TCA Cycle

History

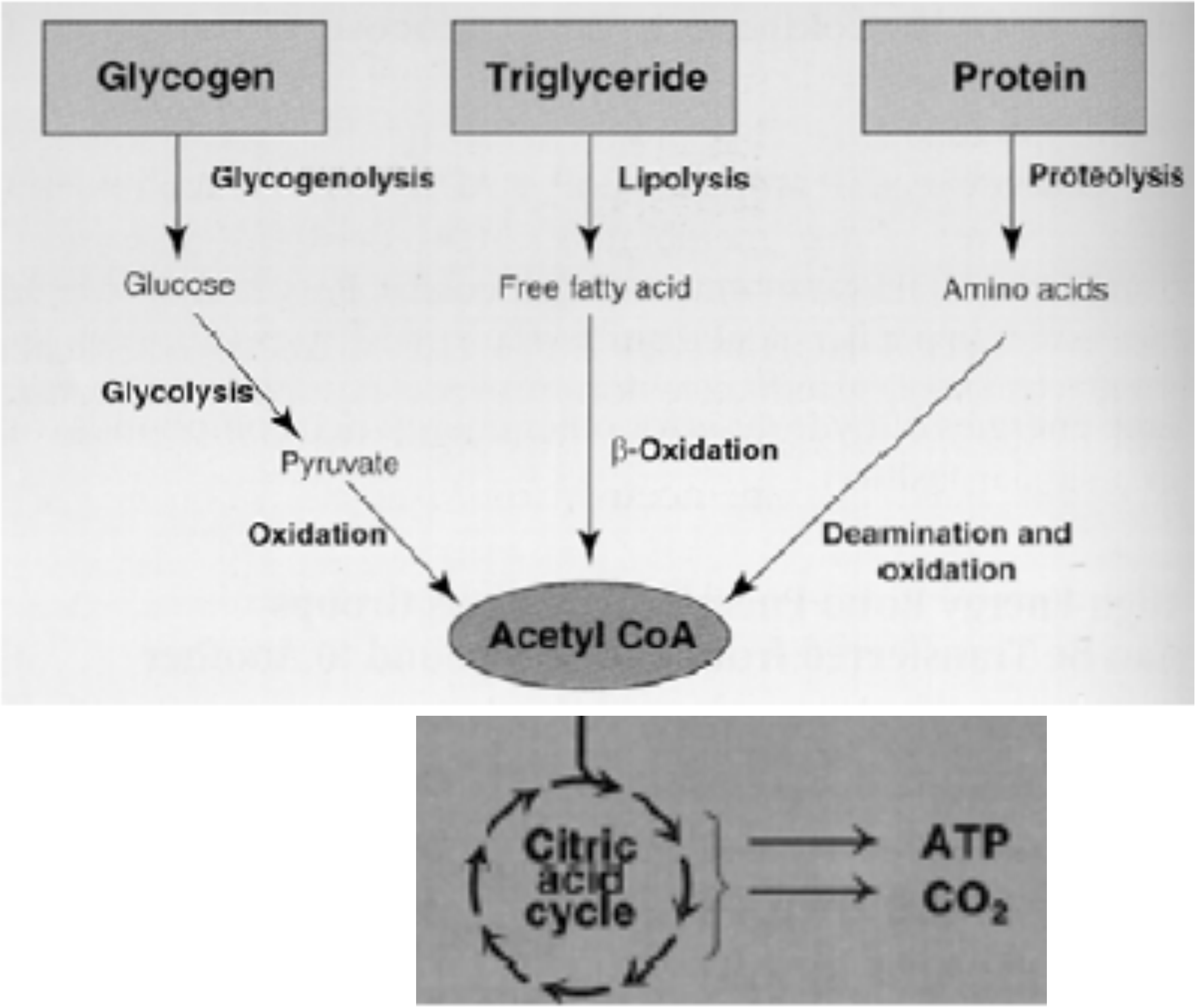
Discovered by Hans Krebs in 1937

He received the Nobel Prize in physiology or medicine in 1953 for his discovery

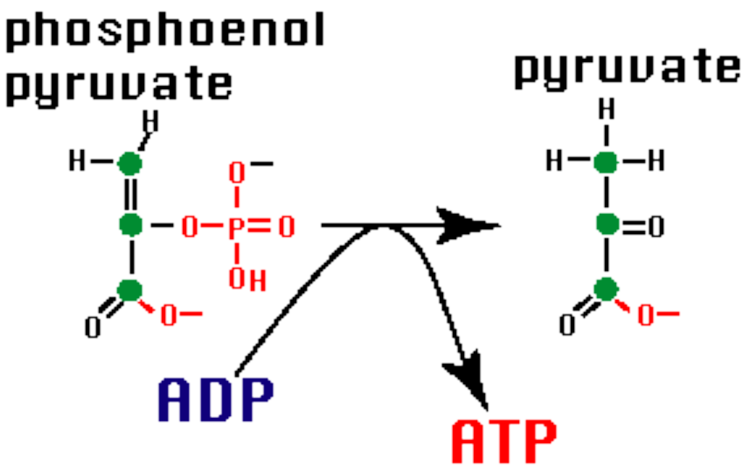
Forced to leave Germany prior to WWII because he was Jewish

- Most of cells energy comes from oxidation of A.CoA in mitochondria
- Glycolysis oxidizes sugar to pyruvate which is converted to A.CoA in mitochondria
- Proteins and fatty acid are also broken down to yield A.CoA
- Acetyl units oxidized to CO2 in mitochondrial matrix by TCA cycle
- Energy released during oxidation captured by NAD+ and FAD

