The Respiratory Chain & Oxidative Phosphorylation

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BIOMEDICAL IMPORTANCE

Aerobic organisms are able to capture a far greater proportion of the available free energy of respiratory substrates than anaerobic organisms. Most of this takes place inside mitochondria, which have been termed the "powerhouses" of the cell. Respiration is coupled to the generation of the high-energy intermediate, ATP, by **oxidative phosphorylation,** and the **chemiosmotic theory** offers insight into how this is accomplished. A number of drugs (eg, **amobarbital**) and poisons (eg, **cyanide, carbon monoxide**) inhibit oxidative phosphorylation, usually with fatal consequences. Several inherited defects of mitochondria involving components of the respiratory chain and oxidative phosphorylation have been reported. Patients present with **myopathy** and **encephalopathy** and often have **lactic acidosis.**

SPECIFIC ENZYMES ACT AS MARKERS OF COMPARTMENTS SEPARATED BY THE MITOCHONDRIAL MEMBRANES

Mitochondria have an **outer membrane** that is permeable to most metabolites, an **inner membrane** that is selectively permeable, and a **matrix** within (Figure 12–1). The outer membrane is characterized by the presence of various enzymes, including acyl-CoA synthetase and glycerolphosphate acyltransferase. Adenylyl kinase and creatine kinase are found in the intermembrane space. The phospholipid cardiolipin is concentrated in the inner membrane together with the enzymes of the respiratory chain.

THE RESPIRATORY CHAIN COLLECTS & OXIDIZES REDUCING EQUIVALENTS

Most of the energy liberated during the oxidation of carbohydrate, fatty acids, and amino acids is made available within mitochondria as reducing equivalents (—H or electrons) (Figure 12–2). Mitochondria contain the **respiratory chain,** which collects and transports reducing equivalents directing them to their final reaction with oxygen to form water, the machinery for trapping the liberated free energy as high-energy phosphate, and the enzymes of β-oxidation and of the citric acid cycle (Chapters 22 and 16) that produce most of the reducing equivalents.

Components of the Respiratory Chain Are Arranged in Order of Increasing Redox Potential

Hydrogen and electrons flow through the respiratory chain (Figure 12–3) through a redox span of 1.1 V from NAD^+/NADH to $O_2/2H_2O$ (Table 11–1). The respiratory chain consists of a number of redox carriers that proceed from the NAD-linked dehydrogenase systems, through flavoproteins and cytochromes, to molecular oxygen. Not all substrates are linked to the respiratory chain through NAD-specific dehydrogenases; some, because their redox potentials are more positive (eg, fumarate/succinate; Table 11–1), are linked directly to flavoprotein dehydrogenases, which in turn are linked to the cytochromes of the respiratory chain (Figure 12–4).

Ubiquinone or Q (coenzyme Q) (Figure 12–5) links the flavoproteins to cytochrome *b*, the member of the cytochrome chain of lowest redox potential. Q exists in the oxidized quinone or reduced quinol form under aerobic or anaerobic conditions, respectively. The structure of Q is very similar to that of vitamin K and vitamin E (Chapter 45) and of plastoquinone, found in chloroplasts. Q acts as a mobile component of the respiratory chain that collects reducing equivalents from the more fixed flavoprotein complexes and passes them on to the cytochromes.

An additional component is the **iron-sulfur protein** (**FeS;** nonheme iron) (Figure 12–6). It is associated with the flavoproteins (metalloflavoproteins) and with cytochrome *b*. The sulfur and iron are thought to take part in the oxidoreduction mechanism between flavin and Q, which involves only a single e^- change, the iron atom undergoing oxidoreduction between Fe^{2+} and Fe^{3+}.

Pyruvate and α-ketoglutarate dehydrogenase have complex systems involving lipoate and FAD prior to the passage of electrons to NAD, while electron trans-

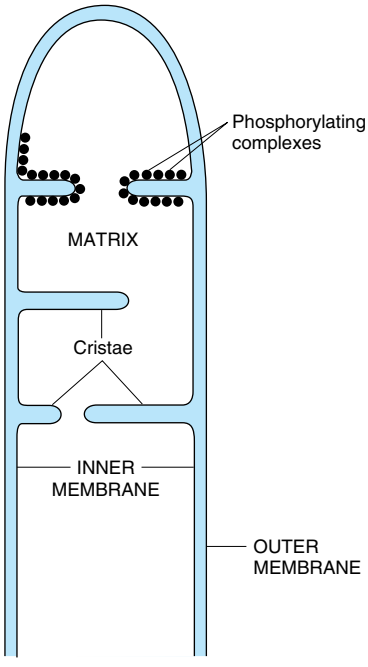

Figure 12–1. Structure of the mitochondrial membranes. Note that the inner membrane contains many folds, or cristae.

fers from other dehydrogenases, eg, L(+)-3-hydroxyacyl-CoA dehydrogenase, couple directly with NAD.

The reduced NADH of the respiratory chain is in turn oxidized by a metalloflavoprotein enzyme—**NADH dehydrogenase.** This enzyme contains FeS and FMN, is tightly bound to the respiratory chain, and passes reducing equivalents on to Q.

Electrons flow from Q through the series of cytochromes in order of increasing redox potential to molecular oxygen (Figure 12–4). The terminal cytochrome aa_3 (cytochrome oxidase), responsible for the final combination of reducing equivalents with molecular oxygen, has a very high affinity for oxygen, allowing the respiratory chain to function at maximum rate until the tissue has become depleted of O_2. Since this is an irreversible reaction (the only one in the chain), it gives direction to the movement of reducing equivalents and to the production of ATP, to which it is coupled.

