insulin release** and promotes energy metabolism by mobilizing energy-yielding compounds—glucose from liver and fatty acids.

Degradation of insulin

In the plasma, insulin has a normal **half-life of 4-5 minutes**. This **short half-life permits rapid metabolic changes** in accordance to the alterations in the circulating levels of insulin. This is advantageous for the **therapeutic purposes**. **A protease enzyme, namely insulinase** (*mainly found in **liver and kidney***), **degrades insulin**.

Metabolic effects of insulin

Insulin plays a ***key role*** in the *regulation of carbohydrate, lipid and protein metabolisms*. Insulin exerts anabolic and anticatabolic influences on the body metabolism.

1. Effects on carbohydrate metabolism: In a normal individual, about **half** of the ingested **glucose is utilized** to meet the **energy demands of the body (mainly through glycolysis**). The **other half is converted to fat (~ 40%) and glycogen (~ 10%). This relation is severely impaired in insulin deficiency**. Insulin influences glucose metabolism in many ways. The net effect is that insulin lowers blood glucose level (**hypoglycemic effect**) by promoting its utilization and storage .

***Effect on glucose uptake by tissues**: Insulin is required for the **uptake of glucose by muscle (skeletal, cardiac and smooth), adipose tissue, leukocytes and mammary glands**. **Tissues into which glucose can freely enter** *include brain, kidney, erythrocytes, retina, nerve, blood vessels and intestinal mucosa*. As **regards liver**, **glucose entry into hepatocytes does not require insulin**.

***Effect on glucose utilization**: Insulin **increases glycolysis** in **muscle and liver**.

***Effect on glucose production**: *Insulin decreases gluconeogenesis*

2. Effects on lipid metabolism: The net effect of insulin on lipid metabolism is to **reduce the release of fatty acids from the stored fat and decrease the production of ketone bodies.** Among the tissues, **adipose tissue** is the *most sensitive to the action of insulin*.

* **Effect on lipogenesis**: Insulin **favours the synthesis** *of triacylglycerols from glucose*

* **Effect on lipolysis:** Insulin **decreases the activity** *of hormone-sensitive lipase* and thus **reduces the release of fatty acids** from stored fat in adipose tissue.

* **Effect on ketogenesis**: Insulin **reduces ketogenesis** by ***decreasing the activity of HMG CoA synthetase.***

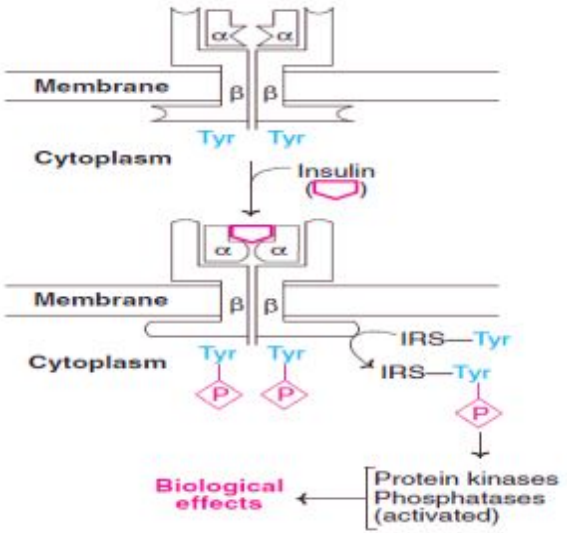
3. **Effects on protein metabolism**: Insulin is an anabolic hormone. It **stimulates the entry of amino acids into the cells**, *enhances protein synthesis* **and** *reduces protein degradation*. Besides the metabolic effects described above, ***insulin promotes cell growth and replication***

Mechanism of action of insulin

It is now recognized that insulin binds to specific plasma membrane receptors present on the target tissues, such as muscle and adipose. This results in a series of reactions ultimately leading to the biological action. **Three distinct mechanisms of insulin action are known**. **One** concerned with the induction of transmembrane signals (**signal transduction**),

second with the glucose transport across the membrane

and the third with induction of enzyme synthesis.



Classification Of Diabetes Mellitus

Diabetes mellitus is a metabolic disease, more appropriately a **disorder of fuel metabolism**. It is mainly characterized by hyperglycemia that leads to several long term complications. Diabetes mellitus is broadly divided into 2 groups, namely **insulin-dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM)**. This classification is mainly based on the requirement of insulin for treatment.

Hypoglycemia

When the blood glucose concentration falls to **less than 45 mg/dl**, *the symptoms of hypoglycemia appear. The manifestations include headache, anxiety, confusion, sweating, slurred speech, seizures and coma*, **and, if not corrected, death**. All these symptoms are directly and indirectly related to the **deprivation of glucose supply to the central nervous system** (**particularly the brain**) due to a fall in blood glucose level. The following three types of hypoglycemia are encountered by physicians.

