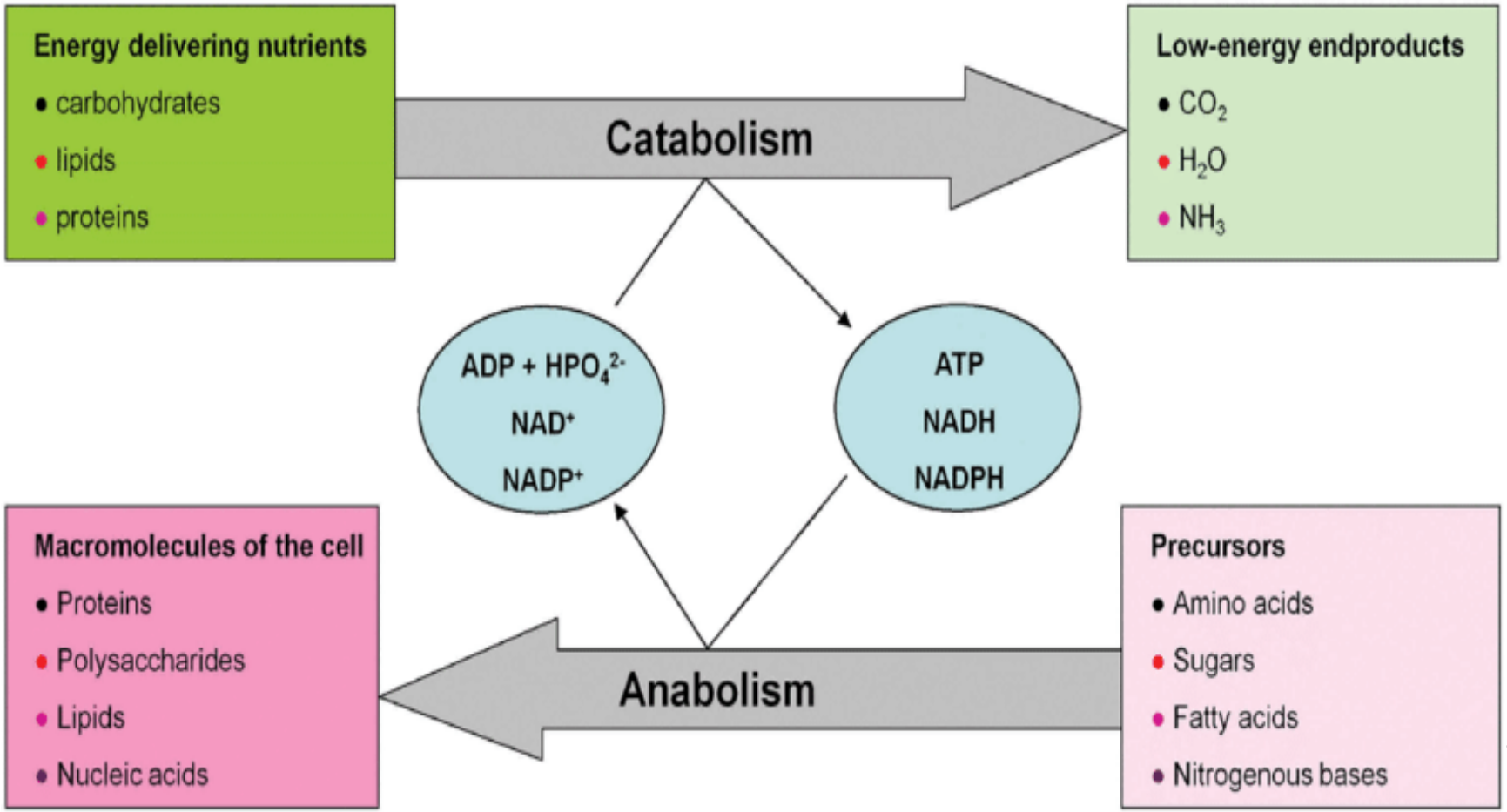
Bioenergetics: general pathways of carbohydrates, lipids and amino acids metabolism. Tricarboxylic acid cycle. Biological oxidation and oxidative phosphorylation.

Assoc. Prof.
Bilets M.V.

Ministry of Public Health of Ukraine
Poltava State Medical University

- Catabolism as a set of processes of splitting of biomolecules (glucose, amino acids, fatty acids up to end-products).
- Anabolism as a synthesis of the biomolecules necessary for construction of cellular structures.
- Stages of catabolism.
- Ways of synthesis of ATP in cells.
- General characteristic of a tricarboxylic acid cycle.
- The chemiosmotic theory of oxidative phosphorylation – the molecular mechanism of generation of ATP during biological oxidation.
- Inhibitors and uncouplers of tissue respiration.

Metabolism


Energy delivering nutrients
• carbohydrates
• lipids
• proteins
Catabolism
Low-energy endproducts
• CO_2
• H_2O
• NH_3
ADP + HPO_4^{2-}
NAD^+
$NADP^+$
ATP
NADH
NADPH
Macromolecules of the cell
• Proteins
• Polysaccharides
• Lipids
• Nucleic acids
Anabolism
Precursors
• Amino acids
• Sugars
• Fatty acids
• Nitrogenous bases

DIFFERENCES BETWEEN CATABOLISM AND ANABOLISM

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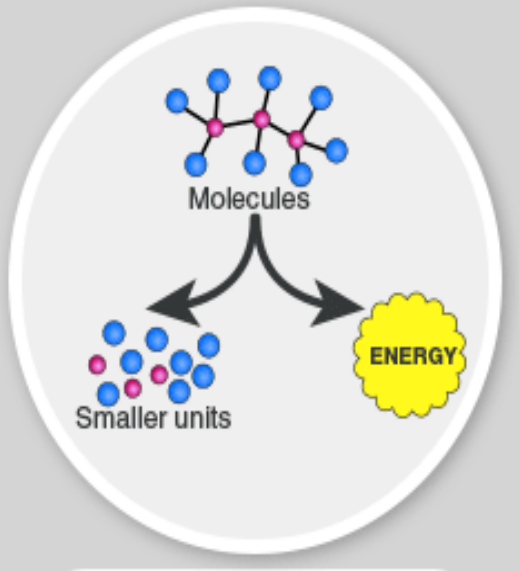
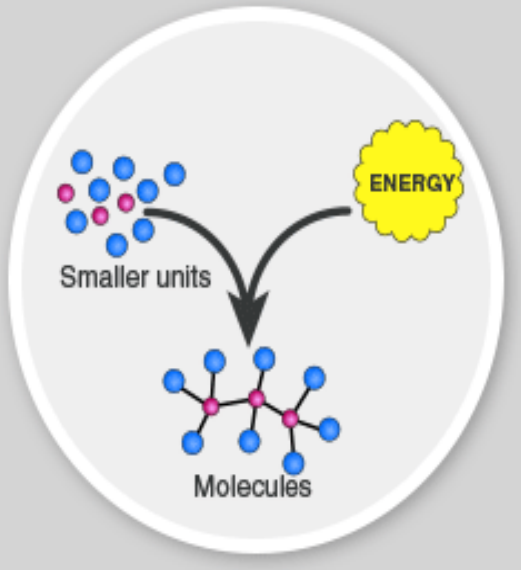


CATABOLISM

CATABOLISM IS THE SET OF METABOLIC PATHWAYS THAT BREAKS DOWN MOLECULES INTO SMALLER UNITS THAT ARE EITHER OXIDIZED TO RELEASE ENERGY OR USED IN OTHER ANABOLIC REACTIONS.