Functionally and structurally, the components of the respiratory chain are present in the inner mitochondrial membrane as four **protein-lipid respiratory chain complexes** that span the membrane. Cytochrome *c* is the only soluble cytochrome and, together with Q, seems to be a more mobile component of the respiratory chain connecting the fixed complexes (Figures 12–7 and 12–8).

THE RESPIRATORY CHAIN PROVIDES MOST OF THE ENERGY CAPTURED DURING CATABOLISM

ADP captures, in the form of high-energy phosphate, a significant proportion of the free energy released by catabolic processes. The resulting ATP has been called the energy "currency" of the cell because it passes on this free energy to drive those processes requiring energy (Figure 10–6).

There is a net direct capture of two high-energy phosphate groups in the glycolytic reactions (Table 17–1), equivalent to approximately 103.2 kJ/mol of glucose. (In vivo, ΔG for the synthesis of ATP from ADP has been calculated as approximately 51.6 kJ/mol. (It is greater than $\Delta G^{0'}$ for the hydrolysis of ATP as given in Table 10–1, which is obtained under standard

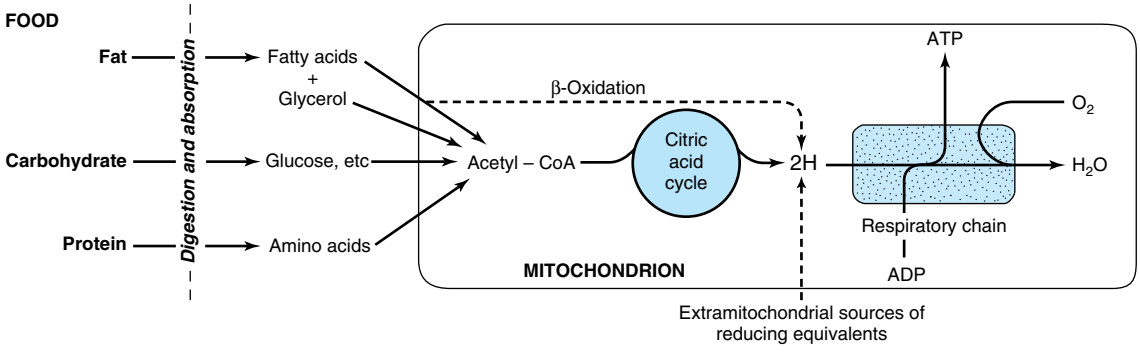

Figure 12–2. Role of the respiratory chain of mitochondria in the conversion of food energy to ATP. Oxidation of the major foodstuffs leads to the generation of reducing equivalents (2H) that are collected by the respiratory chain for oxidation and coupled generation of ATP.

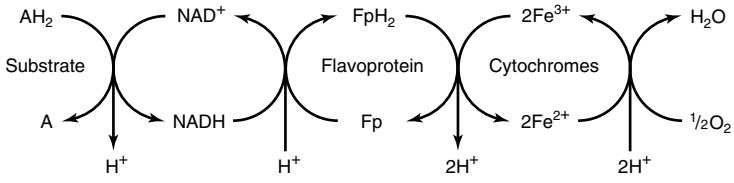

Figure 12–3. Transport of reducing equivalents through the respiratory chain.

concentrations of 1.0 mol/L.) Since 1 mol of glucose yields approximately 2870 kJ on complete combustion, the energy captured by phosphorylation in glycolysis is small. Two more high-energy phosphates per mole of glucose are captured in the citric acid cycle during the conversion of succinyl CoA to succinate. All of these phosphorylations occur at the **substrate level.** When substrates are oxidized via an NAD-linked dehydrogenase and the respiratory chain, approximately 3 mol of inorganic phosphate are incorporated into 3 mol of ADP to form 3 mol of ATP per half mol of O_2 consumed; ie, the P:O ratio = 3 (Figure 12–7). On the other hand, when a substrate is oxidized via a flavoprotein-linked dehydrogenase, only 2 mol of ATP are formed; ie, P:O = 2. These reactions are known as **oxidative phosphorylation at the respiratory chain level.** Such dehydrogenations plus phosphorylations at the substrate level can now account for 68% of the free energy resulting from the combustion of glucose, captured in the form of high-energy phosphate. It is evident that the respiratory chain is responsible for a large proportion of total ATP formation.

Respiratory Control Ensures a Constant Supply of ATP

The rate of respiration of mitochondria can be controlled by the availability of ADP. This is because oxidation and phosphorylation are tightly coupled; ie, oxidation cannot proceed via the respiratory chain without concomitant phosphorylation of ADP. Table 12–1 shows the five conditions controlling the rate of respiration in mitochondria. Most cells in the resting state are in state 4, and respiration is controlled by the availability of ADP. When work is performed, ATP is converted to ADP, allowing more respiration to occur, which in turn replenishes the store of ATP. Under certain conditions, the concentration of inorganic phosphate can also affect the rate of functioning of the respiratory chain. As respiration increases (as in exercise),

