BCHM 270: Module 7

INTEGRATION OF METABOLISM

Content Outline

Section 1..... Insulin and Glucagon

Section 2..... The Feed-Fast Cycle

Section 3..... Diabetes Mellitus

Section 4..... Obesity

Section 1: Insulin and Glucagon

Concept 1.1: Overview of Energy Metabolism

- The body's energy metabolism is regulated by 4 main tissues:
  - The liver
  - The brain
  - Adipose tissue
  - Skeletal muscle
- These tissues communicate with one another via the **nervous system** to provide substrates and specialized fuels to one another
  - Substrate release stimulates insulin or glucagon release

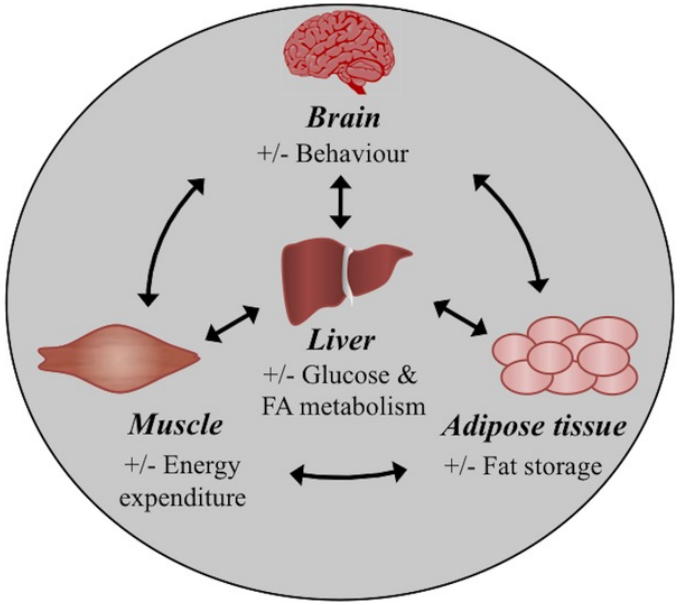


Figure 1. The intersection between the 4 main tissues that regulate metabolism.

Concept 1.2: Insulin - Structure

Structure

- Composed of 51 amino acids in 2 peptide chains → A chain and B chain
- Support:
  - Intramolecular disulfide bonds in the A chain
  - 2 Intermolecular disulfide bonds connecting both chains

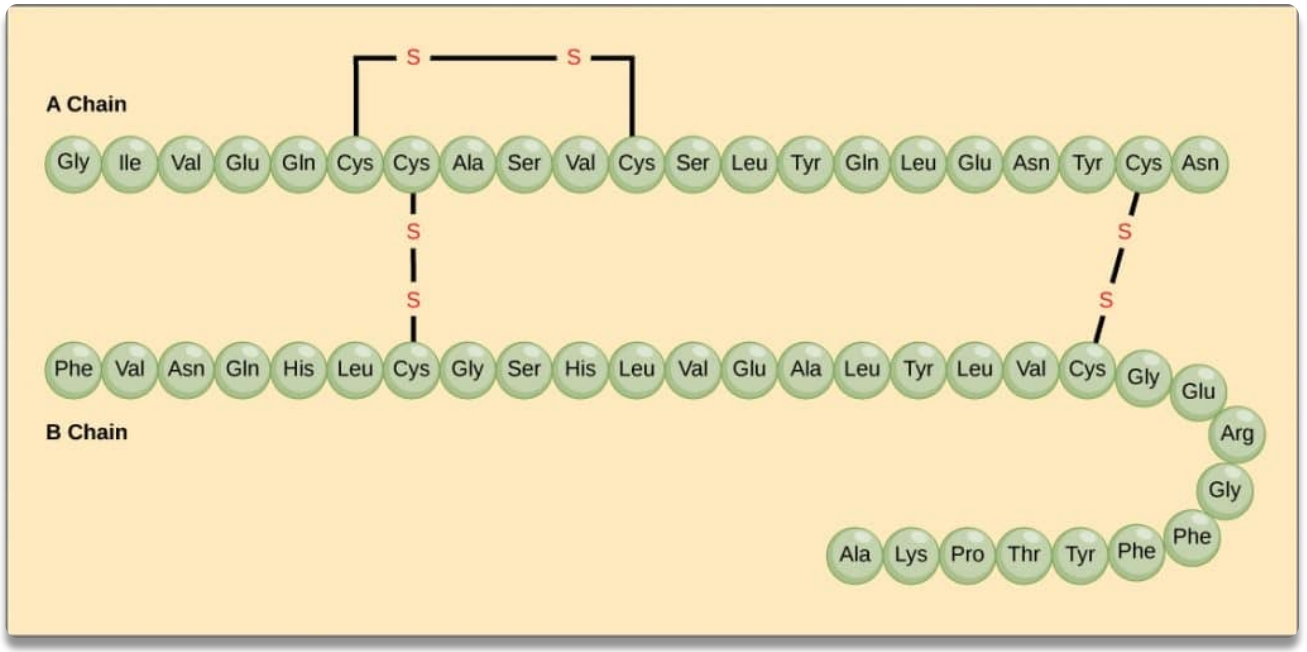


Figure 2. Structure of Insulin.

Concept 1.2: Insulin - Synthesis

1. Insulin mRNA is transcribed from DNA, and transported into the cytosol after processing
2. A signal sequence is made first during translation, directing the ribosome and mRNA to the rough ER
3. Preproinsulin is made in the ER
4. Signal sequence is cleaved and proinsulin is made
5. Proinsulin is sent to the Golgi complex. It is cleaved, forming mature insulin and the C-peptide
6. Insulin and C-peptide are stored in cystolic granules
7. Upon stimulation, insulin and C-peptide are released by exocytosis

Concept 1.2: Insulin – Stimulation

Blood Glucose

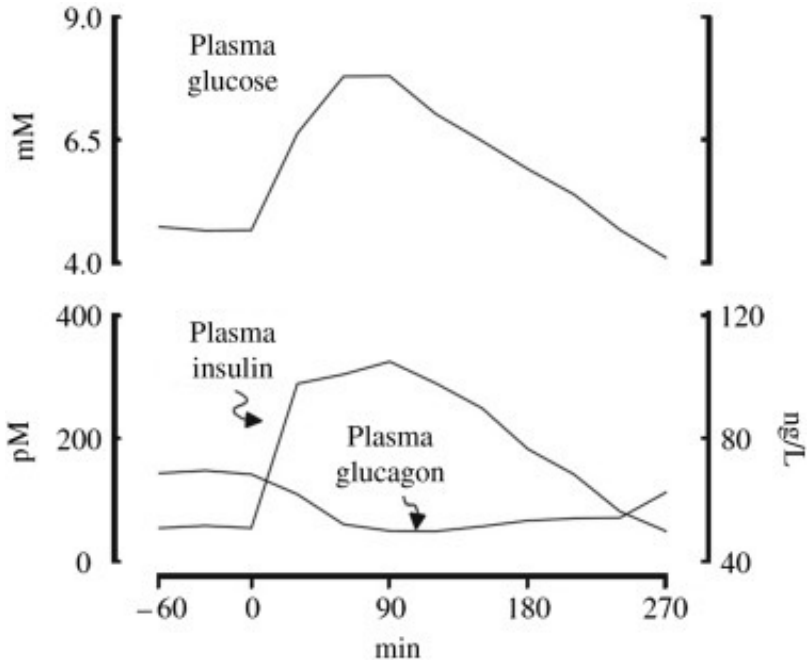
- Most important signal for increased insulin secretion
- Plasma levels of insulin will mirror plasma levels of glucose

Amino Acids

- Consuming protein causes a temporary rise in plasma amino acids
  - Enhancing glucose-induced insulin secretion (fatty acids have a similar effect)

GI Hormones

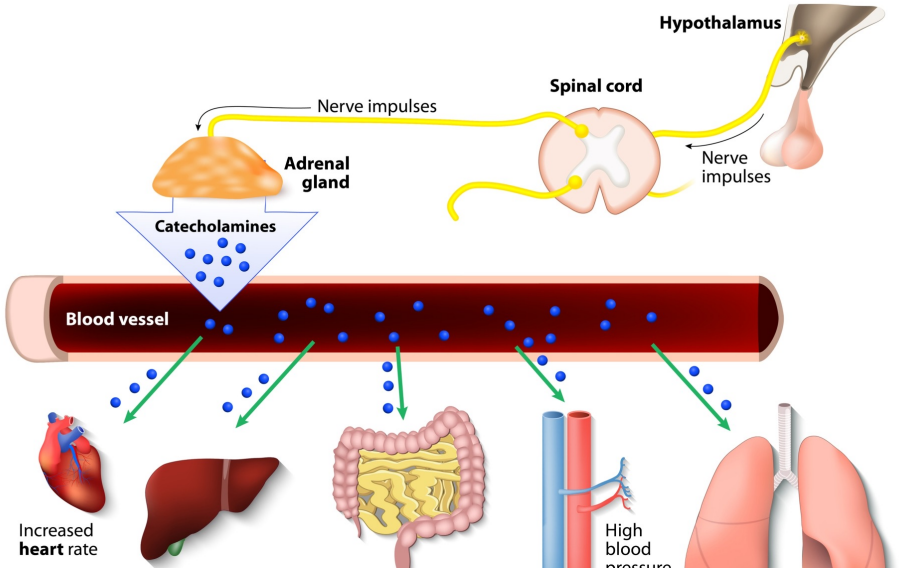
- Ingestion of food causes the release of intestinal hormones such as GLP-1 and GIP, stimulating insulin secretion by increasing the sensitivity of beta-cells to glucose



