# The Endocrine System

## PHYSIOLOGY

☑ Sheet ☐ Slide ☐ Handout

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| Number: | **9** |
| Subject: | **Pancreas + insulin** |
| Done By: | **Sinamis Drei** |
| Corrected by: | **Basel Noufal** |
| Doctor: | |

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| Date: | **20/6/2016** |
| Price: | |

بسم الله الرحمن الرحيـــم

This lecture is going to discuss the pancreas; its structure, function and pathology.

Note 1: this sheet was written according to the recording of section 2.

Note 2: things written in *italic* were not mentioned during the lecture. READ THEM to understand.

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- As we all know, pancreas is a unique organ as it contains both endocrine and exocrine portions. It produces hormones (endocrine) as well as enzymes and ions (exocrine), and there is coordination between the enzymes and hormones.

- **These hormones and enzymes are both stimulated by:**
  1. The ingestion of food.
  2. Gastrointestinal hormones.

***Physiologic anatomy of the pancreas:***

*Pancreas is composed of two major types of tissues:*

*(1) Acini which secrete the digestive juices into the duodenum (enzymes/ exocrine portion).*

*(2) Islets of Langerhans which secrete insulin and glucagon directly into the blood (hormones/endocrine portion).*

- Substrates of the nutrients ingested, pancreatic hormones and pancreatic enzymes are released into the portal vein and then transferred into the liver.

  - ✓ *Let's clarify this point :*
    - ➔ *The food ingested and gastrointestinal hormones stimulate the pancreatic acini to secrete the pancreatic juice (enzymes) into the duodenum where the **substrates** of the food ingested are present.*

➔ *The food ingested and gastrointestinal hormones also stimulate the islets of Langerhans to secrete the hormones insulin and glucagon.*

➔ *Now, the substrates and pancreatic enzymes in the duodenum will travel through the mesenteric vein. The hormones insulin and glucagon will travel through the splenic vein.*

➔ *These two veins then unite to form the portal vein, which transfers them into the liver.*

- In the liver, food constituents are metabolized under the effect of hormones (mainly insulin and glucagon) → the substrates that result from metabolism are then transferred through the peripheral arteries into the peripheral tissues, where they act to feedback the secretion of the hormones insulin and glucagon.

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❖ **Islets of Langerhans :**

These are specialized types of cells in the liver that secrete hormones. the percentage of these cells in the pancreas is only 2%.

- Islets of Langerhans contain four types of cells: A, B, D and F.

Table 19–1. Cell types in pancreatic islets of Langerhans.

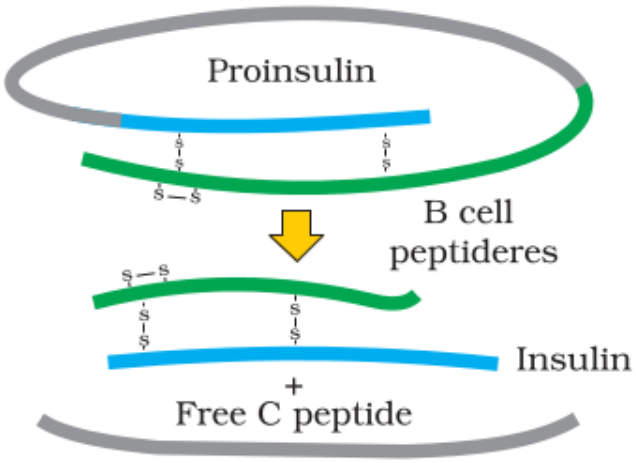
| Cell Types | Approximate % of Islet Mass | Secretory Products |
|---|---|---|
| A cell ($\alpha$) | 20% | Glucagon, proglucagon |
| B cell ($\beta$) | 75% | Insulin, C peptide, proinsulin |
| D cell ($\delta$) | 3–5% | Somatostatin |
| F cell (PP cell) | < 2% | Pancreatic polypeptide |

Note: Beta cells also secrete amylin hormone which complements the action of insulin. F cells also secrete ghrelin.

