Problem 1 – Unit 4 – Biochemistry: Metabolic Effects of Insulin and Glucagon

Overview:

- **There are four organs for fuel metabolism**: liver, adipose, muscle & brain. They communicate by hormones, nervous system & availability of circulating substrates.
- **Integration of energy metabolism is controlled mainly by:**
  - **Insulin (anabolic) & glucagon (catabolic).**
  - **Catecholamines (epinephrine & NE), cortisol, growth hormone** → supporting role.

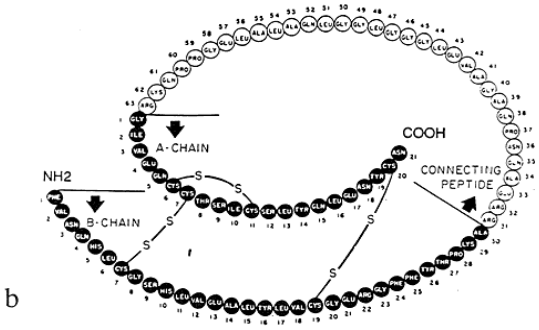
  These hormones allow:
  - Storage of energy when food is available (insulin).
  - Or make stored energy available (through catabolic reactions by counter-regulatory hormones).

Insulin:

- It is a polypeptide hormone produced by β-cells of islets of Langerhans.
- It is the most important hormone coordinating the use of fuels by tissues.
- It is anabolic favoring (e.g. Synthesis of glycogen by glycogenesis in liver and muscles, TAG & proteins).

A. Structure of insulin:

- Composed of 51 amino acids arranged in two polypeptide chains, designated A & B (C-peptide is removed). A & B are linked by disulfide bridges.
- C-peptide is a good indicator of insulin production and secretion.



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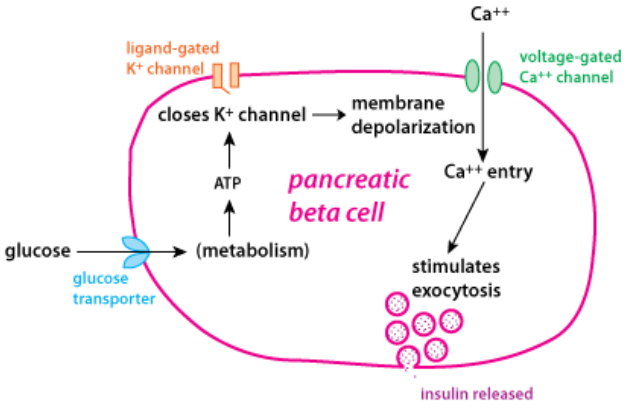
B. Synthesis if insulin:

- **There are two inactive precursors**: preproinsulin and proinsulin.
- Insulin is stored in the cytosol in granules that, given the proper stimulus it will be released by exocytosis (stimulus: increased uptake of glucose by GLUT-2 in β-cells).
- Insulin is degraded by: insulinase.
- The half-life of insulin is 6 minutes.

C. Regulation of insulin secretion:

- **Stimulation of insulin secretion: insulin secretion is increased by:**
  - Glucose: ingestion of glucose or a carbohydrate-rich meal leads to a rise in blood glucose (most important).
  - Amino acids.
  - Gastointestinal hormones: CCK & gastric-inhibitory polypeptide.