Concept 1.2: Insulin – Inhibition

Factors to know:

- Decreased food ingestion (lower blood glucose) → stimulate glucagon, inhibit insulin release
- Periods of physiological stress
  - Injury or infection
  - NorEpi and Epi mediated through the nervous system
  - Catecholamines can override glucose-stimulated release in emergencies (fight or flight for instance)



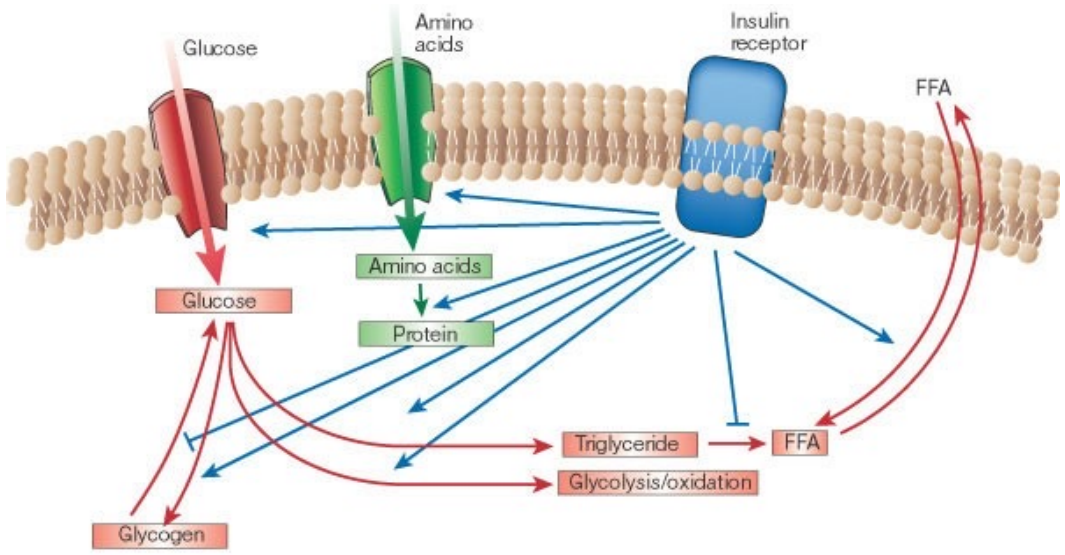
Concept 1.2: Insulin – Degradation

- Short-half life
- Circulates for 6 minutes before taken up by the liver and degraded by the enzyme *insulinase*
- **Significance:**
  - Quick turnover allows for rapid changes in the amount of circulating insulin, and tight control of energy metabolism

Concept 1.2: Insulin – Carbohydrates

Effects are most prominent in Liver, muscle, and adipose tissue:

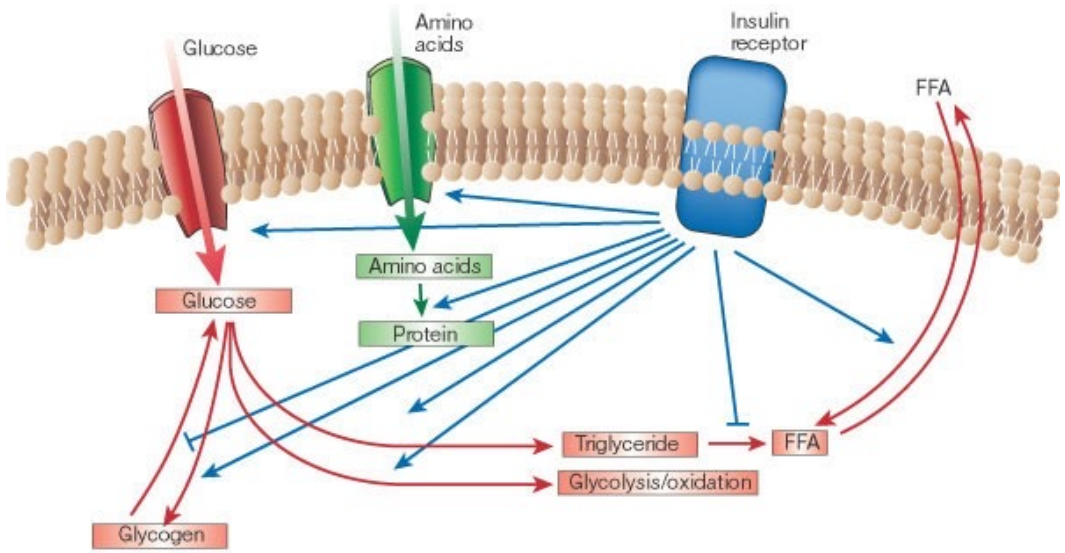
- Liver and muscle
  - Glycogen synthesis is increased
- Muscle and adipose
  - Glucose uptake is increased by increasing the amount of glucose transporters in the membrane
- Liver
  - Glycogen degradation is inhibited, as well as gluconeogenesis, thus reducing glucose production



Concept 1.2: Insulin – Lipid

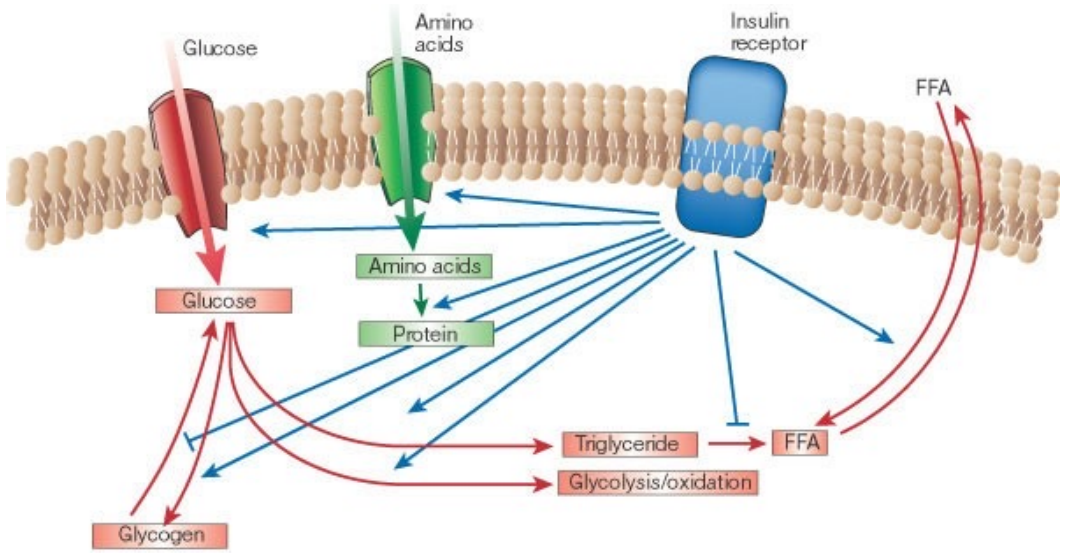
Insulin causes a decrease in the release of FA from adipose tissue, via 2 methods:

- *Hormone sensitive lipase:* inhibited, decreased TAG breakdown
- Due to increased glucose transport and metabolism in fat cells, there is increased TAG synthesis



Concept 1.2: Insulin – Protein

- Amino Acids
  - Entry of amino acids into cells for use in synthesis of new proteins, as well as for degradation
  - The gene expression and synthesis of many of the key regulatory enzymes in the metabolic pathways are **increased** in response to insulin



Concept 1.3: Insulin's Mechanism of Action

- Insulin binds to the a-subunit of the insulin receptor (on the surface of most tissues)
- The receptor undergoes a conformational change that activates a tyrosine kinase in the β-subunit
- The tyrosine kinase autophosphorylates a tyrosine residue in the β-subunit
- Initiates the signal transduction cascade that causes phosphorylation of insulin receptor substrates
- Dephosphorylation of the receptor occurs and the signal is stopped

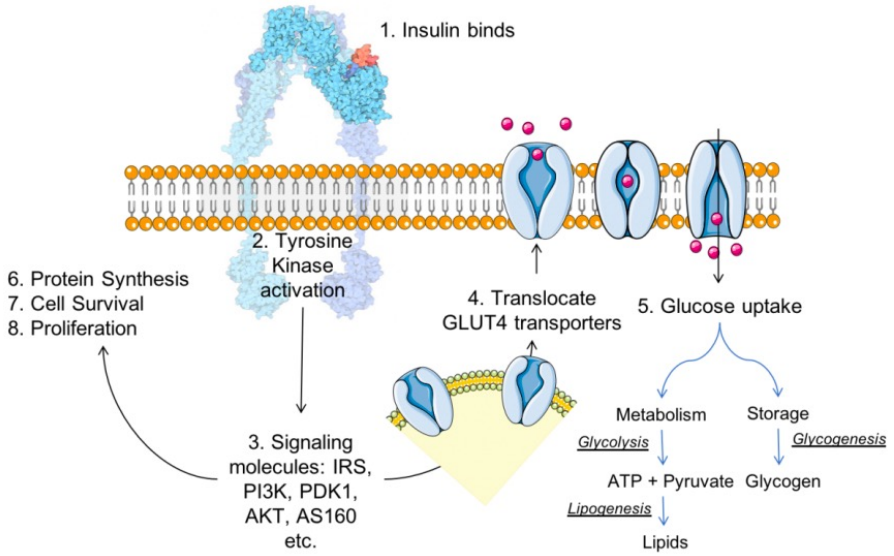


Figure 3. Insulin's mechanism of action.

