BME 2901-BIOCHEMISTRY

Metabolism

by Assist. Prof. Görke Gürel Peközer

Yıldız Technical University
Biomedical Engineering Department
Fall 2019

Metabolism

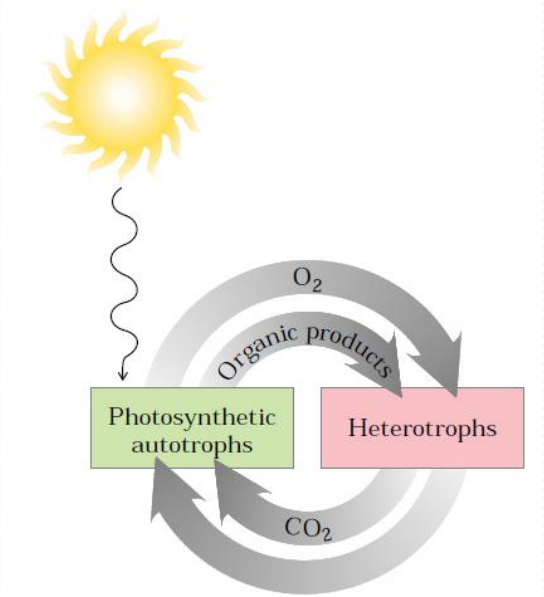
- Metabolism is a highly coordinated cellular activity in which many multienzyme systems (metabolic pathways) cooperate to:

1. obtain chemical energy by capturing solar energy or degrading energy-rich nutrients from the environment;
2. convert nutrient molecules into the cell's own characteristic molecules, including precursors of macromolecules;
3. polymerize monomeric precursors into macromolecules: proteins, nucleic acids, and polysaccharides
4. synthesize and degrade biomolecules required for specialized cellular functions, such as membrane lipids, intracellular messengers, and pigments.

- Living organisms can be divided into two large groups according to the chemical form in which they obtain carbon from the environment:
  - **Autotrophs** (such as photosynthetic bacteria and vascular plants) can use carbon dioxide from the atmosphere as their sole source of carbon, from which they construct all their carbon containing biomolecules. Many autotrophic organisms are photosynthetic and obtain their energy from sunlight.
  - **Heterotrophs** cannot use atmospheric carbon dioxide and must obtain carbon from their environment in the form of relatively complex organic molecules such as glucose. They obtain their energy from the degradation of organic nutrients produced by autotrophs.
- Multicellular animals and most microorganisms are heterotrophic. Autotrophic cells and organisms are relatively self-sufficient, whereas heterotrophic cells and organisms, with their requirements for carbon in more complex forms, must subsist on the products of other organisms.

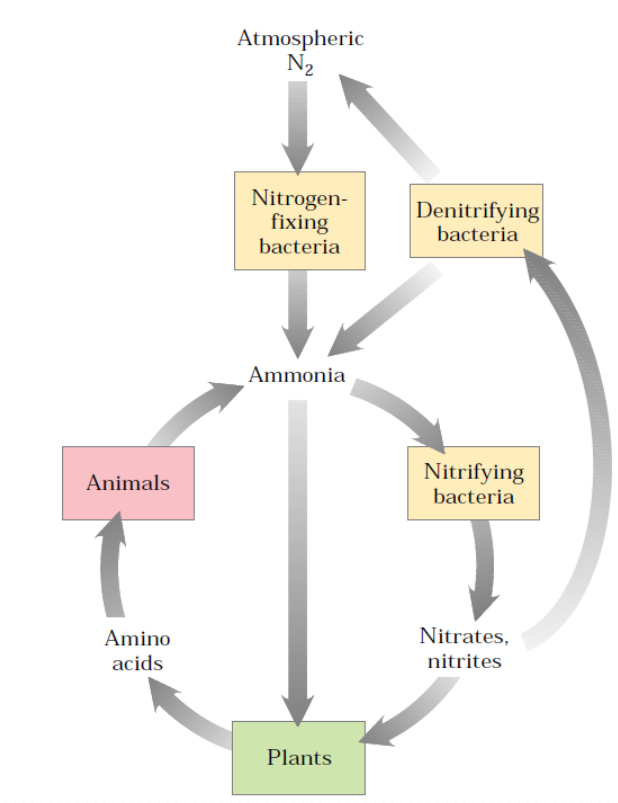
Carbon Cycle

- Autotrophs and heterotrophs live together in a large, coinciding, interdependent cycle in which autotrophic organisms use atmospheric carbon dioxide to build their organic biomolecules, some of them generating oxygen from water in the process.
- Heterotrophs in turn use the organic products of autotrophs as nutrients and return carbon dioxide to the atmosphere.
- Some of the oxidation reactions that produce carbon dioxide also consume oxygen, converting it to water.
- Thus carbon, oxygen, and water are constantly cycled between the heterotrophic and autotrophic worlds with solar energy as the driving force for this global process.



Nitrogen Cycle

- All living organisms also require a source of nitrogen, which is necessary for the synthesis of amino acids, nucleotides, and other compounds.
- Plants can generally use either ammonia or nitrate as their sole source of nitrogen, but vertebrates must obtain nitrogen in the form of amino acids or other organic compounds.
- Only a few organisms—the cyanobacteria and many species of soil bacteria that live symbiotically on the roots of some plants—are capable of converting ("fixing") atmospheric nitrogen (N2) into ammonia.
- Other bacteria (the nitrifying bacteria) oxidize ammonia to nitrites and nitrates; and convert nitrate to N2.
- Thus, in addition to the global carbon and oxygen cycle, a nitrogen cycle operates in the biosphere, turning over huge amounts of nitrogen.

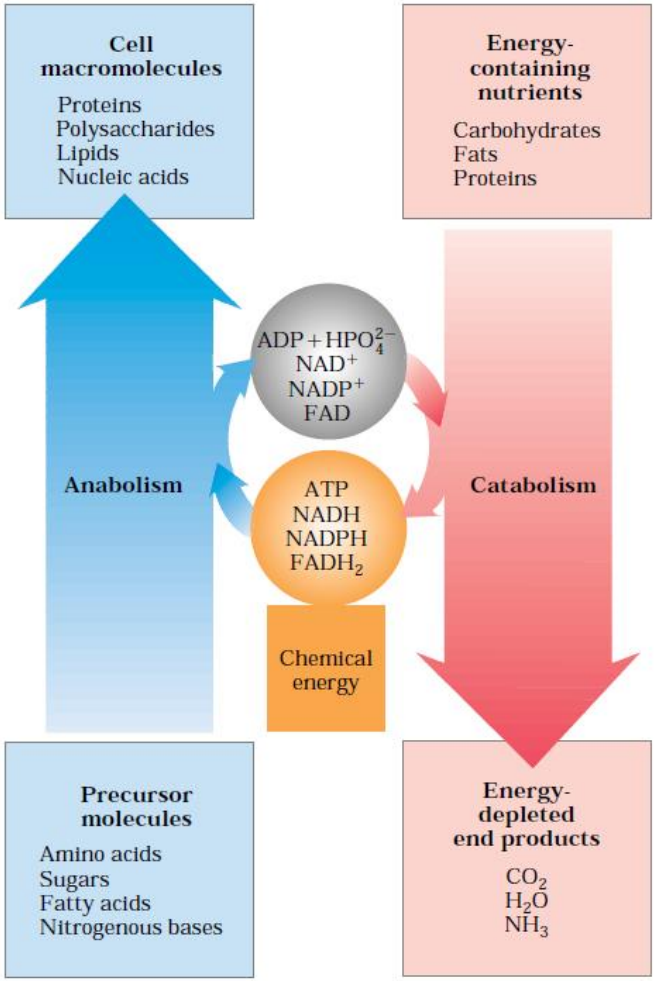


- The cycling of carbon, oxygen, and nitrogen, which ultimately involves all species, depends on a proper balance between the activities of the producers (autotrophs) and consumers (heterotrophs).
- These cycles of matter are driven by an enormous flow of energy into and through the biosphere, beginning with the capture of solar energy by photosynthetic organisms and use of this energy to generate energy rich carbohydrates and other organic nutrients; these nutrients are then used as energy sources by heterotrophic organisms.

