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Chapter 18

Metabolism Overview

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Metabolism

- Metabolism is the sum of all the chemical changes occurring in the cell.

Nutrients ® Cellular Constituents, Energy

- Metabolic Maps summarize the intermediates of metabolism, and the reactions connecting them.
  - See Figure 18.1
  - Explore the Boehringer-Mannheim maps under External Links

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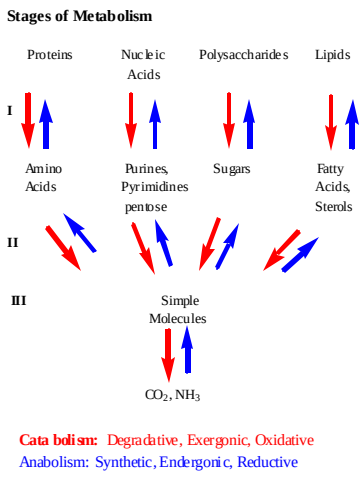

Some reactions can be either catabolic or anabolic, depending on the circumstances. Such reactions are called **amphibolic** reactions. Many of the reactions interconverting the "simple molecules" fall in this category. Catabolic and anabolic pathways are interrelated in three ways:
Matter (catabolic pathways furnish the precursor compounds for anabolism0
Energy (catabolic pathways furnish the energy to "drive" anabolism)
Electrons (catabolic pathways furnish the reducing power for anabolism)

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Topology of Metabolic Pathways

- There are four ways that pathways can be organized "topologically"
  1. Linear
  2. Branched
  3. Cyclic
  4. Equilibrium pool

Linear pathways convert one compound through a series of intermediates to another compound. An example would be glycolysis, where glucose is converted to pyruvate.

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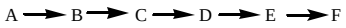
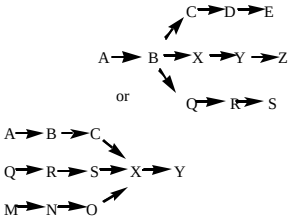
Pathway Topology, con't.

1. Linear Pathway:



2. Branched Pathway:



Branched pathways may either be divergent (an intermediate can enter several linear pathways to different end products) or convergent (several precursors can give rise to a common intermediate). Biosynthesis of purines and of some amino acids are examples of divergent pathways. There is usually some regulation at the branch point. The conversion of various carbohydrates into the glycolytic pathway would be an example of convergent pathways.

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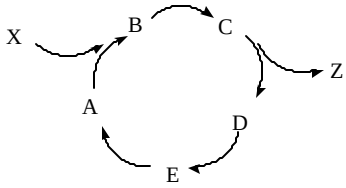
Pathway Topology, con't.

3. Cyclic Pathway



In a cyclic pathway, intermediates are regenerated, and so some intermediates act in a catalytic fashion. In this illustration, the cyclic pathway carries out the net conversion of X to Z. The Tricarboxylic Acid Cycle is an example of a cyclic pathway.

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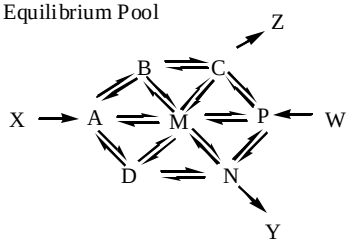
Pathway Topology, con't.

4. Equilibrium Pool



A pool of compounds in equilibrium with each other provides the intermediates for converting compounds to a variety of products, depending on what is fed "into" the pool and what is "withdrawn" from the pool. The phosphogluconate pathway is an example of such a pool of intermediates. The pathway can convert glucose to CO_2, hexoses to pentoses, pentoses to hexoses, pentoses to trioses, etc. depending on what the cell requires in a particular situation. NADPH as a source of reducing power for anabolic reactions is also a main product of the phosphogluconate pathway.

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Enzyme Organization in Pathways

- Some pathway enzymes are organized in a **multienzyme complex**.
  - The complex may consist of dissociable subunits, multiple domains on a single polypeptide chain, or a membrane associated complex.
  - See Figure 18.5
- Enzymes that are isolated as individual soluble entities may in some cases be associated in the cell.
- This arrangement allows **metabolic channeling**, where the product of one step does not have to diffuse through the cell to find the next enzyme.

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Cellular Compartmentalization

- Some pathways are compartmentalized in the cell.
  - TCA cycle occurs in mitochondria, glycolysis is in the cytoplasm
  - Fatty acid oxidation is in mitochondria, fatty acid synthesis is in the cytoplasm
  - Formation of urea uses enzymes in both compartments

The necessity for intermediates to cross membrane boundaries between cellular compartments adds another layer of complexity to the regulation of and interactions between metabolic pathways.

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Energetics of Pathways

- If reaction through a pathway occurs spontaneously, the overall process must have a negative ΔG.
- In fact, **each step** in the pathway must have a negative ΔG.
  - Remember:
    - $\Delta G = \Delta G^{o'} + RT\ln Q$, or $\Delta G = RT\ln(Q/K)$
- For each step, Q must be < K.

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Energetics of Pathways, con't.

- If Q is only a little smaller than K (i.e. larger than about 0.05 K), this step of the pathway is **near equilibrium**.
  - The rate through such a step depends on substrate and product concentrations, but doesn't change much with a change in the activity of the enzyme.

There is nothing special about the number 0.05, it only represents an approximate distinction between the two extremes. The ΔG when Q = 0.05 K is –7.4 kJ/mol.

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Energetics of Pathways, con't.