Concept 1.3: Insulin and Glucagon: Compare and Contrast

Insulin

- Produced by β-cells in pancreatic Islets of Langerhans
- Release is stimulated by increased blood glucose levels (**well-fed state**)
- Has anabolic effects:
  - Promotes protein, lipid, and glycogen synthesis
  - Promotes storage of energy

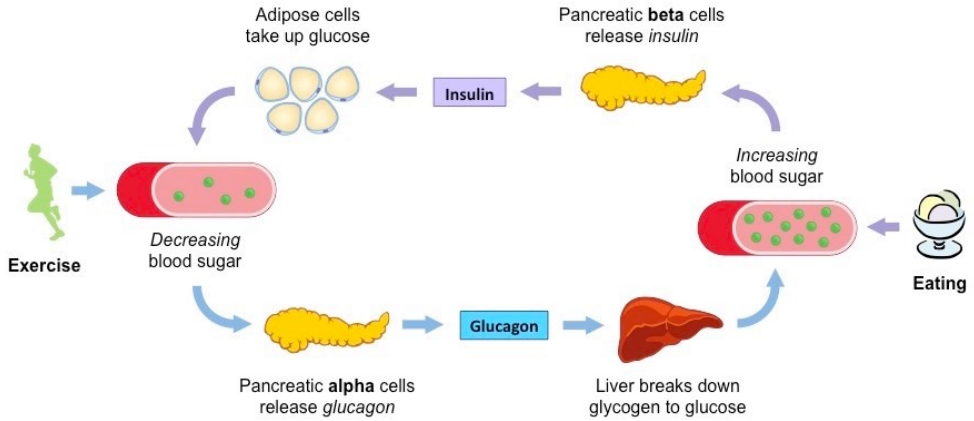


Figure 2. The cycle of insulin and glucagon release.

Concept 1.3: Insulin and Glucagon: Compare and Contrast

Glucagon

- Produced by a-cells in pancreatic Islets of Langerhans
- Release is stimulated by decreased blood glucose levels (**fasting state**)
- Has catabolic effects:
  - Activates gluconeogenesis and liver glycogen degradation

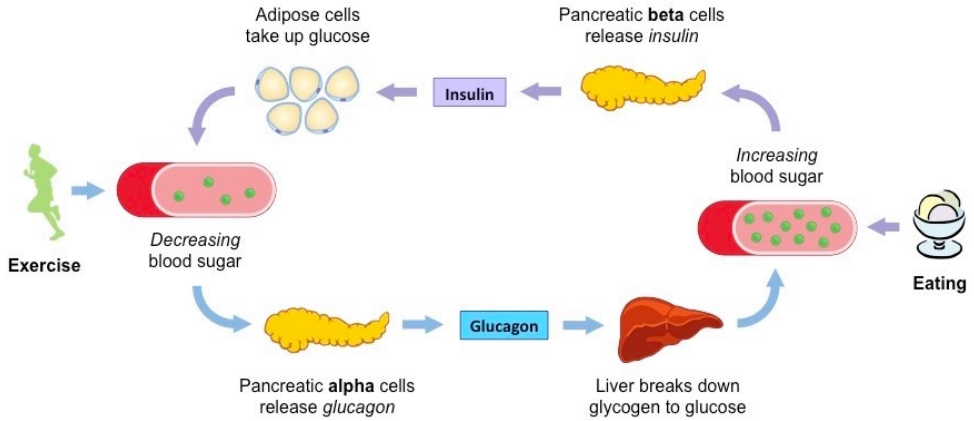


Figure 2. The cycle of insulin and glucagon release.

Concept 1.4: Glucagon

Location of production:

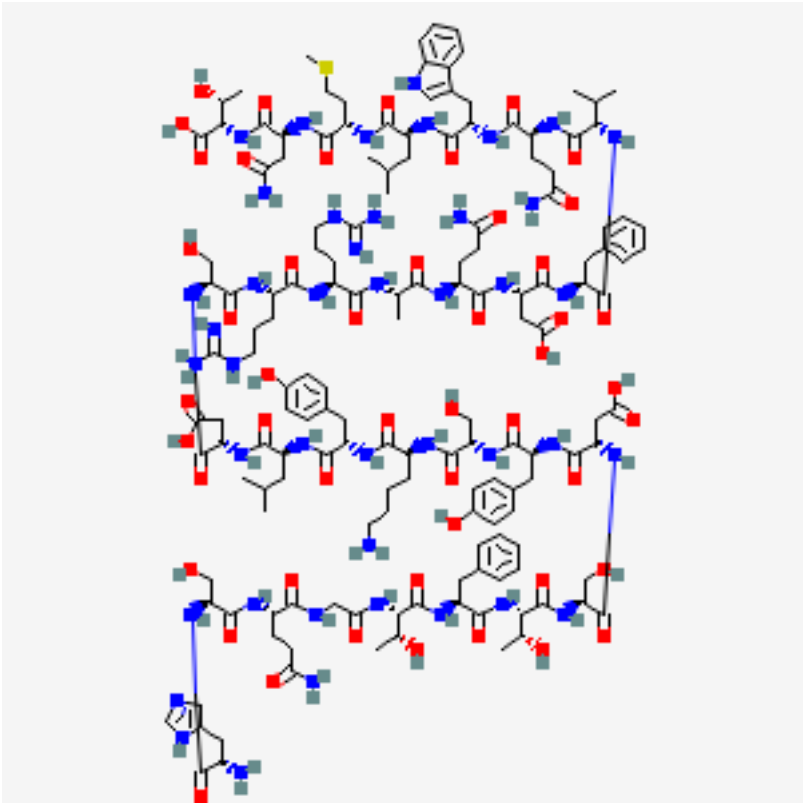
- Alpha-cells in the pancreatic islets of Langerhans
- Single peptide of 29 amino acids

Similar to insulin:

- Starts as preproglucagon, and is converted to glucagon by a series of proteolytic cleavages

Important Role:

- Maintain blood glucose levels by activating glycogen degradation and gluconeogenesis in the liver
- Glucagon, Epi, NorEpi, cortisol, and growth hormone, all oppose actions of insulin (**counterregulatory hormones**)



Concept 1.4: Glucagon – Stimulation

Low Glucose

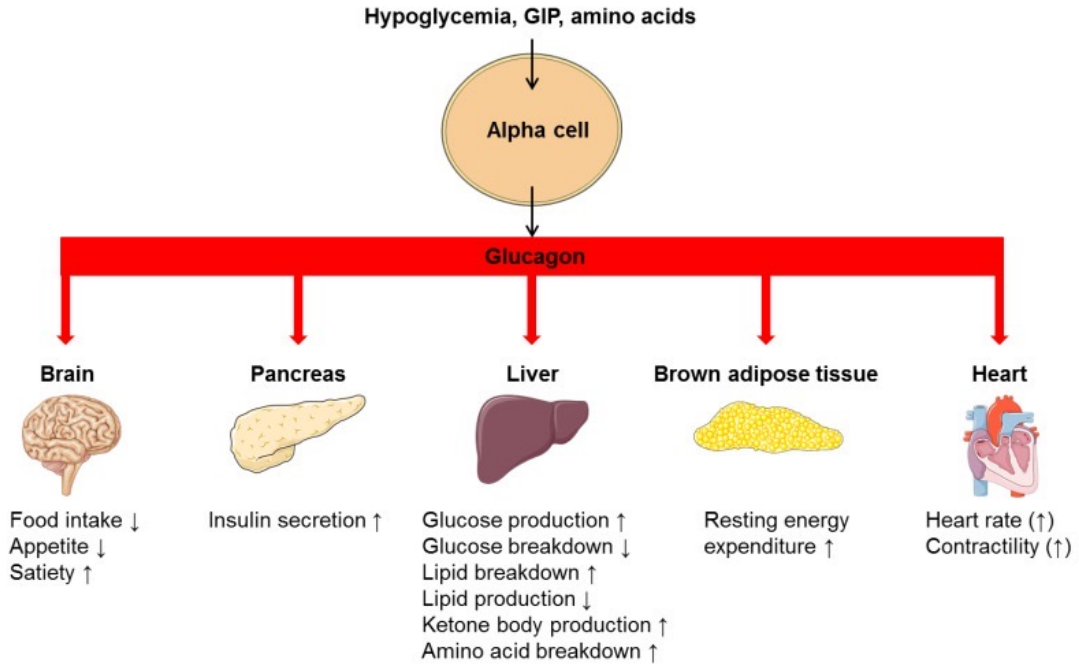
- Primary stimulus
- Overnight or prolonged fasting, glucagon prevents hypoglycemia
- High glucose levels stop glucagon release