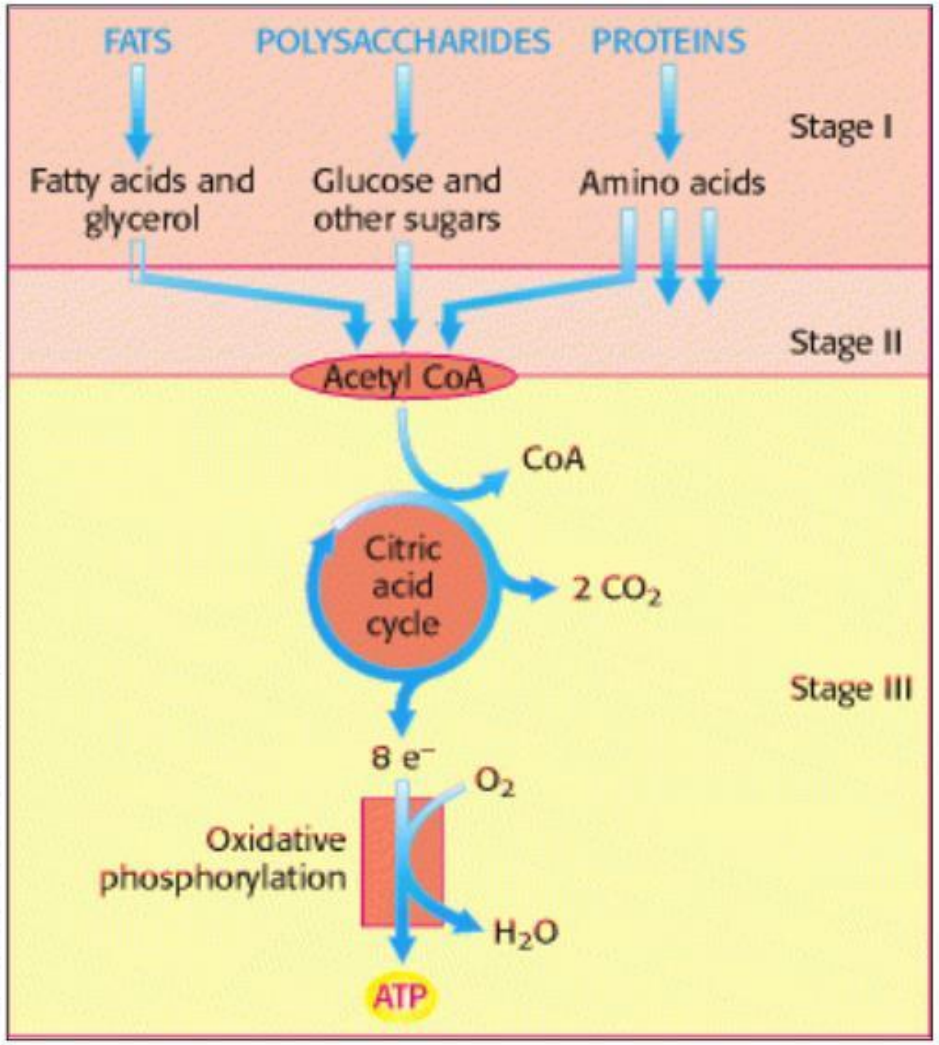
ANABOLISM

ANABOLISM IS THE SET OF METABOLIC PATHWAYS THAT CONSTRUCT MOLECULES FROM SMALLER UNITS, THESE REACTIONS REQUIRE ENERGY, KNOWN ALSO AS AN ENDERGONIC PROCESS.

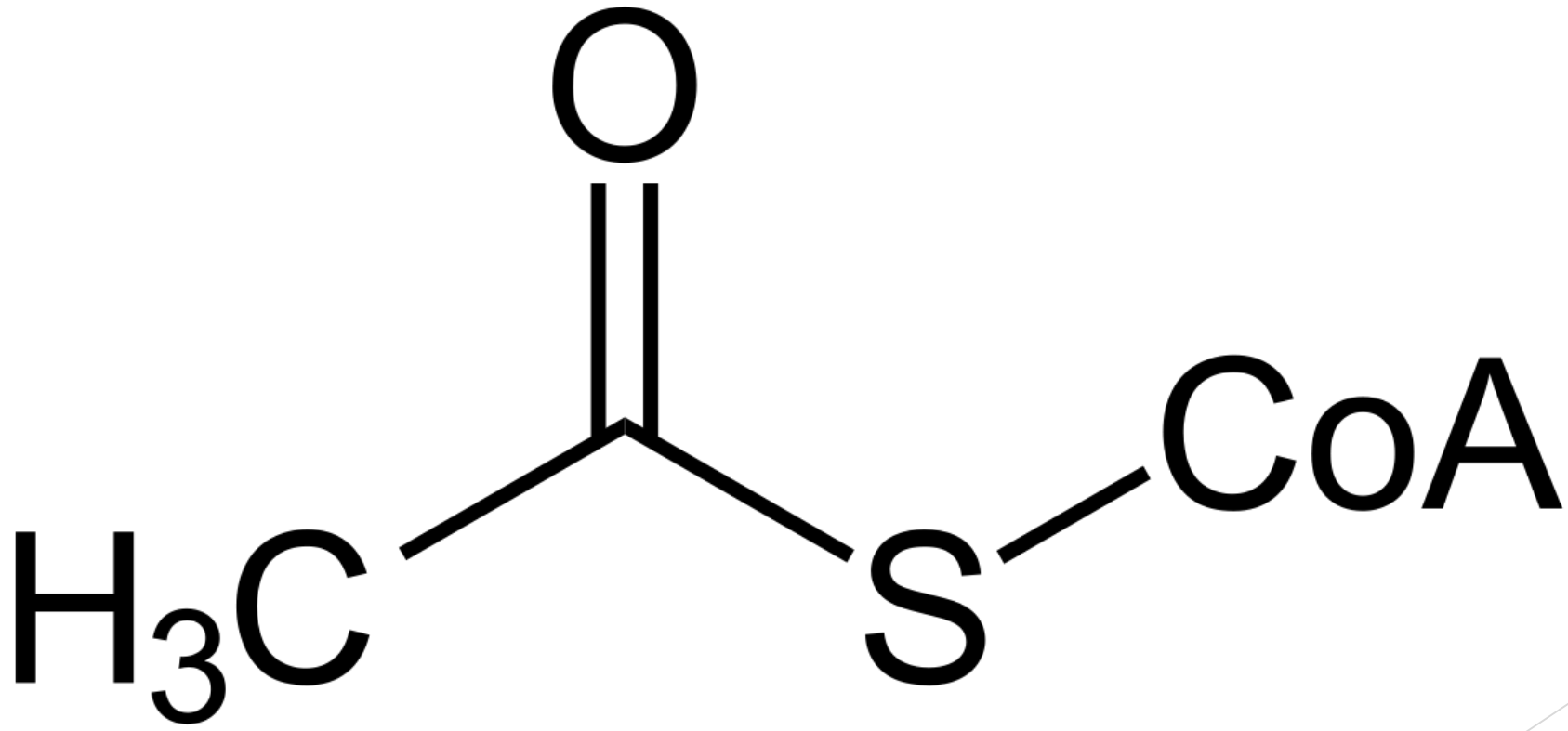
Catabolism	Anabolism
Catabolism breaks down big complex molecules into smaller.	Anabolism builds molecules required for the body's functionality.
The process of catabolism releases energy.	Anabolic processes require energy.
Hormones involved in the processes are adrenaline, cytokine, glucagon, and cortisol.	Hormones involved in the process are estrogen, testosterone, growth hormones and insulin.
Examples of catabolic processes are proteins becoming amino acids, glycogen breaking down into glucose and triglycerides breaking up into fatty acids.	Examples include the formation of polypeptides from amino acids, glucose forming glycogen and fatty acids forming triglycerides.
In catabolism, potential energy is changed into kinetic energy.	In anabolism, kinetic energy is converted into potential energy.
It is required to perform different activities in living entities.	It is required for maintenance, growth, and storage.

