Endocrine Physiology/ Endocrine Pancreas

Extra note: Pancreas is composed of two major tissues:

1. Acini, which secrete digestive juices into the duodenum.
2. Islets of Langerhans, which secrete insulin and glucagon directly in to the blood. The islets contain three types of cells (alpha, beta, and delta) which are distinguished from one another by their morphological and staining characteristics. [1]

Figure (37.1)

- Pancreas has two functions :
  1. Exocrine function (enzymes).
  2. Endocrine function (hormones).
- The enzymes and hormones of pancreas are stimulated by :
  1. Ingestion of nutrients.
  2. Intestinal hormones.

Both (nutrients and intestinal hormones) stimulate acini and islet cells of pancreas to secrete enzymes and hormones. Then, islet hormones and the substrates (products of nutrient digestion) are secreted in to the portal vein and reach the. Within the liver the hormones (especially insulin and glucagon) will affect the metabolism of the ingested substrates. After metabolism, the substrates will be transferred to peripheral tissues and deposited there, from there, the (substrates) will feed back on the pancreatic islets to modulate the secretion of insulin and glucagon (by inhibition or stimulation).

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 and proglucagon
Beta	75%	Insulin, amylin, C peptide, Proinsulin
Delta	3 -5%	Somatostatin
F cells (pp cells)	<2%	Pancreatic polypeptide

- **Epsilon cells**: are endocrine cells found in the islets of Langerhans and they produce the hormone **Ghrelin** (hunger stimulating peptide and hormone. It is produced mainly in

[1] GYTON & HALL medical physiology book.

stomach and a little in the intestines and as newly discovered; in the pancreas, also from some cells in hypothalamus. They were recently discovered.

- **Amylin**: is a peptide hormone that is co- secreted with insulin in the ratio of (100:1). (Complement the action of insulin –as the doctor Said -). ***Extra note:** It plays a role in glycemic regulation by slowing gastric emptying and promoting satiety, thereby preventing postprandial (after eating a meal) spikes in blood level.[2]

Proinsulin

- Proinsulin consists of :
  1. A chain (21 amino acids).
  2. B chain (30 amino acids).
  3. C peptide (31 amino acids), connects insulin's A chain to its B chain.
- Proinsulin is secreted in small amounts and it has 10% of insulin's activity.
- C peptide and insulin are secreted in equal amounts.
- (50 – 60)% of insulin is captured by the liver (is not released in to the circulation), but C peptide is secreted in to the circulation (is not captured by liver). Therefore, if we want to measure the activity of beta cells (to know how much insulin is secreted) we depend on C peptide level not the Insulin level; since c peptide is **secreted** in the same amount as insulin.
- Another advantage of measuring C peptide: we measure c peptide level in diabetic patients instead of Insulin level because C peptide can assess a person's **own** insulin secretion even if they receive insulin injections[3] (its level equals just endogenous insulin level NOT both exogenous and endogenous levels).

Regulation of Glucose Concentration

- Minute by minute, hour by hour, Glucose concentration is controlled mainly by Glucagon and Insulin (short term regulation), but there are other hormones that play role in the homeostasis of glucose in the body (Growth hormone, cortisol, catecholamines and thyroid hormones).
- Insulin is the only natural **hypoglycemic** hormone in the body.

***Hypoglycemic agents**: agents that decrease the level of glucose in the blood.[4]

- Glucagon is the most potent **hyperglycemic** hormone in the body.

[2] Rn.wikipedia.org/wiki/Amylin
[3] En.wikipedia.org/wiki/c-peptide
[4] www.thefreedectionary.com/hypoglycemic+agent

So we have only one hypoglycemic hormone in the body and the other hormones work to normalize the glucose concentration in blood.

Summary of Glucose counter regulatory controls.

- Glucagon stimulates:
  1. Glycogenolysis.
  2. Gluconeogenesis.
- Adrenalin stimulates:
  1. Glycogenolysis.
  2. Gluconeogenesis.
  3. Lipolysis.
- Both Cortisol and Growth hormone stimulates:
  1. Gluconeogenesis.
  2. Lipolysis.
  3. Inhibition of glucose up take.

Please notice that all of the mentioned hormones have **opposite** effects on glucose level in comparison with insulin.

Insulin Receptor

- Insulin's receptor and its second messenger mechanism are unique.
- It has 4 subunits (2 alpha and 2 beta), connected to each other 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).

Functions of insulin:

- 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.

Both: receptor associated tyrosine kinase second messenger and PLC products second messengers stimulate amino acid uptake for protein synthesis and ions (k+, Mg^{+2}, PO_4^{-3}) uptake.