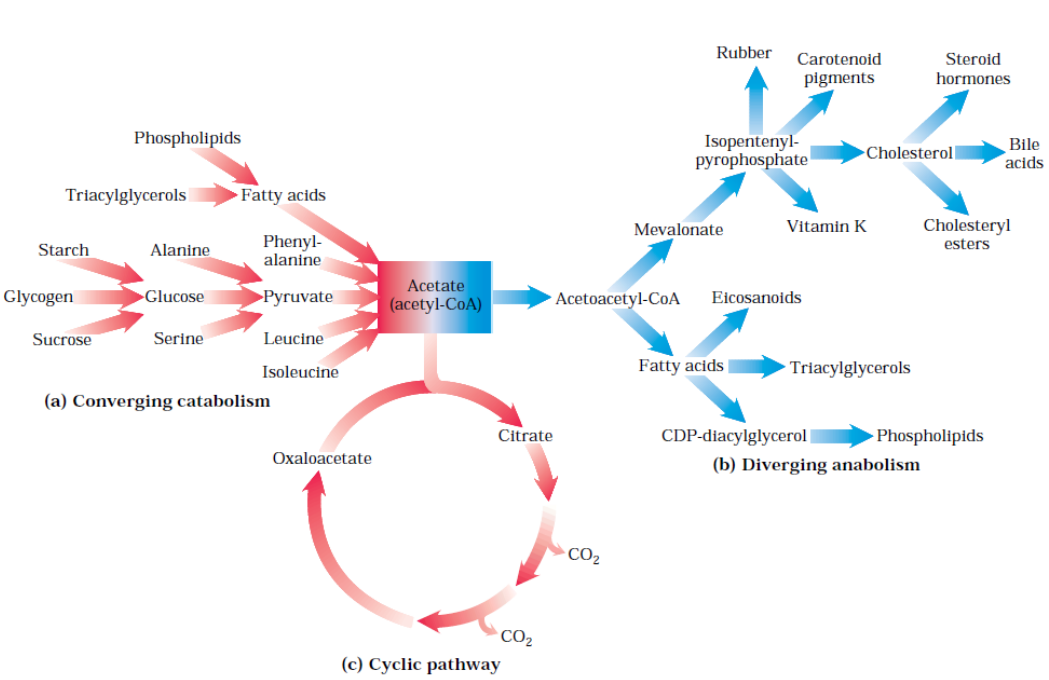
Metabolism

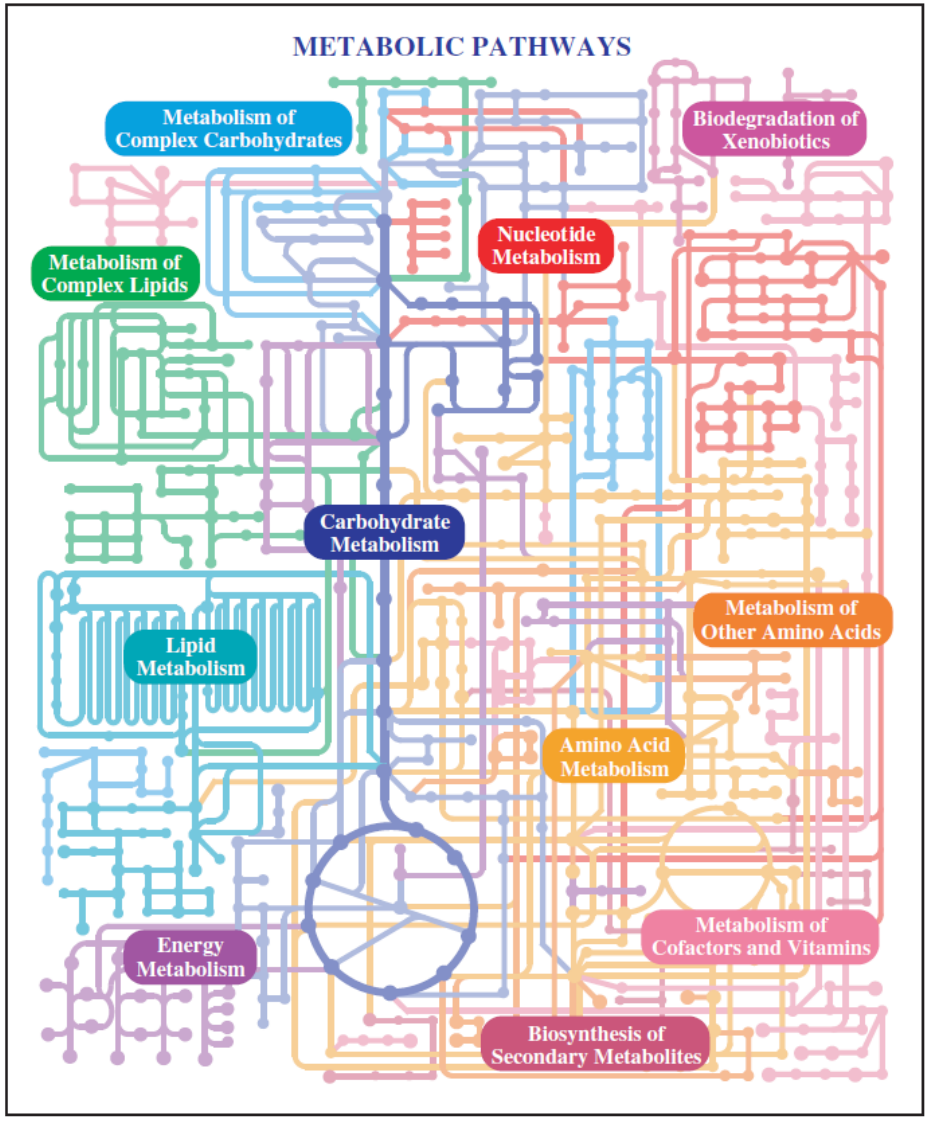
- **Metabolism,** the sum of all the chemical transformations taking place in a cell or organism, occurs through a series of enzyme-catalyzed reactions that constitute **metabolic pathways.**
- Each of the consecutive steps in a metabolic pathway brings about a specific, small chemical change, usually the removal, transfer, or addition of a particular atom or functional group.
- The precursor is converted into a product through a series of metabolic intermediates called **metabolites.**

- **Catabolism** is the degradative phase of metabolism in which organic nutrient molecules (carbohydrates, fats, and proteins) are converted into smaller, simpler end products (such as lactic acid, CO2, NH3).
- Catabolic pathways release energy, some of which is conserved in the formation of ATP and reduced electron carriers (NADH, NADPH, and FADH2); the rest is lost as heat.
- In **anabolism,** also called biosynthesis, small, simple precursors are built up into larger and more complex molecules, including lipids, polysaccharides, proteins, and nucleic acids.
- Anabolic reactions require an input of energy, generally in the form of the phosphoryl group transfer potential of ATP and the reducing power of NADH, NADPH, and FADH2.

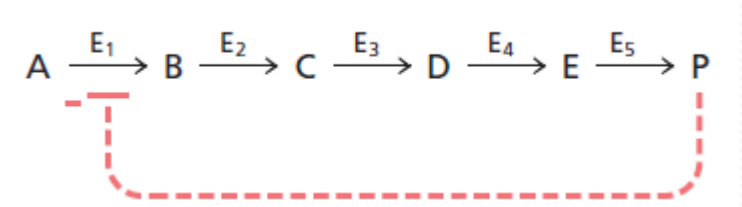


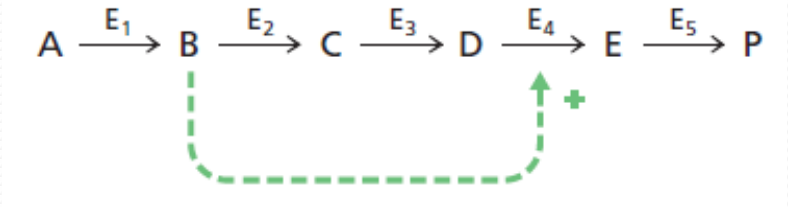
- Some metabolic pathways are linear, and some are branched, yielding multiple useful end products from a single precursor or converting several starting materials into a single product.
- In general, catabolic pathways are convergent and anabolic pathways divergent.
- Some pathways are cyclic: one starting component of the pathway is regenerated in a series of reactions that converts another starting component into a product.




METABOLIC PATHWAYS
Metabolism of Complex Carbohydrates
Biodegradation of Xenobiotics
Nucleotide Metabolism
Metabolism of Complex Lipids
Carbohydrate Metabolism
Metabolism of Other Amino Acids
Lipid Metabolism
Amino Acid Metabolism
Metabolism of Cofactors and Vitamins
Energy Metabolism
Biosynthesis of Secondary Metabolites

- Metabolism is highly regulated. Organisms react to changing environmental conditions such as the availability of energy or nutrients. Organisms also respond to genetically programmed instructions.
- The responses of organisms to changing conditions range from small changes to drastically reorganizing the metabolic processes that govern the synthesis or degradation of biomolecules and the generation or consumption of energy.
- Metabolic pathways can be regulated by the signals within the cell and from outside.
- The most immediate regulation is by the availability of substrate.
- A second type of rapid control from within the cell is allosteric regulation by a metabolic intermediate or coenzyme.



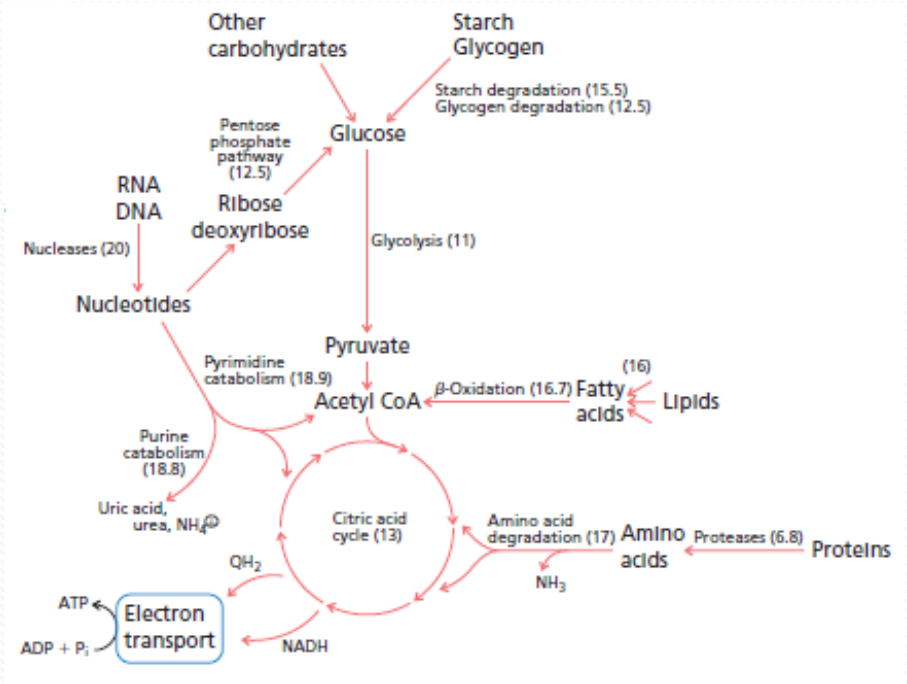


- The activity of enzymes can also be rapidly and reversibly altered by covalent modification, commonly by the addition and removal of phosphoryl groups.
- Phosphorylation, catalyzed by protein kinases at the expense of ATP, is reversed by the action of protein phosphatases, which catalyze the hydrolytic removal of phosphoryl groups.
- Individual enzymes differ in whether their response to phosphorylation is activation or deactivation.
- Enzymes in catabolic pathways are generally activated by phosphorylation and deactivated by dephosphorylation; most enzymes in anabolic pathways are inactivated by phosphorylation and reactivated by dephosphorylation.
- The activation of kinases with multiple specificities allows coordinated regulation of more than one metabolic pathway by one signal.
- Regulation of metabolic processes can also be at the gene expression or protein synthesis level although slower.
- In multicellular organisms the metabolic activities of different tissues are regulated and integrated by growth factors and hormones that act from outside the cell.

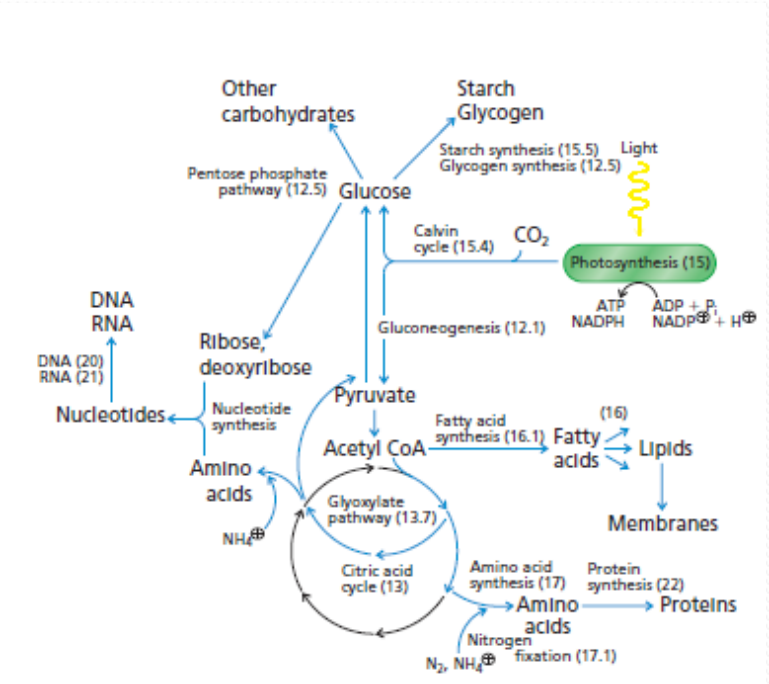
- The activity of enzymes can also be rapidly and reversibly altered by covalent modification, commonly by the addition and removal of phosphoryl groups.
- Phosphorylation, catalyzed by protein kinases at the expense of ATP, is reversed by the action of protein phosphatases, which catalyze the hydrolytic removal of phosphoryl groups.
- Individual enzymes differ in whether their response to phosphorylation is activation or deactivation.
- Enzymes in catabolic pathways are generally activated by phosphorylation and deactivated by dephosphorylation; most enzymes in anabolic pathways are inactivated by phosphorylation and reactivated by dephosphorylation.
- The activation of kinases with multiple specificities allows coordinated regulation of more than one metabolic pathway by one signal.

Major Pathways in Cells

Overview of Catabolic Pathways



Overview of Anabolic Pathways

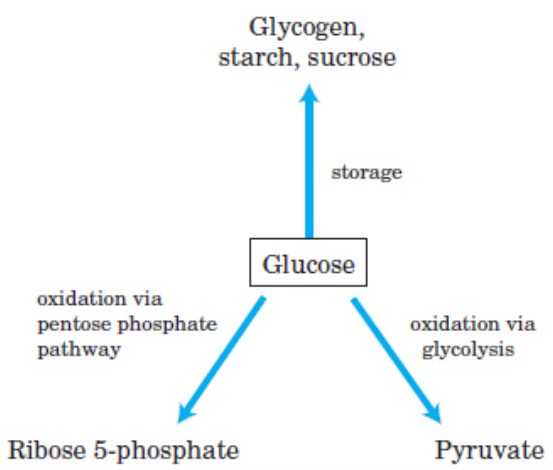


Central Role of Glucose in Metabolism

- Glucose occupies a central position in the metabolism of plants, animals, and many microorganisms.
- It is relatively rich in potential energy, and thus a good fuel; the complete oxidation of glucose to carbon dioxide and water proceeds with a standard free-energy change of 2,840 kJ/mol.
- By storing glucose as a high molecular weight polymer such as starch or glycogen, a cell can stock large quantities of hexose units while maintaining a relatively low cytosolic osmolarity.
- When energy demands increase, glucose can be released from these intracellular storage polymers and used to produce ATP either aerobically or anaerobically.
- Glucose is not only an excellent fuel, it is also a remarkably versatile precursor, capable of supplying a huge array of metabolic intermediates for biosynthetic reactions. A cell can obtain from glucose the carbon skeletons for every amino acid, nucleotide, coenzyme, fatty acid, or other metabolic intermediate it needs for growth.
- Autotrophs make glucose via photosynthesis or chemosynthesis. Heterotrophs make glucose from simpler three and four-carbon precursors.