- If Q is less than about 0.05 K, this step of the pathway is **removed from equilibrium**.
  - The rate through such a step will vary by changing the activity of the enzyme.
  - Such a step is a **rate limiting step**.
  - Most pathway regulation occurs at such steps.
  - (Regulation at equilibrium steps does occur, usually by availability of a **coenzyme cosubtrate**.)

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Anabolic and Catabolic Pathways Differ

- Because ΔG must always be negative, the path from A $\rightarrow$ X must differ from the path from X $\rightarrow$ A.
  - Either completely different (Figure 18.7a)
  - Or different in at least one step (Figure 18.7b)
- In the latter case, it is usually the steps **removed from equilibrium** which are different.

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Role of ATP in Metabolism

- ATP (and closely related compounds with high negative free energies of hydrolysis) is considered the **energy currency** of the cell.
  - Catabolic reactions generate ATP.
  - Photosynthesis stores some light energy ATP.
  - ATP coupling helps make some anabolic reactions spontaneous.
  - The relative concentrations of ATP, ADP, and AMP regulate many enzymes where these nucleotides serve as **allosteric effectors**.

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Role of Nicotinamide Nucleotides in Metabolism

- See Figure 18.19 for the structure of NAD^+ and $NADP^+$
- Reduction adds a hydrogen atom and two electrons to the nicotinamide ring to form NADH and NADPH.
- Hydrogen addition and removal is stereospecific.

NAD^+ was first called **cozymase**, the dialyzable cofactor needed for yeast extracts to carry out fermentation. When its structure was determined, it was first named **diphosphopyridine nucleotide (DPN$^+$)**. The dinucleotide nomenclature was adopted for consistency with naming of other compounds such as flavin adenine dinucleotide (FAD). Some enzymes add and remove the pro-R hydrogen, some add and remove the pro-S hydrogen.

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Nicotinamide Nucleotides

- NAD^+ and $NADP^+$ are **coenzyme cosubstrates.**
- NAD^+ is the electron acceptor in most catabolic oxidation reactions.
- NADH reoxidation by the electron transport chain is a major source of ATP production.
- NADPH is the electron donor for most anabolic reduction reactions.

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Vitamins and Coenzymes

- Many vitamins are components of important coenzymes.
- Chapter 18 shows the structure, key reactions, and vitamin components of most coenzymes.
- Review these coenzymes and be able to:
  - Recognize the structure.
  - Describe the chemical change the coenzyme undergoes.
  - Classify as **cosubstrate** or **prosthetic group**.
  - Name the vitamin component.

We will return to discussion of individual coenzymes as we encounter them in metabolism. To be prepared for those discussions, it will be helpful if you become familiar with their structures now.

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Summary of Coenzymes

Coenzyme	Vitamin	Class	Figure
Thiamine Pyrophosphate	Thiamine (B_1)	Prosthetic Group	18.17
NAD^+ and $NADP^+$	Niacin	Cosubstrate	18.19
FAD and FMN	Riboflavin (B_2)	Prosthetic Group	18.21 and 18.22
Pyridoxal Phosphate	Pyridoxine (B_6)	Prosthetic Group	18.25 and 18.27

Deficiency of thiamine (vitamin B_1) is found in **beriberi.**
Deficiency of niacin (nicotinic acid and nicotinamide) is found in **pellegra** (humans) and **blacktongue** (dogs).

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Summary of Coenzymes, con't.

Coenzyme	Vitamin	Class	Figure
Coenzyme A	Pantothenic Acid (B_3)	Cosubstrate	18.23
Phospho-pantetheine	Pantothenic Acid (B_3)	Prosthetic Group	18.23
5'-Deoxyadenosyl-Cobalamin	Cyanocobalamin (B_{12})	Prosthetic Group	18.28
Ascorbic Acid	Vitamin C	Cosubstrate	18.30

Both coenzyme A and phosphopantetheine are carriers of acyl groups which are attached in thiolester linkage to the terminal SH. The thiol esters have high negative free energies of hydrolysis, and they also help to labilize the hydrogens on the alpha carbon. 5'-Deoxyadenosylcobalamin has a carbon-cobalt bond, and it is the making and breaking of this bond which is involved in its mechanism of action. Ascorbic acid deficiency is found in the disease **scurvy**.

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Summary of Coenzymes, con't.

Coenzyme	Vitamin	Class	Figure
Biotin	Biotin	Prosthetic Group	18.32
Lipoic Acid	Not a Vitamin	Prosthetic Group	18.33
Tetrahydrofolate	Folic Acid (B-complex)	Prosthetic Group	18.35

Ascorbic acid is a necessary cofactor in hydroxylation and proper maturation of collagen.

Biotin cured dermatitis and paralysis in rats fed large amounts of egg white (called **egg white syndrome**). A protein in egg white called **avidin** binds biotin very tightly and was responsible for the deficiency.

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Summary of Coenzymes, con't.

Coenzyme	Vitamin	Class	Figure
Retinal	Retinol (A)	Prosthetic Group	18.36
1,25-Dihydroxy-Vitamin D_3	Ergo- and Cholecalciferol (D)	Hormone-like action	18.37
Alpha Tocopherol	(E)	Antioxidant	18.38
Phylloquinone	(K)	Carboxylation Cofactor	18.39 and 18.40

Vitamins A, D, K and E are fat-soluble vitamins. Deficiency of Vitamin A can lead to night blindness. Deficiency of vitamin D leads to **rickets** in children, or a weakness in bones known as **osteomalacia** in adults.

Vitamin E is a family of substances like alpha-tocopherol that are potent antioxidants.

Vitamin K is a cofactor in the carboxylation of glutamyl residues in several blood clotting proteins. Vitamins D, E, and K don't fit the "cosubstrate/prosthetic group" classification scheme.