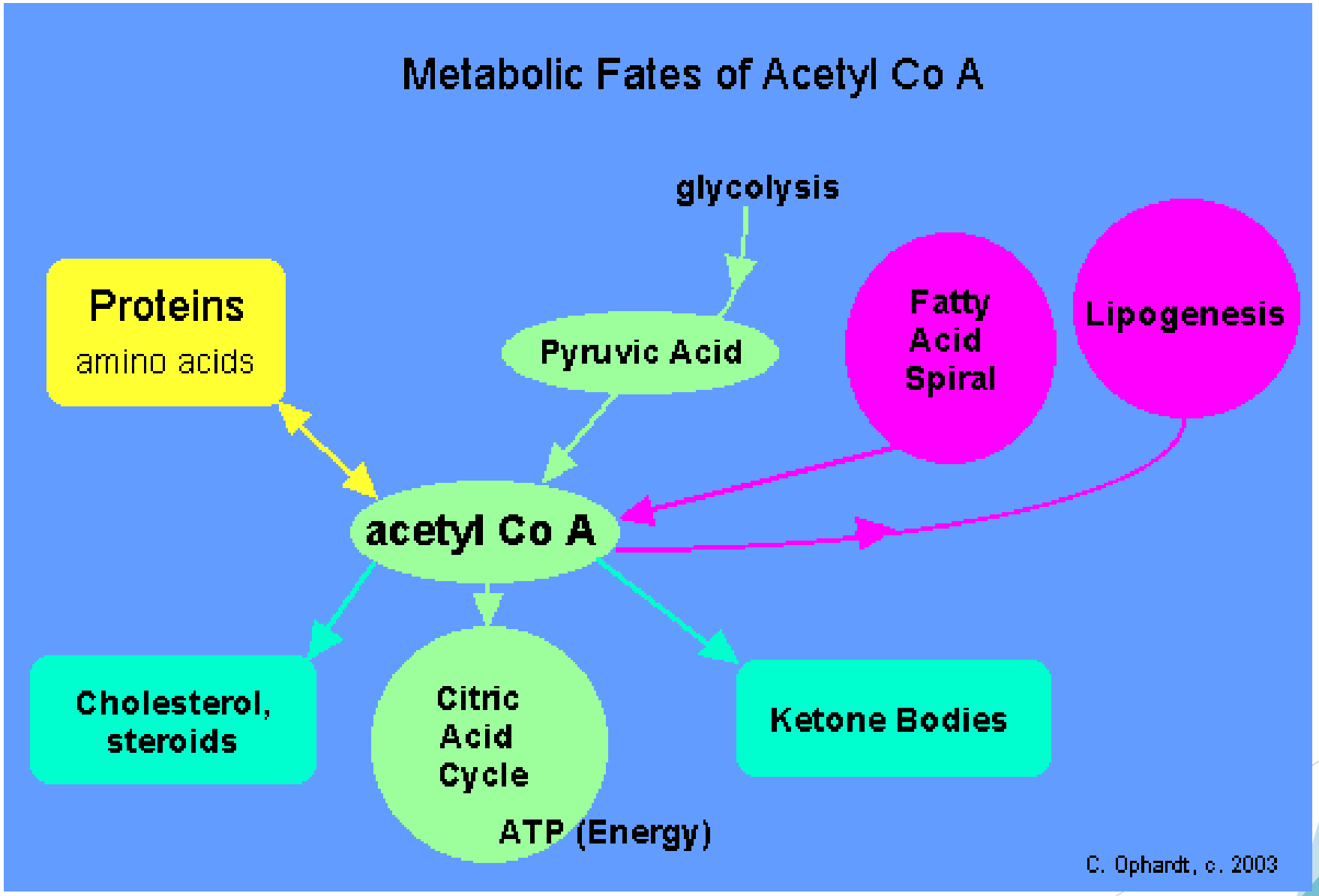
Stages of catabolism

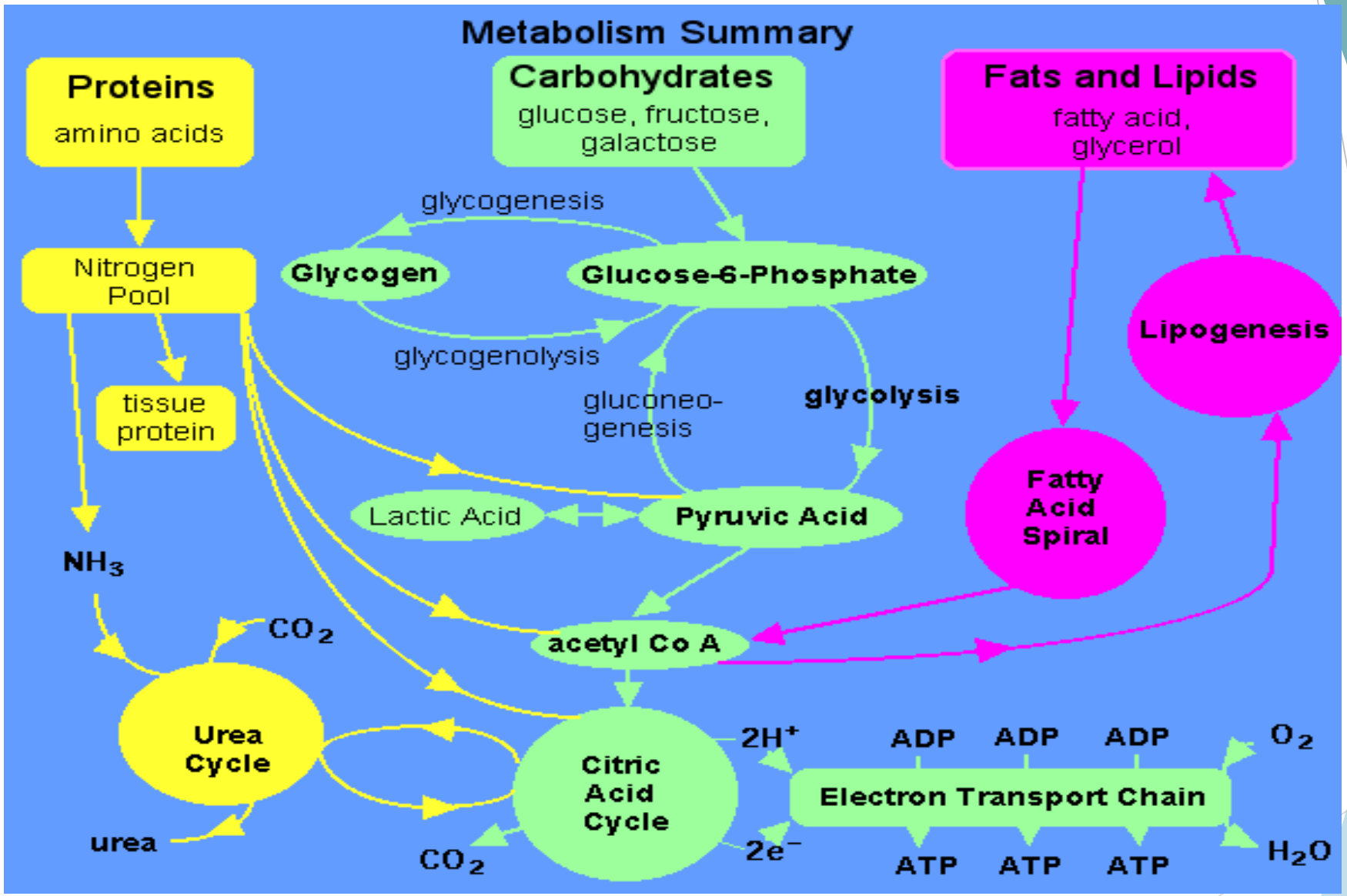
- **1st stage:** Large molecules in food are broken down into smaller units. Preparation stage without capture of energy.
  - Proteins -> amino acids,
  - Polysaccharides -> monosaccharides (glucose, ...)
  - Fats -> glycerol, fatty acids.
- **2nd stage:** Molecules are degraded to simple units that play a central role in metabolism. Most of them are converted into the acetyl unit of acetyl CoA. Some ATP is generated in this anaerobic stage, but amount is small compared with 3rd stage.
- **3rd stage:** ATP is produced from the complete oxidation of the acetyl unit of acetyl CoA. Acetyl CoA brings acetyl units into the citric acid cycle, where they are completely oxidized to CO_2. Four pairs of electrons are transferred (three to NAD^+ and one to FAD) for each acetyl group that is oxidized. Then, a proton gradient is generated as electrons flow from the reduced forms of these carriers to O_2, and this gradient is used to synthesize ATP.



