# The normal endocrine pancreas

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| describe the structure-function relationships in the endocrine pancreas, identifying the sites of insulin, glucagon and somatostatin secretion |
| outline the structure of insulin |
| define the general control mechanisms for the synthesis and secretion of insulin and glucagon |
| describe the metabolic actions of insulin and glucagon |

## Structure-Function Relationships in the Endocrine Pancreas

The pancreas has two main functions: **exocrine** (digestive) and **endocrine** (hormonal).

The **endocrine pancreas** is composed of the **Islets of Langerhans**, which make up about 2% of the pancreas by mass.

The Islets of Langerhans contain several cell types:

- Alpha cells (α-cells): Secrete glucagon.
- Beta cells (β-cells): Secrete insulin.
- Delta cells (δ-cells): Secrete somatostatin.
- PP cells: Secrete pancreatic polypeptide.

The Islets are highly vascularised, allowing hormones to be secreted directly into the bloodstream.
The pancreas receives both sympathetic (via splanchnic nerve) and parasympathetic (via vagus nerve) inputs, which regulate hormone secretion.

## Sites of Hormone Secretion

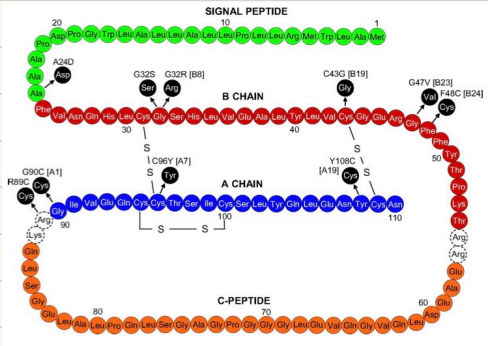
- Insulin: Secreted by beta cells in the Islets of Langerhans.
- Glucagon: Secreted by alpha cells in the Islets of Langerhans.
- Somatostatin: Released by δ cells, acting as a paracrine suppressor of insulin and glucagon.

## Structure of Insulin:

Synthesized in pancreatic β cells as a single-chain precursor called preproinsulin.

Conversion steps:

- Removal of signal peptide → Forms proinsulin.
- Proinsulin consists of:
  - B-chain (N-terminal).
  - A-chain (C-terminal).
  - C-peptide (middle section).
- Three disulfide bonds stabilize its structure.

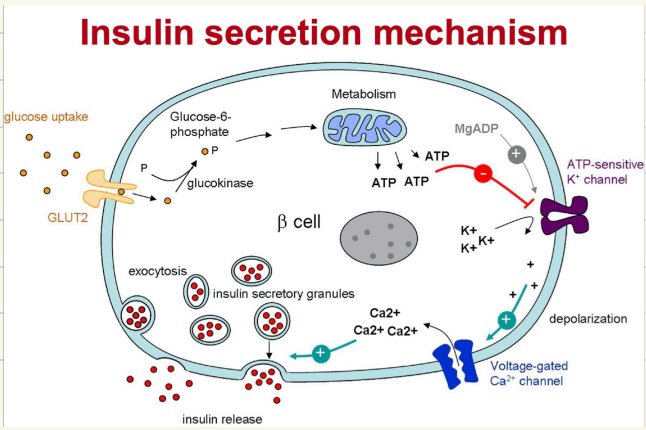



Proinsulin is cleaved by prohormone convertases into mature insulin and free C-peptide

## Control Mechanisms for Insulin and Glucagon Secretion

**Insulin Secretion:**

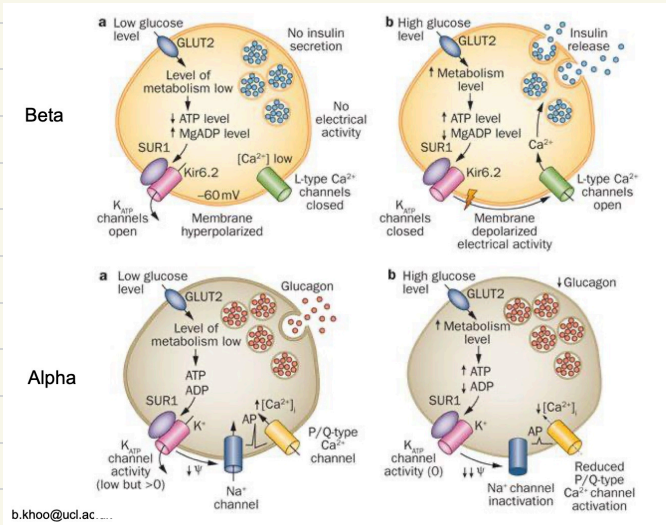
- Stimulated by: High blood glucose (hyperglycemia), amino acids, gut hormones (GLP-1, GIP), acetylcholine, and glucagon.
- Inhibited by: Low blood glucose (hypoglycemia), somatostatin, and activation of alpha-adrenergic receptors.
- Mechanism: Glucose enters beta cells via GLUT2 transporters, is metabolized, and increases the ATP:ADP ratio, leading to the closure of KATP channels. This causes membrane depolarisation, opening of voltage-gated Ca2+ channels, and insulin secretion via exocytosis.



**Glucagon Secretion:**

- Stimulated by: Low blood glucose (hypoglycemia), amino acids, adrenaline, and GIP.
- Inhibited by: High blood glucose, GLP-1, and insulin.
- Mechanism: Glucagon is released in response to low glucose levels, stimulating the liver to produce glucose via glycogenolysis and gluconeogenesis.

General mechanisms of secretion:




## Incretin Effect

- GLP-1 and GIP are gut hormones released in response to eating. They enhance insulin secretion and inhibit glucagon release, known as the incretin effect.
- This effect is reduced in type 2 diabetics, contributing to impaired glucose regulation.

# Metabolic Actions of Insulin and Glucagon

## Insulin:

**Role**: **Anabolic hormone** promoting nutrient storage (fed state).

- **Carbohydrates**:
  - ↑ **Glucose uptake** into muscle/adipose via **GLUT4 translocation**.
    - Hexokinase activated to trap glucose
  - Activates **glycogen synthase** (liver/muscle) for glycogen storage.
  - Inhibits **gluconeogenesis** (liver) and **glycogenolysis**. (inhibitis glucose-6-phosphotase)
- **Lipids**:
  - ↑ **Lipogenesis**: Activates **acetyl-CoA carboxylase** (ACC) → fatty acid synthesis.
  - ↓ **Lipolysis**: Inactivates hormone-sensitive lipase (HSL) → reduces fat breakdown.
- **Proteins**:

  ↑ **Amino acid uptake** (muscle) and **protein synthesis**; inhibits proteolysis.

## Glucagon

**Role**: **Catabolic hormone** mobilizing energy stores (fasting state).

- **Carbohydrates**:
  - ↑ **Glycogenolysis** (liver): Activates glycogen phosphorylase via cAMP-PKA pathway.
  - ↑ **Gluconeogenesis**: Upregulates PEP carboxykinase, glucose-6-phosphatase.
- **Lipids**:
  - ↑ **Lipolysis**: Activates HSL → releases free fatty acids for energy.
  - ↓ **Lipogenesis**: Inactivates ACC → reduces malonyl-CoA, promoting fatty acid oxidation.
- **Proteins**:

  ↑ **Amino acid catabolism** (liver): Provides substrates for gluconeogenesis; activates urea cycle.