Chapter 68 + 69: Metabolism Part 1: Metabolism of carbohydrates and lipids and formation of adenosine triphosphate

Lec 03

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- A great proportion of the chemical reactions in the cells is concerned with making the energy in foods available to the various physiologic systems of the cell.
- For instance, energy is required for muscle activity, secretion by the glands, maintenance of membrane potentials by the nerve and muscle fibers, synthesis of substances in the cells, absorption of foods from gastrointestinal tract, and many other functions.

Coupled Reactions

- All the energy in foods- carbohydrates, fats and proteins can be oxidized in cells and during this process, large amounts of energy are released. These same foods in fact could also be burned with pure oxygen outside the body in an actual fire, also releasing large amounts of energy; in this case, however, the energy is released suddenly, all in the form of heat.
- The energy needed by the physiologic processes of cells is not heat but energy to cause mechanical movement, for example, as well as other processes.
- To provide this energy, the chemical reactions must be coupled with the systems responsible for these physiologic functions. This coupling is accomplished by special cellular enzyme and energy transfer systems.

Free Energy

- The amount of energy liberated by complete oxidation of a food is called the ***free energy*** of oxidation of the food, and this is generally represented by the symbol ΔG.
- Free energy is usually expressed in terms of *calories per mole* of substance. For instance, the amount of free energy liberated by complete oxidation of 1 mole (180 grams) of glucose is 686,000 calories.

Role of ATP in metabolism

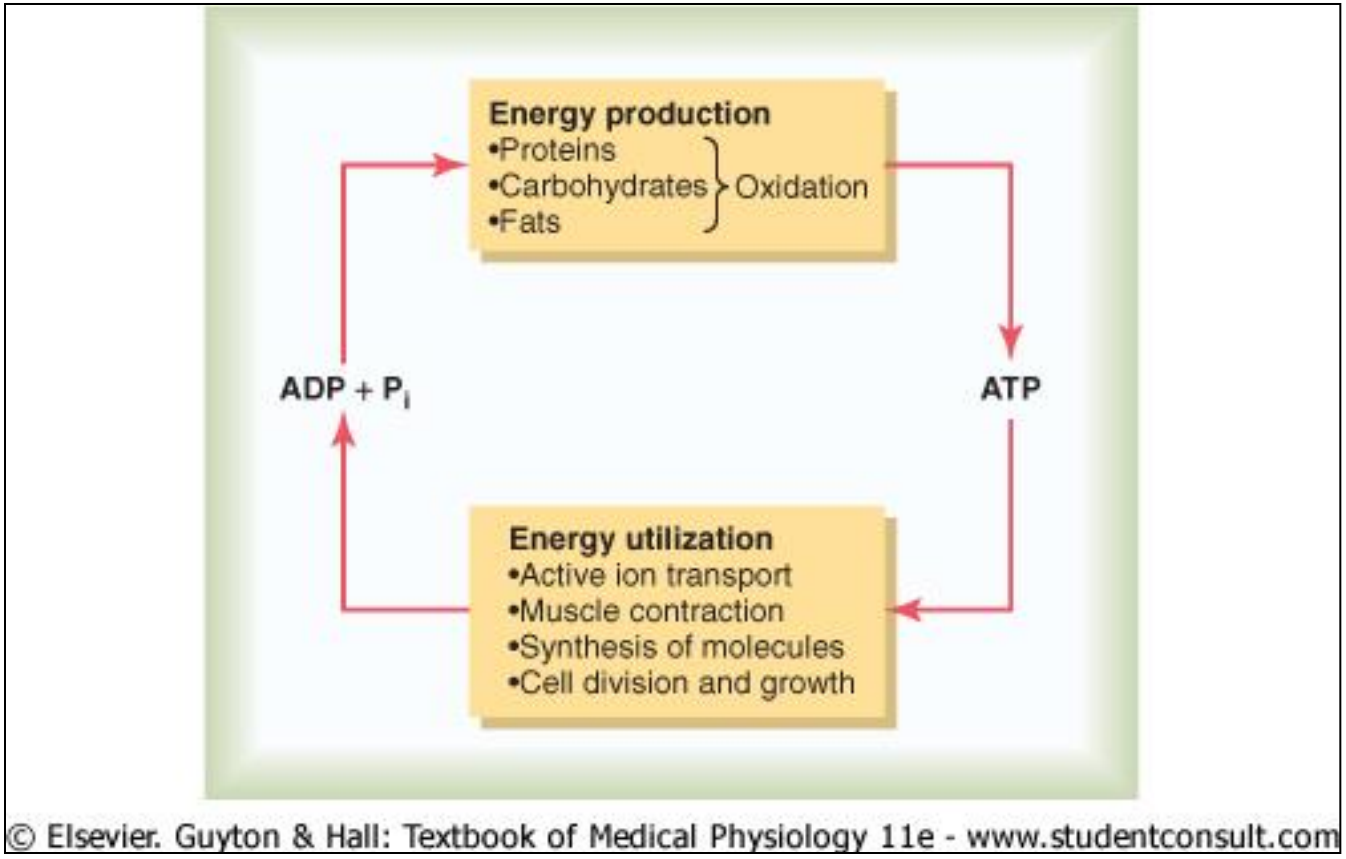


Figure 67-1 Adenosine triphosphate (ATP) as the central link between energy-producing and energy-utilizing systems of the body. ADP, adenosine diphosphate; Pi, inorganic phosphate. ATP is a labile chemical compound that is present in all cells

Central role of glucose in carbohydrate metabolism

- As explained in chapter 65, the final products of carbohydrate digestion in the alimentary tract are almost entirely glucose, fructose, and galactose- with glucose representing, on average, about 80 percent of these.
- After absorption from the intestinal tract, much of the fructose and almost all the galactose are rapidly converted into glucose in the liver. Therefore little fructose and galactose are present in the circulating blood.
- Glucose thus becomes the final common pathway for the transport of almost all carbohydrates to the tissue cells.