Glucose is the most potent stimulus for insulin secretion, but there are many other secondary stimuli which are:

- Increased blood glucose.
- Increased blood free fatty acids and ketoacids.
- ·Increased blood amino acids.
- Gastrointestinal hormones
  (Gastrin, cholecystokinin, secretin, gastric inhibitor peptide).
- Glucagon, growth hormone.
- Cortisol.
- Parasympathetic (vagal) stimulation (Ach).
- Insulin resistance (obesity).
- Sulfonylurea drugs.
- Ghrelin.

Conditions that decrease insulin secretion:

- Decreased blood glucose
- Fasting
- Excersise.
- Somatostatin
- Alpha adrenergic activity
- Leptin hormone from the adipose tissue

How glucose stimulates secretion?

-First glucose is should be metabolized,(*extra note: glucose is oxidized to ATP, which closes K+ channels in the cell membrane), this leads to **depolarization** of beta cells. Depolarization opens Ca+2 channels, which leads to an increase in intracellular Ca+2 and then secretion of insulin.[5]

Figure (78-8)

- 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.

Mechanism of Insulin receptor down regulation

Figure (50-7)

[5] Costanzo physiology BRS.

After exposing the receptors to elevated levels of insulin, they will be down regulated; they will decrease in no., which means that we will need more insulin now to maintain the normal level of glucose concentration.

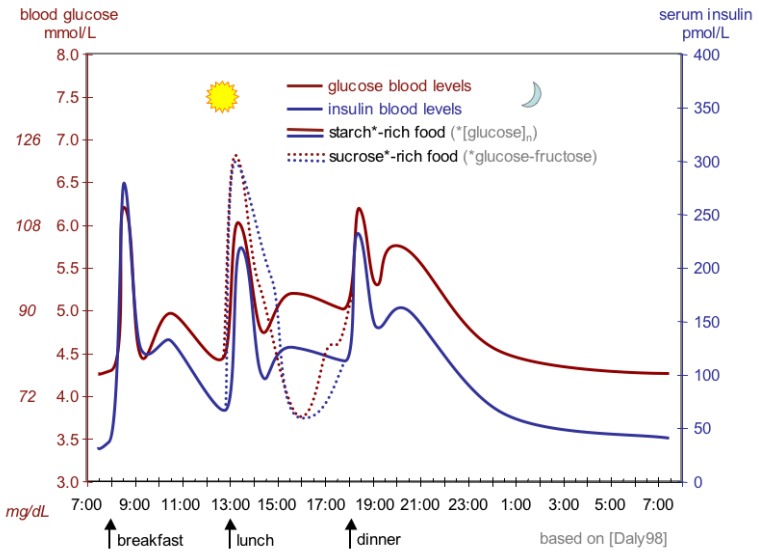
***Extra note**: The process of down regulation occurs when there are elevated levels of the hormone insulin in the blood. When insulin binds to its receptors on the surface of a cell, the hormone receptor complex undergoes endocytosis and is subsequently attacked by intracellular lysosomal enzymes. The internalization of the insulin molecules provides a pathway for degradation of the hormone as well as for regulation of the number of sites that are available for binding on the cell surface. At high plasma concentrations, the number of surface receptors for insulin is gradually reduced by the accelerated rate of receptor internalization and degradation brought about by increased hormonal binding. The rates of synthesis of new receptors within the endoplasmic reticulum and their insertion in the plasma membrane do not keep pace with their rate of destruction. Over time, this self-induced loss of target cell receptors for insulin reduces the target cell's sensitivity to the elevated hormone concentration. The process of decreasing the number of receptor sites is virtually the same for all hormones; it varies only in the receptor hormone complex.[6]

- **Diabetes mellitus 2** (when the insulin receptors are down regulated or desensitized). Mainly DM2 occurs in obese and old individuals, but sometimes it can also occur in old people (with normal weight) but this is rare.

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 presynthesized 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).

[6] http://en.wikipedia.org/wiki/Downregulation_and_upregulation



Note: Some organs take glucose continuously and spontaneously- without the need of insulin- (Brain, kidney tubules, red blood cells and intestinal mucosa); because those are vital organs, while other organs need insulin to take glucose.

Figure (17-14):

- The normal blood glucose level (tested while fasting) for non-diabetics, should be between 90 and 100 milligrams per deciliter (mg/dL)and rarely 70-80 .(this was what the doctor said but in the internet it is 70-100), if above 100 but less than 110, still fine
- Fasting glucose level above 110mg/dl have considered abnormal (pre-diabetic or diabetic).
- 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.