Amino Acids

- Protein rich meal increases concentration of plasma amino acid
- Stimulates **both** insulin and glucagon
- Glucagon prevents hypoglycemia be ensuring that the blood glucose doesn't drop too low if the meal was low in carbohydrates

Catecholamines

- Elevated Epi or NorEpi increase glucagon secretion
- Remember that catecholamines inhibit insulin secretion



Concept 1.4: Glucagon – Inhibition

- Glucagon secretion is inhibited by elevated blood glucose and insulin

Concept 1.4: Glucagon – Metabolic Effects

Carbohydrate Metabolism

- Stimulates the breakdown of liver glycogen and increases gluconeogenesis

Lipid Metabolism

- Increases rate of oxidation of fatty acids and formation of ketone bodies from acetyl-CoA

Protein Metabolism

- Increases uptake of amino acids of amino acids from the blood by the liver
- This enhances gluconeogenesis and reduces amino acid plasma levels

Concept 1.4: Glucagon's Mechanism of Action

- Glucagon binds to glucagon receptor on hepatic cells
- Adenylyl cyclase is activated
  - Increases cAMP concentration
- cAMP-dependent kinase is activated
  - Phosphorylates proteins to cause:
    - Increased ketogenesis
    - Increased gluconeogenesis
    - Increased glycogen degradation
    - Increased amino acid uptake
    - Decreased glycogen synthesis

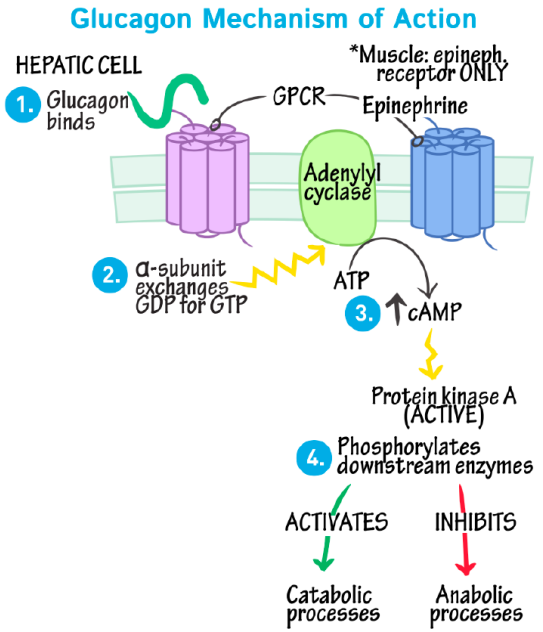


Figure 4. Glucagon's mechanism of action.

Spotlight on Disease: Hypoglycemia – 4 Types

The 4 Types:

- Insulin-induced hypoglycemia
- Fasting
- Alcohol-related hypoglycemia
- Postprandial hypoglycemia

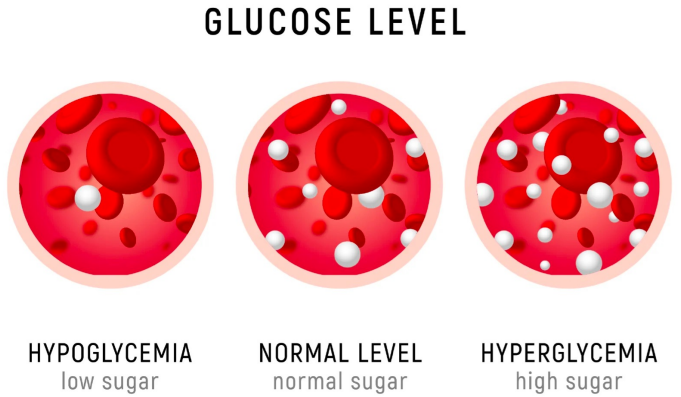


Figure 5. A comparison between different blood-glucose levels.

Spotlight on Disease: Hypoglycemia – Characterization

Characterization:

- CNS
  - Confusion, Aberrant Behavior, Coma
- Blood glucose level <= 40 mg/dL
- Symptoms resolve within minutes of administration of glucose

Clinical Significance:

- MEDICAL EMERGENCY

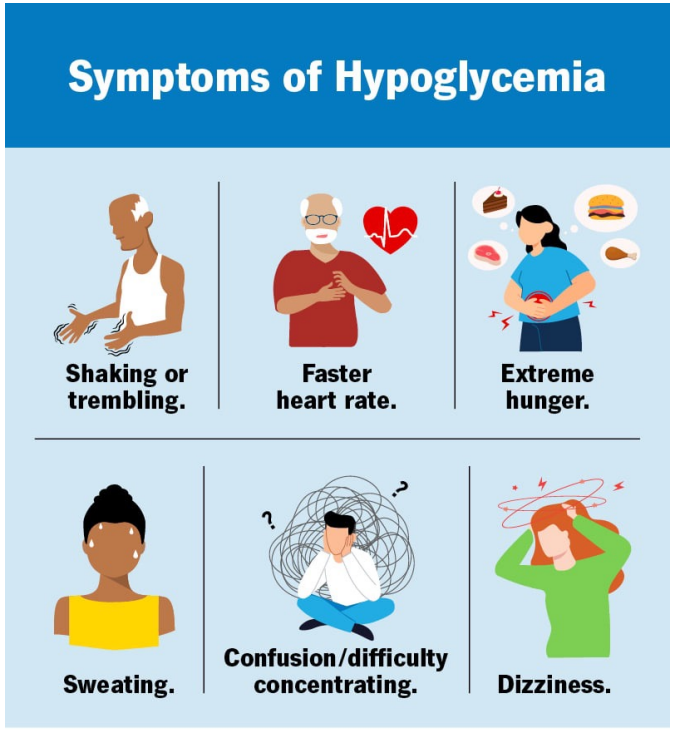


Figure 6. Hypoglycemia Overiew.

Spotlight on Disease: Hypoglycemia – Question

Why do you think hypoglycemia is a medical emergency?

Spotlight on Disease: Hypoglycemia – Question

Answer: CNS has an absolute requirement for the continuous supply of glucose. As a result, the body has many redundant systems in place to prevent and correct hypoglycemia

Spotlight on Disease: Hypoglycemia – Insulin Induced and Fasting

Insulin-induced hypoglycemia

- Commonly caused by insulin injections in diabetes
- Mild cases are treated with oral glucose
- Severe cases are treated with injected glucagon

Fasting

- Can be caused by hepatic damage, insufficient adrenal gland function, pancreatic β-cell cancer, large consumptions of alcohol, or fasting
- Causes neuroglycopenic symptoms

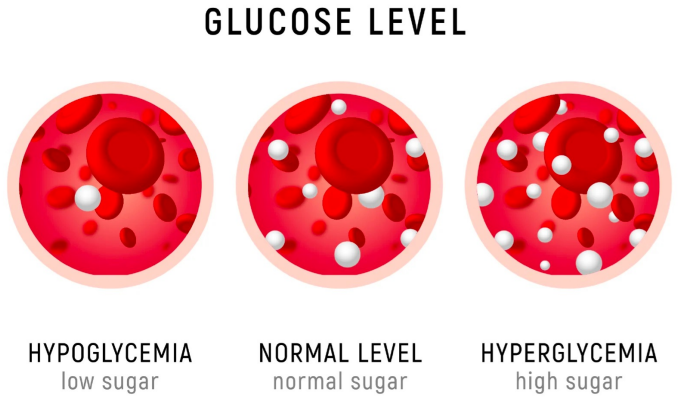


Figure 5. A comparison between different blood-glucose levels.