Central role of glucose in carbohydrate metabolism

- In liver cells, appropriate enzymes are available to promote interconversions among the monosaccharides- glucose, fructose, and galactose. Futhermore, the dynamics of the reactions are such that when the liver releases the monosaccharides back into the blood, the final product is almost entirely glucose.
- Usually more than 95 percent of all the monosaccharides that circulate in the blood are the final conversion product, glucose.

Transport of glucose through the cell membrane

- Before glucose can be used by the body's tissue cells, it must be transported through the tissue cell membrane into the cellular cytoplasm.
- However, glucose cannot easily diffuse through the pores of the cell membrane because the maximum molecular weight of particles that can diffuse readily is about 100, and glucose has a molecular weight of 180.
- Yet glucose does pass to the interior of the cells with a reasonable degree of freedom by the mechanism of *facilitated diffusion*. (discussed in chapter 4).

Transport of glucose through the cell membrane

- Penetrating through the lipid matrix of the cell membrane are large numbers of *protein carrier molecules that can bind with glucose*. In this bound form, the glucose can be transported by the carrier from one side of the membrane to the other side and then released.
- Thus if the concentration of glucose is greater on one side of the membrane than on the other side, more glucose will be transported from the high-concentration area to the low-concentration area than in the opposite direction.

Insulin increases facilitated diffusion of glucose

- The rate of glucose transport as well as transport of some other monosaccharides is greatly increased by insulin. When large amounts of insulin are secreted by the pancreas, the rate of glucose transport into most cells increases to 10 or more times the rate of transport when no insulin is secreted.
- Except for brain and liver, without insulin far too little glucose would enter the cell to support normal metabolism.
- In effect, the rate of carbohydrate utilization by most cells is controlled by the rate of insulin secretion from the pancreas.

Phosphorylation of Glucose

- In most tissues of the body, phosphorylation serves to capture the glucose in the cell.
- Phosphorylation is carried out by the enzymes gluco**kinase** or hexo**kinase**. The enzyme ***phosphatase*** can reverse the reaction.
- Glycogen is stored in liver and muscle: After absorption into a cell, glucose can be used immediately for release of energy to the cell, or it can be stored in the form of glycogen, which is a large polymer of glucose.
- All cells can store at least some glycogen, but liver and muscle have the greatest capability.
- ***Glycogenesis*** is the process of glycogen formation

Removal of stored glycogen- glycogenolysis= the breakdown of the cell's stored glycogen to re-form glucose in the cells

- Glycogenolysis occurs by splitting away each succeeding glucose molecule on each branch of the glycogen polymer by phosphorylation, catalyzed by the enzyme phosphorylase.
- In resting conditions, the phosphorylase is in an inactive form, so that glycogen will remain stored.
- *When it is necessary to reform glucose from glycogen, the phosphorylase must first be activated*. This can be accomplished in several ways, including the following two—

Activation of phosphorylase by epinephrine or by glucagon

- = two hormones that can activate phosphorylase and thereby cause rapid glycogenolysis.
- The initial effect of each of these hormones is to promote the formation of cyclic AMP in the cells, which then initiates a cascade of chemical reactions that activates the phosphorylase.
- Epinephrine is released by the adrenal medullae when the sympathetic nervous system is stimulated. This in effect prepares the body “for action”.
- Glucagon is a hormone secreted by the alpha cells of the pancreas when the blood glucose concentration falls too low. It stimulates cyclic AMP mainly in liver cells.

Release of energy from the glucose molecule by the glycolytic pathway

- Because complete oxidation of 1 mole of glucose releases 686,000 calories of energy and only 12,000 calories are required to form 1 mole of ATP, energy would be wasted if glucose were decomposed all at once into water and carbon dioxide while forming only a single ATP molecule.
- Fortunately, all cells of the body contain special protein enzymes that cause the glucose molecule to split a little at a time in many successive steps, so that its energy is released in small packets to form one molecule of ATP at a time, forming a total of 38 moles of ATP for each mole of glucose metabolized by the cells.

