Learning Objectives:
- Identify primary energy stores of the body
- Differentiate the metabolic processes of the fed and fasted states
- Explain how insulin and glucagon maintain glucose homeostasis

CHAPTER 22
I. METABOLISM (intro)

i. Metabolism
   1. Sum of all chemical reactions in the body
      Reactions making up these pathways
      i. (1) extract energy from nutrients
      ii. (2) use energy for work
      iii. (3) store excess energy so that it can be used later
   2. Anabolic pathways (synthesize large molecules from smaller ones)
   3. Catabolic pathways (break large molecules into smaller ones)

ii. Metabolism can be divided into two states
   1. Fed State (absorptive state)
      a. Anabolic state
      b. Energy of nutrient biomolecules is transferred to high-energy compounds or be stored in chemical bonds of other molecules
      c. Glucose utilization (glycolysis)
   2. Fasted State (postabsorptive state)
      a. Catabolic state
      b. Once nutrients from meal are no longer in bloodstream and available for use by tissues
      c. Glucose sparing metabolism
      d. Pool of available nutrients in blood decreases so body taps into its stored reserves by catabolic processes of chemical bond breakdown

II. ENERGY FROM INGESTED NUTRIENTS MAY BE USED IMMEDIATELY OR STORED

i. Biomolecules are destined to meet one of three fates
   1. Energy (Metabolized immediately; with energy released from broken chemical bonds trapped in ATP, phosphocreatine, and other high-energy compounds; energy used for mechanical work)
   2. Synthesis (Biomolecules used to synthesize basic components needed for growth/maintenance of cells and tissues)
   3. Storage (Excess energy goes into storage in bonds of glycogen and fat; storage energy available for times of fasting)

ii. Nutrient Pools
   1. Nutrients that are available for immediate use
   2. Located primary in plasma
   3. Glucose
      a. Glycogenesis
         i. Synthesis of glycogen from glucose
         ii. Additional excess glucose is converted to fat (lipogenesis)
      b. Glycogenolysis
         i. When plasma glucose concentration decrease, body reaks down glycogen to glucose
      c. Gluconeogenesis
         i. Synthesis of glucose from a noncarbohydrate precursor
2
HORMONES CONTROL METABOLIC PATHWAYS BY CHANGING ENZYME ACTIVITY

i. Most important biochemical pathways for energy production

ii. Metabolic regulation is the use of different enzymes to catalyze forward and reverse reactions

1. *Duel-Control*, referred to as *push-pull control*, allows close regulation of reaction
FATES OF NUTRIENTS IN FED STATE

CARBOHYDRATES (absorbed primarily as glucose)
1. Used immediately for energy through aerobic pathways
2. Lipoprotein synthesis in liver
3. Stored as glycogen in liver and muscle
4. Excess converted to fat and stored in adipose tissue
   (glucose $\rightarrow$ pyruvate $\rightarrow$ acetyl CoA $\rightarrow$ Fatty Acids)

PROTEINS (absorbed primarily as amino acids)
1. Most amino acids go to tissues for protein synthesis
2. If needed for energy, AA converted in liver to intermediates for aerobic metabolism
3. Excess converted to fat and stored in adipose tissue
   (amino acids $\rightarrow$ acetyl CoA $\rightarrow$ Fatty Acids)

FATS (absorbed primarily as triglycerides)
1. Stored as fats primarily in liver and adipose tissue

IV. HOMEOSTATIC CONTROL OF METABOLISM
   i. Endocrine system has primary responsibility for metabolic regulation
   ii. Nervous system as some influence, particularly in terms of governing food intake
   iii. Hour-to-hour regulation depends primarily on ration of insulin to glucagon (pancreas hormones secreted by endocrine cells)