Spotlight on Disease: Hypoglycemia – Alcohol Related and Post-Prandial

Alcohol-related hypoglycemia

- Alcohol metabolism depletes gluconeogenesis substrates
- High alcohol consumption causes hypoglycemia in those with low levels of glycogen

Postprandial hypoglycemia

- Caused by over-release of insulin after a meal
- Results in mild adrenergic symptoms
- Treated with smaller, but more frequent meals

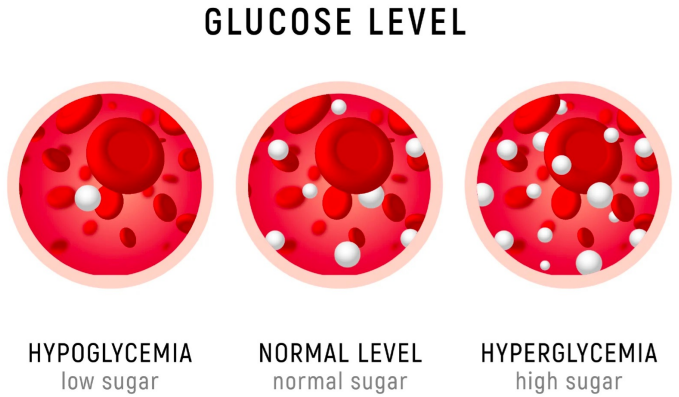


Figure 5. A comparison between different blood-glucose levels.

Section 1 Quiz: 1 MC

Ethanol-induced hypoglycemia is caused by the inhibition of which process?

A) Pentose phosphate pathway

B) Glycogenolysis

C) Gluconeogenesis

D) Glycogenesis

Answer

Answer: C

Section 1 Quiz: 1 Short Answer

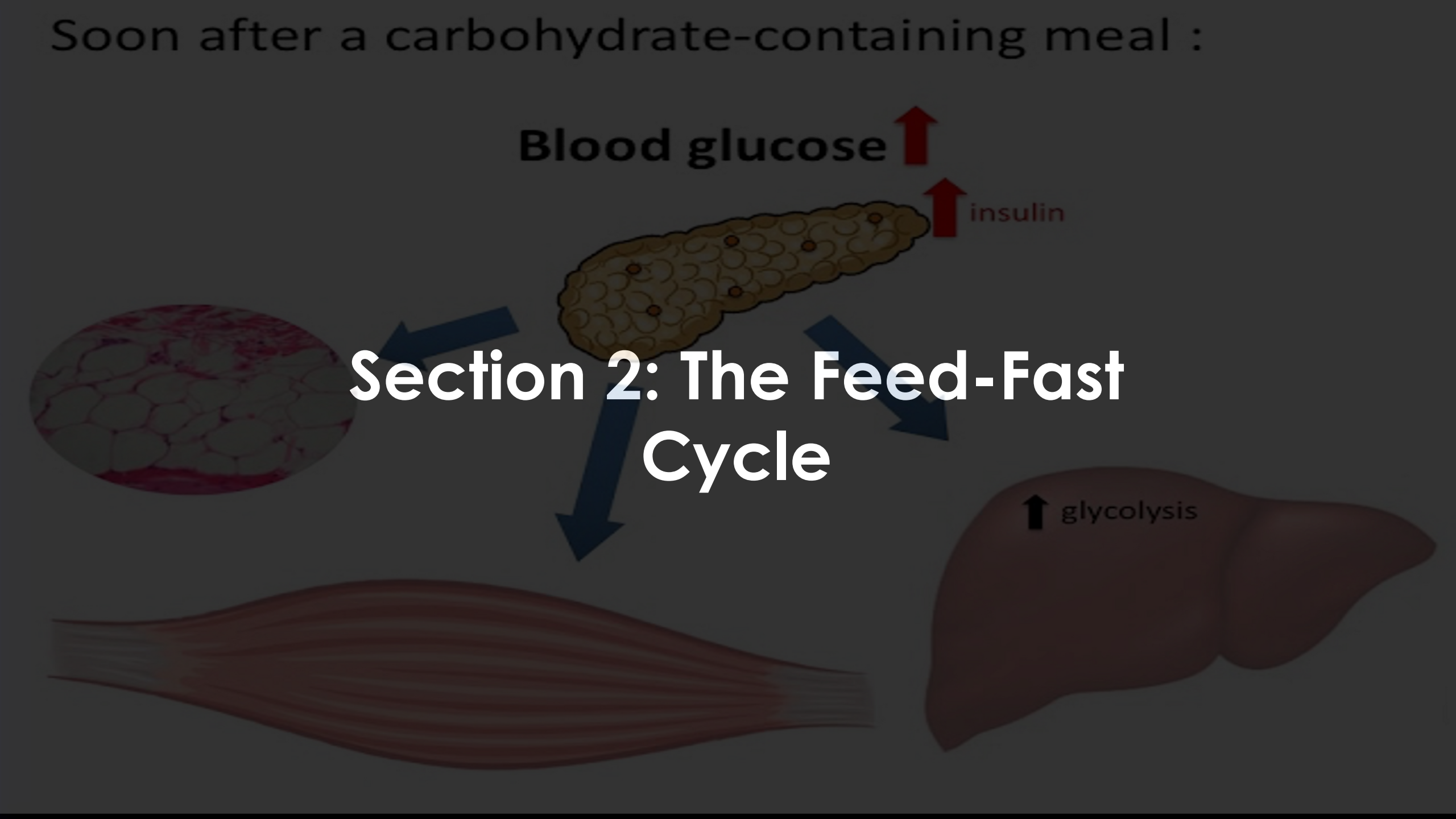
Compare and contrast insulin and glucagon

Insulin

- Produced by β-cells
- Induces anabolism
- Reduces blood-glucose levels when they are high

Glucagon

- Produced by a-cells
- Induces catabolism
- Increases blood-glucose levels when they are high



Section 2: The Feed-Fast Cycle

Concept 2.1: Enzyme Regulation

- **Availability of substrates**
  - Enzyme activity --> proportional to substrate concentration
  - Cells can regulate substrate availability via compartmentalization
- **Allosteric effectors**
  - Regulation of enzymes involved in catalysis of committed/rate-limiting step or irreversible reactions
- **Covalent modification of enzymes**
  - Usually addition/removal of phosphate group on enzyme to activate/inactivate enzyme
- **Induction and repression of enzyme synthesis**
  - Hormonal signalling influencing gene expression and enzyme degradation

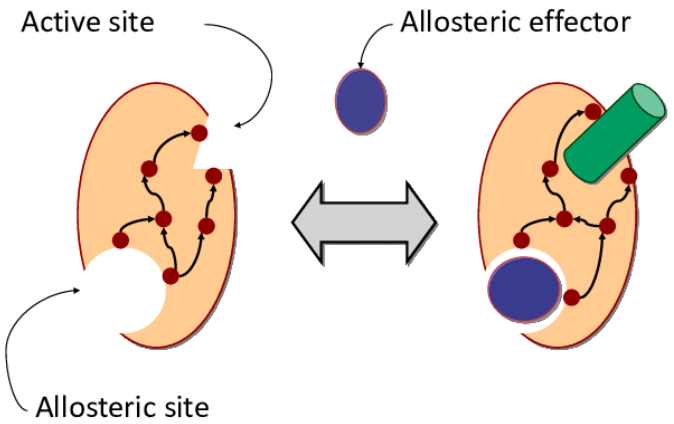


Figure 1. Allosteric effector

Concept 2.2: Compare and contrast the fed and fasting states

Fasting State

- Occurs when no food ingestion following completion of absorptive period
- Causes: can't find food, weight loss program, etc.
- Catabolic period

Fed State

- Occurs 2-4 hours following consumption of meal
- Increased availability of substrates
- Anabolic period

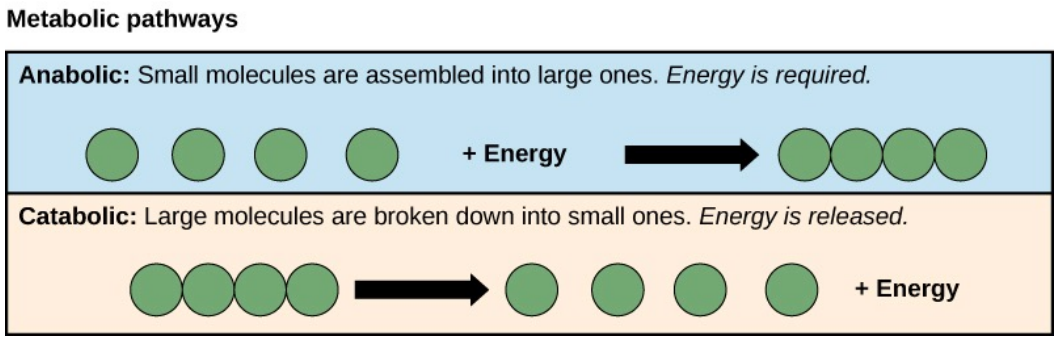


Figure 2. Anabolism vs. catabolism

Concept 2.3: Metabolic Changes Across the 4 Key Tissues During the Fed State

- **Liver**
  - Increased FA & TAG synthesis
  - Increased PPP activity, glucose phosphorylation, glycogen synthesis, glycolysis
  - Decreased glucose production
- **Adipose tissue**
  - Increase in glucose transport into adipocytes
  - Upregulation of lipoprotein lipase
- **Muscle tissue**
  - Increase in glucose transport into skeletal muscle
  - Increased release of fats from lipoproteins
  - Increase in protein synthesis (and uptake of branched-chain amino acids)
- **Brain**
  - Glucose is exclusive fuel source