## ❖ Insulin :

*It's a polypeptide, composed of two amino acid chains that are connected to each other by disulfide bridges. When the two amino acid chains are split apart, the functional activity of insulin is lost .It is first synthesized in the beta cells as* ***preproinsulin*** *, which is then cleaved in the endoplasmic reticulum into* ***proinsulin*** *consisting of three chains of peptieds, A ,B , and C .Most of the proinsulin is further cleaved in Golgi apparatus to form (1) insulin , composed of the A and B chains connected by disulfide linkage and the (2) C peptide. The insulin and C peptide are packaged in secretory granules and secreted in equimolar amounts (refer to Guyton and Hall) .*

- *The difference btween insulin and proinsulin is the presence or absence of C peptide.*
- *In proinsulin, A and B peptide chains are connected by C peptide.*
- *A chain: 21 amino acids*
  *B chain: 30 amino acids*

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❖ *Here are some very important points scientifically :*

➢ In vivo, proinsulin performs 10% of the activity of insulin (some books even say that proinsulin has no biological activity at all).

- It is of clinical significance that insulin and C peptide are secreted in equal amounts from the secretory granules. (we'll see why later)
- Very important: 50-60% of the insulin produced by the pancreas is extracted by the liver, without even reaching the systemic circulation (ineffective).
- In contrast, the liver doesn't extract the C peptide.
- Thus, as C peptide is secreted in equimolar amounts with insulin and is NOT extracted by the liver → Beta cells insulin secretion rate can be calculated.
- The amount of insulin secreted by the pancreas is measured using C peptide not insulin (as high percentage of insulin is extracted by the liver/ 40-50% only reach the blood).
- In diabetic patients treated with insulin, measuring insulin level doesn't tell the rate of secretion of insulin by the pancreas. On the other hand, by measuring C peptide level, one can distinguish between endogenous and exogenous insulin since insulin injected doesn't contain C peptide.
- This is another advantage of measurement using the C peptide

## Insulin effects

### ❖ Carbohydrates metabolism :

- **Short-term regulation of plasma glucose levels**: By insulin and glucagon (minute by minute).
- **Long – term regulation of plasma glucose levels** :

✓ Adrenal corticosteroids
✓ Growth hormone
✓ Catecholamine ( Adrenalin )
✓ Thyroid hormones

Note: The only hypoglycemic hormone in the body is insulin.

The most important hyperglycemic hormone in the body is glucagon.

## ❖ Summary of Glucose – counter regulatory controls :

**Summary of Glucose-Counterregulatory Controls**

| | Glucagon | EPI | Cortisol | GH | $T_3$ |
|---|---|---|---|---|---|
| Glycogenolysis | X | X | | | X |
| Gluconeogenesis | X | X | X | X | X |
| Lipolysis | X | X | X | X | X |
| Blockade of Glucose Uptake | | X | X | X | |

- Cortisol has no role to play in glycogenolysis; glucagon does.
- Cortisol has permissive action with glucagon is stimulating gluconeogenesis.

## ❖ Mechanisms of insulin action on cells.

- Insulin receptor is made up of two alpha subunits and two beta subunits connected together by disulfide bridges.
- Alpha subunits lie entirely outside the cell membrane, while beta subunits penetrate through the cell membrane.
- To initiate its effects on the target cell, insulin first binds with Alpha subunits outside the cell membrane , but because of the linkages with beta subunits , the portions of beta subunits protruding towards the cytoplasm become autophosphorylated (insulin receptor is an example of enzyme linked receptor) . Autophosphorylation of the beta subunits activates the local tyrosine kinase which, in turn, causes phosphorylation of multiple other intracellular enzymes. ( refer to Guyton and Hall )
- **The main actions of Insulin :**

  1. Activation of glucose transporters, the most important ones being glucose transporter 4 (GLUT4).
  2. Stimulates protein synthesis
  3. Stimulates fat synthesis
  4. Inhibits gluconeogenesis
  5. Promotes growth and gene expression (remember that growth does not occur in the absence of insulin)

- In addition to tyrosine kinase , insulin may also activate phospholipase C to produce the two second messengers ( IP3 and DAG ), and it's most probably due to the action of these two second messengers that the entry of amino acids occurs → hence, insulin plays a role in protein synthesis. This is the action of insulin in growth, synergizing with GH.