PANCREAS
   A. Endocrine cells of pancreas make up less than 2% of organs mass
   B. Islets of Langerhans (Contain 4 distinct cell types; each associated with secretion of one or more peptide hormones)
      a. Beta Cells
         i. Produce hormone insulin
         ii. Produce peptide amylin
      b. Alpha Cells
         i. Produce hormone glucagon
      c. D Cells
         i. Produce Somatostatin
      d. F (PP) Cells
         i. Produce pancreatic polypeptide
   C. Islets closely associated with capillaries into which hormones are released; both sympathetic/parasympathetic neurons terminate on islets providing means by which NS can influence metabolism

V. INSULIN-to-GLUCAGON RATION REGULATES METABOLISM
   i. FED STATE
      1. Absorption of nutrients occurring
      2. Insulin dominates
      3. Body undergoes anabolism
      4. Ingested glucose used for energy production
      5. Excess glucose stored as glycogen or fat
      6. Proteins go primarily to protein synthesis
ii. FASTED STATE
1. Metabolic regulation prevents low plasma glucose concentrations (hypoglycemia)
2. Glucagon predominates
3. Liver uses glycogen and nonglucose intermediates to synthesize glucose for release into blood

(Short-Term Control of Metabolism)

<table>
<thead>
<tr>
<th></th>
<th>FED STATE</th>
<th>FASTED STATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Insulin &gt;&gt; Glucagon</td>
<td>Insulin &gt; Glucagon</td>
</tr>
<tr>
<td>Glucose</td>
<td>More elevated</td>
<td>Less elevated</td>
</tr>
<tr>
<td>Metabolism</td>
<td>More Anabolic</td>
<td>More Catabolic</td>
</tr>
</tbody>
</table>

VI. INSULIN (Dominant Hormone of the Fed State)

i. Peptide hormone
ii. Synthesized as an inactive prohormone and activated prior to secretion

<table>
<thead>
<tr>
<th>INSULIN</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell of origin</td>
<td>Beta cells of pancreas</td>
</tr>
<tr>
<td>Chemical nature</td>
<td>51-amino acid peptide</td>
</tr>
<tr>
<td>Biosynthesis</td>
<td>Typical peptide</td>
</tr>
<tr>
<td>Transport in the circulation</td>
<td>Dissolved in plasma</td>
</tr>
<tr>
<td>Half-life</td>
<td>5 minutes</td>
</tr>
<tr>
<td>Factors affecting release</td>
<td>Plasma [glucose] &gt; 100 mg/dL; ↑ blood amino acids; GLP-1 (feedforward reflex); and parasympathetic activity amplifies. Sympathetic activity inhibits</td>
</tr>
<tr>
<td>Target cells or tissues</td>
<td>Liver, muscle, and adipose tissue primarily; brain, kidney, and intestine not insulin depend</td>
</tr>
<tr>
<td>Target receptor</td>
<td>Membrane receptor with tyrosine kinase activity; pathway with insulin receptor substrates</td>
</tr>
<tr>
<td>Whole body or tissue action</td>
<td>↓ Plasma [glucose] by ↑ transport into cells or ↑ metabolic use of glucose</td>
</tr>
<tr>
<td>Action at cellular level</td>
<td>↑ Glycogen synthesis; ↑ aerobic metabolism of glucose; ↑ protein and triglyceride synthesis</td>
</tr>
<tr>
<td>Action at molecular level</td>
<td>Inserts GLUT transporters in muscle and adipose cells; alters enzyme activity. Complex signal transduction pathway involved</td>
</tr>
<tr>
<td>Feedback regulation</td>
<td>↓ Plasma [glucose] shuts off insulin release</td>
</tr>
<tr>
<td>Other information</td>
<td>Growth hormone and Cortisol are antagonistic</td>
</tr>
</tbody>
</table>
iii. Stimulating factors for insulin release
   1. Increased glucose concentrations
   2. Increased amino acid concentrations
      a. Increased AA following a meal
   3. Feedforward effects of GI hormones
      a. As much as 50% of insulin secretion stimulated by glucagon-like-peptide-1 (GLP-1) and gastric inhibitory peptide (GIP) which are incretin hormones
         i. Produced y cells of ileum/jejunum in response to nutrient ingestion
         ii. Incretin travels through circulation to pancreatic beta cells
   4. Parasympathetic activity
iv. Inhibitory factors for insulin
   1. Sympathetic activity
      a. In times of stress sympathetic input to the endocrine pancreas increases, reinforced by catecholamine release from adrenal medulla
      b. E and NE inhibit insulin secretion and switch metabolism to Gluconeogenesis to provide extra fuel for NS and skeletal muscles
v. Promotes Anabolism
   1. Insulin combines with a membrane receptor on its target cells
      a. Insulin receptor = Tyrosine Kinase
   2. Primary targets for insulin are
      a. Liver
      b. Adipose tissue
      c. Skeletal muscles
   3. Insulin lowers plasma glucose in four ways
      a. Insulin increases glucose transport into most, but not all insulin-sensitive cells
      b. Insulin enhances cellular utilization and storage of glucose
         i. Insulin activates enzymes for
            1. Glycolysis (glucose utilization)
            2. Glycogenesis (glycogen synthesis)
            3. Lipogenesis (fat synthesis)
         ii. Insulin inhibits enzymes for
            1. Gluconeogenesis (glucose synthesis)
            2. Glycogenolysis (glycogen breakdown)
            3. Lipolysis breakdown)
      c. Insulin enhances utilization of amino acids
         i. Insulin activates enzymes for protein synthesis