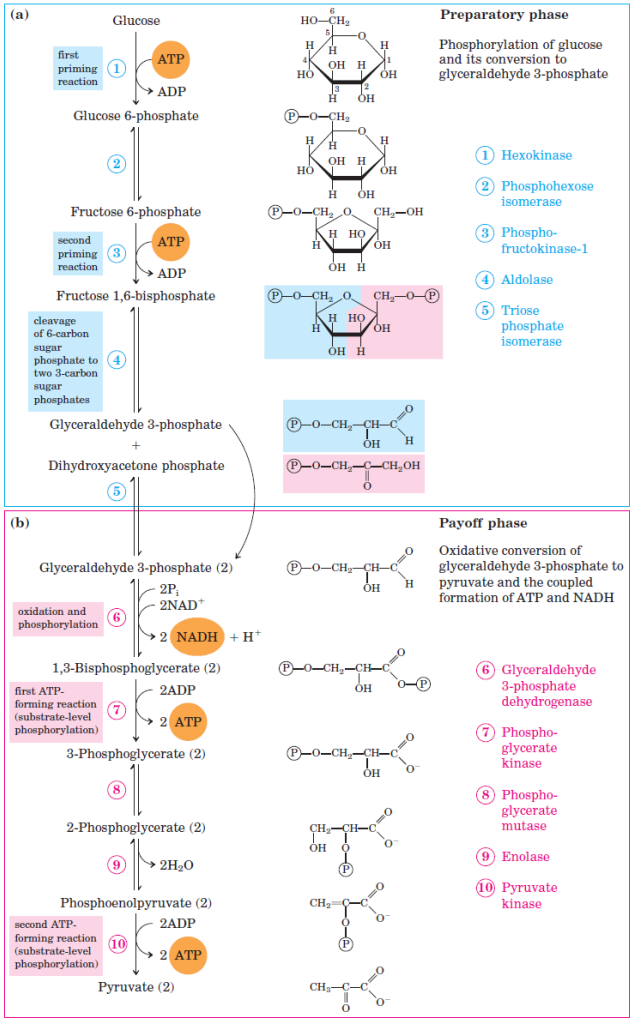
Fate of glucose

- In animals and vascular plants, glucose has three major fates:
  - it may be stored (as a polysaccharide or as sucrose);
  - oxidized to a three-carbon compound (pyruvate) via glycolysis to provide ATP and metabolic intermediates;
  - oxidized via the pentose phosphate (phosphogluconate) pathway to yield ribose 5-phosphate for nucleic acid synthesis and NADPH for reductive biosynthetic processes.

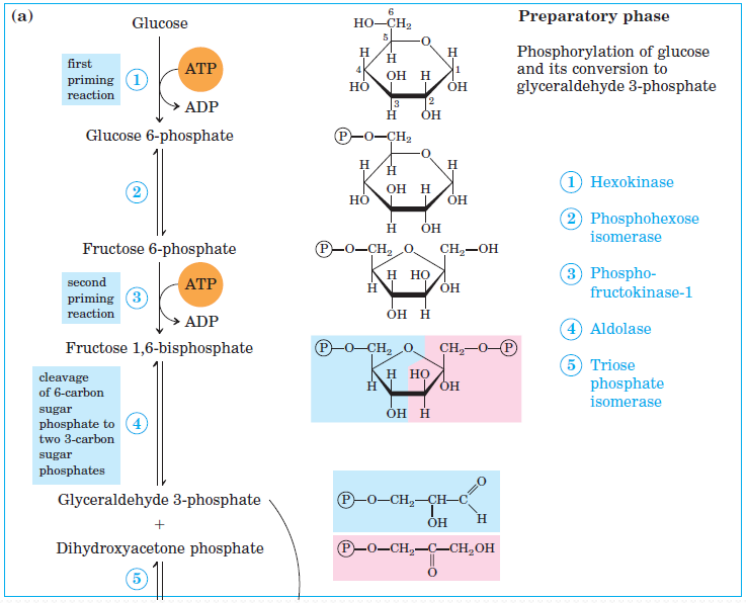


Glycolysis

- In **glycolysis**, a molecule of glucose is degraded in a series of enzyme-catalyzed reactions to yield two molecules of the three-carbon compound pyruvate.
- During the sequential reactions of glycolysis, some of the free energy released from glucose is conserved in the form of ATP and NADH.
- Glycolysis is an almost universal central pathway of glucose catabolism, the pathway with the largest flux of carbon in most cells.

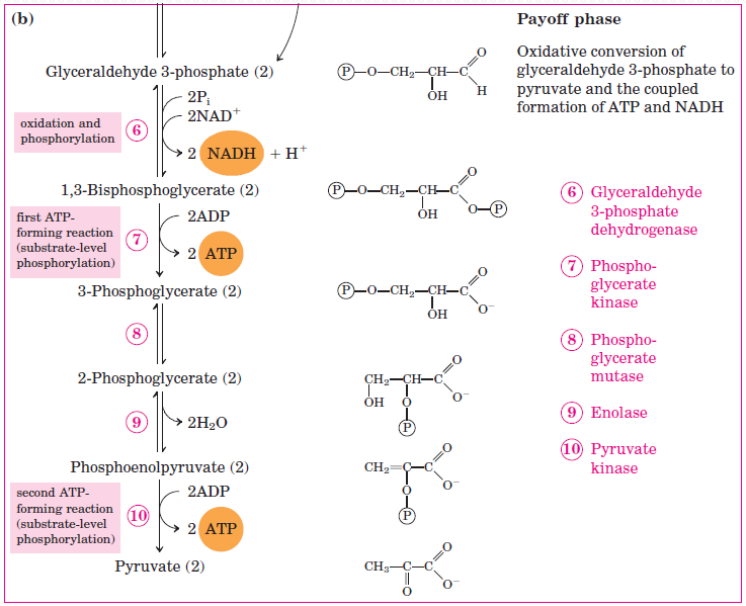


- The breakdown of the six-carbon glucose into two molecules of the three-carbon pyruvate occurs in ten steps, the first five of which constitute the *preparatory phase*.



- In the preparatory phase of glycolysis the energy of 2 ATP is invested, raising the free-energy content of the intermediates, and the carbon chains of all the metabolized hexoses are converted into a common product, glyceraldehyde 3-phosphate.

- The energy gain comes in the *payoff phase* of glycolysis.
- Much of this energy is conserved by the coupled phosphorylation of four molecules of ADP to ATP.
- The net yield is two molecules of ATP per molecule of glucose used, because two molecules of ATP were invested in the preparatory phase.
- Energy is also conserved in the payoff phase in the formation of two molecules of NADH per molecule of glucose.



- Each of the nine glycolytic intermediates between glucose and pyruvate is phosphorylated. The phosphoryl groups appear to have three functions:

1. Because the plasma membrane generally lacks transporters for phosphorylated sugars, the phosphorylated glycolytic intermediates cannot leave the cell. After the initial phosphorylation, no further energy is necessary to retain phosphorylated intermediates in the cell, despite the large difference in their intracellular and extracellular concentrations.
2. Phosphoryl groups are essential components in the enzymatic conservation of metabolic energy. Energy released in the breakage of phosphoanhydride bonds (such as those in ATP) is partially conserved in the formation of phosphate esters such as glucose 6-phosphate. High-energy phosphate compounds formed in glycolysis (1,3-bisphosphoglycerate and phosphoenolpyruvate) donate phosphoryl groups to ADP to form ATP.
3. Binding energy resulting from the binding of phosphate groups to the active sites of enzymes lowers the activation energy and increases the specificity of the enzymatic reactions. The phosphate groups of ADP, ATP, and the glycolytic intermediates form complexes with Mg^{2+}, and the substrate binding sites of many glycolytic enzymes are specific for these Mg^{2+}complexes. Most glycolytic enzymes require Mg^{2+} for activity.

- In the sequential reactions of glycolysis, three types of chemical transformations are particularly noteworthy:

1. degradation of the carbon skeleton of glucose to yield pyruvate,
2. phosphorylation of ADP to ATP by high-energy phosphate compounds formed during glycolysis,
3. transfer of a hydride ion to NAD, forming NADH.

Feeder Pathways for Glycolysis

- Glycogen and starch, polymeric storage forms of glucose, enter glycolysis in a two-step process. Phosphorolytic cleavage of a glucose residue from an end of the polymer, forming glucose 1-phosphate, is catalyzed by glycogen phosphorylase or starch phosphorylase. Phosphoglucomutase then converts the glucose 1-phosphate to glucose 6-phosphate, which can enter glycolysis.
- Ingested polysaccharides and disaccharides are converted to monosaccharides by intestinal hydrolytic enzymes, and the monosaccharides then enter intestinal cells and are transported to the liver or other tissues.
- A variety of D-hexoses, including fructose, galactose, and mannose, can be funneled into glycolysis. Each is phosphorylated and converted to either glucose 6-phosphate or fructose 6-phosphate.

Net gain of Glycolysis

- The overall equation of glycolysis is:

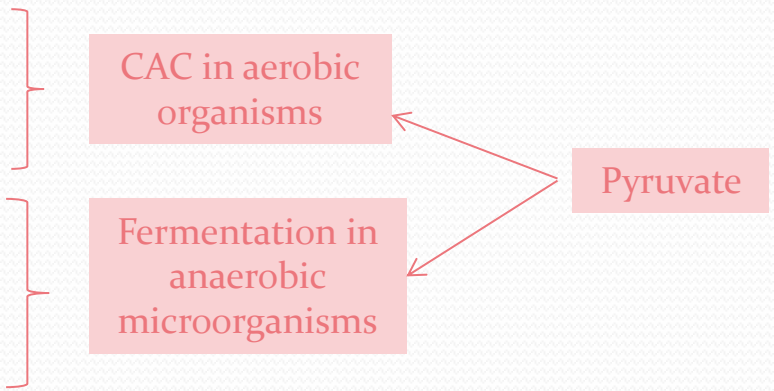
Glucose + $2NAD^+$ + 2ADP + 2Pi → 2 Pyruvate + 2NADH + $2H^+$ + 2ATP + $2H_2O$

