endocrine system

physiology

Sheet Slide

number	7
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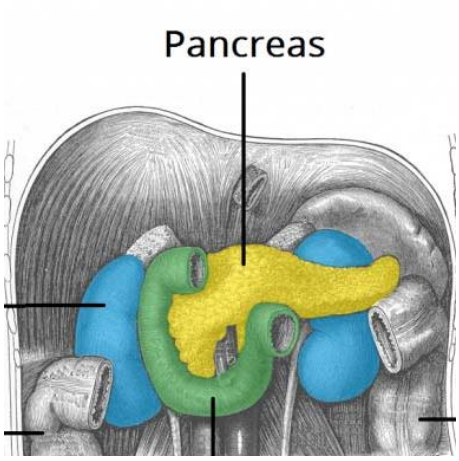
Pancreatic Hormones

The Pancreas is a very important organ because it is the only organ in our body that produces enzymes that work on the digestion of lipids, proteins, and carbohydrates.

The enzymes your body secret are secreted in certain amount and concentration. When you change your diet and food style (like moving to another country), your body will need at least six months to adapt to the new situation.

This is the strategic location of the pancreas:

"The pancreas is located in the upper abdomen behind the stomach"



It is a mixed organ, Pancreas has:

1. **Exocrine** function (Acinar cells): **Enzymes**, digestion of food by secreting the enzymes into the duodenum.

2. **Endocrine** function (Islets of Langerhans): **Hormones**, they secrete insulin and glucagon into the blood directly.

There is coordination between these two functions (the release of the enzymes and the release of the hormones), both stimulated by **the entry of nutrients into the GI tract** and **by GI hormones**; GI hormones stimulate the enzymes as well as the hormones, nutrient stimulate the hormones, and both (nutrient and hormones) stimulate enzymes and hormones.

You see hormones (hormones which affect the metabolism of elements (carbohydrate, protein, and lipid)) are secreted into the **portal vein** and thereby reach the **liver** with the substrate products of nutrient digestion. Within the liver, the hormones affect the metabolism of the ingested substrates. Islet hormones that pass through the liver with substrates affect the disposition of

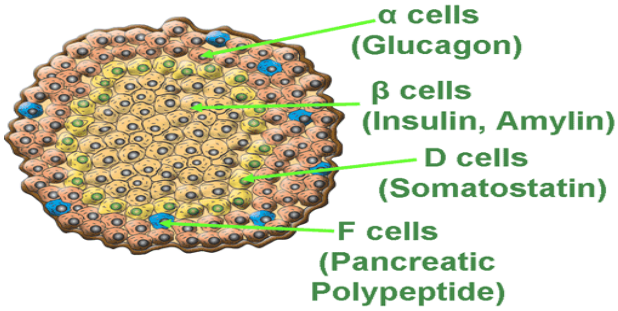
these substrates by peripheral tissues. So, the result is transferring substrates into **peripheral tissues by the effect of hormones**, the level of the hormones and the substrates in the peripheral tissues affect the secretory function of the endocrine level by feedback mechanisms.

There are many cells in the Langerhans islet, these groups of cells function to secrete hormones. Of course, these islets scattered in the pancreas (we don't find them together in one population), and the percentage of these cells to the organ is just 1-2% (very little compared to the important function).

There are 5 types of cells in the islet of Langerhas:-

Beta cells	Alpha cells	Delta cells	PP cells	Epsilon cells
75% of all the cells of the islet, secrete **insulin** and **amylin**	20% of all the cells of the islet, secrete **glucagon**	3-5% of all the cells of the islet, secrete **somatostatin**	Less than 2% of all the cells of the islet, secrete **pancreatic polypeptide**	Secrete **ghrelin**

Beta cells are present in the center of the islet, alpha in the peripheral and delta in between.