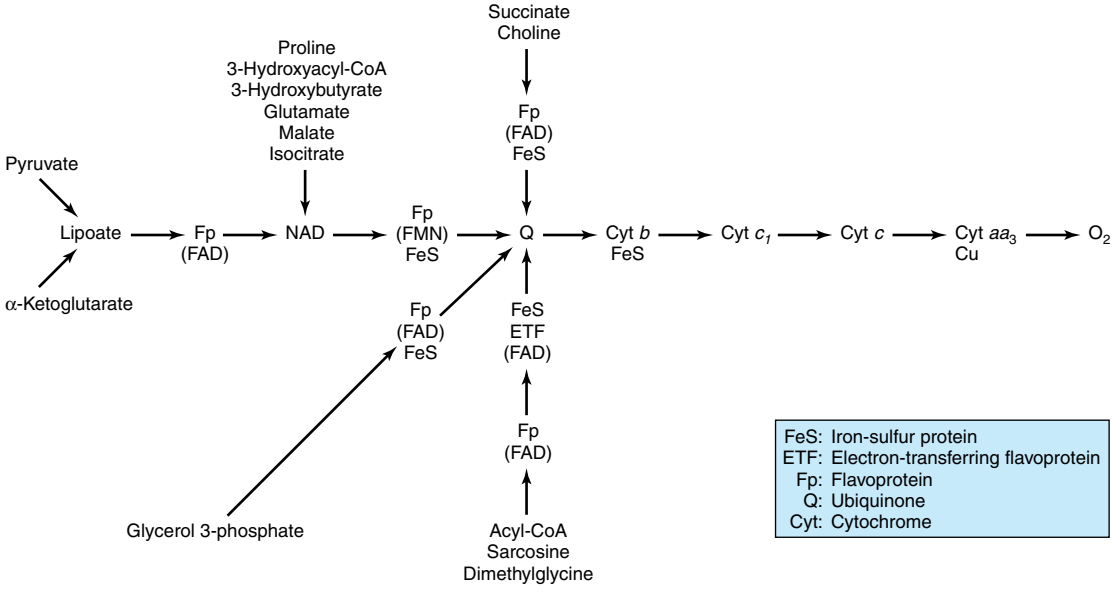

Figure 12–4. Components of the respiratory chain in mitochondria, showing the collecting points for reducing equivalents from important substrates. FeS occurs in the sequences on the O_2 side of Fp or Cyt *b*.

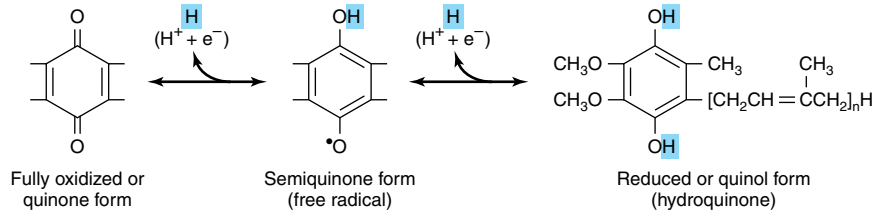

Figure 12–5. Structure of ubiquinone (Q). n = Number of isoprenoid units, which is 10 in higher animals, ie, Q_{10}.

the cell approaches state 3 or state 5 when either the capacity of the respiratory chain becomes saturated or the P_{O_2} decreases below the K_m for cytochrome a_3. There is also the possibility that the ADP/ATP transporter (Figure 12–9), which facilitates entry of cytosolic ADP into and ATP out of the mitochondrion, becomes rate-limiting.

Thus, the manner in which biologic oxidative processes allow the free energy resulting from the oxidation of foodstuffs to become available and to be captured is stepwise, efficient (approximately 68%), and controlled—rather than explosive, inefficient, and uncontrolled, as in many nonbiologic processes. The remaining free energy that is not captured as high-energy phosphate is liberated as **heat.** This need not be considered "wasted," since it ensures that the respiratory system as a whole is sufficiently exergonic to be removed from equilibrium, allowing continuous unidirectional flow and constant provision of ATP. It also contributes to maintenance of body temperature.

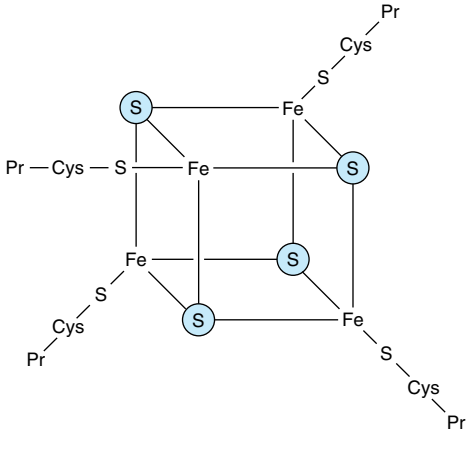

Figure 12–6. Iron-sulfur-protein complex (Fe_4S_4). Ⓢ, acid-labile sulfur; Pr, apoprotein; Cys, cysteine residue. Some iron-sulfur proteins contain two iron atoms and two sulfur atoms (Fe_2S_2).

MANY POISONS INHIBIT THE RESPIRATORY CHAIN

Much information about the respiratory chain has been obtained by the use of inhibitors, and, conversely, this has provided knowledge about the mechanism of action of several poisons (Figure 12–7). They may be classified as inhibitors of the respiratory chain, inhibitors of oxidative phosphorylation, and uncouplers of oxidative phosphorylation.

Barbiturates such as amobarbital inhibit NAD-linked dehydrogenases by blocking the transfer from FeS to Q. At sufficient dosage, they are fatal in vivo. **Antimycin A** and **dimercaprol** inhibit the respiratory chain between cytochrome *b* and cytochrome *c*. The classic poisons **H_2S**, **carbon monoxide,** and **cyanide** inhibit cytochrome oxidase and can therefore totally arrest respiration. **Malonate** is a competitive inhibitor of succinate dehydrogenase.