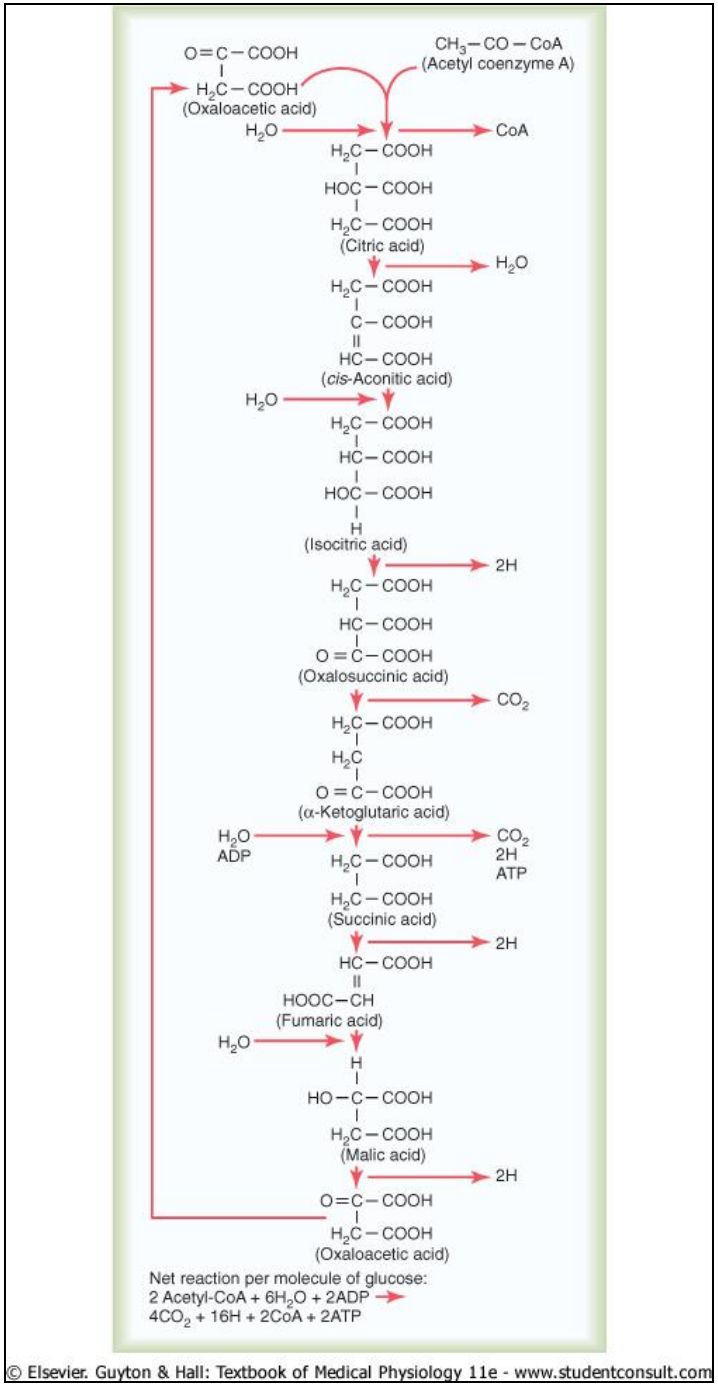
Glycolysis and the formation of pyruvic acid

- The most important means of releasing energy from the glucose molecule is initiated by glycolysis.
- The end products of glycolysis are then oxidized to provide energy. Glycolysis means splitting of the glucose molecule to form two molecules of pyruvic acid.
- Formation of ATP during glycolysis. The net gain of ATP molecules by the entire glycolytic process is only 2 moles of ATP for each mole of glucose utilized.

Glucose Metabolism-cont.

- Conversion of pyruvic acid to acetyl Coenzyme A. The 3-carbon pyruvic acid is converted into the two carbon Acetyl coenzyme A.
- Citric Acid cycle (Krebs Cycle). Figure 67-6. Occurs in the matrix of the mitochondria. Note that this metabolic cycle begins with oxaloacetic acid and ends with the same, thus the cycle can continue over and over again as long as sufficient metabolic components are available.
- Formation of ATP in the citric acid cycle. *Not a great amount of energy is released during the citric acid cycle itself:* only 2 ATPs per glucose.

Figure 67-6 Chemical reactions of the citric acid cycle, showing the release of carbon dioxide and a number of hydrogen atoms during the cycle.



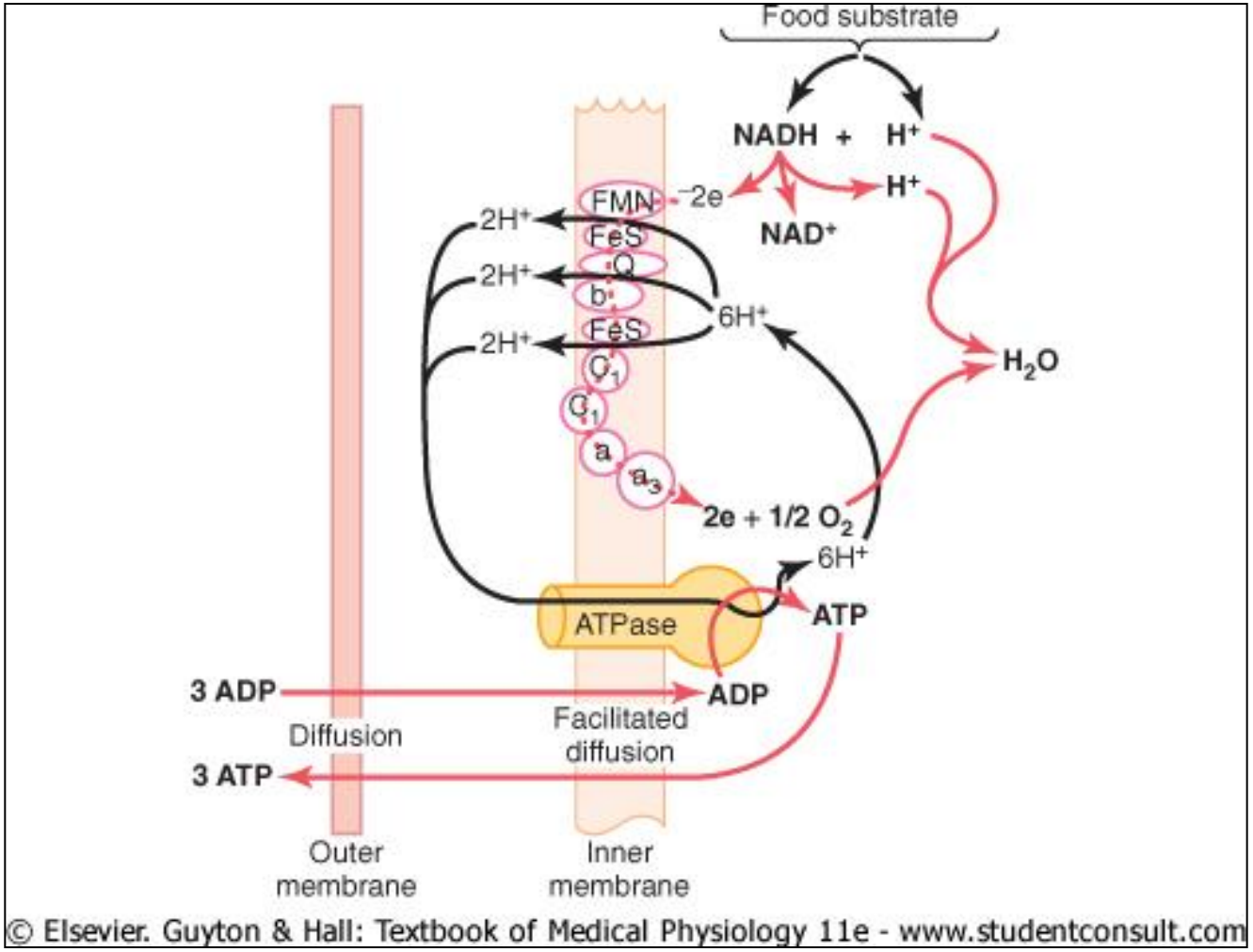
Glucose Metabolism-cont.