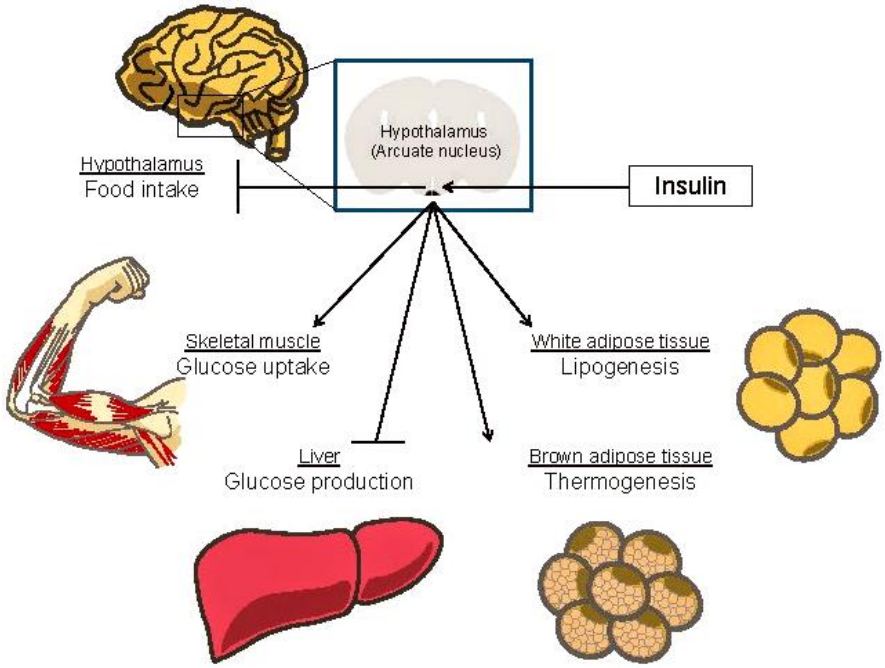


Note: glucose taken into β-cells is metabolized, with subsequent production of ATP. ATP-sensitive K^+ channels close, causing depolarization of the plasma membrane, activation of voltage-gated Ca^{+2} channels, and influx of calcium into the cell. Ca^{+2} causes vesicles containing insulin to be released from the β-cell by exocytosis.

- **Inhibition of insulin secretion: insulin secretion is decreased by:**
  - Scarcity of dietary fuels (↓ glucose, ↓amino acids).
  - Periods of stress → ↑ epinephrine → inducing glycogenolysis & gluconeogenesis.

D. Metabolic effects of insulin:

- **Effects on carbohydrate metabolism:**
  - Glucose storage in: liver, muscle adipose.
  - In liver & muscle: insulin increases glycogen synthesis.
  - In muscle & adipose: insulin increases glucose uptake by increasing the number of glucose transporters (GLUT-4).
- **Effects on lipid metabolism:**
  - Decreased triacylglycerol metabolism: inhibiting the activity of hormone-sensitive lipase that degrades TAG.
  - Increased triacylglycerol synthesis: increases the transport & metabolism of glucose providing the substrate glycerol 3-phosphate for TAG synthesis.
- **Protein synthesis:**
  - Increased uptake of amino acids by muscles.

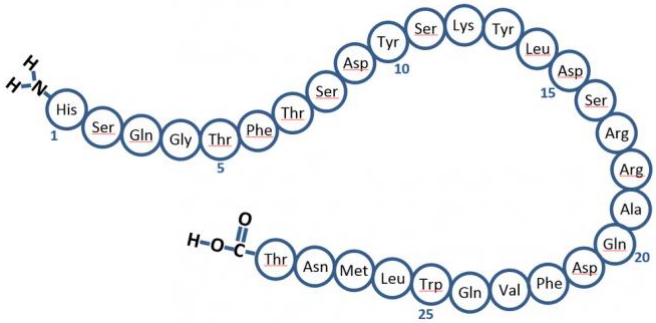


E. Mechanism of insulin action:

- **Insulin receptor**: has 2α & 2β subunits assembled into a tetramer. α-subunit contains the insulin binding site. β-subunit is a tyrosine kinase.
- **Signal transduction:**
  - Insulin binding activates receptor tyrosine kinase activity in the intracellular domain of the β subunit of the insulin receptor.
  - Tyrosine residues of the β subunit are autophosphorylated.
  - Receptor tyrosine kinase phosphrylates other proteins such as insulin receptor substrate (IRS).
  - Phosphorylated IRS promote activation of other protein kinases and phosphatases, leading to biologic actions of insulin.
- **Membrane effects of insulin**: glucose transport in some tissues, such as skeletal muscle and adipocyte, increases in the presence of insulin (by the expression of glucose transport proteins on the cell membrane GLUT-4).

Glucagon:

- It is a polypeptide hormone secreted by the α-cells of the islets of Langerhans.
- Glucagon along with epinephrine, cortisol & GH (counter-regulatory hormones) opposes many of the actions of insulin.
- Glucagon function is mainly in activating glycogenolysis & gluconeogenesis.
- Preproglucagon is converted to glucagon through a series of selective proteolytic cleavages.



A. Stimulation of glucagon secretion: glucagon secretion is increased by:

- **Low blood glucose**: a decrease in plasma glucose concentration is the primary stimulus for glucagon release.
- **Amino acids.**
- **Epinephrine**: during periods of stress, trauma, or severe exercise, the elevated epinephrine levels can override the effect of the α-cell of circulating substrates.

B. Inhibition of glucagon secretion: glucagon secretion is decreased by:

- Elevated blood glucose & insulin.

C. Metabolic effects of glucagon:

- **Effects on carbohydrate metabolism**: the IV administration of glucagon leads to an immediate rise in blood glucose by glycogenolysis & gluconeogenesis.
- **Effects on lipid metabolism**: lipolysis & ketone body synthesis.

D. Mechanism of action of glucagon:

- Glucagon binds to high-affinity G protein-coupled receptors on the cell membrane of hepatocytes.
- Leading to activation of adenylyl cyclase.
- Which will lead to a rise in cAMP.
- Activating cAMP-dependent protein kinase.
- And increasing the phosphrylation of specific enzymes or other proteins.