Atractyloside inhibits oxidative phosphorylation by inhibiting the transporter of ADP into and ATP out of the mitochondrion (Figure 12–10).

The action of **uncouplers** is to dissociate oxidation in the respiratory chain from phosphorylation. These compounds are toxic in vivo, causing respiration to become uncontrolled, since the rate is no longer limited by the concentration of ADP or P_i. The uncoupler that has been used most frequently is **2,4-dinitrophenol,** but other compounds act in a similar manner. The antibiotic **oligomycin** completely blocks oxidation and phosphorylation by acting on a step in phosphorylation (Figures 12–7 and 12–8).

THE CHEMIOSMOTIC THEORY EXPLAINS THE MECHANISM OF OXIDATIVE PHOSPHORYLATION

Mitchell's chemiosmotic theory postulates that the energy from oxidation of components in the respiratory chain is coupled to the translocation of hydrogen ions (protons, H^+) from the inside to the outside of the inner mitochondrial membrane. The electrochemical potential difference resulting from the asymmetric dis-

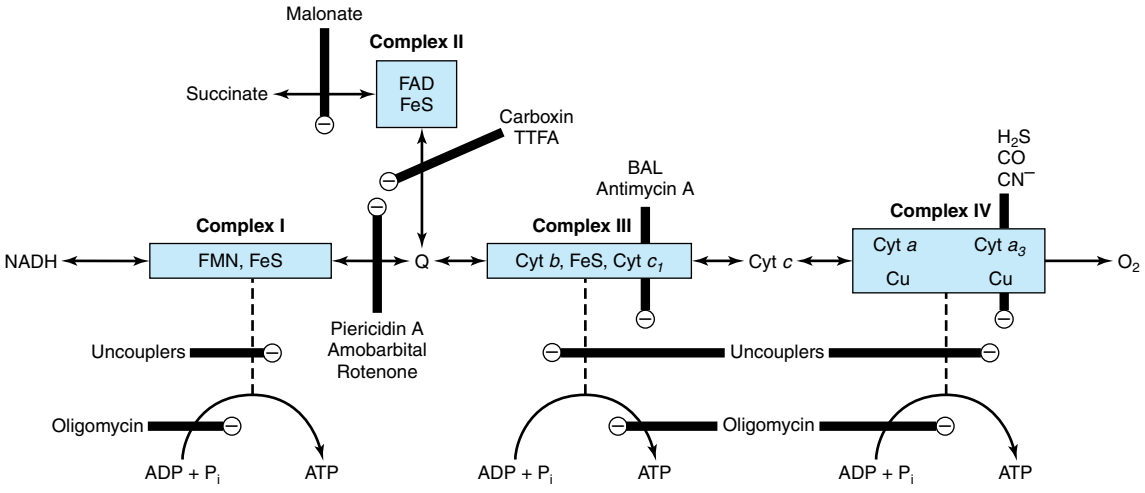

Figure 12–7. Proposed sites of inhibition (⊖) of the respiratory chain by specific drugs, chemicals, and antibiotics. The sites that appear to support phosphorylation are indicated. BAL, dimercaprol. TTFA, an Fe-chelating agent. Complex I, NADH:ubiquinone oxidoreductase; complex II, succinate:ubiquinone oxidoreductase; complex III, ubiquinol:ferricytochrome c oxidoreductase; complex IV, ferrocytochrome c:oxygen oxidoreductase. Other abbreviations as in Figure 12–4.

tribution of the hydrogen ions is used to drive the mechanism responsible for the formation of ATP (Figure 12–8).

The Respiratory Chain Is a Proton Pump

Each of the respiratory chain complexes I, III, and IV (Figures 12–7 and 12–8) acts as a **proton pump.** The inner membrane is impermeable to ions in general but particularly to protons, which accumulate outside the membrane, creating an **electrochemical potential difference** across the membrane ($\Delta\mu_{H^+}$).This consists of a chemical potential (difference in pH) and an electrical potential.

A Membrane-Located ATP Synthase Functions as a Rotary Motor to Form ATP

The electrochemical potential difference is used to drive a membrane-located **ATP synthase** which in the presence of P_i + ADP forms ATP (Figure 12–8). Scattered over the surface of the inner membrane are the phosphorylating complexes, ATP synthase, responsible for the production of ATP (Figure 12–1). These consist of several protein subunits, collectively known as F_1, which project into the matrix and which contain the phosphorylation mechanism (Figure 12–8). These subunits are attached to a membrane protein complex known as F_0, which also consists of several protein subunits. F_0 spans the membrane and forms the proton channel. The flow of protons through F_0 causes it to rotate, driving the production of ATP in the F_1 complex (Figure 12–9). Estimates suggest that for each NADH oxidized, complex I translocates four protons and complexes III and IV translocate 6 between them. As four protons are taken into the mitochondrion for each ATP exported, the P:O ratio would not necessarily be a complete integer, ie, 3, but possibly 2.5. However, for simplicity, a value of 3 for the oxidation of NADH + H^+ and 2 for the oxidation of $FADH_2$ will continue to be used throughout this text.

Experimental Findings Support the Chemiosmotic Theory

(1) Addition of protons (acid) to the external medium of intact mitochondria leads to the generation of ATP.

(2) Oxidative phosphorylation does not occur in soluble systems where there is no possibility of a vectorial ATP synthase. A closed membrane must be present in order to achieve oxidative phosphorylation (Figure 12–8).