- Release of Hydrogen atoms in the citric acid cycle. A total of 24 hydrogen atoms are released for original molecule of glucose entering the cycle. However, these hydrogen atoms are not simply released- both free hydrogen and that bound by NAD+ subsequently enter into multiple oxidative chemical reactions that form tremendous quantities of ATP.
- Carbon dioxide formed in the Krebs cycle is dissolved in the body fluids and transported to the lungs, where it is expired from the body. (see chapter 40).

Formation of large quantities of ATP by oxidation of hydrogen (the process of oxidative phosphorylation).

- Almost 90 percent of the total ATP created through glucose metabolism is formed during ***subsequent oxidation of the hydrogen atoms*** that were released at early stages of glucose degradation.
- Oxidation of hydrogen is accomplished by a series of enzymatically catalyzed reactions in the mitochondria (Fig. 67-7).
- During this sequence of oxidative reactions, tremendous quantities of energy are released for ATP production. This occurs entirely in the mitochondria by a highly specialized process called the chemiosmotic mechanism.

Figure 67-7 Mitochondrial chemiosmotic mechanism of oxidative phosphorylation for forming large quantities of ATP. This figure shows the relationship of the oxidative and phosphorylation steps at the outer and inner membranes of the mitochondrion.



Chemiosmotic mechanism of the mitochondria to form ATP

- Ionization of hydrogen, the electron transport chain, and formation of water. Ionization of hydrogen from NADH also reconstitutes NAD+ that will be reused again and again.
- The electrons that are removed from the hydrogen atoms to cause the hydrogen ionization immediately enter the electron transport chain of electron acceptors that are an integral part of the inner membrane (the shelf membrane) of the mitochondria.
- The electron acceptors can be reversibly reduced or oxidized by accepting or giving up electrons. Important members of this electron transport chain include the cytochromes. Thus, as Fig. 67-7 shows, the ultimate fate of the electrons is their use by cytochrome oxidase to cause the formation of water molecules.

Pumping of hydrogen ions into the outer chamber of the mitochondrion, caused by the electron transport chain

- As the electrons pass through the electron transport chain large amounts of energy are released. This energy is used to pump hydrogen ions from the inner matrix of the mitochondria into the outer chamber between the inner and outer mitochondrial membranes (Fig. 67-7, left).
- This creates a high concentration of positively charged hydrogen ions in this chamber; it also creates a strong negative electrical potential in the inner matrix.

