Digestion and Metabolism

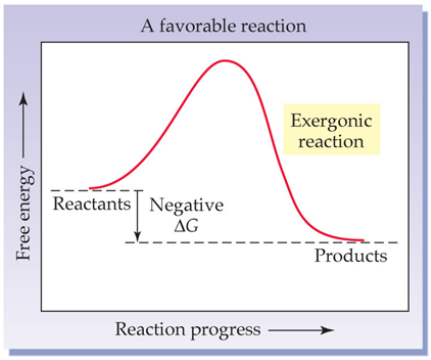
Metabolism

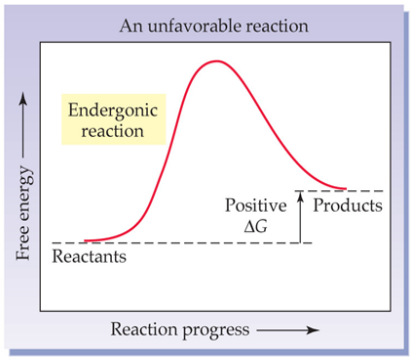
The complete set of reactions living organisms carry out in order to:

- obtain energy
- synthesize the compounds they require

Three requirements on Energy

- Must be released from food ***GRADUALLY***. (Why?)
  - Glucose → 687kcal/mol
- Must be ***stored*** in ***readily accessible*** forms. (Why?)
- Must be ***finely controlled***. (Why?)





Spontaneous reactions (Exergonic)

- A reaction that will occur "on its own."

E.g.

$ATP + H_2O \rightarrow ADP + Pi + 7.3\ kcal/mol$

Nonspontaneous reactions (Endergonic)

- "Does not occur without the addition of energy".
  It needs to be "pushed".

E.g.

$Glucose + Pi + 3.3kcal/mol \rightarrow Glucose\text{-}6\text{-}P + H_2O$

Coupled Reactions

- Endergonic reactions can be *pushed* by exergonic (spontaneous), through a shared intermediate.

$$ATP + H_2O \rightarrow ADP + Pi + 7.3\ kcal/mol$$
$$Glucose + Pi + 3.3kcal/mol \rightarrow Glucose\text{-}6\text{-}P + H_2O$$
$$ATP + Glucose \rightarrow ADP + Glucose\text{-}6\text{-}P + 4.0\ kcal/mol$$

ATP and Energy

- Is the energy form stored in cells.
- Is obtained from the oxidation of food.
- Requires 7.3 (31 kJ) per mole to convert ADP + P_i to ATP.

Stages of Metabolism:

Stage 1. Digestion
Stage 2. Acetyl-SCoA Production
Stage 3. Citric Acid Cycle
Stage 4. ATP Production

Redox reactions

- The net result of catabolism is the oxidation of food to release energy.
- A steady supply of redox agents must be available.

Reduced	Oxidized	
$NADH + H^+$	NAD^+	Produces a carbon-oxygen double bond (C=O)
$FADH_2$	FAD	Produces a carbon-carbon double bond (C=C).
HSCoA	Acetyl-SCoA	Activates acyl groups for transfer.

Metabolic Pathways

- ❖ Sequences of reactions (catalyzed by enzymes) that produce intermediates (called metabolites).
- ❖ Major three traits of metabolic pathways:
  - Individual rxns may be reversible, but not the overall pathway.
  - The first rxn is often the rate-limiting step.
  - Can be turned on and off when needed.
- ❖ Not always linear.

Stage 2: Glycolysis

- A metabolic pathway that uses glucose.
- Degrades 6C glucose molecules to 3C molecules (pyruvate).
- Takes place in the cytoplasm
- Is an anaerobic (no oxygen) process.

Glycolysis: Energy-Investment

Rxns 1-5: Phosphate groups are added and Glucose is converted to two three-carbon molecules.

Glycolysis: Energy-Production

Rxns. 6-10: Sugar phosphates are cleaved and four ATP molecules are produced.