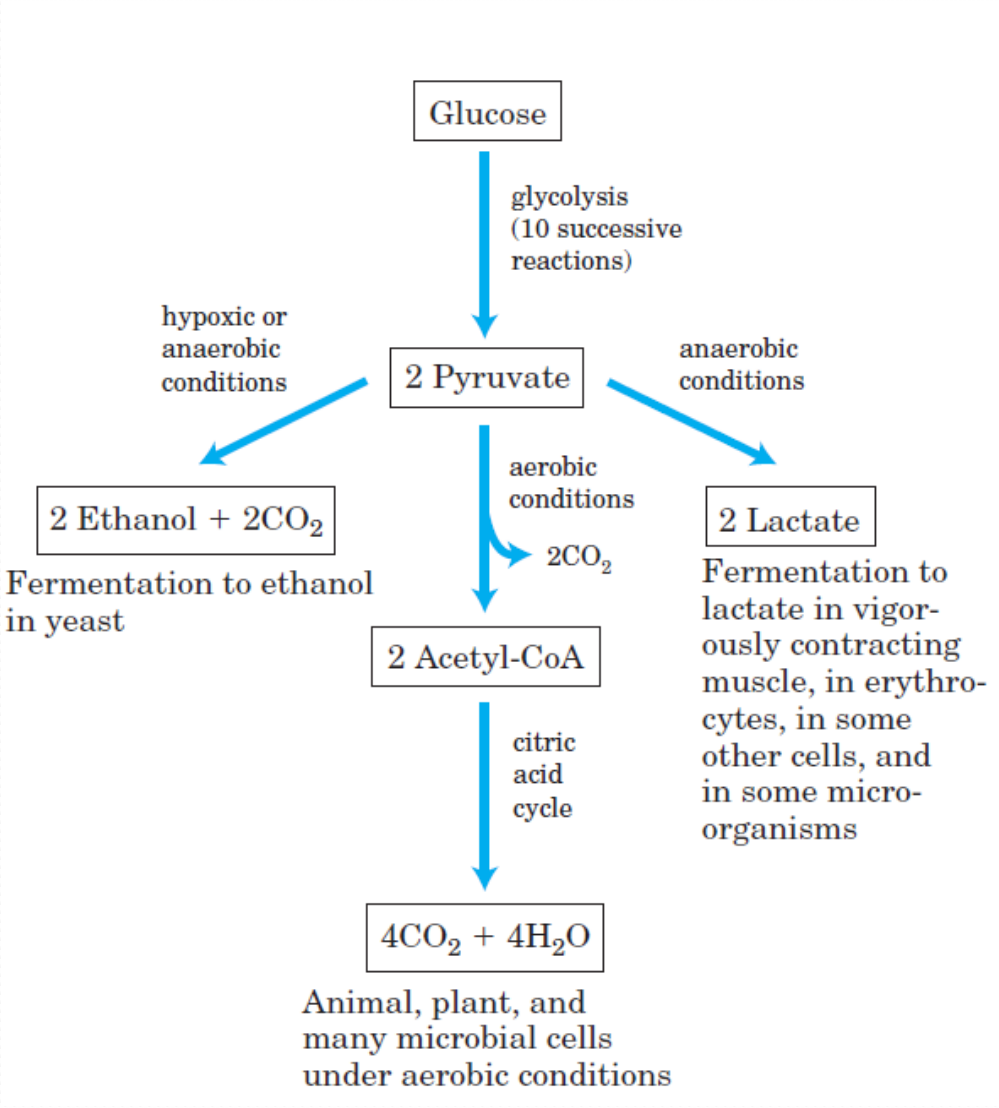
- For 1 glucose (6 C) molecule 2 Pyruvate (3 C) is produced.
- For 1 glucose molecule 2 ATP and 2 NADH is produced.

Fates of Pyruvate

- In aerobic organisms or tissues, under aerobic conditions, glycolysis is only the first stage in the complete degradation of glucose.
- Glycolysis releases only a small fraction of the total available energy of the glucose molecule; the two molecules of pyruvate formed by glycolysis still contain most of the chemical potential energy of glucose, energy that can be further extracted.
- The pyruvate formed by glycolysis is further metabolized via one of three catabolic routes:

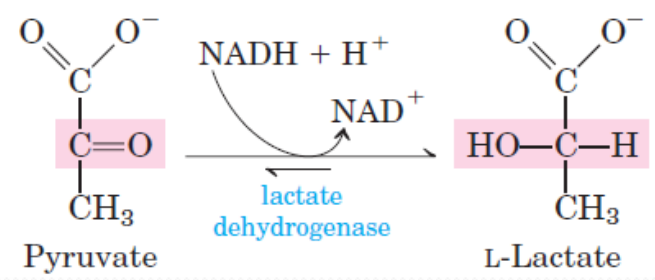
1. Pyruvate is oxidized, with loss of its carboxyl group as CO_2, to yield the acetyl group of acetyl-coenzyme A; the acetyl group is then oxidized completely to CO_2 by the **citric acid cycle**.
2. The second route for pyruvate is its reduction to lactate via **lactic acid fermentation.**
3. The third major route of pyruvate catabolism is **alcohol fermentation** that results in ethanol production.




Glucose
glycolysis (10 successive reactions)
hypoxic or anaerobic conditions
2 Pyruvate
anaerobic conditions
aerobic conditions
$2CO_2$
2 Ethanol + $2CO_2$
Fermentation to ethanol in yeast
2 Acetyl-CoA
2 Lactate
Fermentation to lactate in vigorously contracting muscle, in erythrocytes, in some other cells, and in some microorganisms
citric acid cycle
$4CO_2 + 4H_2O$
Animal, plant, and many microbial cells under aerobic conditions

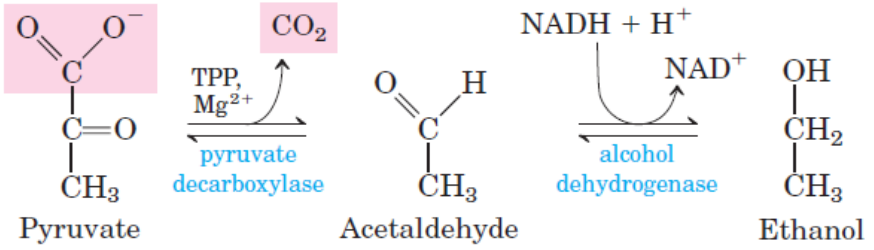
Lactic Acid Fermentation

- The aim of fermentation process is to gain NAD^+ back. Failure to regenerate NAD^+ would leave the cell with no electron acceptor for the oxidation of glyceraldehyde 3-phosphate, and the energy-yielding reactions of glycolysis would stop.
- When animal tissues cannot be supplied with sufficient oxygen to support aerobic oxidation of the pyruvate and NADH produced in glycolysis, NAD is regenerated from NADH by the reduction of pyruvate to **lactate.**
- This occurs also in cells that do not have mitochondria such as erythrocytes.



Alcohol Fermentation

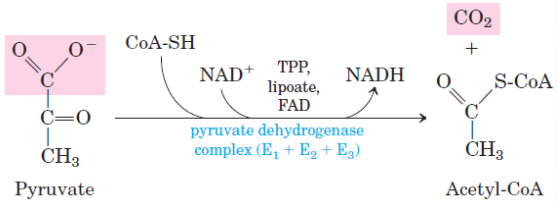
- Yeast and other microorganisms ferment glucose to ethanol and CO2, rather than to lactate.
- Pyruvate is converted to ethanol and CO2.



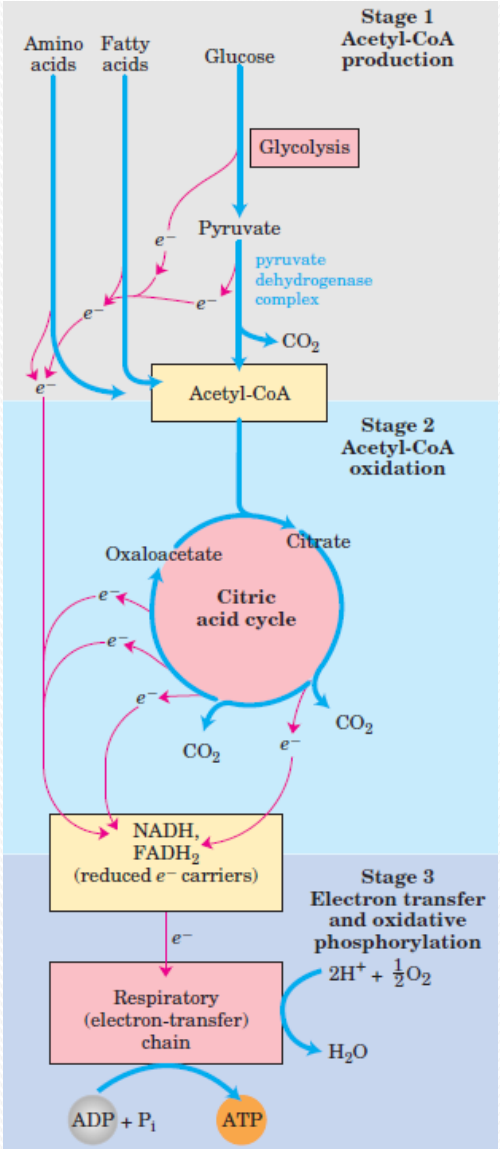
Cellular Respiration

- Some cells obtain energy (ATP) by fermentation, breaking down glucose in the absence of oxygen.
- For most eukaryotic cells and many bacteria, which live under aerobic conditions and oxidize their organic fuels to carbon dioxide and water, glycolysis is but the first stage in the complete oxidation of glucose. Rather than being reduced to lactate, ethanol, or some other fermentation product, the pyruvate produced by glycolysis is further oxidized to H_2O and CO_2.
- This aerobic phase of catabolism is called **respiration.** In the broader physiological or macroscopic sense, respiration refers to a multicellular organism's uptake of O_2 and release of CO_2.
- Biochemists and cell biologists, however, use the term in a narrower sense to refer to the molecular processes by which *cells* consume O_2 and produce CO_2—processes more precisely termed **cellular respiration.**

- Cellular respiration occurs in three major stages:
  - In the first, organic fuel molecules—glucose, fatty acids, and some amino acids—are oxidized to yield two-carbon fragments in the form of the acetyl group of **acetyl-coenzyme A (acetyl-CoA)**.

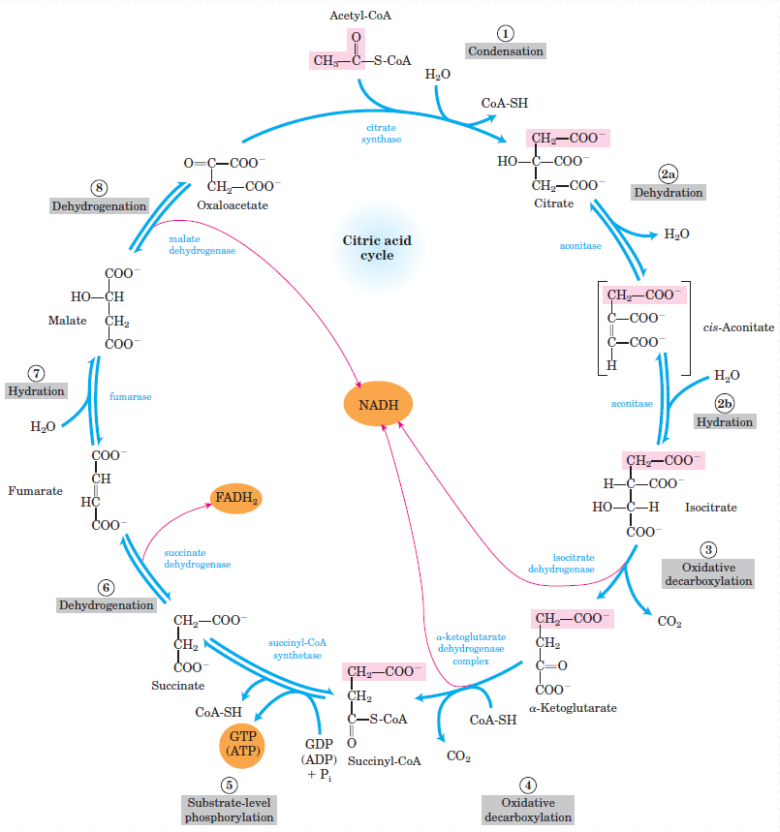


  - In the second stage, the acetyl groups are fed into the **citric acid cycle**, which enzymatically oxidizes them to CO2; the energy released is conserved in the reduced electron carriers NADH and FADH2.
  - In the third stage of respiration, these reduced coenzymes are themselves oxidized, giving up protons (H) and electrons. The electrons are transferred to O2—the final electron acceptor—via a chain of electron-carrying molecules known as the respiratory chain. In the course of electron transfer, the large amount of energy released is conserved in the form of ATP, by a process called **oxidative phosphorylation**.