- As you know, diabetic patients always care about potassium "Be careful about the potassium level!" etc.) due to the essentiality of potassium in the normal heart function. Thus, Insulin also affects the entry of potassium, phosphate and magnesium.

  Note: Banana and radish are rich sources of potassium.

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- **Stimuli and inhibitors of insulin secretion :**

- **Factors that increase insulin secretion :**
  - ✓ Increased blood glucose levels (the main factor), but it has to be utilized to generate ATP to affect insulin secretion (ATP). look at the figure below :

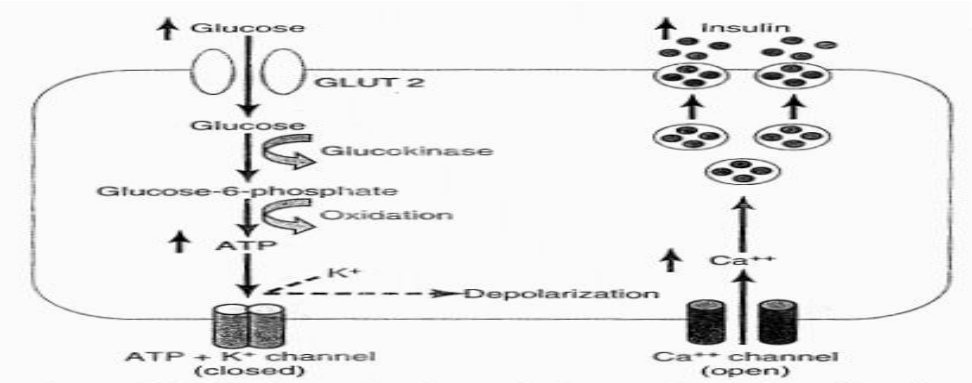

**Figure 78-7** Basic mechanisms of glucose stimulation of insulin secretion by beta cells of the pancreas. GLUT, glucose transporter.

  - ✓ Increased blood free fatty acids.
  - ✓ Increased blood amino acids.

- ✓ Gastrointestinal hormones
- ✓ Glucagon, growth hormone, cortisol.
- ✓ Parasympathetic stimulation by acetylcholine.
- ✓ Insulin resistance, OBESITY.
- ✓ Beta – adrenergic stimulation.

- **Factors that decrease insulin secretion :**
  - ✓ Decresed blood glucose levels.
  - ✓ Fasting
  - ✓ Alpha – adrenergic stimulation.
  - ✓ Leptin

- **Note:** Calcium plays an important role in the secretion of proteins, and Insulin is a protein. Thus, entry of calcium is important for the secretion of insulin.

  - ❖ **Insulin** is not randomly secreted. Rather, it is secreted within limits. The highest limit of insulin secretion is at glucose concentration of 300-400 mg/dl. When plasma glucose concentration is below 50 mg/dl, almost no insulin is secreted as seen in the figure below