Overall Reaction

$C_6H_{12}O_6 + 2ADP + 2Pi + 2NAD^+ \rightarrow 2C_3H_3O_3^- + 2ATP + 2NADH + 2H^+$

Glucose Pyruvate

Regulation of Glycolysis

Three enzymes:

What do these three reactions have in common…???

- Reaction 1 is inhibited by high [glucose-6-phosphate].
- Reaction 3 is inhibited by high [ATP] and activated by high [ADP].
- Reaction 10 inhibited by high [ATP] or [acetyl CoA].

Fates of Pyruvate

1) Pyruvate: Aerobic Conditions (Yields the most energy)

Matrix of the mitochondria.

- Three-carbon pyruvate is decarboxylated.
- Two-carbon acetyl CoA and CO_2 are produced.

pyruvate + HS—CoA + $NAD^+ \rightarrow$ acetyl—S—CoA + CO_2 + NADH + H^+

2) Pyruvate: Anaerobic Conditions

Under anaerobic conditions (without oxygen),

- Pyruvate is reduced to lactate.
- NADH oxidizes to NAD^+ <u>allowing glycolysis to continue</u>.

pyruvate + NADH + $H^+ \rightarrow$ lactate + NAD^+

Lactate in Muscle

During strenuous exercise,

- Anaerobic conditions are produced and lactate accumulates (muscles tire and hurt).
- After exercise, a person breathes heavily.

Cori Cycle

- The flow of lactate and glucose between the muscles and the liver. In the liver lactate is oxidized back to pyruvate; then pyruvate is converted to glucose, which is carried back to the muscles.

3) Fermentation

- Occurs in anaerobic microorganisms such as yeast.
- Decarboxylates pyruvate to acetaldehyde, which is reduced to ethanol.
- Regenerates NAD^+ to continue glycolysis.

$Pyruvate + NADH + H^+ \rightarrow Ethanol + NAD^+ + CO_2$

Citric Acid Cycle (Stage 3)

- Operates under aerobic conditions only.
- Oxidizes the two-carbon acetyl group in acetyl- CoA to $2CO_2$.

Overall Chemical Reaction for the Citric Acid Cycle

$acetylS\text{-}CoA + 3NAD^+ + FAD + ADP + P_i + 2H_2O \rightarrow 2CO_2 + 3NADH + 3H^+ + FADH_2 + HS\text{-}CoA + ATP$

Regulation of Citric Acid Cycle

- Increases when [ATP] or [NADH] are low.
- Decreases [ATP] or [NADH] are high.

Regulation of Electron Transport (For a description of the process, look at your other handout on metabolism.)

- ADP/ATP ratio
- Low levels of ADP, P_i, and oxygen decrease electron transport activity.
- High levels of ADP that activate electron transport.

Utilization of Glucose

Glucose

- Is the primary energy source for the brain, skeletal muscle, and red blood cells.
- Deficiency can impair the brain and nervous system.

Glycogenesis

- Stores glucose by converting glucose to glycogen when [glucose-6-phosphate] is high.
- Stops when energy stores (glycogen) are full. (i.e. *additional glucose is converted to body fat.)*

Glycogenolysis

- Glycogen is broken down to glucose.
- Molecules are removed one by one.

Gluconeogenesis: Glucose Synthesis

- The synthesis of glucose from carbon atoms of noncarbohydrate compounds.
- Required when glycogen stores are depleted.

Regulation of [Glucose]

When [glucose] is high (after eating)

- Insulin (produced in the pancreas) is released into the bloodstream.

Glycolysis	(+)
Glycogenesis	(+)
Gluconeogenesis	(–)
Glycogenolysis	(–)

- If we have enough glycogen, the extra glucose is converted to fat.

Regulation of [Glucose]

When [glucose] is low

- Glucagon (produced in the pancreas) is secreted into the bloodstream.