(3) The respiratory chain contains components organized in a sided manner (transverse asymmetry) as required by the chemiosmotic theory.

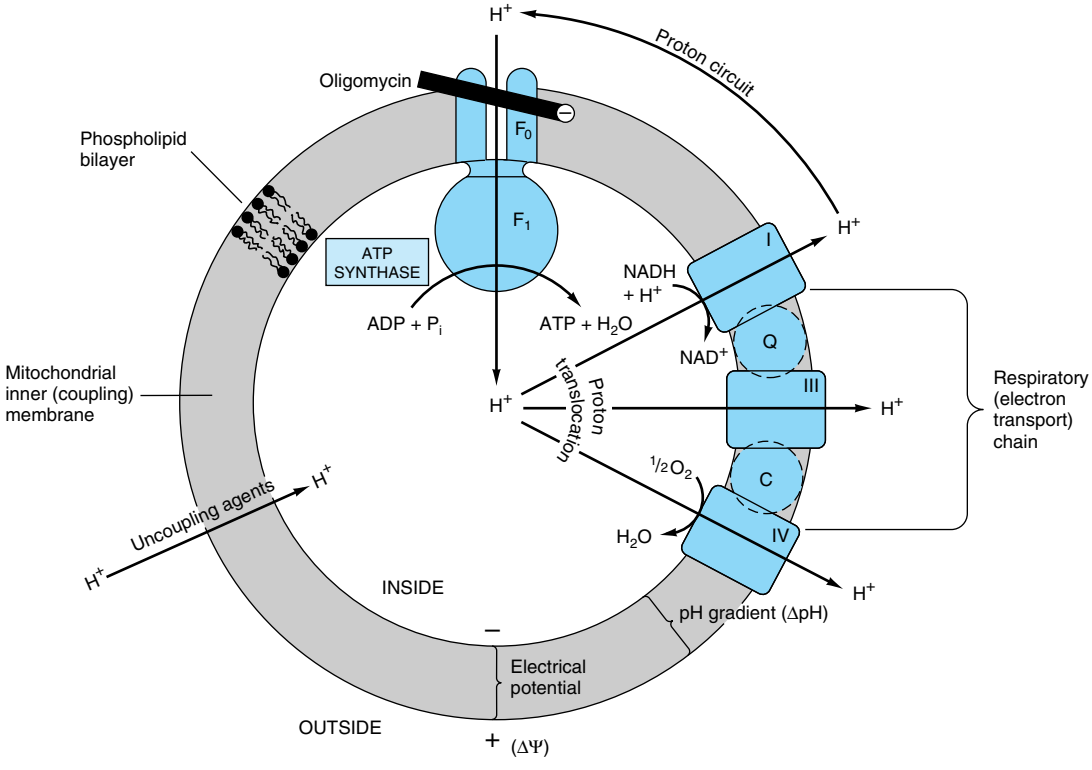

Figure 12–8. Principles of the chemiosmotic theory of oxidative phosphorylation. The main proton circuit is created by the coupling of oxidation in the respiratory chain to proton translocation from the inside to the outside of the membrane, driven by the respiratory chain complexes I, III, and IV, each of which acts as a *proton pump.* Q, ubiquinone; C, cytochrome c; F_1, F_0, protein subunits which utilize energy from the proton gradient to promote phosphorylation. Uncoupling agents such as dinitrophenol allow leakage of H^+ across the membrane, thus collapsing the electrochemical proton gradient. Oligomycin specifically blocks conduction of H^+ through F_0.

The Chemiosmotic Theory Can Account for Respiratory Control and the Action of Uncouplers

The electrochemical potential difference across the membrane, once established as a result of proton translocation, inhibits further transport of reducing equivalents through the respiratory chain unless discharged by back-translocation of protons across the membrane through the vectorial ATP synthase. This in turn depends on availability of ADP and P_i.

Uncouplers (eg, dinitrophenol) are amphipathic (Chapter 14) and increase the permeability of the lipoid inner mitochondrial membrane to protons (Figure 12–8), thus reducing the electrochemical potential and short-circuiting the ATP synthase. In this way, oxidation can proceed without phosphorylation.

Table 12–1. States of respiratory control.

	Conditions Limiting the Rate of Respiration
State 1	Availability of ADP and substrate
State 2	Availability of substrate only
State 3	The capacity of the respiratory chain itself, when all substrates and components are present in saturating amounts
State 4	Availability of ADP only
State 5	Availability of oxygen only