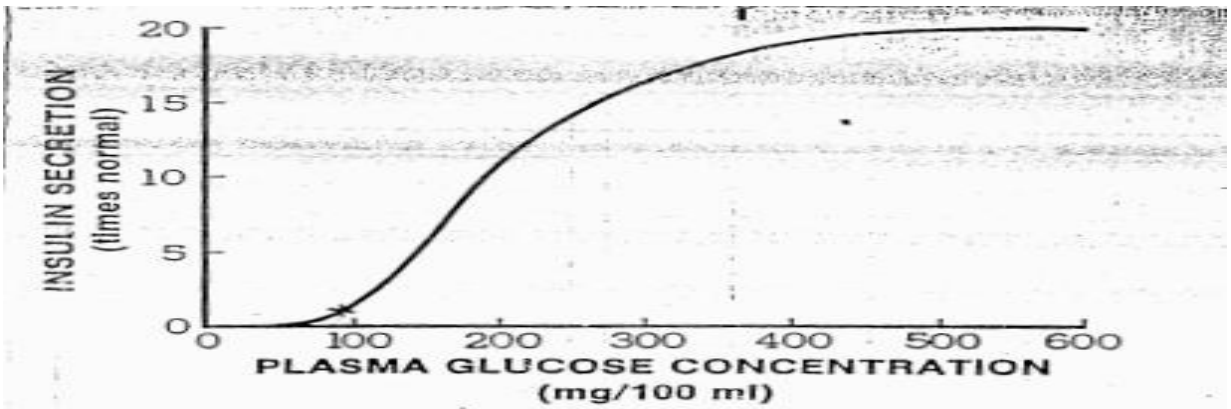

**Figure 78–8.** Approximate increase in insulin secretion at different plasma glucose levels.

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- **Remember**: one of the factors that stimulates and increases insulin secretion is insulin resistance (as in type 2 diabetes mellitus) and obesity.

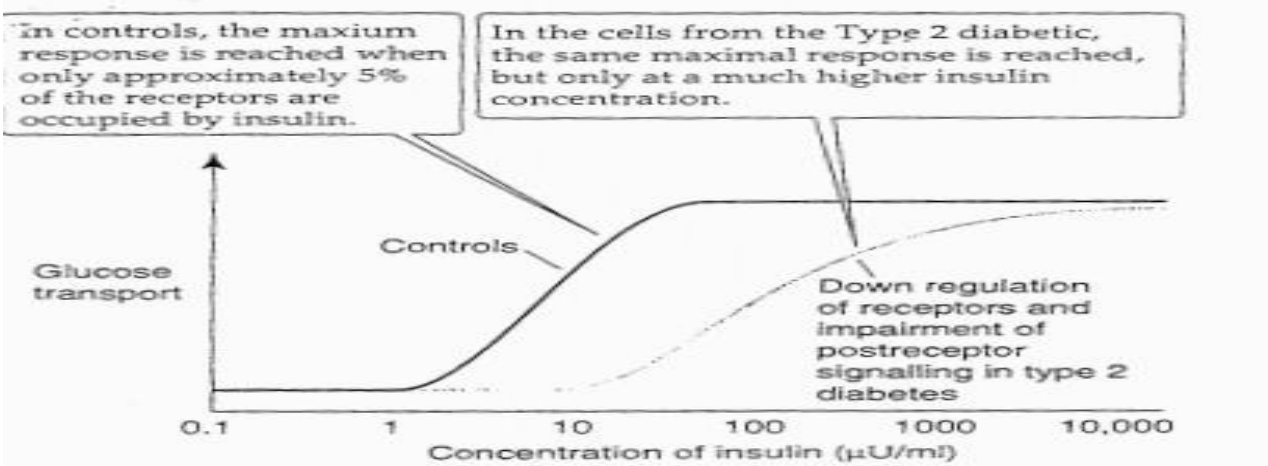


FIGURE 50–7. Response to insulin of normal and "downregulated" adipocytes.

- **Downregulation** of insulin receptors on adipocytes and impairment of postreceptor signaling in type 2 diabetes results in much higher concentration of insulin that is needed to reach the maximum response which is normally reached when only approximately 5% of insulin receptors are occupied in controls.