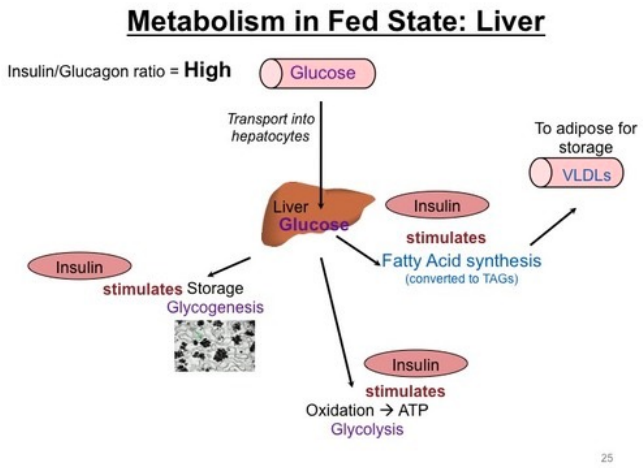


Figure 3. Liver during fed state

Concept 2.4: Metabolic Changes Across the 4 Key Tissues During the Fasting State

- **Liver**
  - Elevated glycogen degradation & gluconeogenesis
  - Elevated FA oxidation and ketone body synthesis
- **Adipose tissue**
  - Decreased glucose transport into adipocytes & FA uptake
  - Increased TAG degradation & FA release
- **Muscle tissue**
  - Decreased GLUT-4 transporters in cell membrane
  - Elevated lipoprotein lipase expression
  - Degradation of muscle protein
- **Brain**
  - Use of ketone bodies and glucose for metabolic fuel

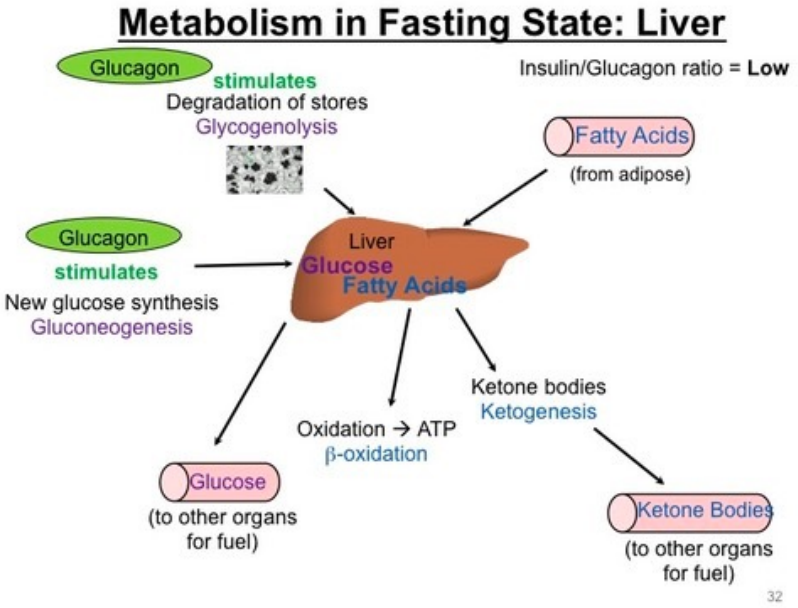


Figure 4. Liver during fasting state

Section 2 Quiz: 1 MC

In what state(s) would the brain use ketone bodies as a fuel source?

a. Fed state
b. Fasting state
c. Both states
d. Neither state

Answer: b.

Section 2 Quiz: 1Short Answer

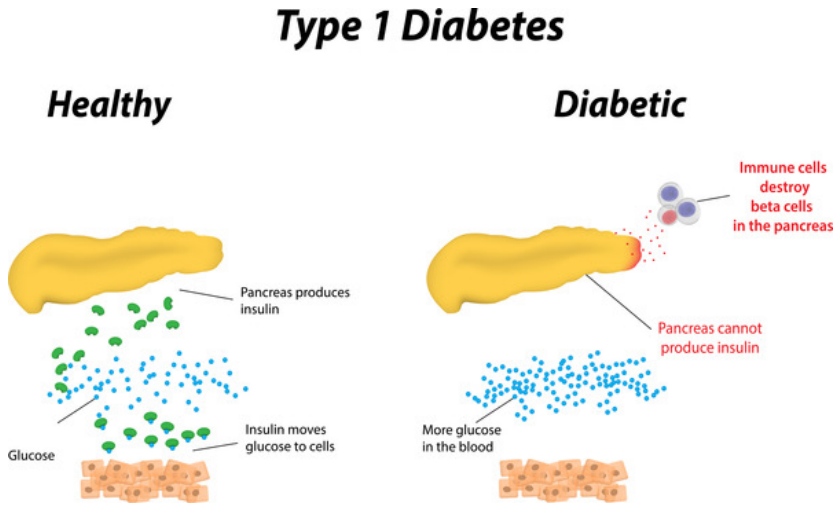
Discuss the similarities and differences between covalent modification and substrate availability.

Answer: Both substrate availability and covalent modification are forms of enzyme regulation. Substrate availability entails how many substrates are present. If less substrates are available, then enzyme activity will be reduced. Covalent modification entails the addition or removal of groups like phosphate to activate or inactivate enzymes.

Section 3: Diabetes Mellitus

Concept 3.1: Type 1 Diabetes

- Absolute insulin deficiency due to autoimmune attack on B-cells of pancreas
  - Insulin Deficiency causes chronic elevated blood glucose
  - Symptoms: polyuria, polydipsia, polyphagia, fatigue, weight loss and weakness
- **Pathogenesis requires:**
  - Environmental stimulus/trigger (e.g., infection)
  - Genetic determinant allowing cells to be targeted by the immune system



Etiology of Type 1 Diabetes.

Concept 3.2: Metabolic Changes in Type 1 Diabetes

Hyperglycemia

- Lack of insulin signalling causes the liver to increase glucose production while muscle/adipose take up less glucose
- (GLUT-4 not activated) -> sugar in urine

Ketoacidosis

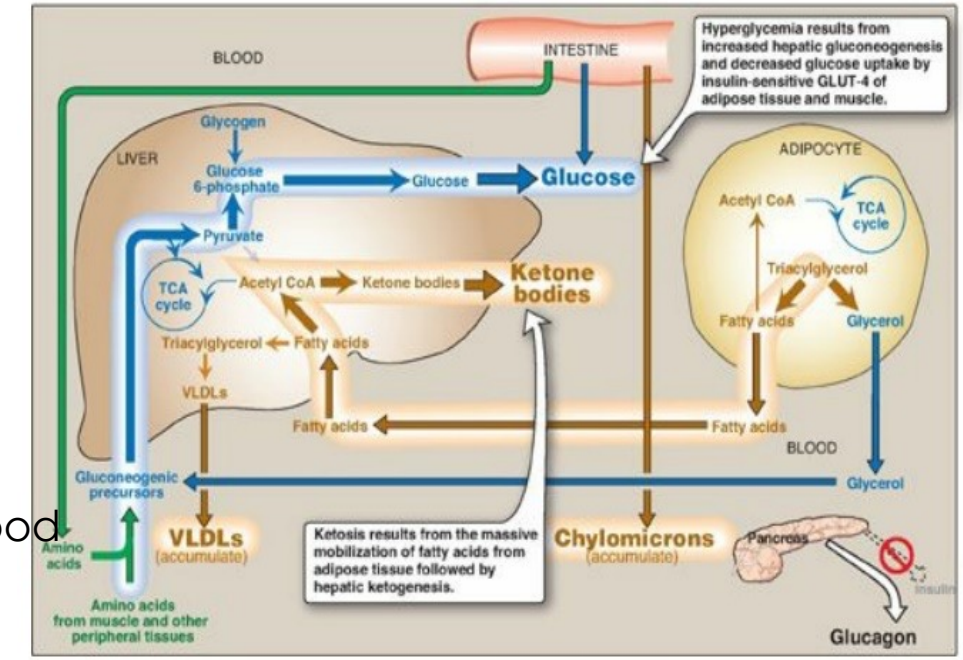
- Increased FA mobilization from adipose tissue
  - increased FA oxidation in liver and increased ketone body synthesis

Hypertriglyceridemia

- Lack of insulin signalling causes mobilization of lipids from adipocytes (via hormone-sensitive lipase activation) leading to elevated TAG in blood

- The liver cannot dispose of all FAs, packages them in VLDL

- Decreased lipoprotein lipase activity prevents adipose tissue from absorbing fats
  - Accumulation of chylomicrons/VLDL



Metabolic changes in Type 1 Diabetes.