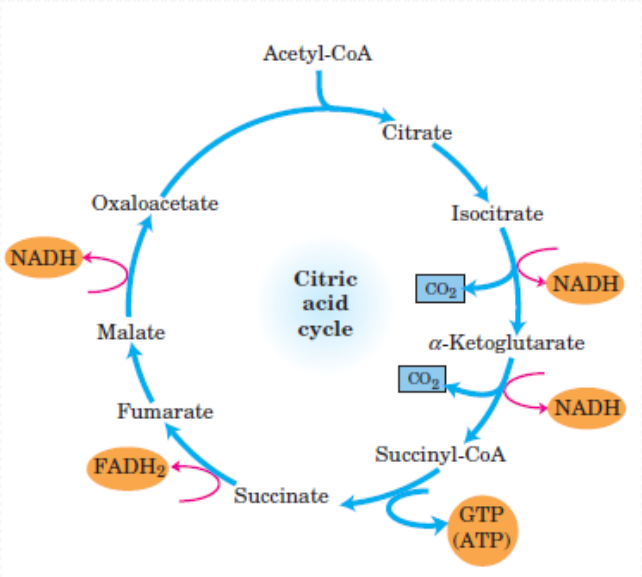
Citric Acid Cycle

- **Citric acid cycle, is** also called the **tricarboxylic acid (TCA) cycle** or the **Krebs cycle.**
- Acetyl-CoA donates its acetyl group to the four-carbon compound oxaloacetate to form the six-carbon citrate.
- Citrate is then transformed into isocitrate, also a six-carbon molecule, which is dehydrogenated with loss of CO_2 to yield the five-carbon compound -ketoglutarate (also called oxoglutarate).
- α-Ketoglutarate undergoes loss of a second molecule of CO_2 and ultimately yields the four-carbon compound succinate.
- Succinate is then enzymatically converted in three steps into the four-carbon oxaloacetate—which is then ready to react with another molecule of acetyl-CoA.
- In each turn of the cycle, one acetyl group (two carbons) enters as acetyl-CoA and two molecules of CO_2 leave; one molecule of oxaloacetate is used to form citrate and one molecule of oxaloacetate is regenerated.



Citric Acid Cycle

- A two-carbon acetyl group entered the cycle by combining with oxaloacetate.
- Two carbon atoms emerged from the cycle as CO_2 from the oxidation of isocitrate and -ketoglutarate.
- The energy released by these oxidations was conserved in the reduction of three NAD and one FAD and the production of one ATP or GTP.
- At the end of the cycle a molecule of oxaloacetate was regenerated.
- Although the citric acid cycle directly generates only one ATP per turn (in the conversion of succinyl-CoA to succinate), the four oxidation steps in the cycle provide a large flow of electrons into the respiratory chain via NADH and $FADH_2$ and thus lead to formation of a large number of ATP molecules during oxidative phosphorylation.

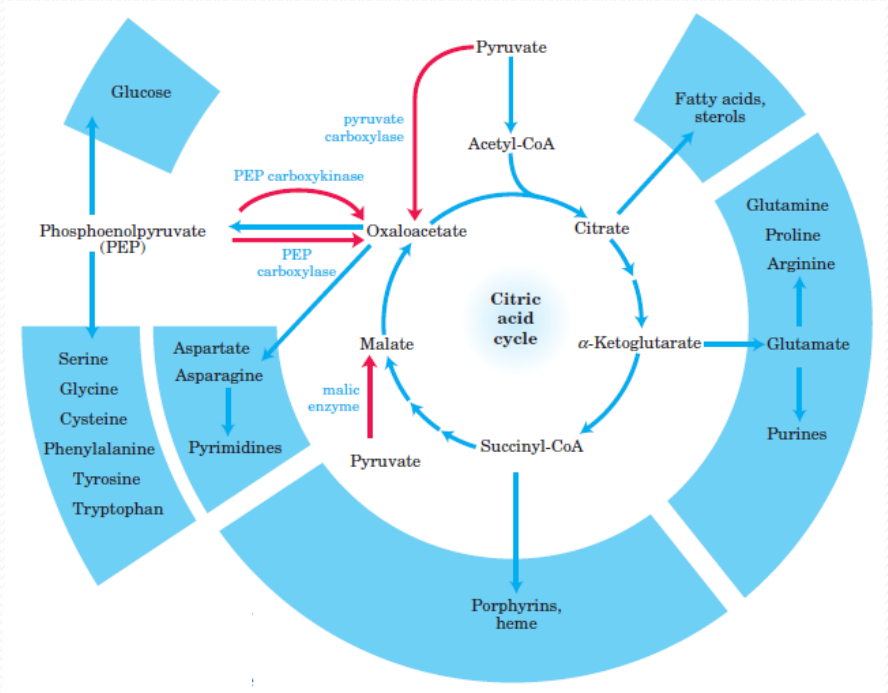


Net gain of Citric Acid Cycle

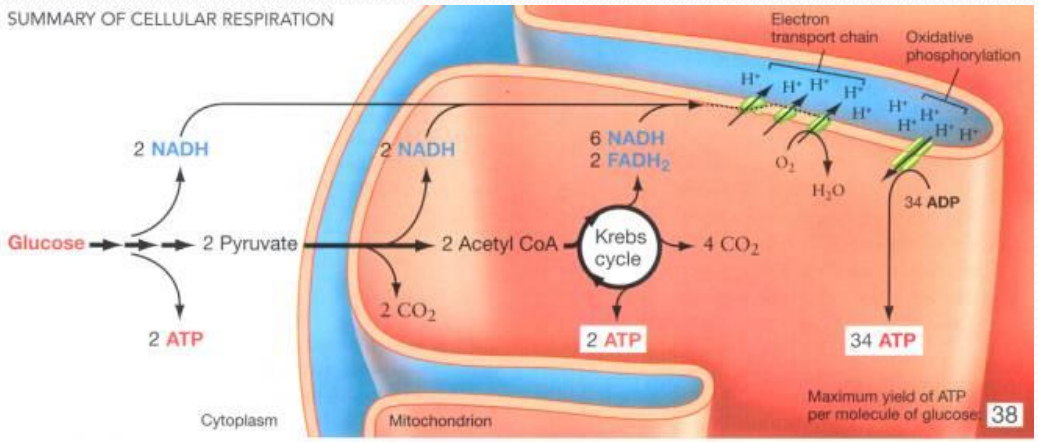
6 NADH + 2 $FADH_2$ + 2 ATP

Citric Acid Cycle Components Are Important Biosynthetic Intermediates

- The eight-step cyclic process for oxidation of simple two carbon acetyl groups to CO_2 may seem unnecessarily long and not in keeping with the biological principle of maximum economy.
- The role of the citric acid cycle is not confined to the oxidation of acetate, however. This pathway is the hub of intermediary metabolism.
- Four- and five-carbon end products of many catabolic processes feed into the cycle to serve as fuels. Oxaloacetate and -ketoglutarate, for example, are produced from aspartate and glutamate, respectively, when proteins are degraded.
- Under some metabolic circumstances, intermediates are drawn out of the cycle to be used as precursors in a variety of biosynthetic pathways.



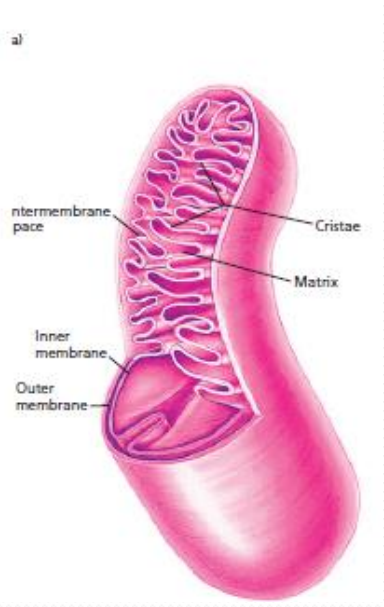
- Glycolysis takes place in cytoplasm.
- The entire set of reactions of the citric acid cycle takes place in mitochondria.
- Isolated mitochondria were found to contain not only all the enzymes and coenzymes required for the citric acid cycle, but also all the enzymes and proteins necessary for the last stage of respiration—electron transfer and ATP synthesis by oxidative phosphorylation.

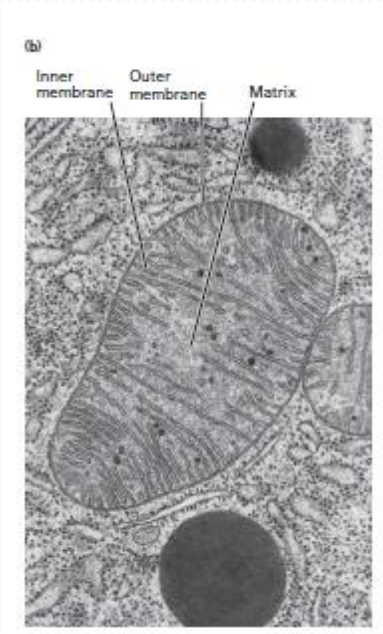


Oxidative Phosphorylation

- Oxidative phosphorylation (OP) is the last step of energy yielding metabolism in aerobic organisms.
- All oxidative steps in the degradation of carbohydrates, fats, and amino acids converge at this final stage of cellular respiration, in which the energy of oxidation drives the synthesis of ATP.
- It involves the *reduction* of O_2 to H_2O with electrons donated by NADH and $FADH_2$.
- Oxidative phophorylation produces energy according to chemiosmotic theory.
- **Chemiosmotic theory** states that transmembrane differences in proton concentration are the reservoir for the energy extracted from biological oxidation reactions.

- In eukaryotes, oxidative phosphorylation occurs in mitochondria.
- Mitochondria have two membranes. The outer mitochondrial membrane is readily permeable to small molecules and ions. The inner membrane is impermeable to most small molecules and ions, including protons (H); the only species that cross this membrane do so through specific transporters.
- The inner membrane bears the components of the respiratory chain and the ATP synthase.
- The mitochondrial matrix, enclosed by the inner membrane, contains the pyruvate dehydrogenase complex and the enzymes of the citric acid cycle, the fatty acid-oxidation pathway, and the pathways of amino acid oxidation—**all the pathways of fuel oxidation except glycolysis, which takes place in the cytosol.**
- The selectively permeable inner membrane segregates the intermediates and enzymes of cytosolic metabolic pathways from those of metabolic processes occurring in the matrix.



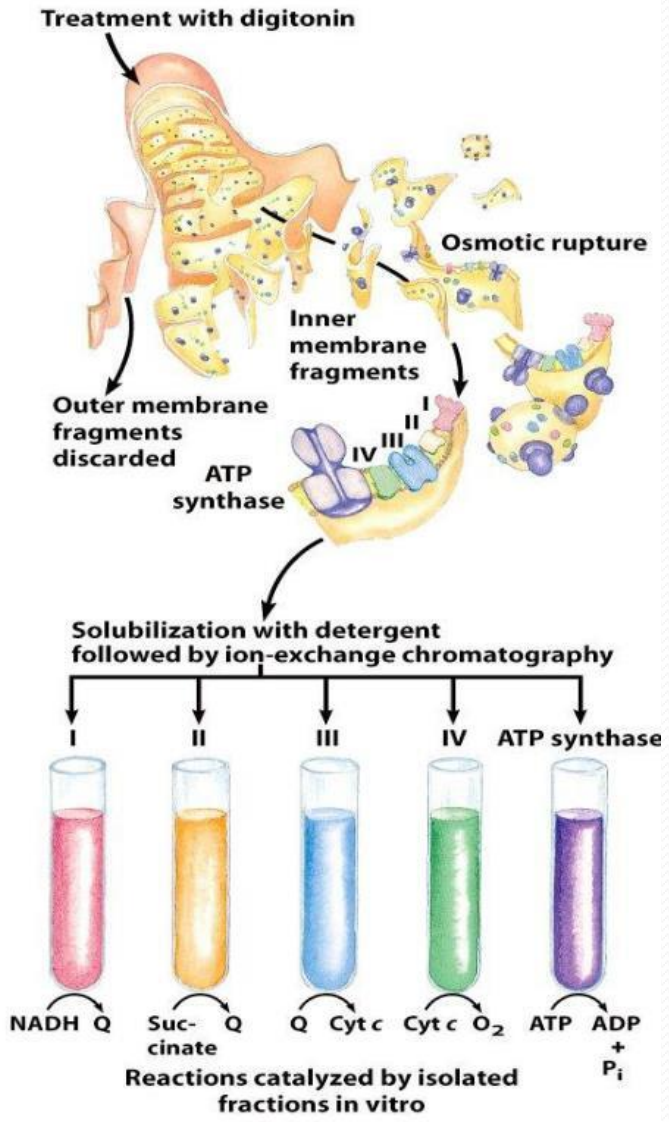


- Oxidative phosphorylation begins with the entry of electrons into the respiratory chain.
- Most of these electrons arise from the action of dehydrogenases that collect electrons from catabolic pathways and funnel them into universal electron acceptors—nicotinamide nucleotides (NAD or NADP) or flavin nucleotides (FMN or FAD).