  - **Insulin secretion rate when the control in injected with Glucose ( in minutes ) :**

- When there is a rapid increase in glucose concentration, beta cells first secrete insulin that is **presynthesized** and stored inside secretory granules. Later, when the insulin stores run out, beta cells **synthesize** insulin for being secreted. This takes some time and, therefore, insulin secretion is delayed after being first maximally secreted. Then, stability of insulin levels is reached within 15 – 20 minutes later. As seen below

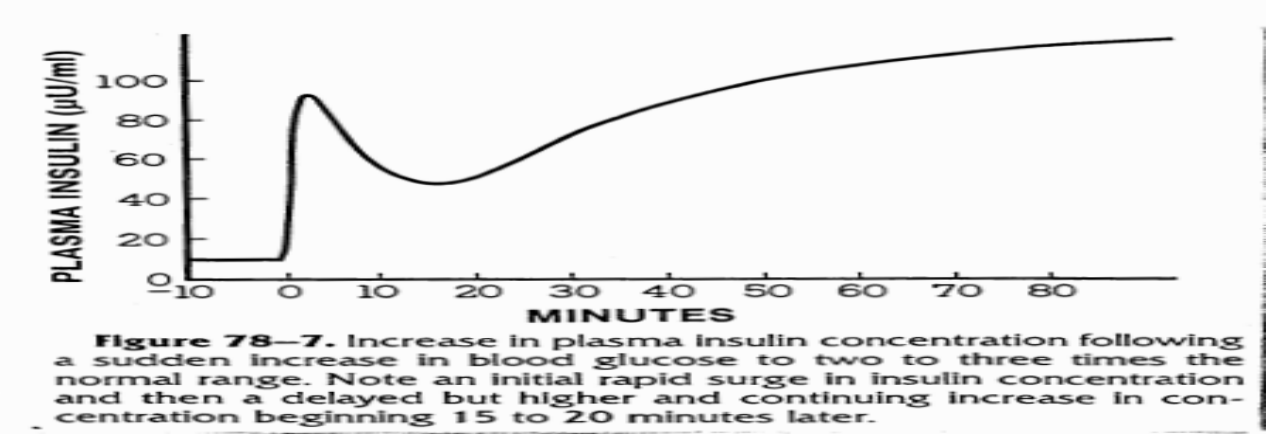


**Figure 78–7.** Increase in plasma insulin concentration following a sudden increase in blood glucose to two to three times the normal range. Note an initial rapid surge in insulin concentration and then a delayed but higher and continuing increase in concentration beginning 15 to 20 minutes later.

- **As said earlier, insulin has effects on:** the metabolism of carbohydrates, proteins and lipids, ion transport (potassium, phosphate and magnesium), and growth (check them in table 7.6 in the slides). It affects organs including: Liver, adipose tissue, muscles and others.

- Some organs and some tissues do not need insulin for glucose uptake; including the brain, kidney tubules, intestinal mucosa and RBCs (erythrocytes). These are vital organs which glucose is crucial for their survival.

- **Normal plasma glucose concentration:** usually it is 90 ± 10 mg/dl.

- In 75% of people, it is 90 mg/dl.
- In some people it is 70 mg/dl. This is normal if it is constant.

- **at normal insulin concentration , glucose is :**
  - ✓ Transferred into liver → 5%
  - ✓ Transferred into fat → 30-40%
  - ✓ Transferred into muscles and other tissues → very low concentration.
  - ✓ Low glucose appears in the urine → no glycosuria

- **In case of insulin deficiency, the following consequences will occur :**
  1. Disordered plasma glucose levels (300 mg/dl)
  2. No Glucose transport to adipose tissue
  3. No glucose transport to muscle cells
  4. Glucose output from the liver is greater than glucose input.
  5. Brain is not affected unless glucose level rises too high (remember, the brain is insulin-independent)
  6. High concentration of glucose transferred to kidneys → glycosuria (Note: glucose is undetectable in urine as long as blood glucose level is lower than the renal threshold (180mg/dl)

القوّة التي تضع حبّات الرمّان واحدة واحدة داخل قشرتها ، تعلم في أيّ قلب تضعك فلا تقلق .