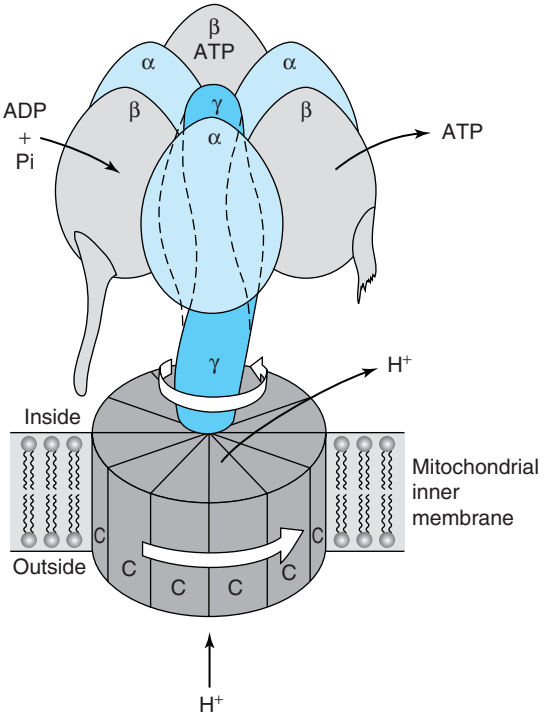

Figure 12–9. Mechanism of ATP production by ATP synthase. The enzyme complex consists of an F_0 subcomplex which is a disk of "C" protein subunits. Attached is a γ-subunit in the form of a "bent axle." Protons passing through the disk of "C" units cause it and the attached γ-subunit to rotate. The γ-subunit fits inside the F_1 subcomplex of three α- and three β-subunits, which are fixed to the membrane and do not rotate. ADP and P_i are taken up sequentially by the β-subunits to form ATP, which is expelled as the rotating γ-subunit squeezes each β-subunit in turn. Thus, three ATP molecules are generated per revolution. For clarity, not all the subunits that have been identified are shown—eg, the "axle" also contains an ε-subunit.

THE RELATIVE IMPERMEABILITY OF THE INNER MITOCHONDRIAL MEMBRANE NECESSITATES EXCHANGE TRANSPORTERS

Exchange diffusion systems are present in the membrane for exchange of anions against OH^- ions and cations against H^+ ions. Such systems are necessary for uptake and output of ionized metabolites while preserving electrical and osmotic equilibrium. The inner bilipoid mitochondrial membrane is freely permeable to uncharged small molecules, such as oxygen, water, CO_2, and NH_3, and to monocarboxylic acids, such as 3-hydroxybutyric, acetoacetic, and acetic. Long-chain fatty acids are transported into mitochondria via the carnitine system (Figure 22–1), and there is also a special carrier for pyruvate involving a symport that utilizes the H^+ gradient from outside to inside the mitochondrion (Figure 12–10). However, dicarboxylate and tri-

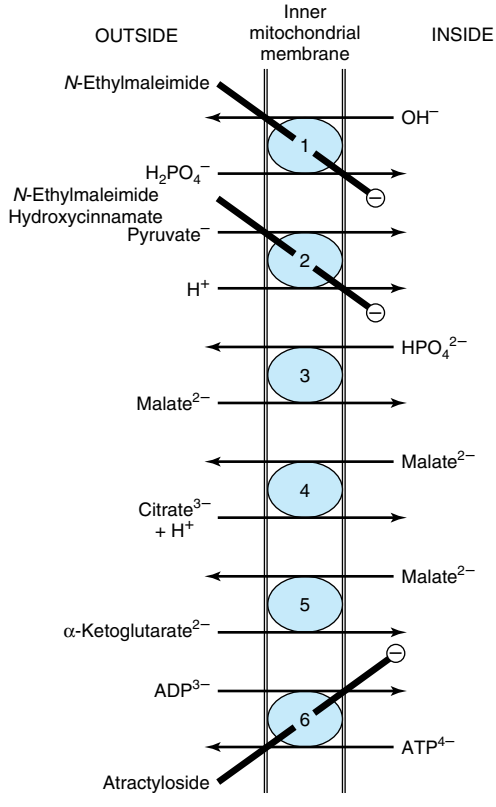

Figure 12–10. Transporter systems in the inner mitochondrial membrane. ①, phosphate transporter; ②, pyruvate symport; ③, dicarboxylate transporter; ④, tricarboxylate transporter; ⑤, α-ketoglutarate transporter; ⑥, adenine nucleotide transporter. *N*-Ethylmaleimide, hydroxycinnamate, and atractyloside inhibit (⊖) the indicated systems. Also present (but not shown) are transporter systems for glutamate/aspartate (Figure 12–13), glutamine, ornithine, neutral amino acids, and carnitine (Figure 22–1).

carboxylate anions and amino acids require specific transporter or carrier systems to facilitate their passage across the membrane. Monocarboxylic acids penetrate more readily in their undissociated and more lipid-soluble form.

The transport of di- and tricarboxylate anions is closely linked to that of inorganic phosphate, which penetrates readily as the $H_2PO_4^-$ ion in exchange for OH^-. The net uptake of malate by the dicarboxylate transporter requires inorganic phosphate for exchange in the opposite direction. The net uptake of citrate, isocitrate, or *cis*-aconitate by the tricarboxylate transporter requires malate in exchange. α-Ketoglutarate transport also requires an exchange with malate. The adenine nucleotide transporter allows the exchange of ATP and ADP but not AMP. It is vital in allowing ATP exit from mitochondria to the sites of extramitochondrial utilization and in allowing the return of ADP for ATP production within the mitochondrion (Figure 12–11). Na^+ can be exchanged for H^+, driven by the proton gradient. It is believed that active uptake of Ca^{2+} by mitochondria occurs with a net charge transfer of 1 (Ca^+ uniport), possibly through a Ca^{2+}/H^+ antiport. Calcium release from mitochondria is facilitated by exchange with Na^+.

