Summary of Metabolism
Basic Strategies of Catabolic Metabolism

• Generate ATP

• Generate reducing power

• Generate building blocks for biosynthesis
ATP

• Universal currency of energy

• High phosphoryl-transfer potential

• ATP hydrolysis drives reactions by changing the equilibrium of coupled reactions by a factor of $10^8$

• Generated from the oxidation of fuel molecules
Reducing Power

- Oxidation of fuel molecules generates NADH for mitochondrial ETC
- NADPH is generated for reducing power for biosynthetic processes
- Pentose phosphate pathway is the major source of NADPH
Biomolecules

- Large number of diverse macromolecules are synthesized from a small number of building blocks.
- Carbon skeletons from generated from the oxidation of macromolecules provide the building blocks for biosynthetic pathways.
- Central metabolic pathways have anabolic as well as catabolic roles.
Figure 18.4

Energy-yielding nutrients
- Carbohydrates
- Fats
- Proteins

Cell macromolecules
- Proteins
- Polysaccharides
- Lipids
- Nucleic acids

Catabolism (oxidative, exergonic)

Energy-poor end products
- $H_2O$
- $CO_2$
- $NH_3$

Anabolism (reductive, endergonic)

Precursor molecules
- Amino acids
- Sugars
- Fatty acids
- Nitrogenous bases

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Relationships between catabolic and anabolic processes

- The pathway leading to the biosynthesis of a compound are distinct from the pathway leading to its breakdown
- This separation ensure that the processes are thermodynamically favorable in both directions
- Allows for reciprocal regulation
Activation of one mode is accompanied by reciprocal inhibition of the other mode.
Themes in Metabolic Regulation

- Allosteric regulation
- Covalent modification
- Control of enzyme levels
- Compartmentalization
- Metabolic specialization of organs
Allosteric regulation

- Typically associated with enzymes that catalyze irreversible reactions
- Allosteric regulators can cause feedback or feedforward regulation
- Allosteric regulators are often related to the energy state of the cell
- This type of regulation allows for immediate response to changes in metabolic flux (milliseconds to seconds)
- Functions at local level
Covalent Modification

- Covalent modification of last step in signal transduction pathway
- Allows pathway to be rapidly up or down regulated by small amounts of triggering signal (HORMONES)
- Last longer than do allosteric regulation (seconds to minutes)
- Functions at whole body level
Enzyme Levels

- Amount of enzyme determines rates of activity
- Regulation occurs at the level of gene expression
- Transcription, translation
- mRNA turnover, protein turnover
- Can also occur in response to hormones
- Longer term type of regulation
Compartmentalization

- One way to allow reciprocal regulation of catabolic and anabolic processes
Specialization of Organs

• Regulation in higher eukaryotes

• Organs have different metabolic roles
  i.e. Liver = gluconeogenesis,
  Muscle = glycolysis

• Metabolic specialization is the result of
  differential gene expression
Glucose

- Glucose 6-phosphate
  - Fructose 6-phosphate
  - Pyruvate (Low ATP, Need skeletons)
  - Glycogen (Lots ATP, G-6-P)
  - 6-Phosphogluconate
  - Ribose 5-phosphate
Metabolic Specialization of Organs
Brain

- Glucose is the primary fuel for the brain.
- Brain lacks fuel stores, requires constant supply of glucose.
- Consumes 60% of whole body glucose in resting state. Required to maintain Na and K membrane potential in nerve cells.
- Fats can't serve as fuel because blood brain barrier prevents albumin access.
- Under starvation can ketone bodies used.
Muscle

- Glucose, fatty acids and ketone bodies are fuels for muscles
- Muscles have large stores of glycogen (3/4 of body glycogen in muscle)
- Muscles do not export glucose (no glucose-6-phosphatase)
- In active muscle glycolysis exceeds citric acid cycle, therefore lactic acid formation occurs
- Cori Cycle required
Muscle

- Muscles can’t do urea cycle. So excrete large amounts of alanine to get rid of ammonia (Glucose Alanine Cycle)

- Resting muscle uses fatty acids to meet 85% of energy needs
Heart Muscle

• Heart exclusively aerobic and has no glycogen stores.

• Fatty acids are the heart's primary fuel source. Can also use ketone bodies. Doesn't like glucose.
Liver

- Major function is to provide fuel for the brain, muscle and other tissues
- Metabolic hub of the body
- Most compounds absorb from diet must first pass through the liver, which regulates blood levels of metabolites
Liver: carbohydrate metabolism

- Liver removes 2/3 of glucose from the blood.
- Glucose is converted to glucose-6-phosphate (glucokinase).
- Liver does not use glucose as a fuel. Only as a source of carbon skeletons for biosynthetic processes.
- Glucose-6-phosphate goes to glycogen (liver stores 1/4 body glycogen).
Liver: lipid metabolism

• Excess glucose-6-phosphate goes to glycolysis to form acetyl-CoA

• Acetyl-CoA goes to form lipids (fatty acids cholesterol)

• Glucose-6-phosphate also goes to PPP to generate NADH for lipid biosynthesis

• When fuels are abundant triacylglycerol and cholesterol are secreted to the blood stream in LDLs. LDLs transfer fats and cholesterol to adipose tissue.

• Liver can not use ketone bodies for fuel.
Liver: protein/amino acid metabolism

- Liver absorbs the majority of dietary amino acids.
- These amino acids are primarily used for protein synthesis.
- When extra amino acids are present the liver or obtained from the glucose alanine cycle amino acids are catabolized.
- Carbon skeletons from amino acids directed towards gluconeogenesis for livers fuel source.
Adipose Tissue

• Enormous stores of Triacylglycerol
• Fatty acids imported into adipocytes from chyromicrons and VLDLs as free fatty acids
• Once in the cell they are esterified to glycerol backbone.
• Glucagon/epinephrine stimulate reverse process
Glucose (from the liver) → Glucose → Glycerol 3-phosphate → Triacylglycerols → Hormone-sensitive lipase → Glycerol (to the liver) → Fatty acid–albumin complexes (to the liver) → Fatty acids → Fatty acyl CoA → VLDL (from the liver)
Well-Fed State

- Glucose and amino acids enter blood stream, triacylglycerol packed into chylomicrons
- Insulin is secreted, stimulates storage of fuels
- Stimulates glycogen synthesis in liver and muscles
- Stimulates glycolysis in liver which generates acetyl-CoA for fatty acid synthesis
Early Fasting State

• Blood glucose levels begin to drop, glucagon is secreted

• Stimulates mobilization of fuels

• Stimulates glycogen breakdown in liver and glucose is released to the blood stream

• Glucose is not taken up by muscle tissues but used primarily to fuel the brain

• Glucagon stimulates release of fatty acids from adipose tissues and the shift of muscle fuel from glucose to fatty acids.

• Gluconeogenesis is stimulated in liver, glucose made from carbon skeletons coming from TAG and amino acid catabolism. New glucose exported to bloodstream
Refed State

- Liver initially does not absorb glucose, lets glucose go to peripheral tissues, and stays in gluconeogenesis mode.
- Newly synthesized glucose goes to replenish glycogen stores.
- As blood glucose levels rise, liver completes replenishment of glycogen stores.
- Excess glucose goes to fat production.
Starvation

- Fuels change from glucose to fatty acids to ketone bodies