Acetyl-CoA




Metabolic Fates of Acetyl Co A
glycolysis
Proteins
amino acids
Pyruvic Acid
Fatty
Acid
Spiral
Lipogenesis
acetyl Co A
Cholesterol,
steroids
Citric
Acid
Cycle
ATP (Energy)
Ketone Bodies
C. Ophardt, c. 2003

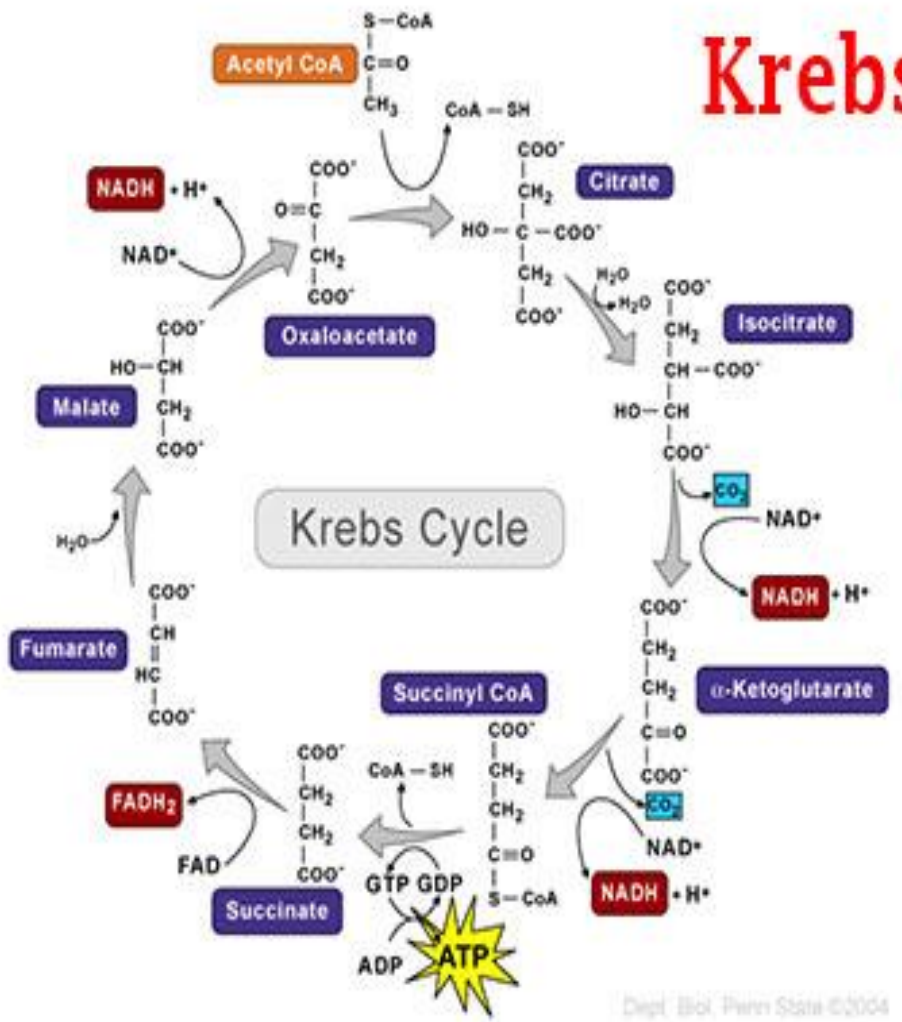

Metabolism Summary
Proteins
amino acids
Carbohydrates
glucose, fructose, galactose
Fats and Lipids
fatty acid, glycerol
glycogenesis
Nitrogen Pool
Glycogen
Glucose-6-Phosphate
Lipogenesis
glycogenolysis
tissue protein
gluconeo-genesis
glycolysis
Fatty Acid Spiral
Lactic Acid
Pyruvic Acid
NH3
CO2
acetyl Co A
Urea Cycle
Citric Acid Cycle
2H+
ADP ADP ADP
O2
Electron Transport Chain
urea
CO2
2e−
ATP ATP ATP
H2O

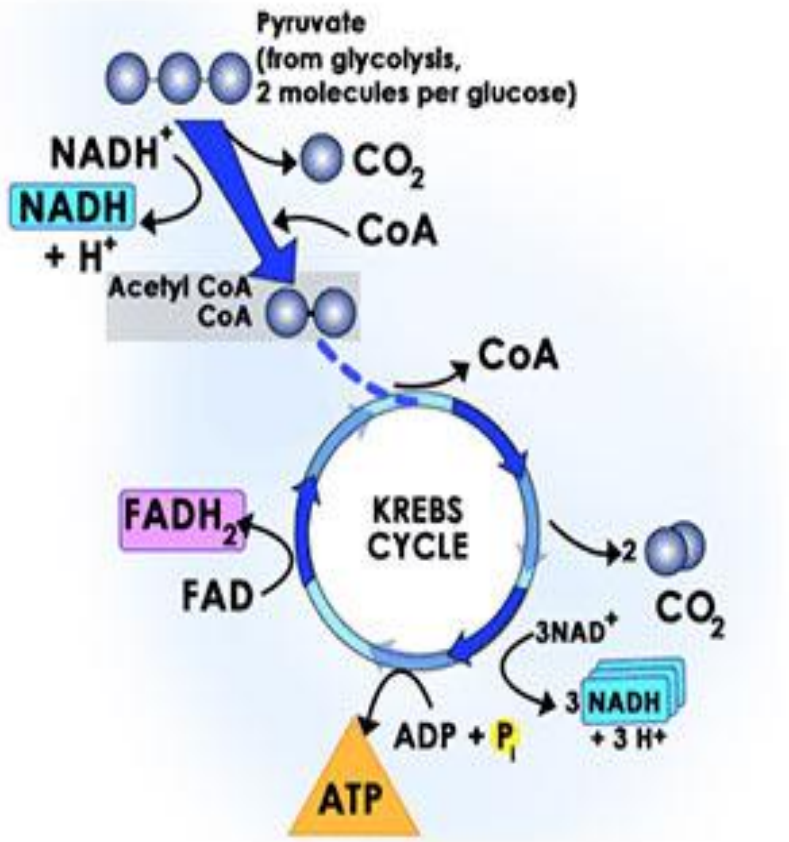
Citric Acid Cycle (Krebs cycle)

Significance of Citric Acid Cycle

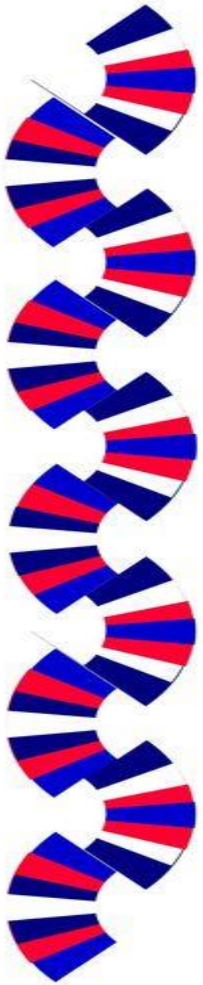
- The primary function is to provide energy (ATP).
- It is the final common pathway for the oxidation of carbohydrate, lipids, and protein via acetyl CoA or intermediates of the cycle.
- Citric acid cycle is an **amphibolic process** i.e, it plays role in both oxidative (catabolic) and synthetic (anabolic) processes. E.g....
  - Gluconeogenesis
  - Transamination
  - Fatty acid synthesis and
  - Porphyrin synthesis.