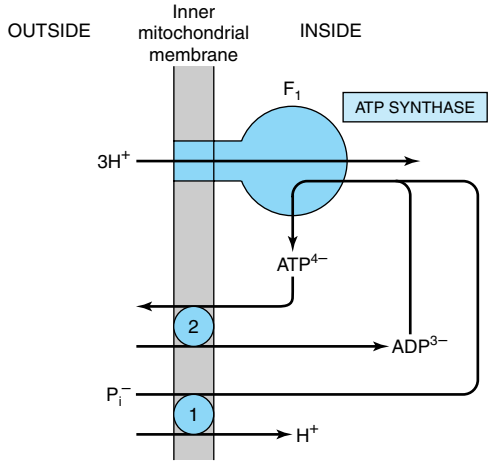

Figure 12–11. Combination of phosphate transporter (①) with the adenine nucleotide transporter (②) in ATP synthesis. The H^+/P_i symport shown is equivalent to the P_i/OH^- antiport shown in Figure 12–10. Four protons are taken into the mitochondrion for each ATP exported. However, one less proton would be taken in when ATP is used inside the mitochondrion.

Ionophores Permit Specific Cations to Penetrate Membranes

Ionophores are lipophilic molecules that complex specific cations and facilitate their transport through biologic membranes, eg, **valinomycin** (K^+). The classic uncouplers such as dinitrophenol are, in fact, proton ionophores.

A Proton-Translocating Transhydrogenase Is a Source of Intramitochondrial NADPH

Energy-linked transhydrogenase, a protein in the inner mitochondrial membrane, couples the passage of protons down the electrochemical gradient from outside to inside the mitochondrion with the transfer of H from intramitochondrial NADH to NADPH for intramitochondrial enzymes such as glutamate dehydrogenase and hydroxylases involved in steroid synthesis.

Oxidation of Extramitochondrial NADH Is Mediated by Substrate Shuttles

NADH cannot penetrate the mitochondrial membrane, but it is produced continuously in the cytosol by 3-phosphoglyceraldehyde dehydrogenase, an enzyme in the glycolysis sequence (Figure 17–2). However, under aerobic conditions, extramitochondrial NADH does not accumulate and is presumed to be oxidized by the respiratory chain in mitochondria. The transfer of reducing equivalents through the mitochondrial membrane requires substrate pairs, linked by suitable dehydrogenases on each side of the mitochondrial membrane. The mechanism of transfer using the **glycerophosphate shuttle** is shown in Figure 12–12). Since the mitochondrial enzyme is linked to the respiratory chain via a flavoprotein rather than NAD, only 2 mol rather than 3 mol of ATP are formed per atom of oxygen consumed. Although this shuttle is present in some tissues (eg, brain, white muscle), in others (eg, heart muscle) it is deficient. It is therefore believed that the **malate shuttle** system (Figure 12–13) is of more universal utility. The complexity of this system is due to the impermeability of the mitochondrial membrane to oxaloacetate, which must react with glutamate and transaminate to aspartate and α-ketoglutarate before transport through the mitochondrial membrane and reconstitution to oxaloacetate in the cytosol.

Ion Transport in Mitochondria Is Energy-Linked

Mitochondria maintain or accumulate cations such as K^+, Na^+, Ca^{2+}, and Mg^{2+}, and P_i. It is assumed that a primary proton pump drives cation exchange.

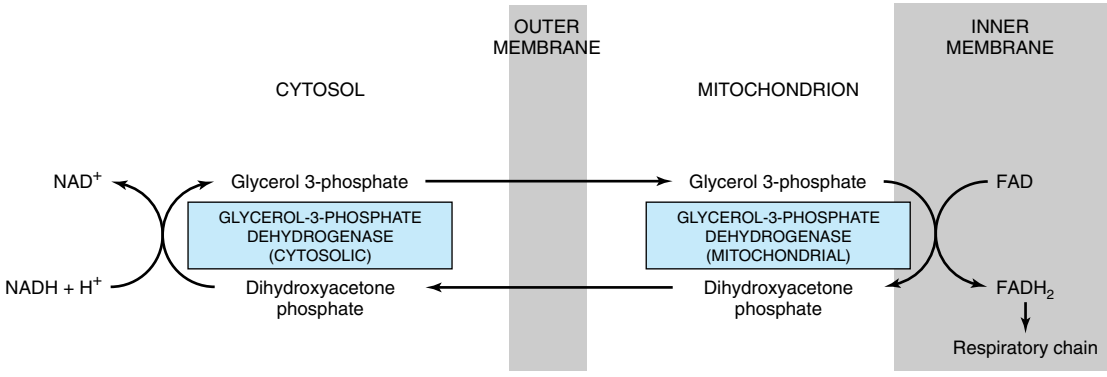

Figure 12–12. Glycerophosphate shuttle for transfer of reducing equivalents from the cytosol into the mitochondrion.

The Creatine Phosphate Shuttle Facilitates Transport of High-Energy Phosphate From Mitochondria

This shuttle (Figure 12–14) augments the functions of creatine phosphate as an energy buffer by acting as a dynamic system for transfer of high-energy phosphate from mitochondria in active tissues such as heart and skeletal muscle. An isoenzyme of creatine kinase (CK_m) is found in the mitochondrial intermembrane space, catalyzing the transfer of high-energy phosphate to creatine from ATP emerging from the adenine nucleotide transporter. In turn, the creatine phosphate is transported into the cytosol via protein pores in the outer mitochondrial membrane, becoming available for generation of extramitochondrial ATP.

