The Pancreas

The pancreas is both an endocrine gland producing several important hormones, including insulin and glucagon, and a digestive organ secreting pancreatic juice containing digestive enzymes.

Pancreas has two main functions:

1- Hormone production and secretion (endocrine pancreas).
2- Digestive enzymes production and secretion (exocrine pancreas).

Both the endocrine and exocrine pancreas is stimulated by:

- Ingestion of food (entry of nutrients).
- GI hormones (as well as GI enzymes).

The endocrine pancreas contains clusters of cells called the **islets of langerhans,** which represent 1-2% of the total mass of the pancreas.
Islets hormones are secreted into the portal vein to reach the liver along with the substrates. Within the liver, they affect the metabolism of the ingested substrates.
In turn, these substrates regulate the secretion of insulin and glucagon via feedback mechanisms.

There are four types of cells in the 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 , and amylin
D cell (delta)	**3-5%**	**Somatostatin**
F cell (PP)	**<2%**	Pancreatic polypeptide

Amylin

Preclinical data indicate that amylin acts as a neuroendocrine hormone that **complements the action of insulin in postprandial glucose homeostasis via several mechanisms.**
These include a suppression of postprandial glucagon secretion and a slowing of the rate at which nutrients are delivered from the stomach to the small intestine for absorption.

Insulin

Human proinsulin is synthesized as a single-chain peptide, which is cleaved in the Golgi apparatus of the pancreatic beta cells to form connecting peptide (C peptide) and insulin , which is composed of A and B chains connected by 2 disulfide bonds.

Insulin is:

- A protein with very short half–life (6 minutes).
- B chain (beta chain) is the **active chain** of insulin.
- A chain is composed of 21 amino acids, whereas B chain is composed of 30 amino acids.
- Insulin amount in the plasma is equal to C peptide plasma amount, thus we can use C peptide amount to measure the amount of insulin in the blood.

Insulin and glucagon play a pivotal role in the fine regulation of plasma glucose levels:

- Insulin is the **ONLY** hormone capable of lowering plasma glucose (i.e. the only hypoglycemic hormone in the body).
- Glucagon is the **most potent** (but not the only one) hyperglycemic hormone that controls the blood glucose level by increasing glycogenolysis and gluconeogenesis.

Other agents also contribute to the maintenance of stable blood glucose as well as mobilizing glucose when necessary. These hormones include:

1- Adrenal corticosteroids.
2- Thyroid hormones.
3- Catecholamines.
4- Growth Hormone.

Insulin Receptor:

- Is a tetramer held together by disulfide linkages (bridges).
- Consists of **two alpha subunits** that lie entirely outside the cell membrane (ON the cell membrane). And **two beta subunits** that span the cell membrane (IN the cell membrane) and have a tyrosine kinase activity.
- Insulin binds to the alpha subunits on the cell membrane.
- Once the insulin binding takes place, the beta subunits is activated, and immediately tyrosine kinase (the second messenger) is activated too, which in turn causes phosphorylation of multiple other intracellular enzymes.
- Other two 2nd messengers *may be* produced by insulin, namely the IP3 and DAG, which facilitate the entry of amino acids, potassium, phosphate and magnesium. Therefore, diabetic people will have heart problems because of the imbalanced potassium level in the blood.

Actions of insulin:

- Growth and increases gene expression.
- Increases minerals (mainly K+) uptake into cells.
- Decreases glucose synthesis
- Increases fat synthesis.
- Increases protein synthesis (stimulates growth by facilitating the entry of amino acids into the cells)
- Increase the insertion of glucose transporters (mainly GLUT-2 and GLUT-4) into the plasma membrane via the effect of insulin.

Note: GH doesn't function properly unless insulin is there.

Insulin–like Growth Factor :

Both IGF-1 and insulin receptors are the same, but IGF-2 receptor is different.

Mechanism of insulin secretion by beta cells of the pancreas:

There are many factors that stimulate insulin secretion, but the most important stimulant is glucose.

1. Glucose binds to GLUT-2 on the beta cells.
2. Glucose is oxidized to ATP.
3. K+ channels are closed by ATP leading to depolarization of the plasma membrane.
4. Voltage-gated Ca++ channels are opened increasing the intracellular level of Ca++.
5. Insulin is released from the beta cells by exocytosis.

Regulation of Insulin Secretion

Stimulatory Factors	Inhibitory Factors
- Increased blood glucose, free fatty acids and amino acids. - GI hormones - Phosphate - Glucagon - GH - Cortisol - Acetylcholine - Sulfonylurea (drugs given to diabetics)	- Decreased blood glucose - Fasting - Exercise - Somatostatin - Alpha adrenergic activity - Digoxin - Leptin (hormone released by adipose tissue)

- If the plasma glucose concentration is equal or less than 50 mg/100 ml there will be no or very little insulin secretion.
- The maximum level of insulin secretion usually appears when the plasma glucose concentration is between 300-400 mg/100 ml.
- Insulin concentration increases 2-3 times after a solid increase in blood glucose.
- The kidney will excrete glucose in the urine when the plasma glucose concentration is **above** 180 mg/100 ml.
- Insulin down-regulates its own receptors, therefore the number of receptors is decreased in obesity, that's why they need higher levels of insulin

Refer to the graph representing insulin vs. glucose concentration for the next few notes.

The graph shows a sudden increase in insulin followed by a decrease in insulin levels then a sustained increase.

Explanation:

When blood glucose **increases**, insulin is secreted from beta cells (sudden increase), but this will **deplete** the storage of insulin in the beta cells causing the **decrease** in insulin levels. But after a while (15-20 minutes) the beta cells will keep synthesizing insulin until glucose levels are back to normal (usually after one hour).

The insulin levels immediately after the meal are low.

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