Concept 3.3: Treatment of Type 1 Diabetes

Supply the body with exogenous insulin therapy to control blood glucose levels

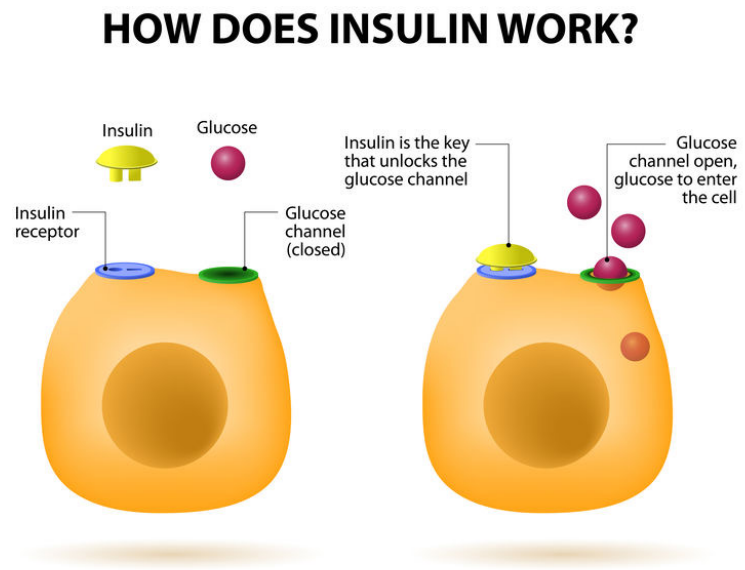
- Standard insulin treatment: 1 or 2 daily injections
  - Used in vulnerable populations like children and the elderly
- Intensive insulin treatment: 3+ injections daily
  - More frequent blood glucose monitoring decreases more than standard
  - More closely mimics non-diabetic insulin secretion (tighter control of blood glucose)

Therapy outcomes

- Standard results in overall higher average blood glucose compared to intensive therapy

Hypoglycemia

- Complication of T1D therapy resulting from too much insulin
- Elevated in intensive therapy compared to standard therapy

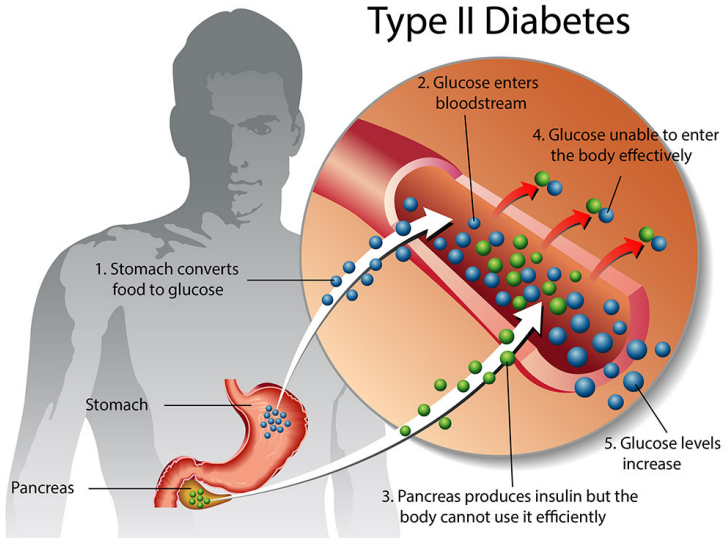


Mechanism of Action of Insulin.

Concept 3.4: Type 2 Diabetes

- Most common form of diabetes (90%)
  - Milder than type 1
  - Caused by:
    - Insulin resistance (usually obesity)
    - Genetic predisposition for non-functional cells

- Non-functional beta-cells
  - If Beta-cells function normally, compensate by increasing insulin secretion



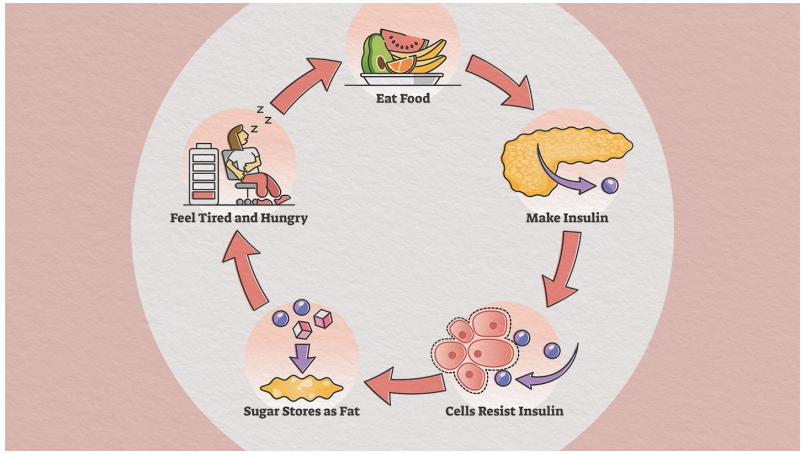
Pathology of Type 2 Diabetes.

Concept 3.4: Type 2 Diabetes Continued

- Risk factors include weight gain, lack of exercise, hypertension, elevated LDL/HDL ratio
- Develops gradually without symptoms (age 35+)
  - Some patients exhibit polyuria, polydipsia, polyphagia
- Diagnosis based on hyperglycemia
  - Most patients do not require insulin injections to live unless beta cells fail
  - Can be controlled by diet and hypoglycemic drugs

Concept 3.5: Insulin Resistance

- Decreased ability of cells to respond to normal insulin levels
- Characterized by uncontrolled glucose production in liver, decreased glucose uptake by muscle/adipose tissue
- Obesity most common cause but most obese insulin-resistant patients do not develop diabetes
- Increased insulin is required to keep blood glucose like normal levels
- Caused by changes in adipose secretions:
  - ↑ inflammatory signalling molecules
  - ↓ leptin
  - ↓ adiponectin



Mechanism of Insulin Resistance.

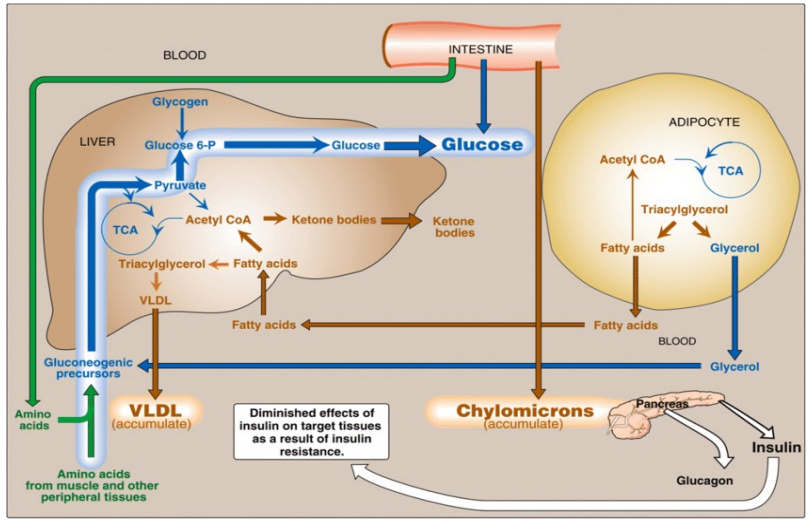
Concept 3.6: Metabolic Changes in T2D

Hyperglycemia

- Increased production of liver glucose via gluconeogenesis/ glycogenolysis and decreased tissue uptake of glucose -> elevated blood glucose
- Ketogenesis minimal because of insulin

Hypertriglyceridemia

- Decreased insulin signalling -> decrease in lipoprotein absorption from chylomicrons and VLDL into adipose tissue
- Increased activity of hormone-sensitive lipase within adipocytes
  - Increases release of lipids from adipose TAG stores
  - TAG accumulation in blood



Mechanism Changes in Type 2 Diabetes.

Section 3 Quiz: 1 MC

What is the etiology of Type 1 diabetes?

a) Destruction of alpha-cells in the pancreas
b) Destruction of beta-cells in the pancreas
c) The inability for peripheral cells to respond to insulin
d) A diet high in saturated and trans fats

B: Destruction of beta-cells in the pancreas

Section 3 Quiz: 1 Short Answer

Compare and contrast Type 1 and 2 Diabetes.

Type 1 Diabetes	Type 2 Diabetes
- Absolute insulin deficiency due to autoimmune attack on B-cells of pancreas - Genetic and/or environmental causes - 10% of cases - Always requires insulin therapy	- Decreased ability of cells to respond to normal insulin levels - Obesity most common cause - 90% of cases - Can be managed with diet or hypoglycemic drugs if beta-cells are functional

Section 4: Obesity

Concept 4.1: Obesity

Obesity: Disorder in regulatory systems for body weight

Results in fat accumulation

Etiology: A multifactorial disorder affected by genetic, environmental, behavioral and social factors

Overall, obesity is caused by increased caloric input and a decreased caloric output.

Symptoms: Breathlessness, Sweating, Joint Pain, Fatigue etc.