Electron Transport Chain

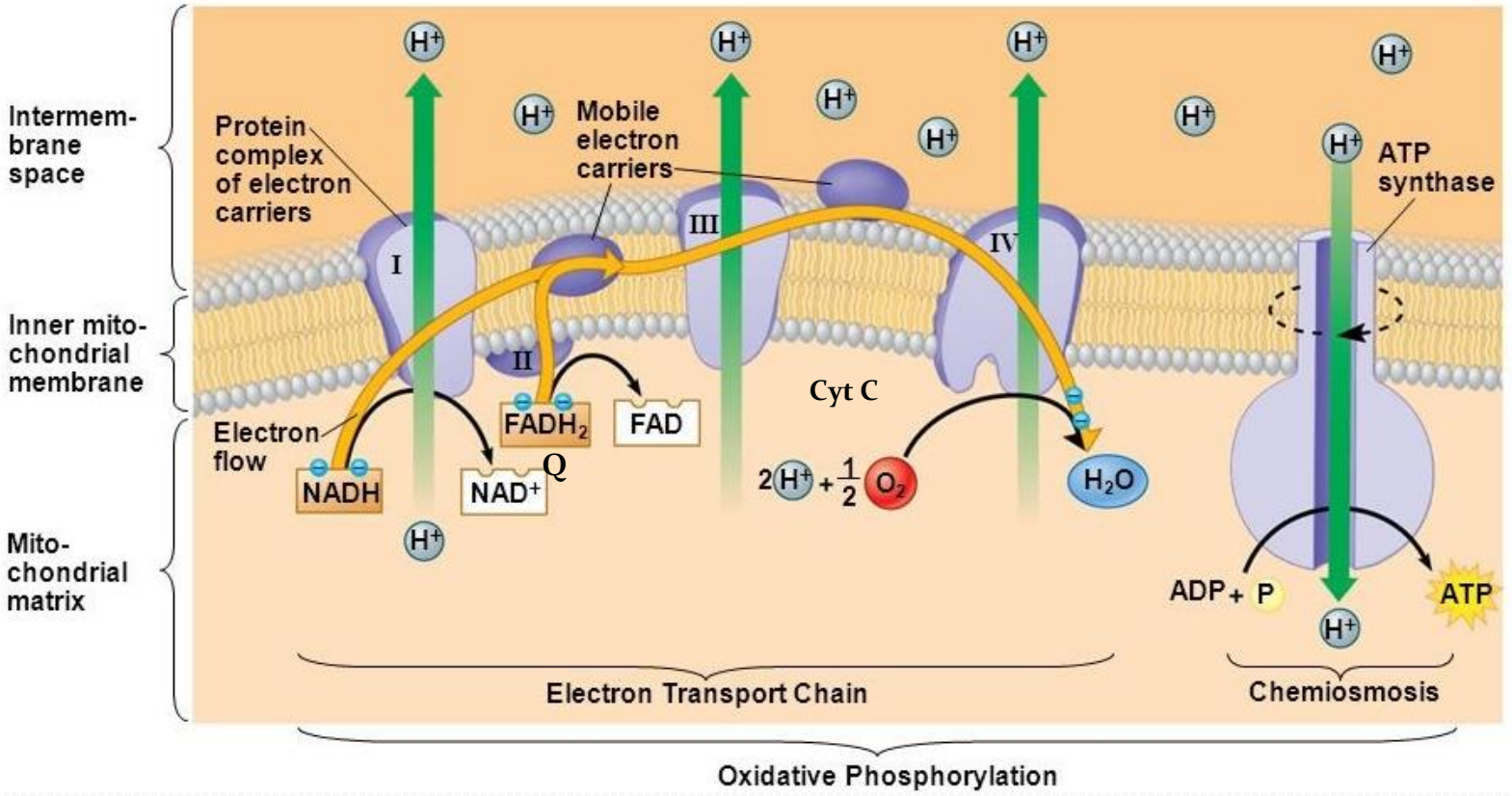
- The mitochondrial respiratory chain consists of a series of sequentially acting electron carriers, most of which are integral proteins with prosthetic groups capable of accepting and donating either one or two electrons.
- Three types of electron transfers occur in oxidative phosphorylation: (1) direct transfer of electrons, as in the reduction of Fe^{+3} to Fe^{+2}; (2) transfer as a hydrogen atom (H + e^-); and (3) transfer as a hydride ion ($:H^-$), which bears two electrons.
- The term **reducing equivalent** is used to designate a single electron equivalent transferred in an oxidation-reduction reaction.

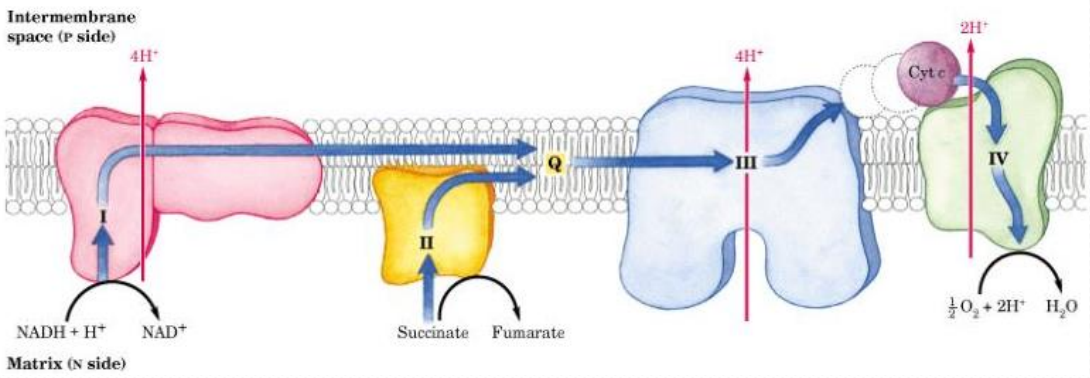
- In addition to NAD and FAD, three other types of electron-carrying molecules function in the respiratory chain: a hydrophobic quinone (ubiquinone or Q) and two different types of iron-containing proteins (cytochromes and iron-sulfur proteins).
- They are located in the inner membrane of mitochondria.

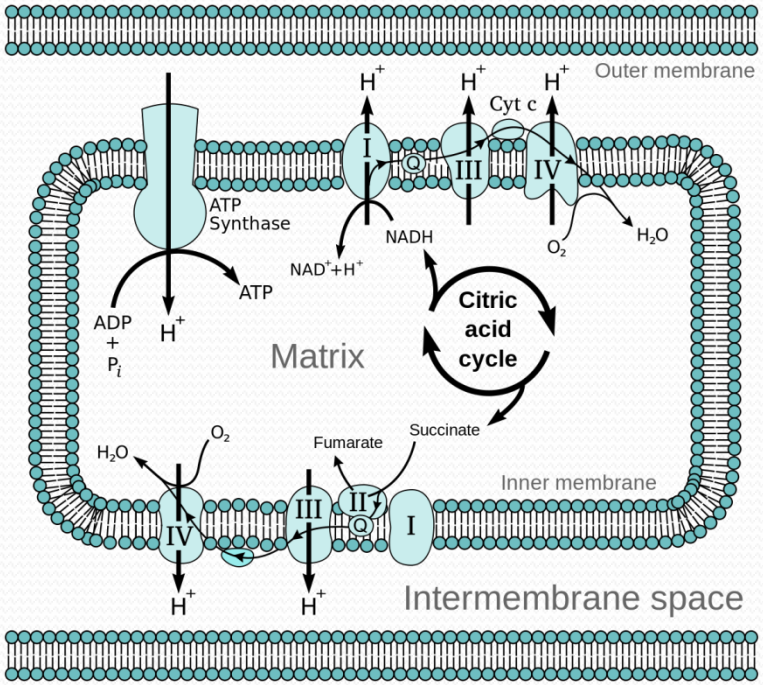


Electron Transfer in OP

- In mitochondria, hydride ions removed from substrates by NAD-linked dehydrogenases donate electrons to the respiratory (electron-transfer) chain, which transfers the electrons to molecular O_2, reducing it to H_2O.
- Reducing equivalents from all NAD-linked dehydrogenations are transferred to mitochondrial NADH dehydrogenase (Complex I). Reducing equivalents are then passed through a series of Fe-S centers to ubiquinone, which transfers the electrons to cytochrome *b*, the first carrier in Complex III.
- Electrons, one at a time, pass through cytochrome *c* and into Complex IV, cytochrome oxidase. This copper-containing enzyme, which also contains cytochromes *a* and *a3*, accumulates electrons, then passes them to O_2, reducing it to H_2O.
- Some electrons enter this chain of carriers through alternative paths. Succinate is oxidized by succinate dehydrogenase (Complex II), in which electrons pass through several Fe-S centers to ubiquinone. Electrons derived from the oxidation of fatty acids pass to ubiquinone via this complex.


Intermem-
brane
space
Inner mito-
chondrial
membrane
Mito-
chondrial
matrix
Protein
complex
of electron
carriers
Mobile
electron
carriers
ATP
synthase
I
II
III
IV
Electron
flow
NADH
NAD+
FADH2
FAD
Q
Cyt C
2H+ + 1/2 O2
H2O
ADP + P
ATP
H+
Electron Transport Chain
Chemiosmosis
Oxidative Phosphorylation


Intermembrane
space (P side)
4H+
2H+
Cyt c
I
II
III
IV
Q
NADH + H+
NAD+
Succinate
Fumarate
½ O2 + 2H+
H2O
Matrix (N side)


Outer membrane
H+
H+
H+
Cyt c
I
III
IV
ATP
Synthase
NADH
NAD+ + H+
O2
H2O
ATP
ADP
+
Pi
H+
Matrix
Citric
acid
cycle
Succinate
Fumarate
O2
H2O
Inner membrane
IV
III
II
I
H+
H+
Intermembrane space

ATP Synthesis through OP

- The flow of electrons through Complexes I, III, and IV results in pumping of protons across the inner mitochondrial membrane, making the matrix alkaline relative to the intermembrane space.
- This proton gradient provides the energy (in the form of the proton-motive force) for ATP synthesis from ADP and Pi by ATP synthase in the inner membrane.