Krebs (Citric Acid) Cycle





Energy balance of Citric Acid Cycle



Energy production

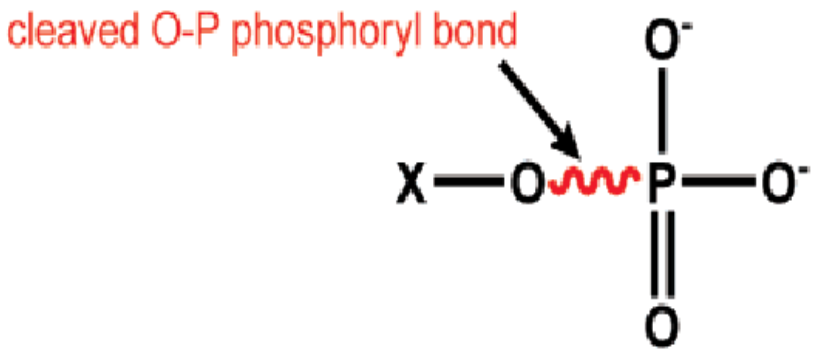
Every one mole of acetyl-CoA produce 12 moles of ATP as follows:

Isocitrate ⟶ α-ketogluterate	3ATP
α-ketogluterate ⟶ succinyl CoA	3ATP
succinyl CoA ⟶ succinate	1ATP
succinate ⟶ fumarate	2ATP
Malate ⟶ O.A.A	3ATP

Total energy production in Kreb's cycle is 12 ATP

High energy molecules

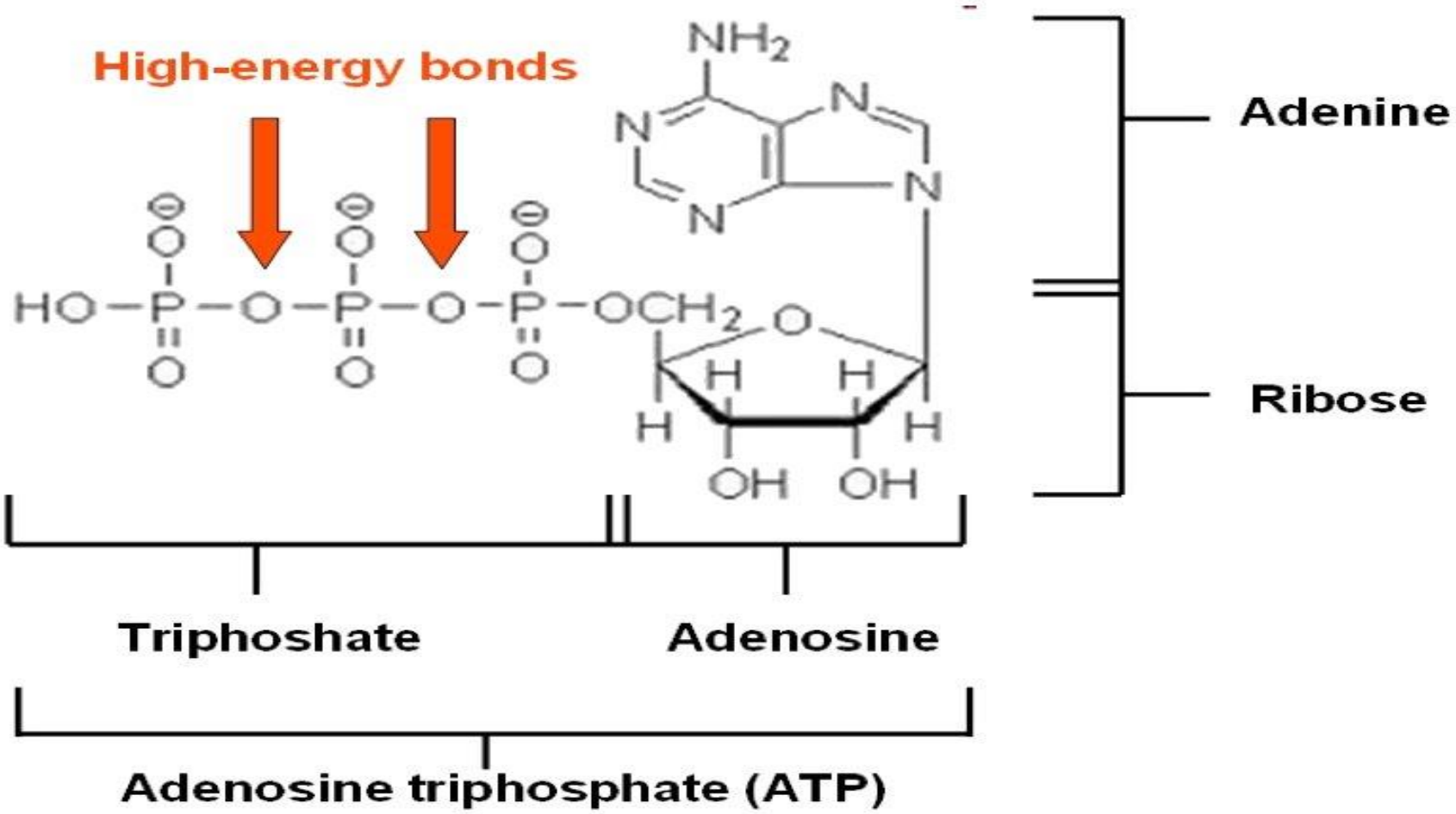
High energy molecules are biological molecules
that are capable of storing and transferring energy during a reaction.
During hydrolysis of one of the bonds, more than 20 kJ/mol (5 kcal/mol) is released.
According to the chemical structure, macroergs are most often anhydrides
of phosphoric and carboxylic acids, as well as weak acids, such as thiols and enols.



Substituent		ΔG hydrolysis (kcal/mol)
X = 1:	glycerate (glycerol-3-phosphate)	-2.2
2:	methanolate (methyl monophosphate)	-2.2
3:	3,4,5,6 tetrahydroxytetrahydropyranyl methanolate (glucose-6-phosphate)	-3.3
4:	3,4,5 trihydroxy 6 tetrahydropyranolate (glucose-1-phosphate)	-5.0
5:	pyruvate enol (phosphoenol pyruvate)	-6.8
6:	methyl monophosphate (methyl diphosphate)	-8.5
7:	methyl diphosphate (methyl triphosphate)	-8.5
8:	acetate (acetyl phosphate)	-10.3
9:	3-phosphoglycerate (1,3 bisphosphoglycerate)	-11.8
10:	carbamate (carbamyl phosphate)	-12.5

