Endocrine pancreas and the regulation of blood glucose

Simge Aykan, PhD

Department of Physiology

Ankara University School of Medicine

Pancreas

- Both an exocrine and endocrine organ
- Cells with exocrine function release an alkaline fluid containing sodium bicarbonate and enzymes →pancreatic duct → small intestine
  - Pancreatic exocrine cells = acinar cells
- Cells of the Islet of Langerhans synthesize and release hormones into the circulation

Pancreatic Endocrine Cells

Regulate carbohydrate, fat, protein metabolism:

- **Alpha cells** –glucagon
- **Beta cells** –insulin and amylin
- **Delta cells** –gastrin and somatostatin
- **F cells** - pancreatic polypeptide

Structure of Insulin

- Insulin is a polypeptide hormone, composed of two chains (A and B)
- Both chains are derived from proinsulin, a prohormone.
- The two chains are joined by disulfide bonds.

Roles of Insulin

- Acts on tissues (especially liver, skeletal muscle, adipose) to increase uptake of glucose and amino acids.
- - without insulin, most tissues do not take in glucose and amino acids well (except brain).
- Increases glycogen production (glucose storage) in the liver and muscle.
- Stimulates lipid synthesis from free fatty acids and triglycerides in adipose tissue.
- Also stimulates potassium uptake by cells (role in potassium homeostasis).

The Insulin Receptor

- The insulin receptor is composed of two subunits, and has intrinsic tyrosine kinase activity.
- Activation of the receptor results in a cascade of phosphorylation events:

Specific Targets of Insulin Action: Carbohydrates

- Increased activity of glucose transporters. Moves glucose into cells.
- Activation of glycogen synthetase. Converts glucose to glycogen.
- Inhibition of phosphoenolpyruvate carboxykinase. Inhibits gluconeogenesis.

Specific Targets of Insulin Action: Lipids

- Activation of acetyl CoA carboxylase. Stimulates production of free fatty acids from acetyl CoA.
- Activation of lipoprotein lipase (increases breakdown of triacylglycerol in the circulation). Fatty acids are then taken up by adipocytes, and triacylglycerol is made and stored in the cell.

Regulation of Insulin Release

- Major stimulus: increased blood glucose levels

  - after a meal, blood glucose increases

  - in response to increased glucose, insulin is released

  - insulin causes uptake of glucose into tissues, so blood glucose levels decrease.

  - insulin levels decline as blood glucose declines

Insulin Action on Cells: Dominates in Fed State Metabolism

- ↑ glucose uptake in most cells
  (not active muscle)
- ↑ glucose use and storage
- ↑ protein synthesis
- ↑ fat synthesis

Other Factors Regulating Insulin Release

- Amino acids stimulate insulin release (increased uptake into cells, increased protein synthesis).
- Keto acids stimulate insulin release (increased glucose uptake to prevent lipid and protein utilization).
- Insulin release is inhibited by stress-induced increase in adrenal epinephrine

  - epinephrine binds to alpha adrenergic receptors on beta cells

  - maintains blood glucose levels
- Glucagon stimulates insulin secretion (glucagon has opposite actions).

Structure and Actions of Glucagon

- Peptide hormone, 29 amino acids
- Acts on the liver to cause breakdown of glycogen (glycogenolysis), releasing glucose into the bloodstream.
- Inhibits glycolysis
- Increases production of glucose from amino acids (gluconeogenesis).
- Also increases lipolysis, to free fatty acids for metabolism.
- Result: maintenance of blood glucose levels during fasting.

Mechanism of Action of Glucagon

- Main target tissues: liver, muscle, and adipose tissue
- Binds to a Gs-coupled receptor, resulting in increased cyclic AMP and increased PKA activity.
- Also activates IP3 pathway (increasing Ca^{++})

Glucagon Action on Cells: Dominates in Fasting State Metabolism

- Glucagon prevents hypoglycemia by ↑ cell production of glucose
- Liver is primary target to maintain blood glucose levels

Targets of Glucagon Action

- Activates a phosphorylase, which cleaves off a glucose 1-phosphate molecule off of glycogen.
- Inactivates glycogen synthase by phosphorylation (less glycogen synthesis).
- Increases phosphoenolpyruvate carboxykinase, stimulating gluconeogenesis
- Activates lipases, breaking down triglycerides.
- Inhibits acetyl CoA carboxylase, decreasing free fatty acid formation from acetyl CoA
- Result: more production of glucose and substrates for metabolism

Regulation of Glucagon Release

- Increased blood glucose levels inhibit glucagon release.
- Amino acids stimulate glucagon release (high protein, low carbohydrate meal).
- Stress: epinephrine acts on beta-adrenergic receptors on alpha cells, increasing glucagon release (increases availability of glucose for energy).
- Insulin inhibits glucagon secretion.

Other Factors Regulating Glucose Homeostasis

- Glucocorticoids (cortisol): stimulate gluconeogenesis and lipolysis, and increase breakdown of proteins.
- Epinephrine/norepinephrine: stimulates glycogenolysis and lipolysis.
- Growth hormone: stimulates glycogenolysis and lipolysis.
- Note that these factors would complement the effects of glucagon, increasing blood glucose levels.

Pancreatic Islets (Islets of Langerhans)

- Alpha cells secrete glucagon.
  - Stimulus is decrease in blood [glucose].
  - Stimulates glycogenolysis and lipolysis.
  - Stimulates conversion of fatty acids to ketones.
- Beta cells secrete insulin.
  - Stimulus is increase in blood [glucose].
  - Promotes entry of glucose into cells.
  - Converts glucose to glycogen and fat.
  - Aids entry of amino acids into cells.

Energy Regulation of Pancreas

- Islets of Langerhans contain 3 distinct cell types:
  - α cells:
    - Secrete glucagon.
  - β cells:
    - Secrete insulin.
  - Δ cells:
    - Secrete somatostatin.

Regulation of Insulin and Glucagon

- Mainly regulated by blood [glucose].
- Lesser effect: blood [amino acid].
  - Regulated by negative feedback.
- Glucose enters the brain by facilitated diffusion.
- Normal fasting [glucose] is 65–105 mg/dl.

Regulation of Insulin and Glucagon (continued)

- When blood [glucose] increases:
  - Glucose binds to GLUT2 receptor protein in β cells, stimulating the production and release of insulin.
- Insulin:
  - Stimulates skeletal muscle cells and adipocytes to incorporate GLUT4 (glucose facilitated diffusion carrier) into plasma membranes.
    - Promotes anabolism.

Hormonal Regulation of Metabolism

- Absorptive state:
  - Absorption of energy.
  - 4 hour period after eating.
  - Increase in insulin secretion.
- Postabsorptive state:
  - Fasting state.
  - At least 4 hours after the meal.
  - Increase in glucagon secretion.

Absorptive State

- Insulin is the major hormone that promotes anabolism in the body.
- When blood [insulin] increases:
  - Promotes cellular uptake of glucose.
  - Stimulates glycogen storage in the liver and muscles.
  - Stimulates triglyceride storage in adipose cells.
  - Promotes cellular uptake of amino acids and synthesis of proteins.

Postabsorptive State

- Maintains blood glucose concentration.
- When blood [glucagon] increased:
  - Stimulates glycogenolysis in the liver (glucose-6-phosphatase).
  - Stimulates gluconeogenesis.
  - Skeletal muscle, heart, liver, and kidneys use fatty acids as major source of fuel (hormone-sensitive lipase).
  - Stimulates lipolysis and ketogenesis.