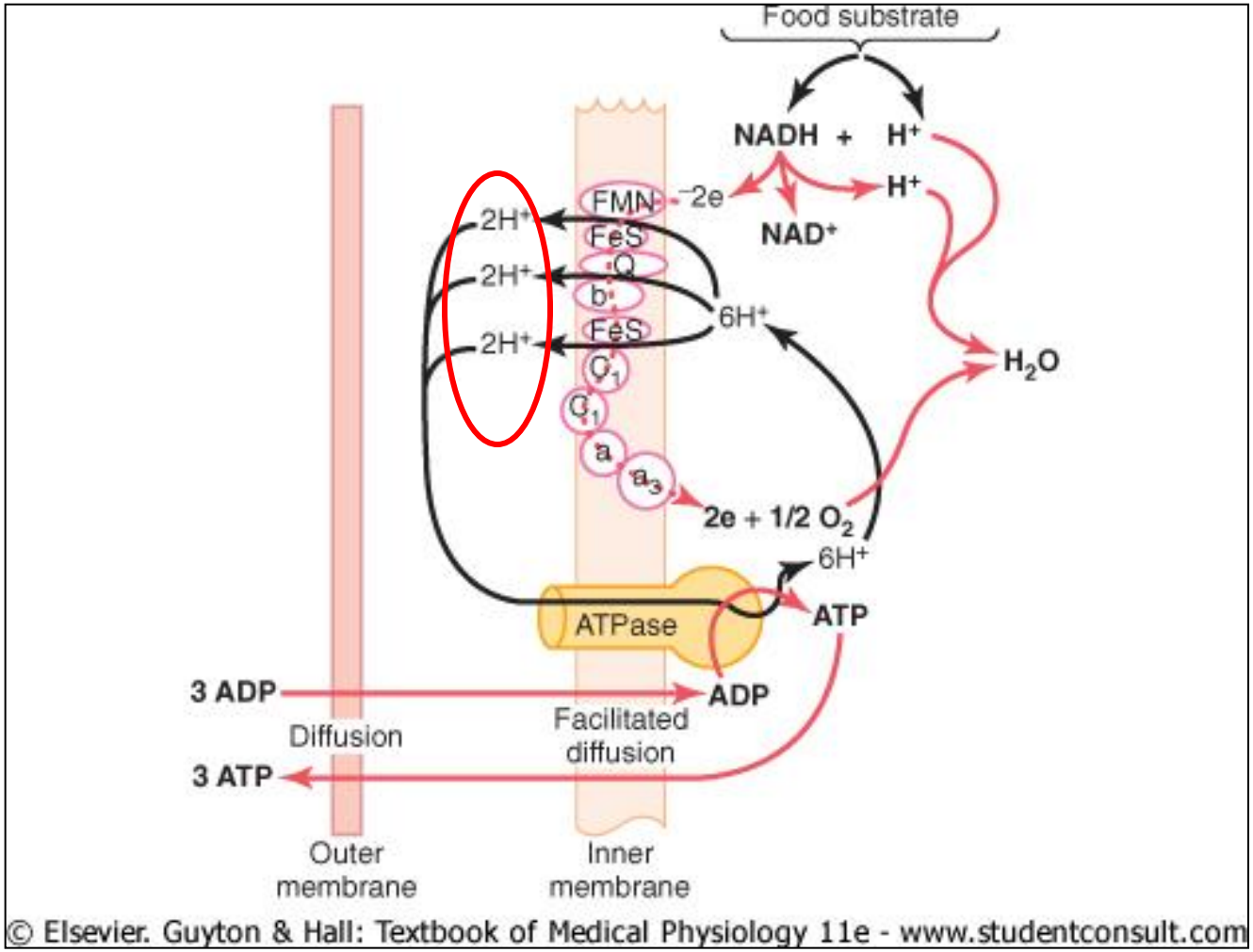
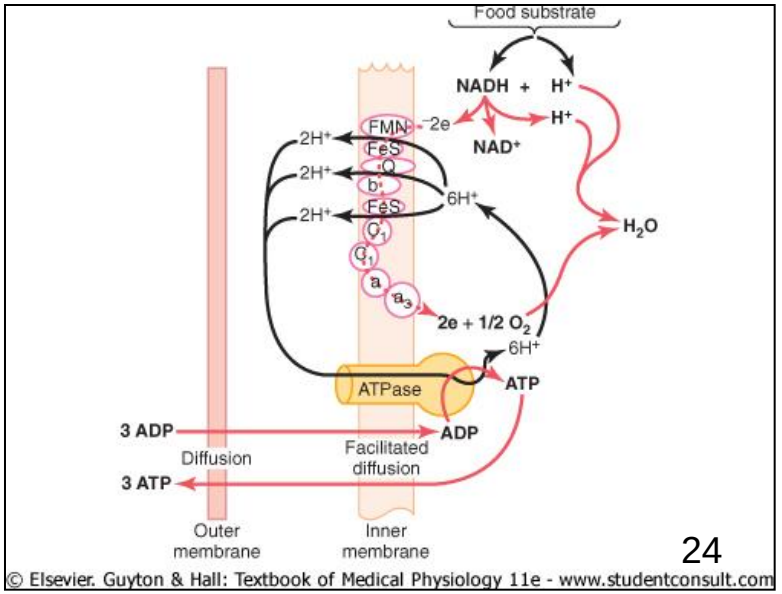


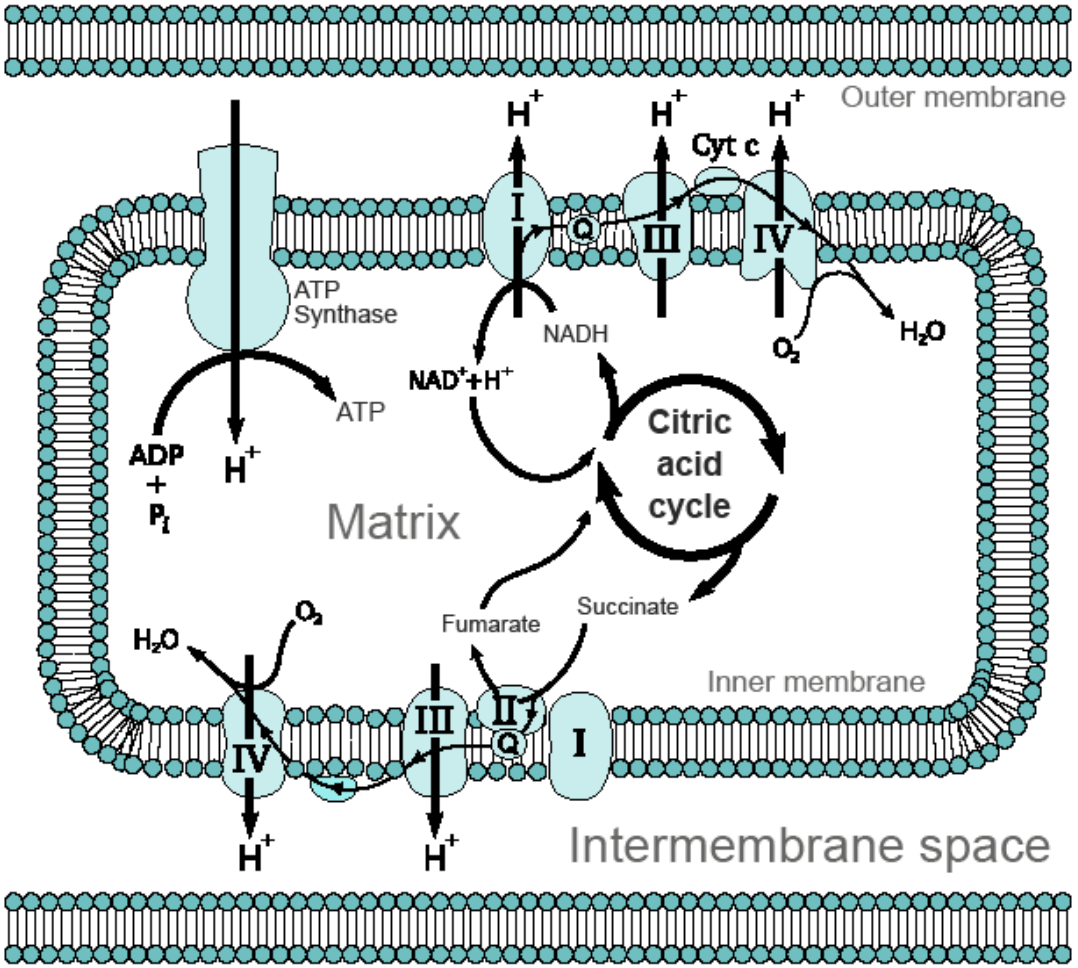
Figure 67-7 Mitochondrial chemiosmotic mechanism of oxidative phosphorylation for forming large quantities of ATP. This figure shows the relationship of the oxidative and phosphorylation steps at the outer and inner membranes of the mitochondrion.