- **Amylin:** 37 amino acid peptide, this hormone produced mainly by the pancreas, in detail, it is a neuroendocrine hormone which complements the action of insulin in postprandial (means after eating a meal) glucose homeostasis via several mechanisms, these include a suppression of postprandial glucagon secretion and slowing of the rate at which nutrients are delivered from the stomach to the small intestine for absorption.

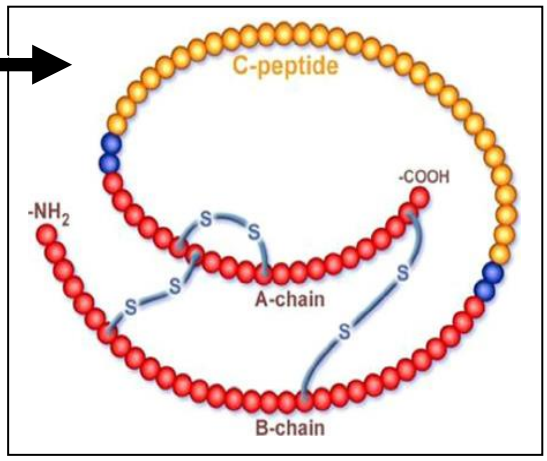
- **Ghrelin:** this hormone is produced also by the stomach as well as the intestine, it stimulates the appetite.

Insulin: is the main hormone from the islet, it is a protein hormone, very special and very important hormone, Insulin has a short half-life (6 minutes) composed of two chains of amino acids: **A chain** (21 Amino Acids, inactive chain) and **B chain** (30 Amino Acids, the active chain), connected to each other by disulfide bridges. There are bridges and there are extra bridges in the chain.

Proinsulin; is insulin with another peptide (**C-peptide/C chain**). And to form mature insulin the C-peptide is removed, and B-peptide remains connected with A-peptide (%10 of insulin activity).

proinsulin

Proinsulin has biological activity equal just 10% of the insulin.



Proinsulin is cleaved in the Golgi apparatus of the pancreatic beta cells to form connecting peptide (C peptide), and insulin (A and B peptides).

In the granules, C chain split from the insulin, secretory granules contain very little amount of the proinsulin. Even when C-peptide leaves the insulin (splits from the insulin) they remain in the granules, they are packaged in granules and secreted in equimolar amounts, along with a small amount of proinsulin (so you see that the secretory granules contain **insulin** and **proinsulin** and C-peptide).

It is of clinical significance that insulin and C-peptide secreted in equal amounts

C-peptide has clinical significance when we want to measure the level of insulin. **50-60%** of the insulin produced by the pancreas extracted by the liver without even reaching the systemic circulation, so just about **40%** is released into the systemic circulation. Why? Because the liver doesn't extract the C-peptide.

Now we know the clinical value of C-peptide; we can measure the C-peptide instead of insulin to know the exact amount of insulin the pancreas secretes. This is more useful in diabetic patients (type 1 DM), these diabetic patients

may take exogenous insulin (injection insulin) and we can't differentiate between the exogenous insulin and the endogenous insulin, so here C-peptide tells us about the exact amount secreted by the pancreas.

Proinsulin= insulin + C-peptide ⟶ equal amounts of insulin and C-peptide

WHY is it actual amount?
BECAUSE: **1. Liver doesn't extract the C-peptide**
2. Insulin and C-peptide secreted in equimolar amounts

The Regulation of Glucose Concentration in Plasma

Glucose homeostasis, it is very important to maintain glucose concentration normally in the body.

When we talk about the insulin actually we are talking about the glucose concentration in the body, glucose is regulated minute by minute by **hormones**, there is short-term regulation and there is long-term regulation.

Short-term regulation: under the effect of the **insulin** and **glucagon**, one **hypoglycemic** and the other **hyperglycemic** opposing each other, the first reduces the glucose level and the later increases the glucose level. There are other hormones involved in the regulation of plasma glucose such as:

1- ***Glucagon*** (in glycolysis and gluconeogenesis).
2- ***Cortisol*** (long gluconeogenesis, lipolysis and on inhibition of glucose uptake; that mean glucose remain in the blood).
3- ***Catecholamine***, adrenalin (lipolysis).