NOTE: It is the ratio of insulin to glucagon that determines the direction of metabolism rather than an absolute amount of either hormone
ii. Insulin inhibits enzymes for protein breakdown
d. Insulin promotes fat synthesis
   i. Insulin promotes conversion of excess glucose or AA into triglycerides (lipogenesis)
   ii. Insulin inhibits beta-oxidation of fatty acids

VII. GLUCAGON
   a. Secreted by pancreatic alpha cells
   b. Antagonistic in insulin I its effects on metabolism
   c. Function
      i. Preventing hypoglycemia
      ii. Stimulates Glycogenolysis and Gluconeogenesis to increase glucose output
d. Primary Stimulus
   i. Plasma glucose concentration
   ii. Accessory Stimulus: Plasma amino acids
e. Primary Target Tissue
   i. Liver

**GLUCAGON**

<table>
<thead>
<tr>
<th>Cell of origin</th>
<th>Alpha cells of pancreas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical nature</td>
<td>29-amino acid peptide</td>
</tr>
<tr>
<td>Biosynthesis</td>
<td>Typical peptide</td>
</tr>
<tr>
<td>Transport in circulation</td>
<td>Dissolved in plasma</td>
</tr>
<tr>
<td>Half-life</td>
<td>4-6 minutes</td>
</tr>
<tr>
<td>Factors affecting release</td>
<td>Stimulated by plasma [glucose] &lt; 200 mg/dL, with maximum secretion below 50 mg/dL; ↑blood amino acids</td>
</tr>
<tr>
<td>Target cells or tissues</td>
<td>Liver</td>
</tr>
<tr>
<td>Target receptor/second messenger</td>
<td>G protein-couple receptor linked to cAMP</td>
</tr>
<tr>
<td>Whole body or tissue action</td>
<td>↑ Plasma [glucose] by Glycogenolysis and Gluconeogenesis; ↑lipolysis leads to ketogenesis in liver</td>
</tr>
<tr>
<td>Action at molecular level</td>
<td>Alters existing enzymes and stimulates synthesis of new enzymes</td>
</tr>
<tr>
<td>Feedback regulation</td>
<td>↑ Plasma [glucose] shuts off glucagon secretion</td>
</tr>
<tr>
<td>Other information</td>
<td>Member of secretin family (along with VIP, GIP, and GLP-1)</td>
</tr>
</tbody>
</table>

![Glucagon diagram](image-url)