Formation of ATP

- Formation of ATP from ADP occurs in conjunction with a large protein molecule which is an ATPase called ATP synthetase. The high concentration of positively charged hydrogen ions in the outer chamber and the large electrical potential difference across the inner membrane cause the hydrogen ions to flow into the inner mitochondrial matrix through the ATPase molecule.
- In doing so, energy derived from this hydrogen ion flow is used by ATPase to convert ADP into ATP by combining ADP with a free ionic phosphate radical (Pi), thus adding another high-energy phosphate bond to the molecule.
- Finally, ATP is transferred from the inside of the mitochondrion back to the cell cytoplasm. This occurs by facilitated diffusion outward through the inner membrane and then by simple diffusion through the permeable outer mitochondrial membrane. In turn, ADP is continually transferred in the other direction for continual conversion into ATP.



Formation of ATP-2



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Summary of ATP formation during the breakdown of glucose

- Glycolysis= two molecules of ATP
- For each turn of the citric acid cycle= 2 ATP
- Hydrogen ions from glycolysis and citric acid cycle make 30 ATP via oxidative phosphorylation
- 4 more hydrogen ions are released beyond the 1st stage shown in Fig. 67-7. = 4ATP.
- Total = maximum of 38 ATP molecules formed for each molecule of glucose degraded to carbon dioxide and water.

Control of energy release from stored glycogen when the body needs additional energy; effect of ATP and ADP cell concentrations in controlling the rate of glycolysis

- . One important way in which ATP helps control energy metabolism is to inhibit the enzyme ***phosphofructokinase***. Because this enzyme promotes one of the initial steps in glycolysis, the net effect of excess cellular ATP is to slow or even stop glycolysis, which in turn stops most carbohydrate metabolism **[+ or – feedback?]**. Conversely, ADP (and AMP as well), causes the opposite change in this enzyme, greatly increasing its activity **[+ or – feedback?]** .
- Another control linkage is the citrate ion formed in the citric acid cycle (***second metabolite in the cycle***). An excess of this ion also strongly inhibits phosphofructokinase, thus preventing the glycolytic process from getting ahead of the citric acid cycle's ability to use the pyruvic acid formed during glycolysis.
- A third way by which the ATP-ADP-AMP system controls carbohydrate metabolism is based on the fact that if all of the ADP in the cell has been already converted to ATP, additional ATP simply cannot be formed, at least not quickly.

Anaerobic release of energy- anaerobic glycolysis

- Occasionally oxygen becomes either unavailable or insufficient, so that oxidative phosphorylation cannot take place. This limits ATP production to glycolysis, which is extremely wasteful because only 2 ATPs are produced per molecule of glucose
- Formation of lactic acid during anaerobic glycolysis allows release of extra anaerobic energy. ***The law of mass action*** states that as the end products of a chemical reaction build up in a reacting medium, the rate of the reaction decreases, approaching zero.
- The two end products of the glycolytic reactions are pyruvic acid and hydrogen ions. The buildup of either or both of these would stop the glycolytic process and prevent further formation of ATP. When their quantities begin to be excessive, these two end products react with each other to form lactic acid, :
-
- Pyruvic acid + NADH + H+ (lactate dehydrogenase) $\rightleftharpoons$ lactic acid + NAD+

Anaerobic release of energy-anaerobic glycolysis-2

- ***Thus, under anaerobic conditions, the major portion of the pyruvic acid is converted into lactic acid***, which diffused out of the cells into the extracellular fluids and even into the intracellular fluids of other less active cells.
- Therefore, lactic acid represents a type of sinkhole, into which the glycolytic end products can disappear, thus allowing glycolysis to proceed far longer than would otherwise be possible. Lactic acid can then be converted back to pyruvic acid when oxygen becomes available again (why is this possible?).

- Use of lactic acid by the heart for energy. Heart muscle is especially capable of converting lactic acid to pyruvic acid and then using the pyruvic acid for energy. This occurs to a great extent during heavy exercise, when large amounts of lactic acid are released into the blood from the skeletal muscles.