Adrenalin in addition to glucagon (permissive hormonal interaction): lipolysis, you remember the adrenalin on lipid tissues.

An example of adrenalin functioning along with another **hormone**: Adrenal does not function if thyroxine is not present.

4- **Thyroid hormones** (Thyroxin).
5- ***Growth hormones*** have actions similar to the cortisol but most probably cortisol is more potent and stronger than growth hormone in providing glucose.

From the past papers

Low insulin level is required for? **Inhibit hepatic gluconeogenesis.**

Opposite hormone in metabolic function to all other's? **Insulin** (most likely)

All these **hormones** are **hyperglycemic**. **Insulin** is the only **hypoglycemic** hormone in the body.

The most potent hyperglycemic hormone in the body is **GLUCAGON** then comes **CORTISOL**, they are essential because when you are fasting those hormones will work to produce glucose from non-carbohydrate sources in order to raise glucose level in plasma preventing death.

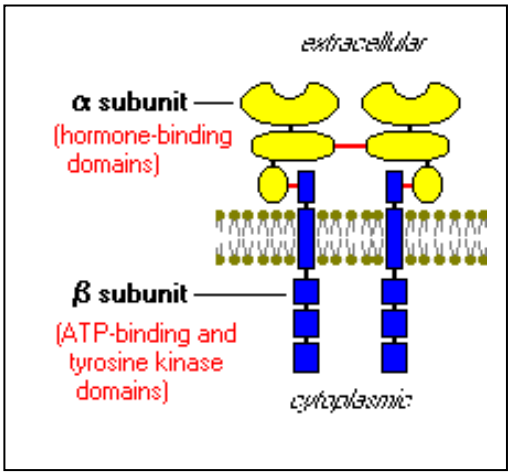
What is the hormone that don't play any role in growth? **Glucagon.**

What is the major hyperglycemic hormone? **Glucagon.**

Insulin Receptors

They are found on many different cells in the body, including cells **in which insulin does not increase glucose uptake.**

When we talked about the mechanism of the hormones as well as the receptors we mentioned exceptions, one of these exceptions is **insulin**, it is an exception from the other hormones in the **receptor structure** as well as on the **second messenger mechanisms**.



You see the receptor for insulin, it has 4 subunits: 2 alpha (on the cell membrane) and 2 beta (penetrating the cell membrane).

They are linked with each other by **disulfide bridges**; bind alpha subunits with each other and alpha with beta.

Mechanism of action

Insulin bind with **alpha subunit**, once it binds with alpha **the beta subunit** is **activated**, consequently, the second messenger **tyrosine kinase** which binds **with beta subunit is activated**, producing autophosphorylation of the beta subunits on tyrosine residues by ATP. **This autophosphorylation is necessary for insulin to exert its biological effect**. Glucose transporters are then **moved to the plasma membrane and facilitate glucose entry**.

The insulin doesn't function unless it finds the receptor and activates the second messenger (tyrosine kinase) so that a physiological response will occur. The main function of insulin is **the activation of glucose transporters**.

There are many types of glucose transporters. The one plays role in transferring glucose in the cell is the glucose transporter **number 4,** they say that number 6 plays a role as well. there are many types of glucose transporters that may function with or against the concentration gradient.

From the past papers

Doesn't use cAMP as second messenger? **Insulin**

The following hormones act by activate tyrosine kinase? **GH + insulin**

Functions of Insulin

1- The main function of insulin is **activation** of glucose transporter,

2- Fat, **protein** and glycogen synthesis,

3- Growth and gene expression, we talked about role of growth hormones in the growth and we also talked about the role of insulin in the growth. we said that if the insulin is deficient or absent **normal growth of musculoskeletal** system and **maturation and growth of other tissues** will be **affected**.