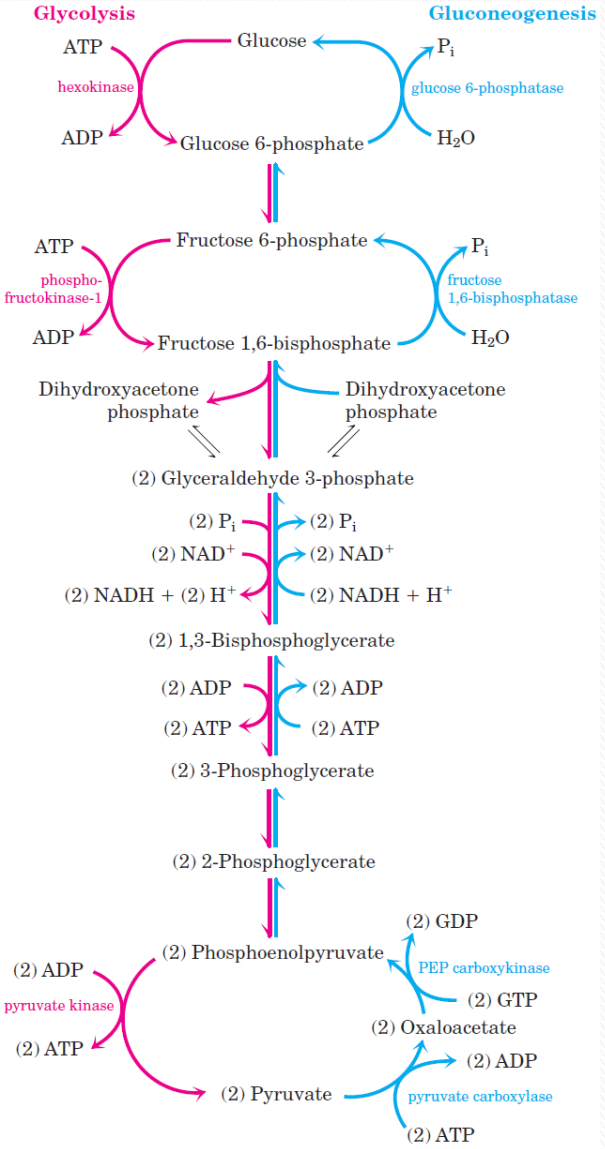
Net gain of 1 glucose

- Glycolysis → 2 NADH + 2 ATP
- Production of Acetyl CoA from pyruvate → 2 NADH
- Citric Acid Cycle → 6 NADH + 2 $FADH_2$ + 2 ATP
- Oxidative Phosphorylation → 10 NADH x 2.5 ATP + 2 $FADH_2$ x 1.5 ATP + 4 ATP

- 32 ATP in total for 1 glucose molecule

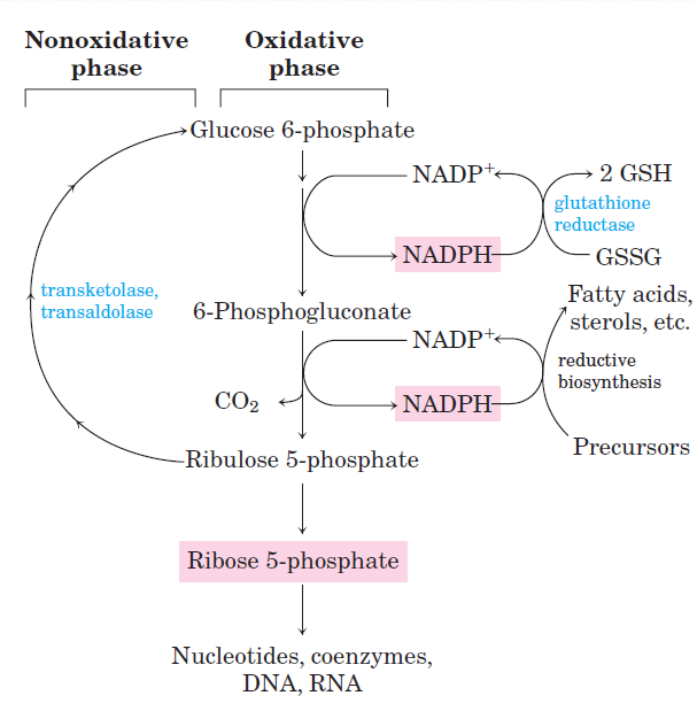
Gluconeogenesis

- Organisms need a method for synthesizing glucose from noncarbohydrate precursors.
- This is accomplished by a pathway called **gluconeogenesis** ("formation of new sugar"), which converts pyruvate and related three- and four-carbon compounds to glucose.



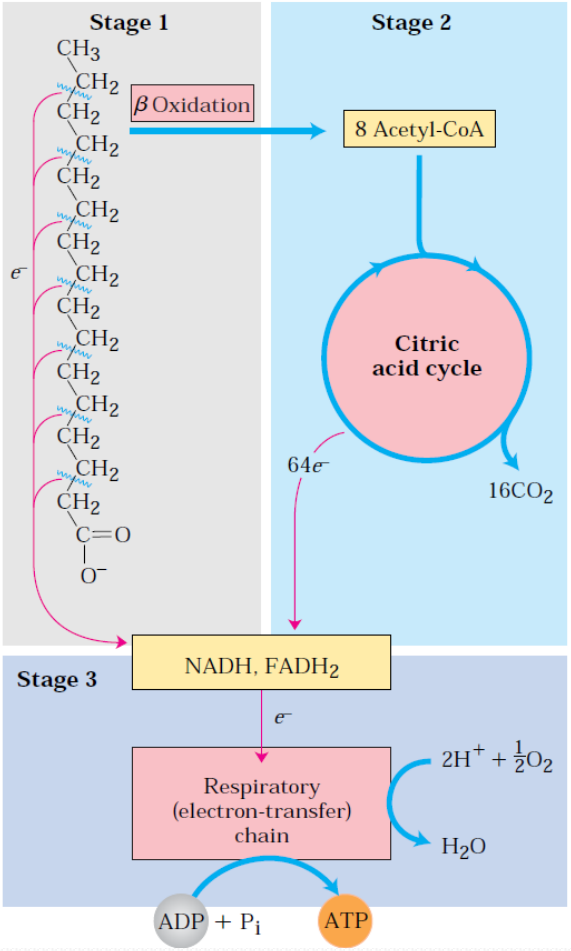
Pentose Phosphate Pathway

- The pentose phosphate pathway is a pathway for the synthesis of pentose phosphates especially ribose-5-phosphate which is essetial for nucleic acid biosynthesis.
- NADPH is produced in the process which is used in biosynthetic pathways.



Lipid Metabolism

- The oxidation of long-chain fatty acids to acetyl-CoA is another central energy-yielding pathway in many organisms and tissues.
- Fatty acids are converted into acetyl-CoA by **β-oxidation**.
- The electrons removed from fatty acids during oxidation pass through the respiratory chain, driving ATP synthesis and the acetyl-CoA produced can be completely oxidized to CO_2 in the citric acid cycle or used in ketone body of fatty acid synthesis.



Ketone Bodies

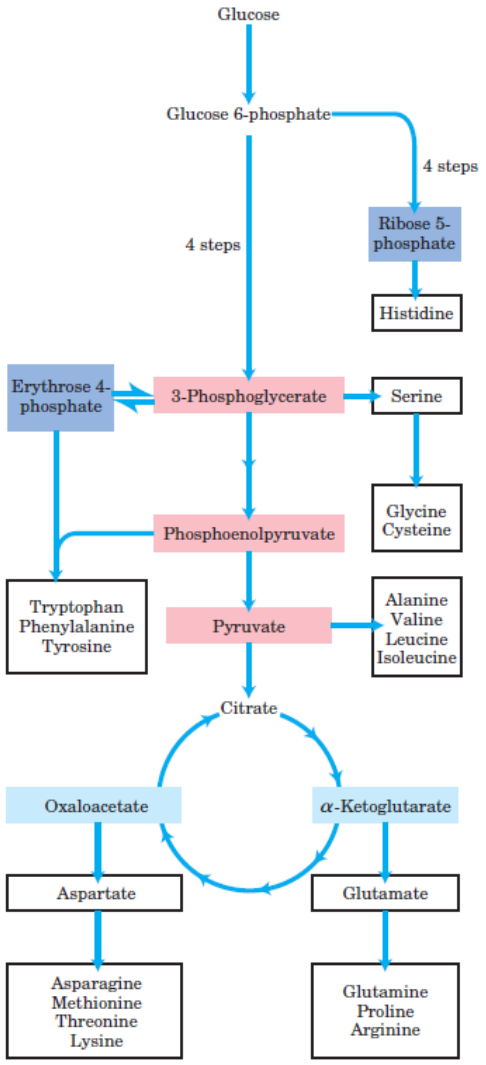
- Acetyl-CoA formed during oxidation of fatty acids can either enter the citric acid cycle or undergo conversion to the **ketone bodies** such as acetone, acetoacetate, and D-β-hydroxybutyrate.
- Acetone, produced in smaller quantities than the other ketone bodies, is exhaled.
- Acetoacetate and D-β-hydroxybutyrate are transported by the blood to tissues other than the liver (extrahepatic tissues), where they are converted to acetyl-CoA and oxidized in the citric acid cycle, providing much of the energy required by tissues such as skeletal and heart muscle and the renal cortex.
- The brain, which preferentially uses glucose as fuel, can adapt to the use of acetoacetate or D-β-hydroxybutyrate under starvation conditions, when glucose is unavailable.

In untreated diabetes

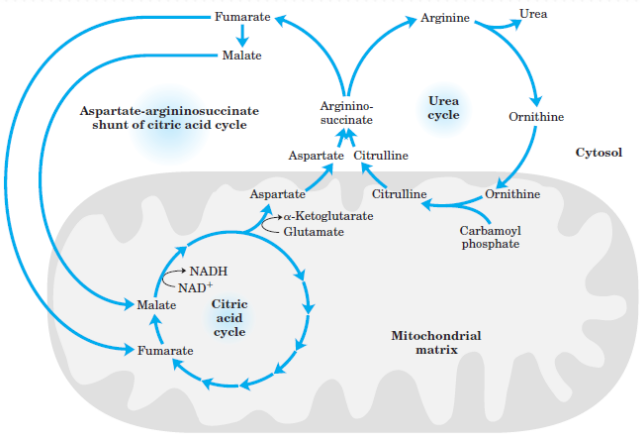
- Starvation and untreated diabetes mellitus lead to overproduction of ketone bodies, with several associated medical problems.
- During starvation, gluconeogenesis depletes citric acid cycle intermediates, diverting acetyl-CoA to ketone body production.
- The increased blood levels of acetoacetate and D-β-hydroxybutyrate lower the blood pH, causing the condition known as **ketoacidosis.**
- Extreme ketoacidosis can lead to coma and in some cases death.

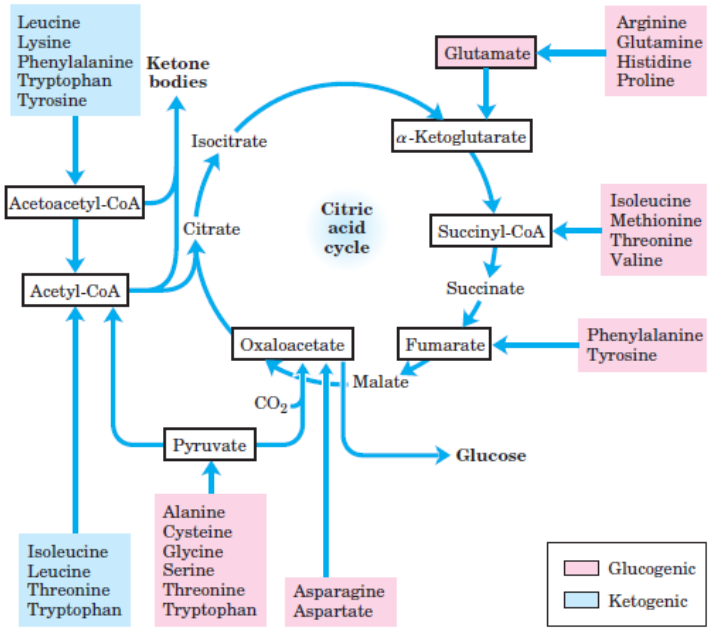
Protein Metabolism

- Proteins are synthesized from aminoacid precursors by ribosomes through translation.
- Aminoacids can be formed from intermediates in glycolysis, the citric acid cycle, or the pentose phosphate pathway.
- Nitrogen enters these pathways by way of glutamate and glutamine.
- Plants and bacteria synthesize all 20 common amino acids.
- Mammals can synthesize about half; the others are required in the diet (essential amino acids).



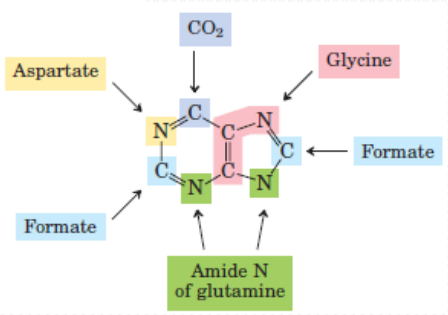
- Amino groups are cleaved during aminoacid catabolism in ammonia form.
- If not reused for the synthesis of new amino acids or other nitrogenous products, amino groups are channeled into a single excretory end product such as urea by urea cycle.
- After removal of their amino groups, the carbon skeletons of amino acids undergo oxidation to compounds that can enter the citric acid cycle for oxidation to CO_2 and H_2O.
- Depending on their degradative end product, some amino acids can be converted to ketone bodies, some to glucose, and some to both.