Release of energy from glucose by the pentose phosphate pathway

- is an alternative pathway for energy metabolism when certain enzymatic abnormalities occur in cells. It can provide energy independently of all the enzymes of the citric acid cycle. Used in liver and fat cells.
- Use of hydrogen to synthesize fat. The hydrogen released during the pentose phosphate pathway does not combine with NAD+, but rather with NADP, which is similar, but has an extra phosphate radical, P.
- however, this difference is extremely significant, because only hydrogen bound with NADP+ in the form of NADPH can be used for the synthesis of fats from carbohydrates and for the synthesis of some other substances.

Glucose conversion to Glycogen or Fat

- When glucose is not immediately required for energy, the extra glucose that continually enters the cells is either stored as glycogen or converted into fat.

- Formation of carbohydrates from proteins and fats-gluconeogenesis. When the body's stores of carbohydrates decrease below normal, moderate quantities of glucose can be formed from amino acids and the glycerol portion of fat.
- This process is called *gluconeogenesis*, and helps keep a steady state of glucose available to the brain, for example between meals.

Gluconeogenesis-2

- About 60 percent of the amino acids in the body proteins can be converted easily into carbohydrates; the remaining 40 percent have chemical configurations that make this difficult or impossible.

- Regulation of gluconeogenesis. Diminished carbohydrates in the cells and decreased blood sugar are the basic stimuli that increase the rate of gluconeogenesis.
- Release of the hormone cortisol from the adrenal glands; this cortisol mobilizes proteins from essentially all cells of the body, making these available in the form of amino acids in the body fluids. These provide substrate for conversion to glucose in the liver.

- Blood glucose. The levels of glucose in the blood are regulated by the pancreatic hormones insulin and glucagon.

Lipid Metabolism

Several chemical compounds in food and in the body are classified as lipids. They include 1) neutral fat, also known as trigycerides; 2) phospholipids; 3) cholesterol; 4) a few other of less abundance.

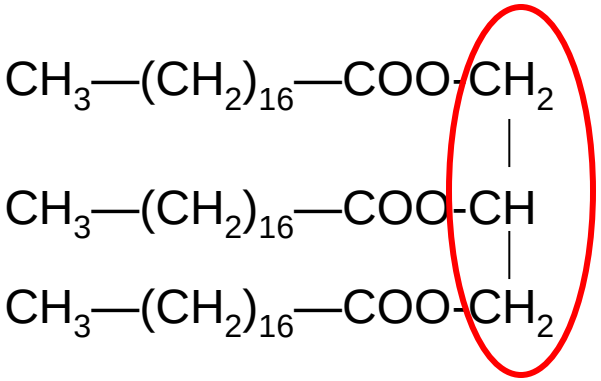
Chemically, the basic lipid moiety of the triglycerides and the phospholipids is fatty acids, which are simple long-chain hydrocarbon organic acids.

A typical fatty acid, palmitic acid, is the following: $CH_3(CH_2)_{14}COOH$. Although cholesterol does not contain fatty acid, its sterol nucleus is synthesized from portions of fatty acid molecules, thus giving it many of the physical and chemical properties of other lipid substances.

The triglycerides

- are used in the body mainly to provide energy for the different metabolic processes, a function they share almost equally with the carbohydrates.
- However, some lipids, especially cholesterol, the phospholipids, and small amounts of triglycerides, are used to form the membranes of all cells of the body and to perform other cellular functions.

Basic chemical structure of triglycerides (Neutral Fat).



- typical structure of the triglyceride molecule
- Note that 3 long-chain fatty acid molecules are bound with one molecule of glycerol.

Transport of Lipids in the Body Fluids

- Almost all the fats in the diet are absorbed from the intestines into the intestinal lymph.
- During digestion, most triglycerides are split into monoglycerides and fatty acids.
- Then, while passing through the intestinal epithelial cells, the monoglycerides and fatty acids are resynthesized into new molecules of triglycerides that enter the lymph as minute, dispersed droplets called chylomicrons, whose diameters are between 0.08 and 0.6 microns.

Removal of chylomicrons from the blood

- About 1 hour after a meal that contains large quantities of fat, the chylomicron concentration in the plasma may rise to 1 to 2 percent of the total plasma.
- However, the chylomicrons have a half-life of less than 1 hour, so the plasma is cleared again within a few hours. The fat of the chylomicrons is removed mainly in the following way.

- Chylomicron triglycerides are hydrolyzed by ***lipoprotein lipase***, and fat is stored in adipose tissue and liver cells.
- The fatty acids, being highly miscible with the membranes of the cells, immediately diffuse into the fat cells of the adipose tissue and into the liver cells.
- Once inside these cells, the fatty acids are again synthesized into triglycerides, with new glycerol being supplied by the metabolic processes of the storage cells.
- ***The lipase also causes hydrolysis of phospholipids***; this too, releases fatty acids to be stored in the cells in the same way.

Free fatty acids are transported in the blood in combination with albumin

- When fat that has been stored in the adipose tissue is to be used elsewhere in the body to provide energy, it must first be transported from the adipose tissue to the other tissue.
- It is transported mainly in the form of free fatty acids. This is achieved by hydrolysis of the triglycerides back into fatty acids and glycerol.

- On leaving fat cells, fatty acids ionize strongly in the plasma, and *the ionic portion combines immediately with albumin molecules of the plasma proteins.* Fatty acids bound in this manner are called **free fatty acids**.