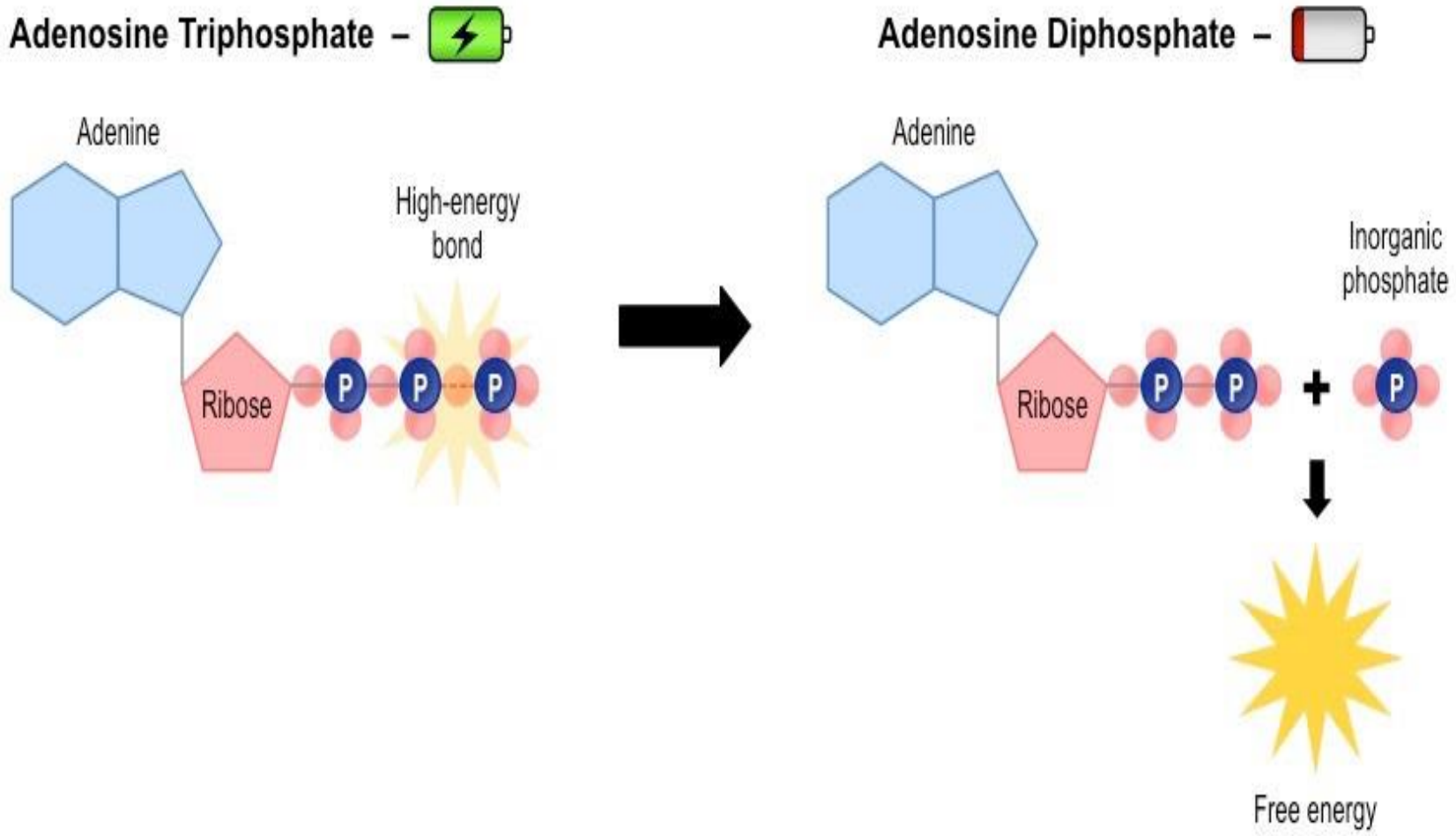
ıosphoryl compounds modeled.

ATP structure



Phosphorylation…

1. **Photophosphorylation** – plants use energy from sun to drive phosphorylation of ADP → ATP
2. **Substrate-level phosphorylation** – glycolysis and Krebs cycle use proteins (substrates) to phosphorylate ADP → ATP
3. **Oxidative phosphorylation** – in ETC, redox reactions drive production of ATP
   - This is where most of ATP generated from cell respiration comes from!


Adenosine Triphosphate –
Adenine
High-energy bond
Ribose
P
P
P
Adenosine Diphosphate –
Adenine
Inorganic phosphate
Ribose
P
P
+
P
Free energy

Oxidative and substrate level phosphorylation

Two Methods of ATP Synthesis

Substrate-level phosphorylation

- direct ATP formation through phosphate transfer from substrate to ADP
- Occurs in glycolysis & Kreb cycle

Oxidative phosphorylation

- indirect ATP formation through redox reactions involving O2 as a final electron acceptor
- Driven by the electron transport chain

Substrate-level phosphorylation

-direct formation of ATP from the transfer of a phosphate from a substrate to ADP.

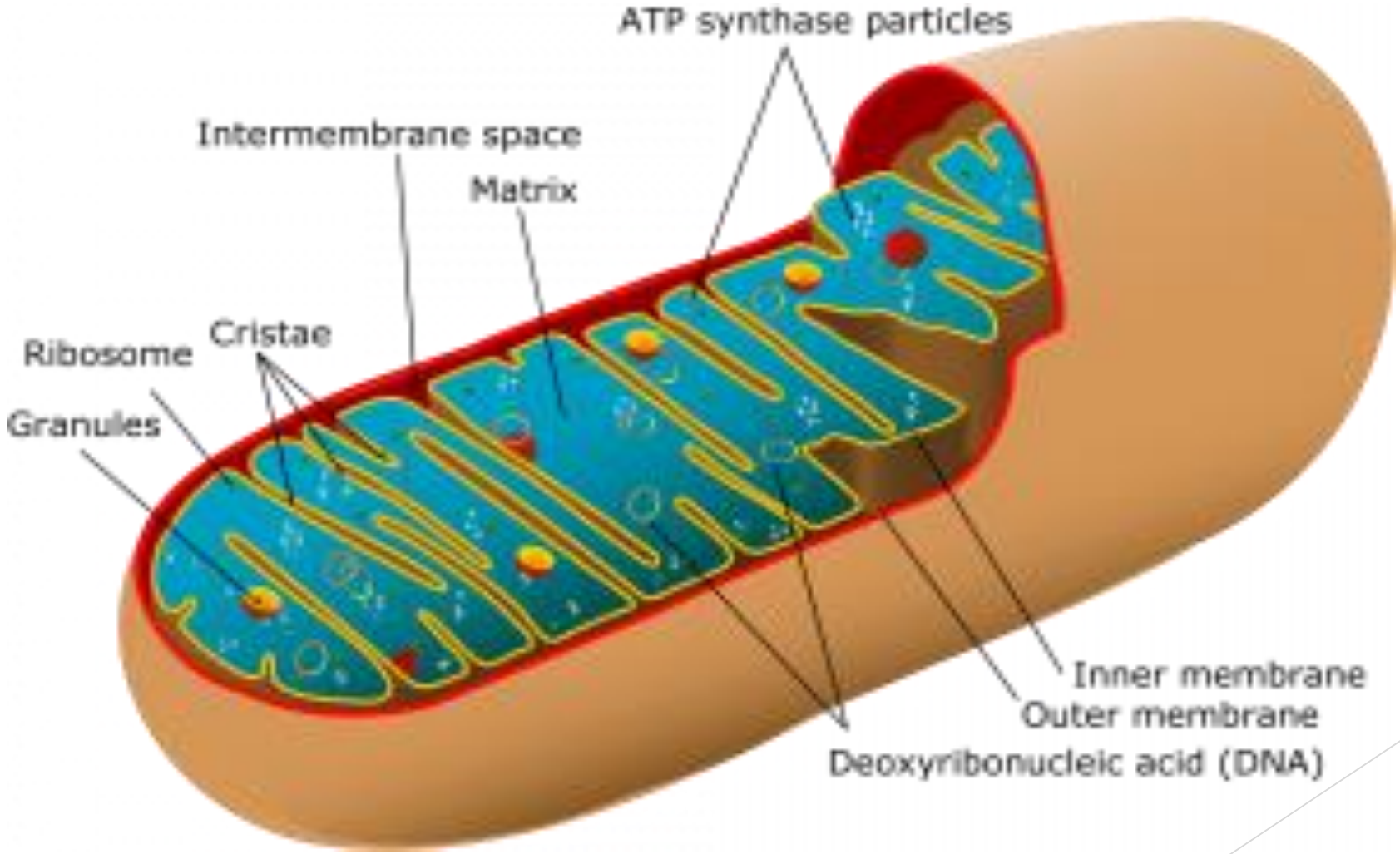
-occurs in glycolysis and the Krebs cycle.