4- Have very important role in the entry of amino acids into the cells, most probably by production of the TWO-second messengers (IP3 & DAG: phospholipase C system) in addition to tyrosine kinase, these two second messengers will help in the entry of amino acids into the cell for **protein synthesis**.

5- Facilitate the entry of electrolytes (potassium, phosphate, magnesium) into the cell.

So these are the functions of insulin (are all results of activation of glucose transporter).

Factors and Conditions that Increase or Decrease Insulin Secretion

There are many stimuli for the insulin, any element any chemical in the body **increase blood glucose** level **stimulate** the insulin.

The increase in glucose level is the **most potent stimuli of insulin secretion** but is have to be metabolized in the cells of the pancreas to cause the release of insulin.

Logically if we know the function of insulin we know the stimuli and the inhibitors for insulin secretion:

Stimulatory Factors	Inhibitory Factors
Increased glucose concentration	Decreased blood glucose
Increased amino acid concentration	Fasting
Increased fatty acid and ketoacid concentration	Exercise
Glucagon	Somatostatin
Cortisol	α-Adrenergic agonists
Glucose-dependent insulinotropic peptide (GIP)	Diazoxide
Potassium	
Vagal stimulation; acetylcholine	
Sulfonylurea drugs (e.g., tolbutamide, glyburide)	
Obesity	

ALSO DOCTOR MENTIONED THOSE:-

- Gastrointestinal hormones: (Gastrin, Cholecystokinin, Secretin, Gastric inhibitory peptide)
- Growth hormone
- β-Adrenergic stimulation
- Insulin resistance; Obesity

From the past papers

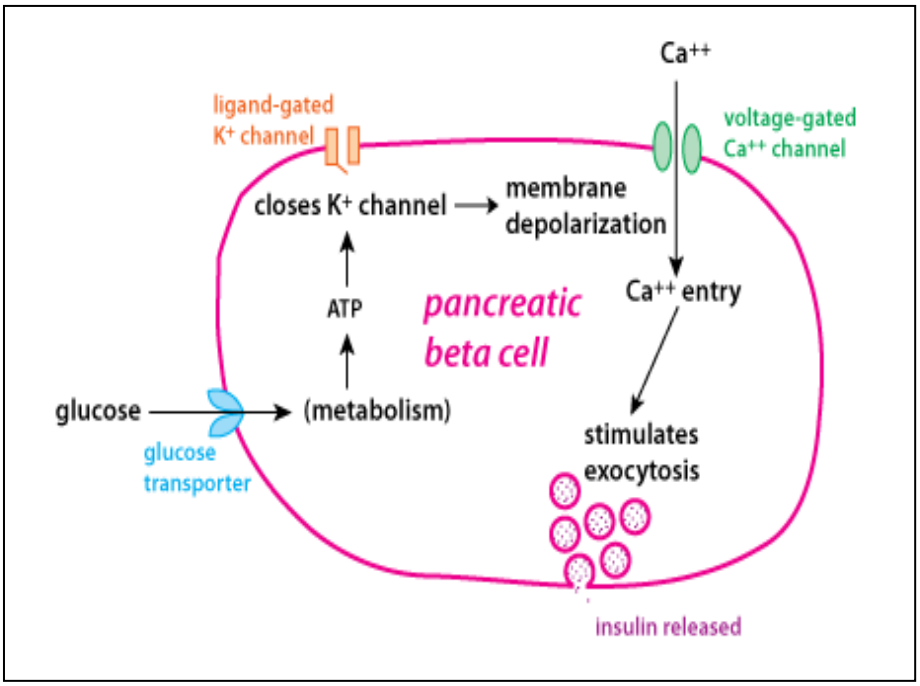
Insulin is stimulated by all the following **except**: **starving**

One of the following **increases** both GH and Insulin: **uptake of protein**

Common between GH and insulin: **uptake of protein**

If you eat 4 sugar-glazed donuts which hormone would you expect to rise: **Insulin**

Insulin Secretion and Calcium Role:



When we talked about the functions of the calcium we said that calcium causes the release of certain proteins or enzymes.