Lipoproteins- their special function in transporting cholesterol and phospholipids

- In the postabsorptive state, after all the chylomicrons have been removed from the blood, more than 95 percent of all the lipids in the plasma are in the form of lipoprotein.
- These are small particles, much smaller than chylomicrons, but qualitatively similar in composition- containing triglycerides, cholesterol, phospholipids, and protein.
- Types of lipoproteins
- Aside from the chylomicrons, ***which are themselves very large lipoproteins***, there are four major types of lipoproteins, classified by their densities as measured by the ultracentrifuge:
- 1) very low density lipoproteins (VLDL); 2)intermediate density lipoproteins;
- 3)low density lipoproteins (**LDL**)- have a high concentration of cholesterol; 4) high-density lipoproteins (**HDL**)- high concentration of protein but lower cholesterol.

Formation and function of lipoproteins

- *Almost all the lipoproteins are formed in the liver*, which is also where most of the plasma cholesterol, phospholipids, and triglycerides are synthesized. The primary function of the lipoproteins is to transport their lipid components in the blood.
- Fat deposits/Adipose tissue
- Large quantities of fat are stored in two major tissues of the body, the adipose tissue and the liver. The adipose tissue is usually called fat deposits or simply tissue fat.
- The major function of adipose tissue is storage of triglycerides until they are needed to provide energy elsewhere in the body. A subsidiary function is to provide heat insulation for the body.

Fat cells (adipocytes).

- The fat cells (adipocytes) of adipose tissue are modified fibroblasts that store almost pure triglycerides in quantities as great as 80 to 95 percent of the entire cell volume. Triglycerides in the fat cells are usually in liquid form.
- When the tissues are exposed to prolonged cold, the fatty acid chains of the cell triglycerides, over a period of weeks, ***become either shorter or more unsaturated to decrease their melting point***, thereby always allowing the fat to remain in a liquid state.
- This is particularly important because only liquid fat can be hydrolyzed and transported from the cells.
- Fat cells can synthesize very small amounts of fatty acids and triglycerides from carbohydrates; this function supplements the synthesis of fat in the liver.

Exchange of fat between the adipose tissue and the blood- tissue lipases

- Large quantities of lipases are present in adipose tissue. Some of the enzymes catalyze the deposition of cell triglycerides from the chylomicrons and lipoproteins.
- Others, when activated by hormones, cause splitting of triglycerides of the fat cells to release free fatty acids.
- Because of the rapid exchange of fatty acids, the triglycerides in fat cells are renewed about once every 2 to 3 weeks, thus emphasizing *the dynamic state of storage fat*.

Liver lipids

- The principle functions of the liver in lipid metabolism are to 1) degrade fatty acids into small compounds that can be used for energy, 2) synthesize triglycerides mainly from carbohydrates, but to a lesser extent from proteins as well, 3) synthesize other lipids from fatty acids, especially cholesterol and phospholipids.
- Large quantities of triglycerides appear in the liver 1)during the early stages of starvation, 2) in diabetes, and 3) in any other condition in which fat instead of carbohydrates is being used for energy.
- In these conditions, large quantities of triglycerides are mobilized from the adipose tissue, transported as free fatty acids in the blood, and redeposited as triglycerides in the liver, where the initial stages of much of fat degradation begin.
- Thus, under normal physiologic conditions, the total amount of triglycerides in the liver is determined to a great extent by the overall rate at which lipids are being used for energy.

Liver Cells

- The liver cells, in addition to containing triglycerides, contain large quantities of phospholipids and cholesterol, which are continually synthesized by the liver.
- Also the liver cells are much more capable than other tissues of *desaturating* fatty acids, so that liver triglycerides normally are much more unsaturated than the triglycerides of adipose tissue.
- This capability of the liver to desaturate fatty acids is functionally important to all tissues of the body, because many structural elements of all cells contain reasonable quantities of unsaturated fats, and their principal source is the liver.

Use of triglycerides for energy: formation of adenosine triphosphate

- About 40 percent of the calories in a typical American diet are derived from fats, which is almost equal to the calories derived from carbohydrates.

- Hydrolysis of triglycerides.
- The first stage in using triglycerides for energy is their hydrolysis into fatty acids and glycerol. Then, both the fatty acids and the glycerol are transported in the blood to the active tissues, where they will be oxidized to give energy. Almost all cells- with the exception of the brain and red blood cells-can use fatty acids for energy.
- Glycerol, on entering the active tissue, is immediately changed by intracellular enzymes into glycerol-3-phosphate, which enters the glycolytic pathway for glucose breakdown and is thus used for energy. Before the fatty acids can be used for energy, they must be processed further in the following way.

Processing of fatty acids

- Entry of fatty acids into mitochondria. Degradation and oxidation of fatty acids occur only in the mitochondria. Therefore the first step for the use of fatty acids is their transport into the mitochondria.
- This is a carrier mediated process that uses carnitine as the carrier substance. Once inside the mitochondria, fatty acids split away from carnitine and are degraded and oxidized for energy formation.

- Degradation of fatty acids to acetyl coenzyme A by beta-oxidation.
- The fatty acid molecule is degraded in the mitochondria by progressive release of two-carbon segments in the form of acetyl coenzyme A (acetyl-CoA).

Oxidation of acetyl-CoA

- The acetyl-CoA molecules formed by beta-oxidation of fatty acids in the mitochondria enter immediately into the citric acid cycle, with the ultimate degradation to carbon dioxide and hydrogen.
- The hydrogen is subsequently oxidized by the chemiosmotic oxidative system of the mitochondria.
- Thus, after initial degradation of fatty acids to acetyl CoA, their final breakdown is precisely the same as that of the acetyl CoA formed from pyruvic acid during the metabolism of glucose.
- And the extra hydrogen atoms are also oxidized by the same chemiosmotic oxidative system of the mitochondria that is used in carbohydrate oxidation, liberating large amounts of ATP.

Shared Pathways

- So, we get energy from sugars and fats!
- (*and the common metabolite is?*)
- The end!