Glycolysis	(–)
Glycogenesis	(–)
Gluconeogenesis	(+)
Glycogenolysis	(+)

- Epinephrine (adrenaline) is released from the adrenal glands when we need a "burst of energy" (the "fight or flight" mode) to signal for glycogenolysis.

Fat Mobilization (Lipids)

- Breaks down TAG's in adipose tissue.
- Forms fatty acids and glycerol.

Fatty Acids and Glycerol

- Glycerol is converted to glyceraldehyde 3-phosphate and dihydroxyacetone phosphate, which participate in:
  - ***Glycolysis***—energy generation
  - ***Gluconeogenesis***—glucose formation
  - Triacylglycerol synthesis
- Fatty acids undergo
  - Resynthesis of triacylglycerols for storage
  - ***Conversion to acetyl-SCoA (The process is known as beta oxidation).***

Summary of Fatty Acid Activation

- Fatty acid activation is complex, but it regulates the degradation and synthesis of fatty acids.
- Two ATP's are invested.

Beta-Oxidation of Fatty Acids

In reaction 1, oxidation

- Forms a trans C=C bond.
- Reduces FAD to $FADH_2$.

In reaction 2 hydration

- Adds water across the trans C=C bond.
- Adds a hydroxyl group to the β carbon.

In reaction 3 is a second oxidation

- Forms a keto group on the β carbon.

In Reaction 4 acetyl CoA is cleaved

- By splitting the bond between the α and β carbons.
- Forms a shortened fatty acyl CoA that repeats β-oxidation.

Fatty Acid Length and β-Oxidation

The length of a fatty acid determines the number of oxidations and of acetyl-CoA groups.

Carbons in Fatty Acid	Acetyl CoA (#C's/2)	β-Oxidation Cycles (#C's/2) –1
12	6	5
14	7	6

The β-Oxidation of Unsaturated Fatty Acid yields less ATP's. Why?

Unsaturated fatty acids already have double bonds in their structures, so reaction number 1 (and formation of $FADH_2$) is not needed. Since the double bonds in nature are cis, reaction one is just an isomerization to the trans structure for the double bond. Due to this factor, for every C=C that appears in the structure of an unsaturated fatty acid, we get 2 ATP's less than we would with a saturated fatty acid with the same number of carbons.

Ketone Bodies

If carbohydratesare not available

- Body fat breaks down to meet energy needs.
- Keto compounds called ketone bodies form. (***Ketogenesis***)

Ketosis occurs

- In diabetes, diets high in fat, and starvation.
- [ketone bodies] is high!!
- Lowers blood pH below 7.4 (acidosis).

Ketosis Causes:

Dehydration (due to increased urine flow).
Labored breathing.
Coma and death (if untreated).

Lipogenesis: Fatty Acid Synthesis

- Is the synthesis of fatty acids from acetyl CoA. (Opposite of beta oxidation.)
- Allows the body to divert the energy of excess carbohydrates and amino acids into storage as TAG's.

In fatty acid synthesis

- A high level of blood glucose and insulin stimulates glycolysis and pyruvate oxidation.
- More acetyl CoA is available to form fatty acids.

Proteins in the Body (Amino Acid Pool)

Proteins provide

- Amino acids for protein synthesis.
- Nitrogen atoms for nitrogen-containing compounds.
- Energy when carbohydrate and lipid resources are not available.

Metabolism of Amino Acids

- Each of the 20 amino acids is degraded via its own unique pathway (when not used for proteins).
- General scheme:
    - Removal of the amino group
    - Use of nitrogen in synthesis of new nitrogen compounds
    - Passage of nitrogen into the urea cycle
    - Incorporation of the carbon atoms into compounds that can enter the citric acid cycle

Urea Cycle

The urea cycle

- Detoxifies ammonium ion from amino acid degradation.
- Converts ammonium ion to urea in the liver.
- Provides 25-30 g urea daily for urine formation in the kidneys.

Sources of Amino Acids

- Essential amino acids must be obtained in the diet.
- Nonessential amino acids are synthesized in the body. (*See your handout on amino acid side chains.*)