1. **Post-prandial hypoglycemia**
2. **Fasting hypoglycemia**
3. **Hypoglycemia due to alcohol intake**
4. **Hypoglycemia due to insulin overdose**
5. **Hypoglycemia in premature infants**

2) Glucagon

Glucagon, secreted by **α-cells of the pancreas, opposes the actions of insulin**. It is a **polypeptide** hormone composed of **29 amino acids** in a **single chain**. Glucagon is actually **synthesized as proglucagon** which on sequential **degradation releases active glucagon**. Glucagon has a **short half-life** in plasma i.e. **about 5 minutes.**

Regulation of glucagon secretion

The secretion of glucagon is **stimulated by**

- **low blood glucose** concentration **,**
- **amino acids** derived from dietary protein and
- **low** levels of **epinephrine.**

Increased blood glucose level markedly **inhibits glucagon** secretion.

Mechanism of action of glucagon

Glucagon binds to the specific receptors on the plasma membrane and acts through the mediation of **cyclic AMP, the second messenger**

Metabolic effects of glucagon

Glucagon influences carbohydrate, lipid and protein metabolisms. In general, the effects of this hormone oppose that of insulin.

1. **Effects on carbohydrate metabolism**: Glucagon is the most potent hormone that enhances the blood glucose level (**hyperglycemic**). Primarily, glucagon acts **on liver** to cause **increased synthesis of glucose** (**gluconeogenesis**) **and enhanced degradation of glycogen** (**glycogenolysis**). The actions of glucagon are mediated **through cyclic AMP**.

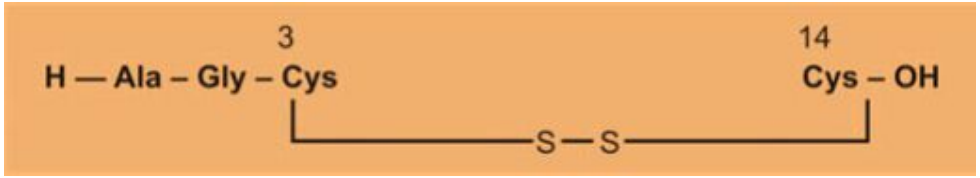
2. **Effects on lipid metabolism**: Glucagon promotes **fatty acid oxidation** resulting in **energy production and ketone body synthesis** (**ketogenesis**).

3. **Effects on protein metabolism**: Glucagon **increases the amino acid uptake** by liver which, in turn, **promotes gluconeogenesis**.

3) Somatostatin

The peptide somatostatin (also **called as** "**GH release inhibiting factor**") was first **isolated from the hypothalamus** and was implicated as **a regulator of GH secretion**.

Chemistry: It is **a peptide** consisting of 14 amino acids. There is an intrachain S–S linkage joining **cysteine 3** and **cysteine at position 14**.



Source: There are **three sources**:

1. **Hypothalamus** as stated above.
2. **Pancreas:** Somatostatin is also **secreted by δ-cells** of islet of Langerhans of pancreas.
3. **GI tract:** It is also **produced by D-cells** of *antral mucosa of stomach and also duodenal mucosa.*

The above suggest that the hypothalamic releasing hormones may actually be more widely distributed.

(a) Hypothalamic Somatostatin:

- Acts as a **regulator** of **growth hormone secretion**
- It **inhibits** GH release
- It may also serve as a **neurotransmitter** substance **in the brain.**

(b) Pancreatic Somatostatin:

- It **inhibits** **both insulin and glucagon secretion** and thus may serve as an "**intra islet**" (**paracrine**) **regulator of secretion of these hormones**. Thus, acts as **intraorgan** "**synaptic transmitters or neuromodulators**.
- Somatostatin is **secreted into the portal vein blood** *as a result of glucose or amino acid stimulus* indicating extra-islet role.
- Also directly **inhibit** secretion of ***both HCO3– and enzymes in pancreatic juice***.

(c) GI Somatostatin:

- **Inhibits** the secretions of **gastrin, CCK, GIP and motilin**.
- **Also inhibits** **gastric acid secretion**, *secretion of Brunner's glands*. Since somatostatin can **inhibit** a variety of GI functions (**gastric emptying, GI motility**), its **major function may be** to **regulate nutritional influx at the level of GI tract**.

Questions

1. What is the second messenger involved in glucagon's mechanism of action?
2. Glucagon promotes which process in lipid metabolism?
3. Which cells secrete somatostatin in the pancreas?

Learning Resources for Hormone Mechanisms

Here are excellent sources to deepen your understanding of this topic:

Medical Textbooks:

"Harper's Illustrated Biochemistry" (Chapter on Hormones & Signal Transduction): Provides a detailed, yet clear, biochemical perspective on second messenger systems.

"Guyton and Hall Textbook of Medical Physiology" (Chapter 74: Introduction to Endocrinology): Excellent for understanding the physiological principles of hormone-receptor interactions and signaling.

"Greenspan's Basic & Clinical Endocrinology": A comprehensive resource that links basic mechanisms to clinical practice.

YouTube Channels:

Armando Hasudungan: His detailed drawings are fantastic for visualizing signal transduction pathways.

Dr. Najeeb Lectures: Provides extremely detailed lectures on the entire process.