CLINICAL ASPECTS

The condition known as **fatal infantile mitochondrial myopathy and renal dysfunction** involves severe diminution or absence of most oxidoreductases of the respiratory chain. **MELAS** (mitochondrial encephalopathy, lactic acidosis, and stroke) is an inherited condition due to NADH:ubiquinone oxidoreductase (complex I) or cytochrome oxidase deficiency. It is caused by a muta-

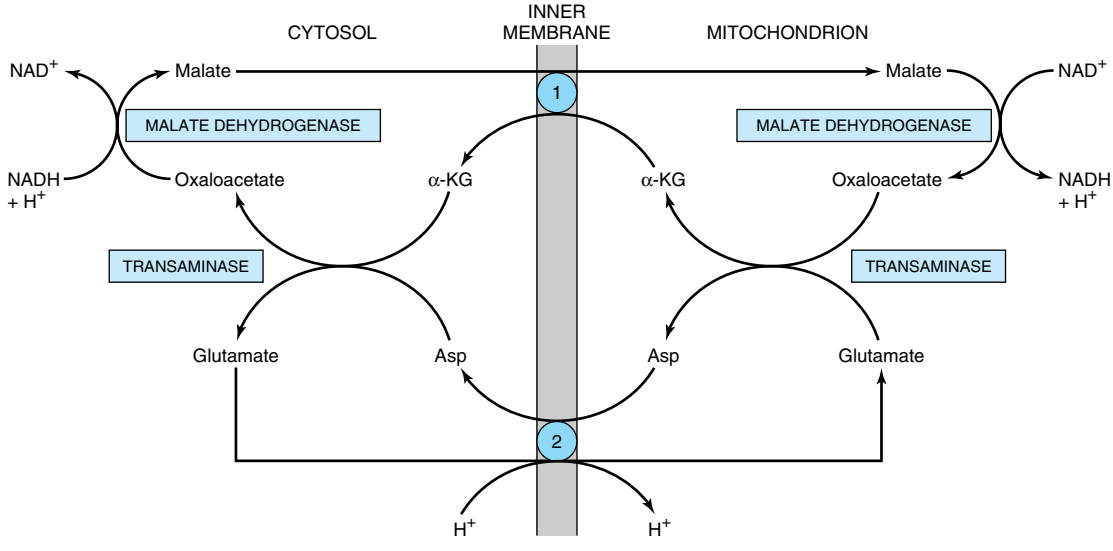

Figure 12–13. Malate shuttle for transfer of reducing equivalents from the cytosol into the mitochondrion. ① Ketoglutarate transporter; ②, glutamate/aspartate transporter (note the proton symport with glutamate).

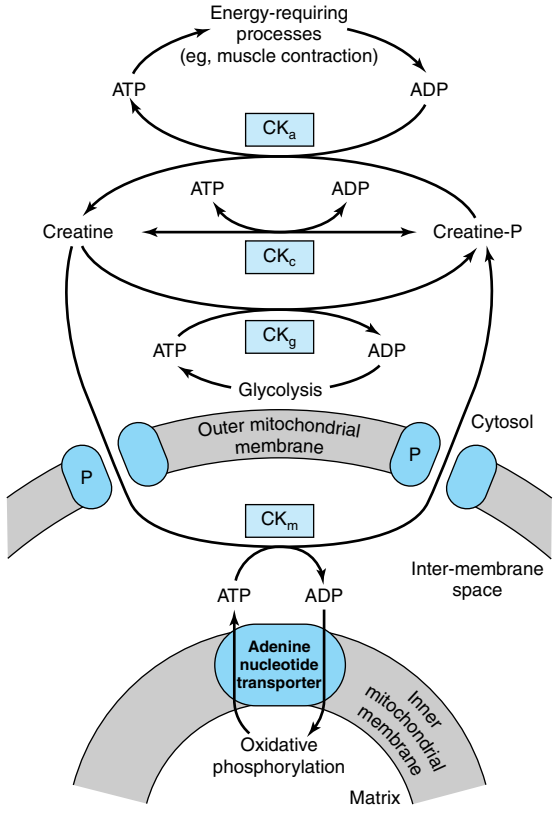

Figure 12–14. The creatine phosphate shuttle of heart and skeletal muscle. The shuttle allows rapid transport of high-energy phosphate from the mitochondrial matrix into the cytosol. CK_a, creatine kinase concerned with large requirements for ATP, eg, muscular contraction; CK_c, creatine kinase for maintaining equilibrium between creatine and creatine phosphate and ATP/ADP; CK_g, creatine kinase coupling glycolysis to creatine phosphate synthesis; CK_m, mitochondrial creatine kinase mediating creatine phosphate production from ATP formed in oxidative phosphorylation; P, pore protein in outer mitochondrial membrane.

tion in mitochondrial DNA and may be involved in Alzheimer's disease and diabetes mellitus. A number of drugs and poisons act by inhibition of oxidative phosphorylation (see above).

SUMMARY

- Virtually all energy released from the oxidation of carbohydrate, fat, and protein is made available in mitochondria as reducing equivalents (—H or e^-). These are funneled into the respiratory chain, where they are passed down a redox gradient of carriers to their final reaction with oxygen to form water.
- The redox carriers are grouped into respiratory chain complexes in the inner mitochondrial membrane. These use the energy released in the redox gradient to pump protons to the outside of the membrane, creating an electrochemical potential across the membrane.
- Spanning the membrane are ATP synthase complexes that use the potential energy of the proton gradient to synthesize ATP from ADP and P_i. In this way, oxidation is closely coupled to phosphorylation to meet the energy needs of the cell.
- Because the inner mitochondrial membrane is impermeable to protons and other ions, special exchange transporters span the membrane to allow passage of ions such as OH^-, P_i^-, ATP^{4-}, ADP^{3-}, and metabolites, without discharging the electrochemical gradient across the membrane.
- Many well-known poisons such as cyanide arrest respiration by inhibition of the respiratory chain.

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