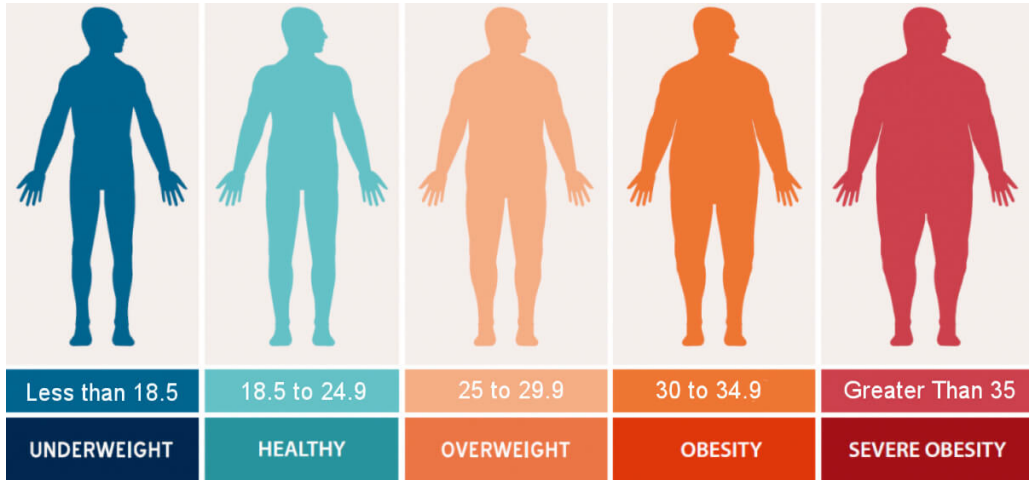


Figure X. diagram showing the classifications of obesity based on BMI.

Concept 4.2: Body Shape and Fat Depots

- Two Body Types
  - Apple Shaped: Increased fat accumulation in upper-body/central abdomen. Increased association with visceral fat
  - Pear Shaped: Increased fat storage in lower-body
- Sites of Fat Deposition
  - Subcutaneous Depots(80-90% of fat): found in abdomen and gluteal-fermoral regions. These adipocytes are bigger, store TAG efficiently, and released fatty acids into the blood slower.
  - Visceral Depots (10-20% of fat): found in abdominal cavity. Have higher mobilization of fatty acids, respond more quickly to hormones. Increase risk of metabolic diseases.q

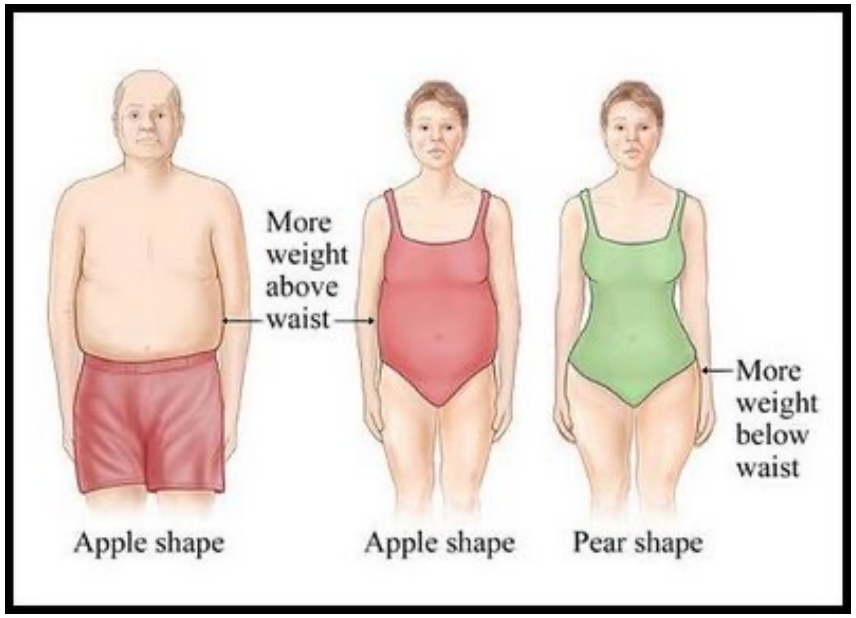


Figure X. Diagram of the differences between apple and pear-shaped body types.

Concept 4.3: Fat Cells: Size and Number

- Adipocytes increase in size with increased storage of TAGs (Up to 3x)
- If the capacity of adipocyte growth is met, more adipocytes are developed from pre-adipocytes
- Obesity is caused by both the hypertrophy and hyperplasia of fat cells.
- Very difficult to lose new fat cells once developed

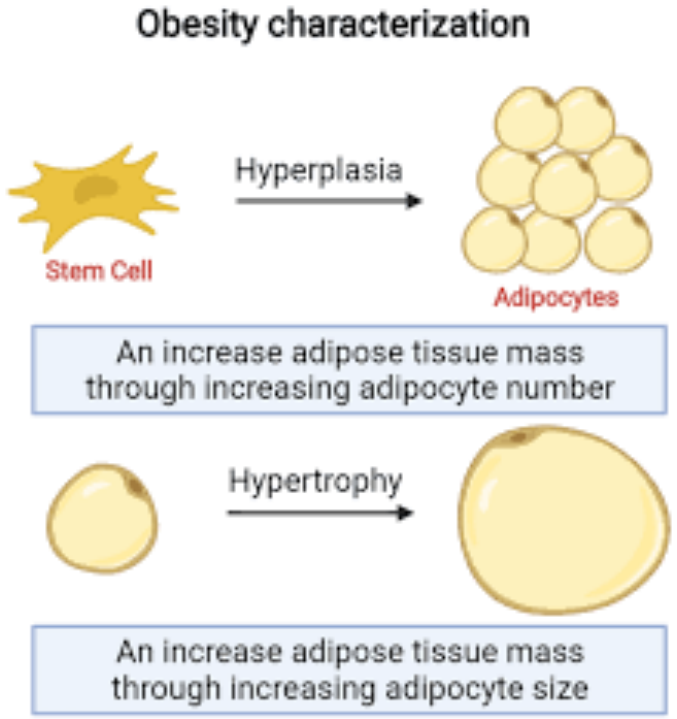


Figure X. Diagrams of hyperplasia and hypertrophy in adipocytes.

Concept 4.4: Satiety Regulating Hormones

Obesity patients tend to have issues in appetite signalling

Two Hormonal Signalling Pathways:

- Leptin: Adipose tissue releases the hormone. Increased release results in increased hunger suppression.
  - Decreased leptin gene expression tends to result in increased obesity.
  - More fat cells = More leptin release
- Insulin: Acts on neurons to suppress appetite.
  - Although obesity patients have high insulin release, insulin resistance means the high insulin levels cannot dampen hunger

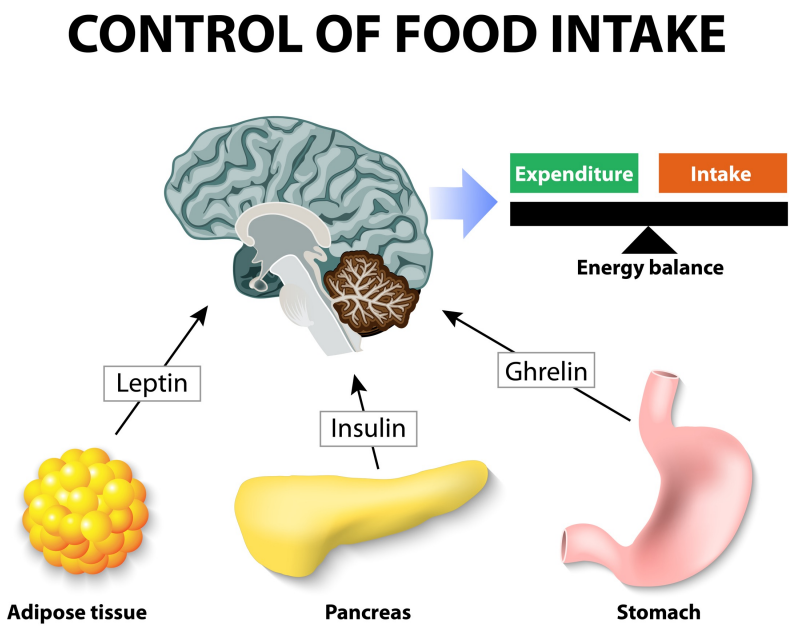


Figure X. Hormones associated with hunger.

Concept 4.5: Metabolic Syndrome

What is it? What is its etiology? What are the five criteria?

- Metabolic Syndrome: Group of disorders that increase the risk of cardiovascular disease, diabetes and death.
- To be diagnosed with metabolic syndrome, you must meet 3/5 criteria:
  - Increased waist circumference
  - Increased TAGs levels
  - Decreased HDL levels
  - Increased Blood Pressure
  - Increased fasting glucose

Figure X. Diagram showing the difference in a healthy weight and metabolic syndrome.

Section 4 Quiz: 1 MC

Choose the correct statement:

a) Leptin release increases hunger
b) Pear-shaped fat is stored in the upper body/central abdomen
c) Obesity is the most common cause of insulin resistance
d) Fat cells are easy to lose