Oxidative Phosphorylation (ETC)

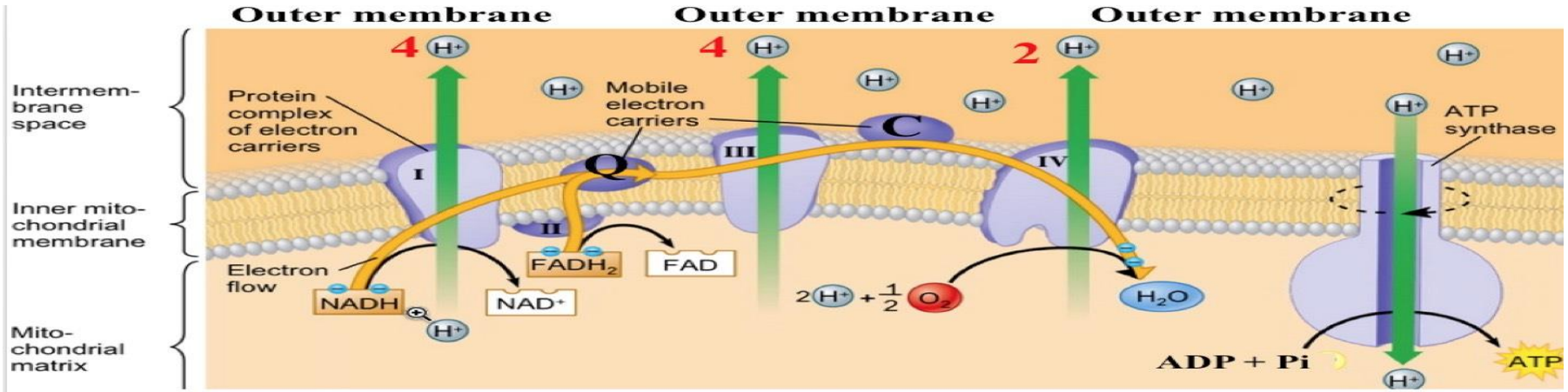
-indirect formation of ATP from the oxidation of NADH and $FADH_2$ and the next step of the transfer of electrons and pumping of protons and using O_2 as a final acceptor

-occurs via the electron transport chain

Mitochondria structure



Electron transport chain



1. **Redox of NADH+H+ at Complex I**, electrons go to Complex I, four protons pumped from matrix to intermembrane space
2. **Redox of $FADH_2$ at Complex II**, Coenzyme Q picks up electrons (from Complex I and II) and transports to Complex III
3. **Redox of Complex III**, four protons pumped from matrix to intermembrane space, carrier C transports electrons to Complex IV
4. **Redox of Complex IV**, two protons pumped from matrix to intermembrane space, formation of H_20 (20% of water in body)
5. **ATP Synthase action**, pumps protons from intermembrane space to matrix, produces ATP from ADP + Pi + energy

- Complex I (NADH dehydrogenase)
- It contains FMN, which accepts 2 electrons and H + from 2 NADH to become the reduced form of $FMNH_2$; also contains iron atoms, which assist in the transfer of the e – and H + to coenzyme Q.
- Complex II (Succinate dehydrogenase)
- Contains iron and succinate, which oxidizes FAD to form $FADH_2$
- Coenzyme Q
- Accepts electrons from $FMNH_2$ (complex I) and $FADH_2$ (complex II) and transfers electrons to complex III.
- Complex III (cytochrome b)
- It contains heme group, in which the Fe 3+ accepts the electrons from coenzyme Q to become Fe 2+. Transfers electrons to cytochrome c.
- Cytochrome c
- It contains the heme group, in which the Fe 3+ accepts the electrons from complex III to become Fe 2+. Transfers electrons to complex IV.
- Complex IV (cytochrome a)
- It contains the heme group, in which the Fe 3+ accepts electrons from cytochrome c to become Fe 2+. Transfers electrons to O_2, which is combined with hydrogen to form H_2O.
- Complex V (ATP synthase)
- It contains a proton channel that allows for protons to cross into the matrix, using the proton gradient energy to form ATP.

Mitochondrial ATP synthase complex

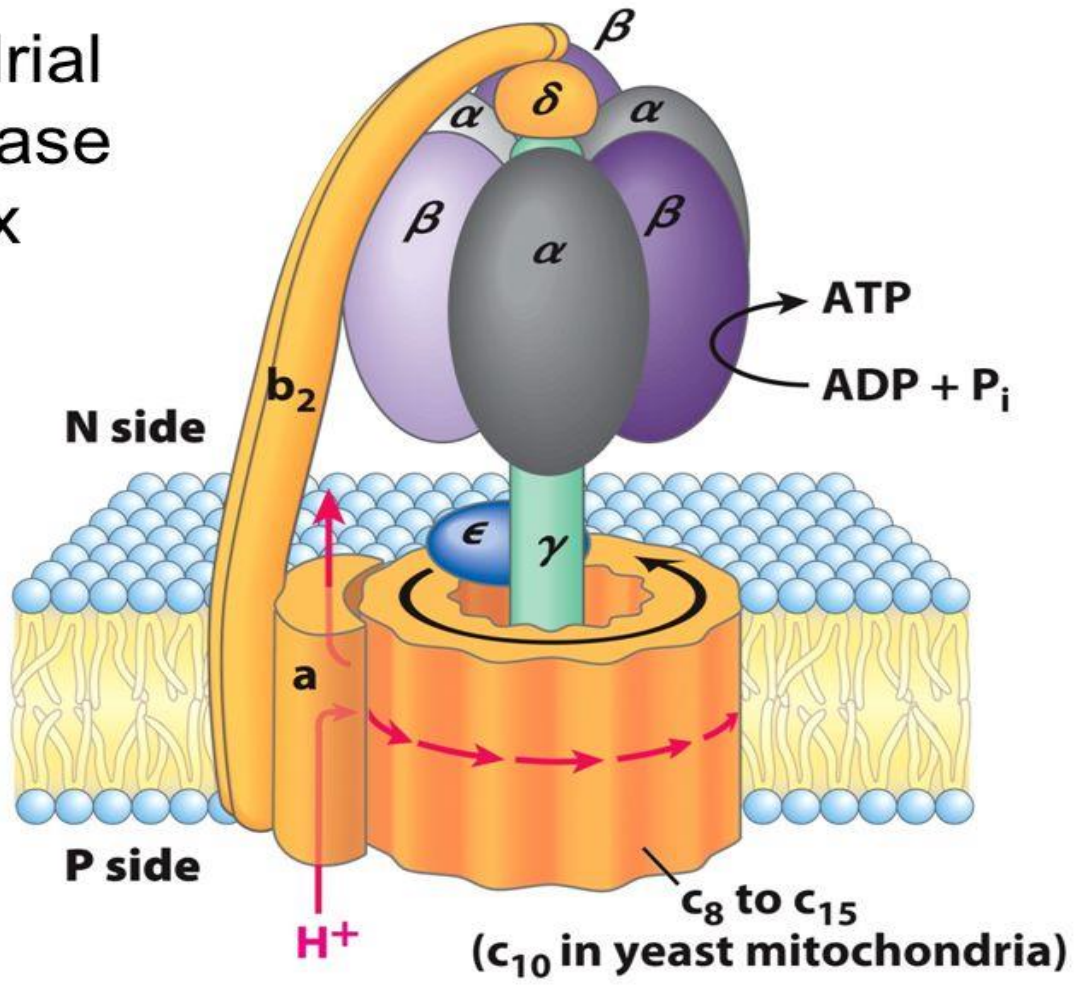
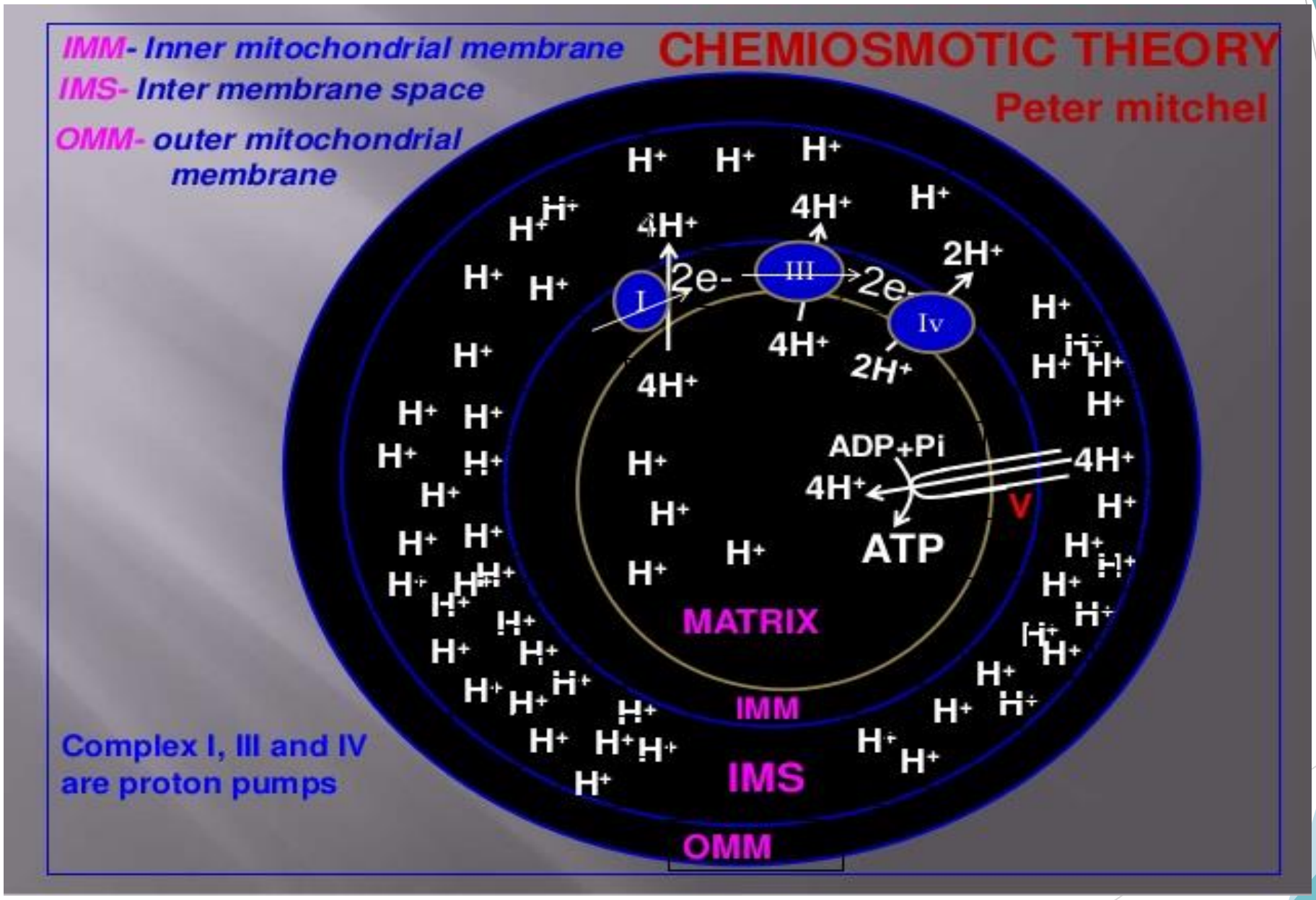