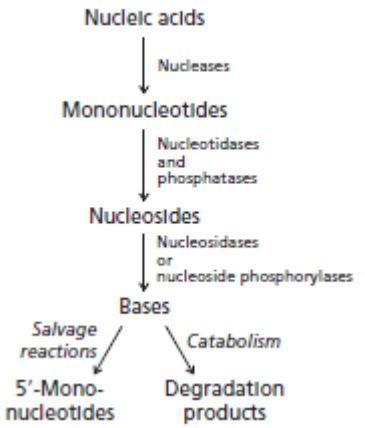


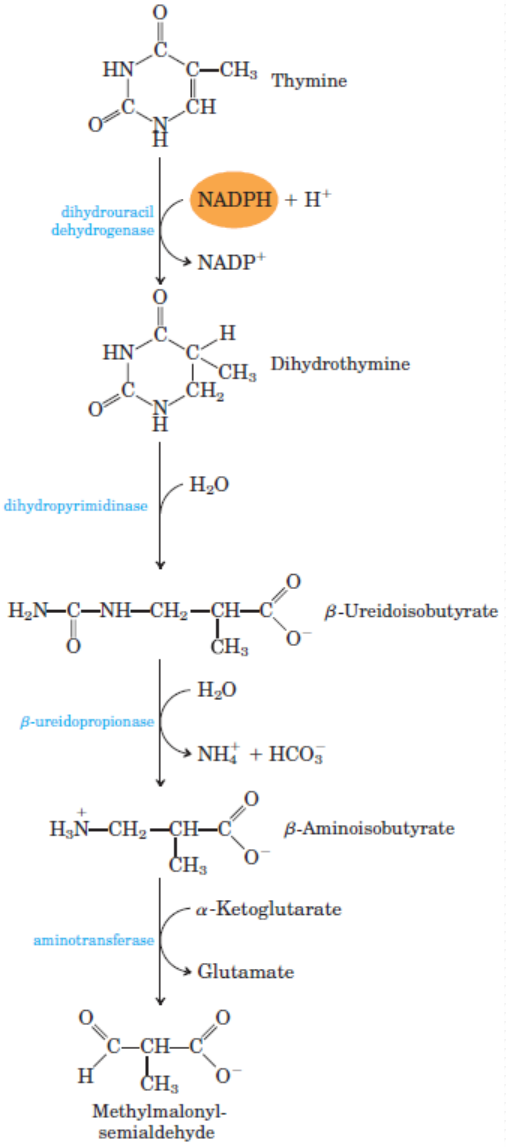
Nucleic Acid Metabolism

- Two types of pathways lead to nucleotides: the **de novo pathways** and the **salvage pathways.**
- De novo synthesis of nucleotides begins with their metabolic precursors: amino acids, ribose 5-phosphate, CO_2, and NH_3.
- Salvage pathways recycle the free bases and nucleosides released from nucleic acid breakdown.



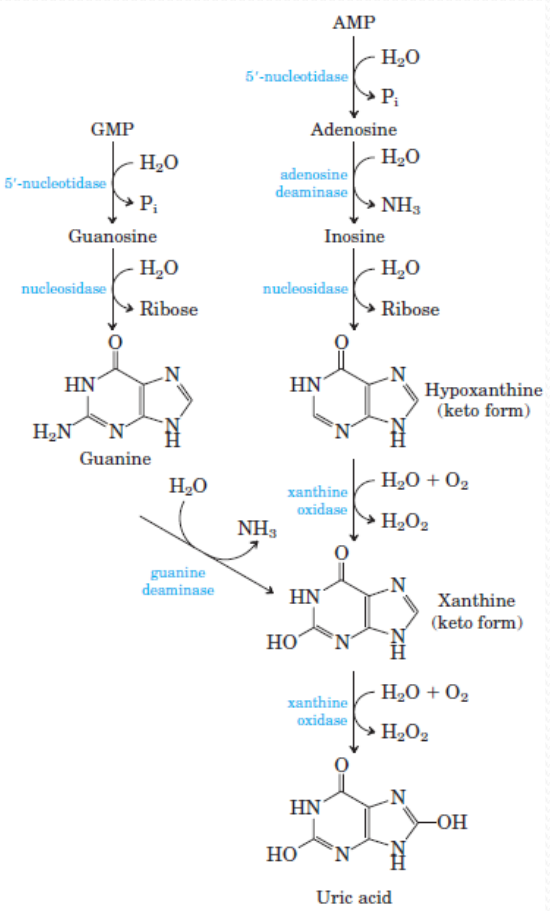
De novo Nucleic Acid Biosynthesis Pathway





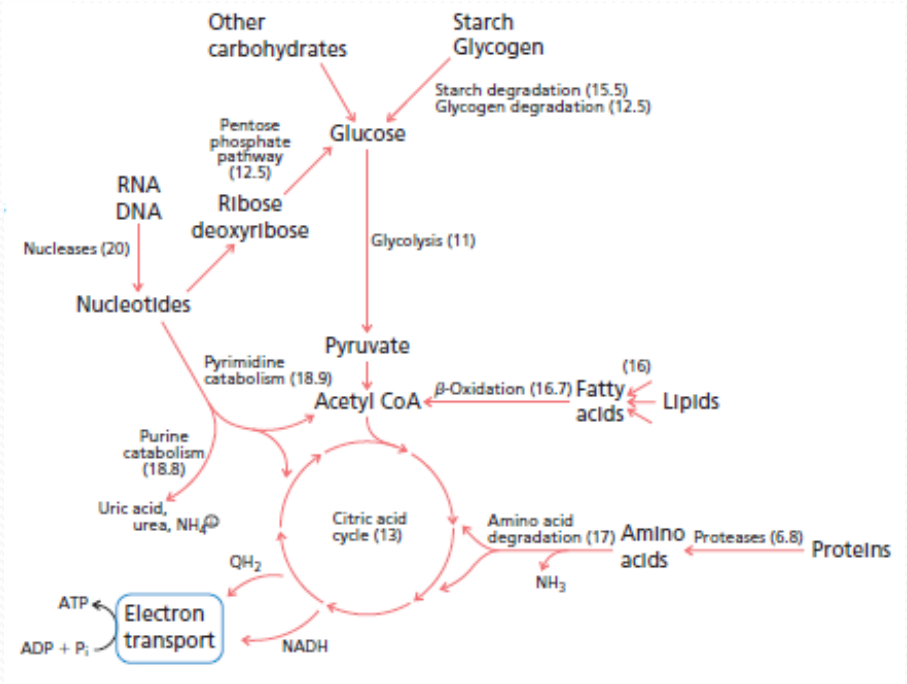
The pathways for degradation of pyrimidines generally lead to NH_4^+ production and thus to urea synthesis.

Purine nucleotides are degraded by a pathway in which uric acid is produced.

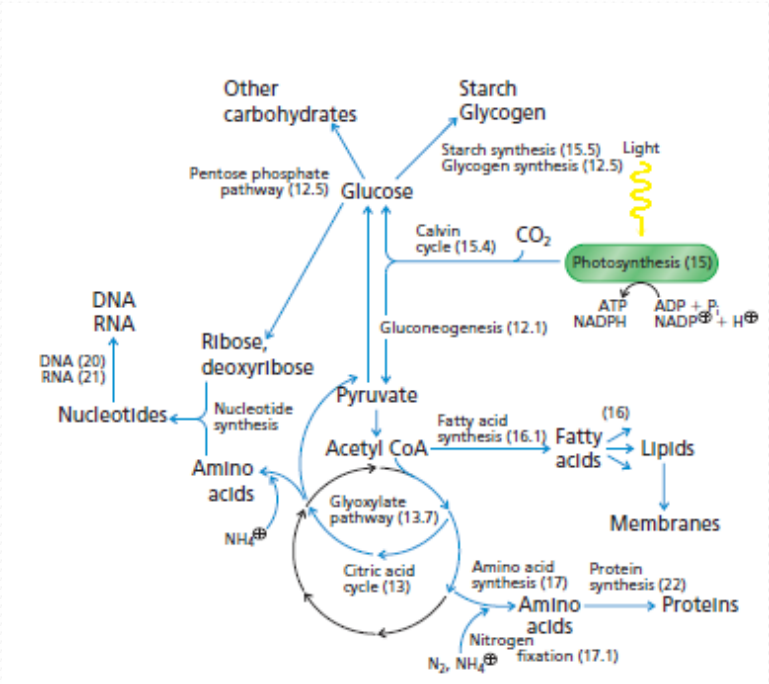


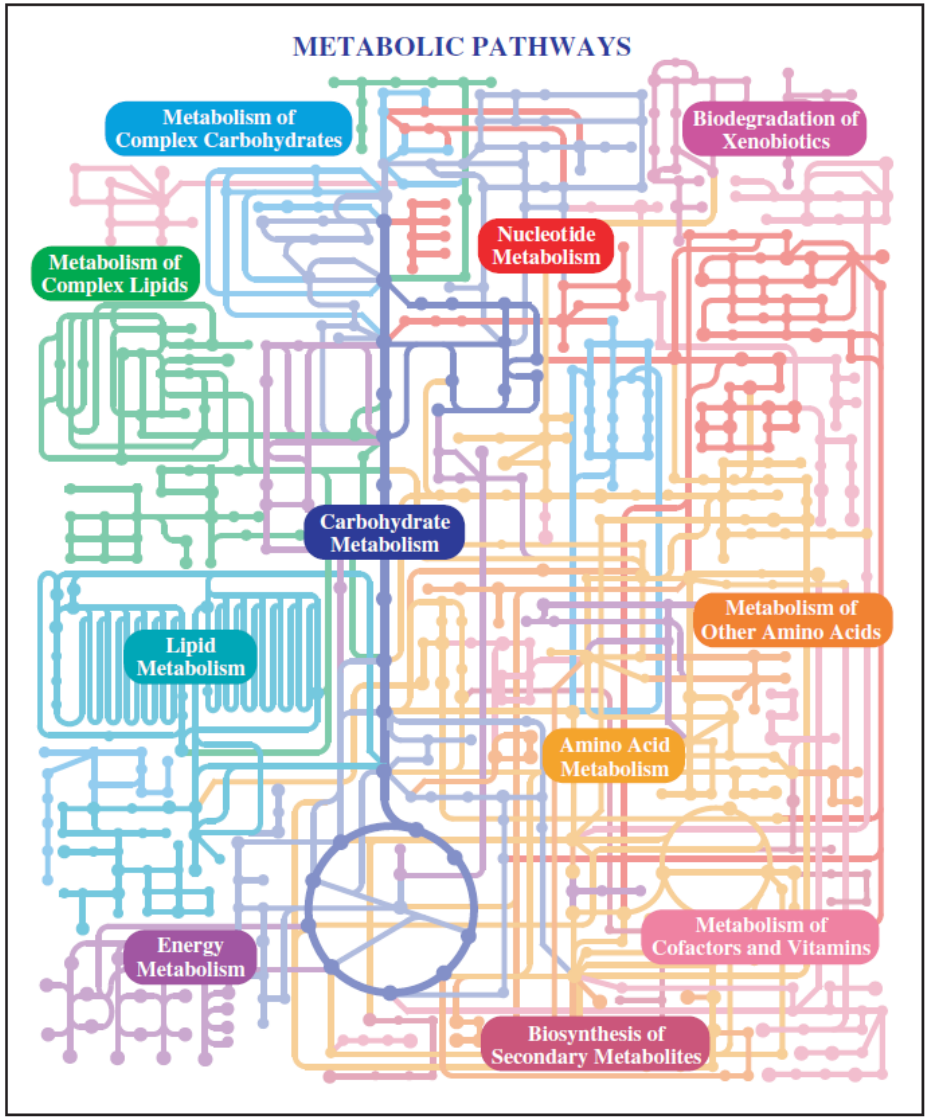
Major Pathways in Cells

Overview of Catabolic Pathways



Overview of Anabolic Pathways




METABOLIC PATHWAYS
Metabolism of Complex Carbohydrates
Biodegradation of Xenobiotics
Nucleotide Metabolism
Metabolism of Complex Lipids
Carbohydrate Metabolism
Metabolism of Other Amino Acids
Lipid Metabolism
Amino Acid Metabolism
Metabolism of Cofactors and Vitamins
Energy Metabolism
Biosynthesis of Secondary Metabolites