If there is no release of calcium there is no insulin, so insulin need calcium, the most important stimulus for insulin secretion is **glucose** but it had to be metabolized in the cell **to cause the entry of calcium into the beta cells** so that insulin can be secreted.

When the **glucose** enters the cell by **glucose transporter GLUT2**, glucokinase converts it to **Glucose-6-phosphate**, this metabolism of glucose increase **ATP** production, ATP **close potassium channels**, causing **depolarization** of the cell (more K+ inside), which leads to open **calcium channels**, then **stimulation of insulin release**.

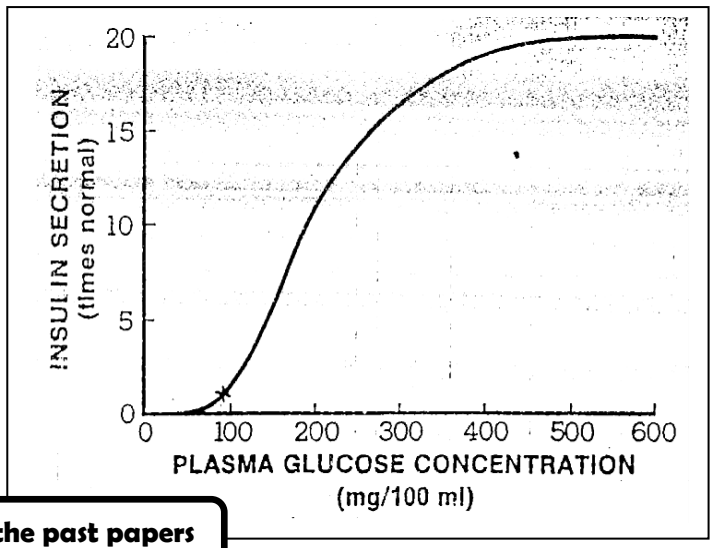
Approximate increase in insulin secretion at different plasma glucose levels

When the glucose concentration is **50mg/100ml** or below almost no insulin is secreted the maximum level secretion of insulin occur when the glucose level between **300-400mg/100ml**

Almost after **400mg/100ml** glucose concentration, the insulin level does not increase.

Normal glucose level range from:

90-100mg/100 ml

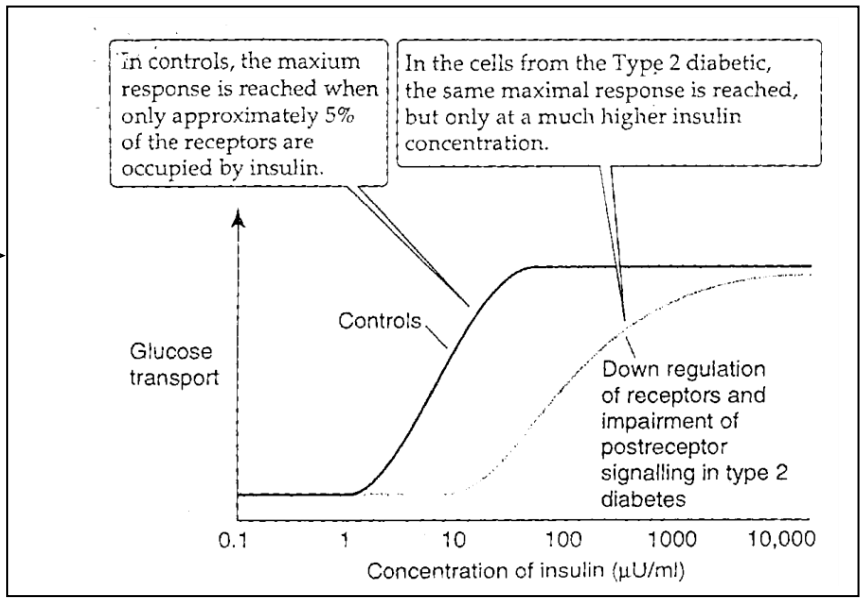


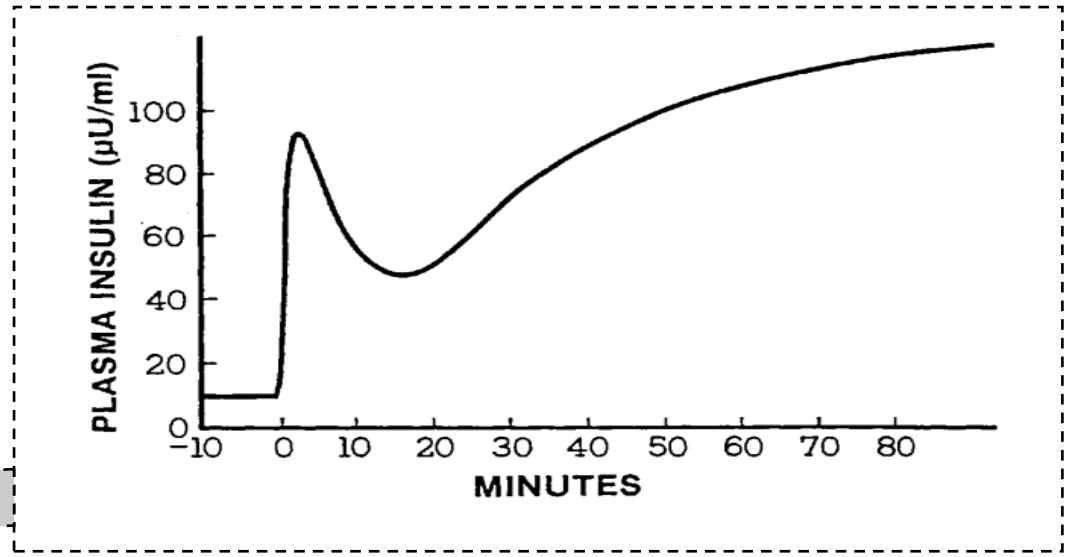
From the past papers

What is the concentration of glucose in diabetic patients?
300mg/100ml

You remember when we talked about the obese old individuals (not always old, sometimes young), these individuals may have normal or high insulin level, so the problem is that these individuals have **down-regulation** of insulin receptors; **number of receptors** and/or **the affinity** decrease, they need more **insulin to produce normal level of glucose and normalize the blood glucose level.** You advise these individuals to do **exercises** and to control their **diet**.

Response to insulin of normal and "down regulated" individuals.





This rat injected with glucose, on the y-axis we found the plasma insulin concentration; immediately the insulin level increase then decrease then normalize.

What is the explanation of this? The first peak **because of the already present insulin** (Not stored but present in the granules), then any new condition is made by **new synthesis**, it needs about 5 minutes to meet the new condition, the new synthesis continues and sometimes the level exceeds the previous level. New synthesis is required to normalize blood glucose.

What is the difference between the already present insulin and storage? Or what is the difference between pancreas and thyroid?

The only gland in the body that stores hormone is the **thyroid gland** (in the colloid not in the cells), the others don't, in pancreas there is insulin in the secretory granules (ONLY small amount), not storage.

Insulin function on carbohydrate, lipid, protein metabolism on liver cells, muscle cells, adipose tissue.

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*When I went to the University, the **medical school** was the only place where one could hope to find the means to study life, its nature, its origins, and its ills. (**Albert Claude**)*

"اللَّهُمَّ انْفَعْنَا بِمَا عَلَّمْتَنَا, وَعَلِّمْنَا مَا يَنْفَعُنَا, وَزِدْنَا عِلْمًا إِلَى عِلْمِنَا"