Figure 19-25a
Lehninger Principles of Biochemistry, Sixth Edition

Chemiosmotic Theory

- Electron Transport: Electrons carried by reduced coenzymes are passed through a chain of proteins and coenzymes to drive the generation of a proton gradient across the inner mitochondrial membrane
- Oxidative Phosphorylation: The proton gradient runs downhill to drive the synthesis of ATP
- Electron transport is coupled with oxidative phosphorylation
- It all happens in or at the inner mitochondrial membrane


IMM- Inner mitochondrial membrane
IMS- Inter membrane space
OMM- outer mitochondrial membrane
CHEMIOSMOTIC THEORY
Peter mitchel
H+
4H+
2H+
2e-
I
III
Iv
V
ADP+Pi
ATP
MATRIX
IMM
IMS
OMM
Complex I, III and IV are proton pumps

Chemiosmosis: The Energy-Coupling Mechanism

- Electron transfer in the electron transport chain causes proteins to pump H^+ from the mitochondrial matrix to the intermembrane space
- H^+ then moves back across the membrane, passing through the protein complex, **ATP synthase**
- ATP synthase uses the exergonic flow of H^+ to drive phosphorylation of ATP
- This is an example of **chemiosmosis**, the use of energy in a H^+ gradient to drive cellular work

Inhibitors and uncouplers of tissue respiration.

Inhibitors and Uncouplers

Table 1. Inhibitors of Respiration and Oxidative Phosphory

Site-Specific	Target Complex
Carbon monoxide	IV
Cyanide	IV
Sodium Azide	IV
Rotenone	I
Antimycin A	III
Amytal	I
Phosphorylation	
Oligomycin	F_o
Uncouplers	
2,4-Dinitrophenol (DNP)	Proton gradient
Trifluorocarbonylcyanide Phenylhydrazone (FCCP)	Proton gradient

Any compound that stops electron transport will stop respiration…this means you stop breathing

Electron transport can be stopped by inhibiting ATP synthesis

An uncoupler breaks the connection between ATP synthesis and electron transport

Inhibitors of Electron Transport:

- These are the inhibitors that arrest respiration by combining with members of the respiratory chain, rather than with the enzymes that may be involved in coupling respiration with ATP synthesis.

- They appear to act at 3 loci that may be identical to the energy transfer sites I, II and III. The given below are the inhibitors of Electron transport chain.

Rotenone

- It inhibits the transfer of electrons from iron-sulfur centers in complex I to ubiquinone.
- This interferes with NADH during the creation of usable cellular energy (ATP)
- Complex I is unable to pass off its electron to CoQ, creating a back-up of electrons within the mitochondrial matrix.
- Cellular oxygen is reduced to the radical, creating reactive oxygen species, which can damage DNA and other components of the mitochondria
- It is the non-toxic inhibitors of Electron transport chain.
- This is non-toxic to mammals because poorly absorbed. Shows toxic effect in fishes.

Inhibitors of Oxidative Phosphorylation:

Oligomycins:

- Is a polypeptide antibiotic are obtained from various species of "Streptomyces".
- The antibiotic is potent inhibitor to ATP synthase complex.
- binds to the Fo domain of ATP synthase, closing the proton channel and preventing reentry of protons into the matrix, there by preventing phosphorylation of ADP to ATP.
- Because the pH and electrical gradients cannot be dissipated in the presence of this drug, electron transport stops because of the difficulty of pumping any more protons against the steep gradients .
- This dependency of cellular respiration on the ability to phosphorylate ADP to ATP is known as respiratory control and is the consequence of the tight coupling of these processes.

Uncouplers of Oxidative Phosphorylation:

- Uncouplers can be defined as *A substance that uncouples phosphorylation of ADP from electron transfer.*

- Uncoupling agents are compounds which dissociate the synthesis of ATP from the transport of electrons through the cytochrome system.

- This means that the electron transport continues to function, leading to oxygen consumption but phosphorylation of ADP is inhibited.

2,4-Dinitrophenol:

- A classic uncoupler of oxidative phosphorylation.
- was used as a weight-loss agent in the 1930s
- The substance carries protons across the inner mitochondria membrane.
- In the presence of these uncouplers, electron transport from NADH to O_2 proceeds normally, but ATP is not formed by the mitochondria.
- Body temperature is elevated as a result of hyper metabolism.
- When phosphorylation is uncoupled from electron flow, a decrease in the proton gradient across the inner mitochondrial membrane and, therefore , impaired ATP synthesis is expected.
- In an attempt to compensate for this defect in energy capture , metabolism and electron flow to oxygen is increased.
- This hyper metabolism will be accompanied by elevated body temperature be cause the energy in fuels is largely wasted, appearing as heat.

Sources of information

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