> Carried to ETC for synthesis of ATP (oxidative phosphorylation)

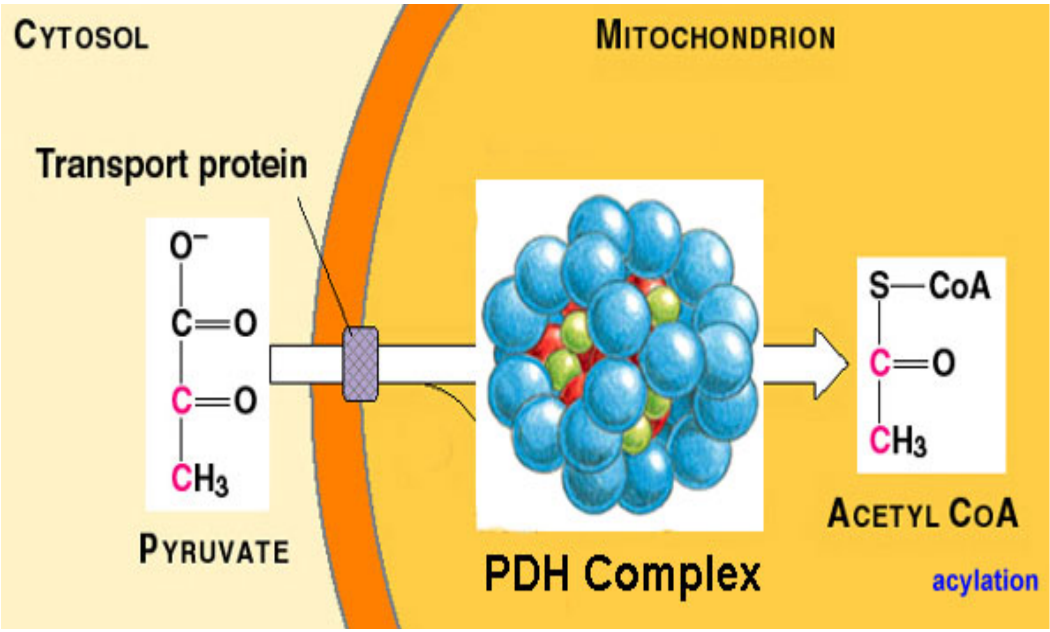

Glycogen
Triglyceride
Protein
Glycogenolysis
Lipolysis
Proteolysis
Glucose
Free fatty acid
Amino acids
Glycolysis
Pyruvate
β-Oxidation
Oxidation
Deamination and oxidation
Acetyl CoA
Citric acid cycle
ATP
CO_2

RXN 10 Glycolysis



Pyruvate produced from glycolysis must be decarboxylated to A. CoA before it enters TCA cycle

Catalyzed by large enzyme
-Pyruvate dehydrogenase complex (mitochondrial matrix)



Pyruvate + CoA + NAD^+ → A. CoA + CO_2 + NADH + H^+

Control of the Pyruvate Dehydrogenase complex

- Regulation by its products

> NADH & Acetyl-CoA : inhibit

While

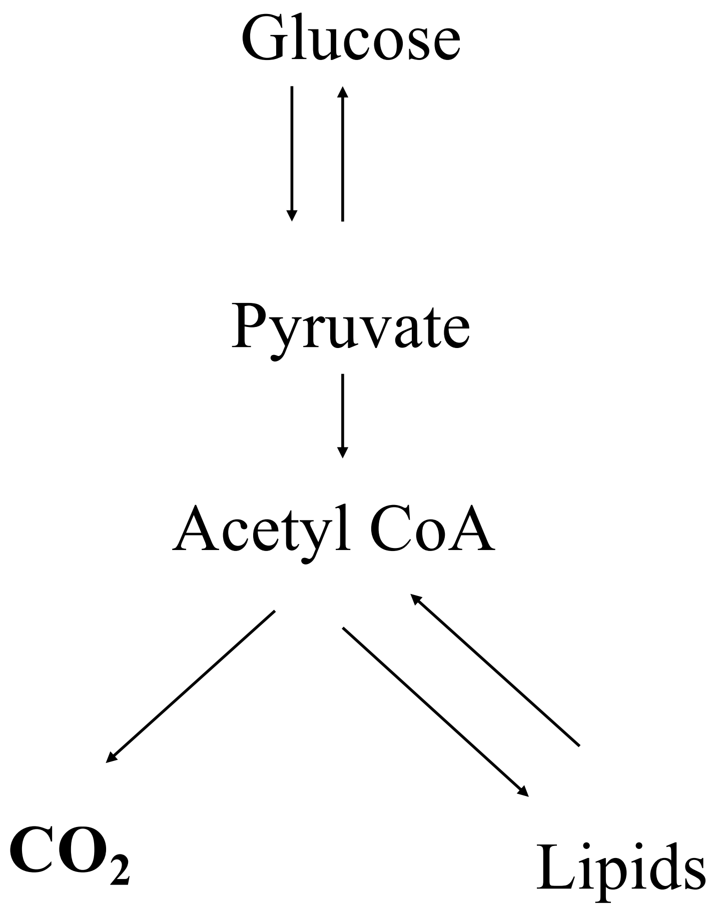
>NAD^+ & CoA stimulate

- Regulation by energy charge

> ATP : inhibit

While

> AMP : stimulate



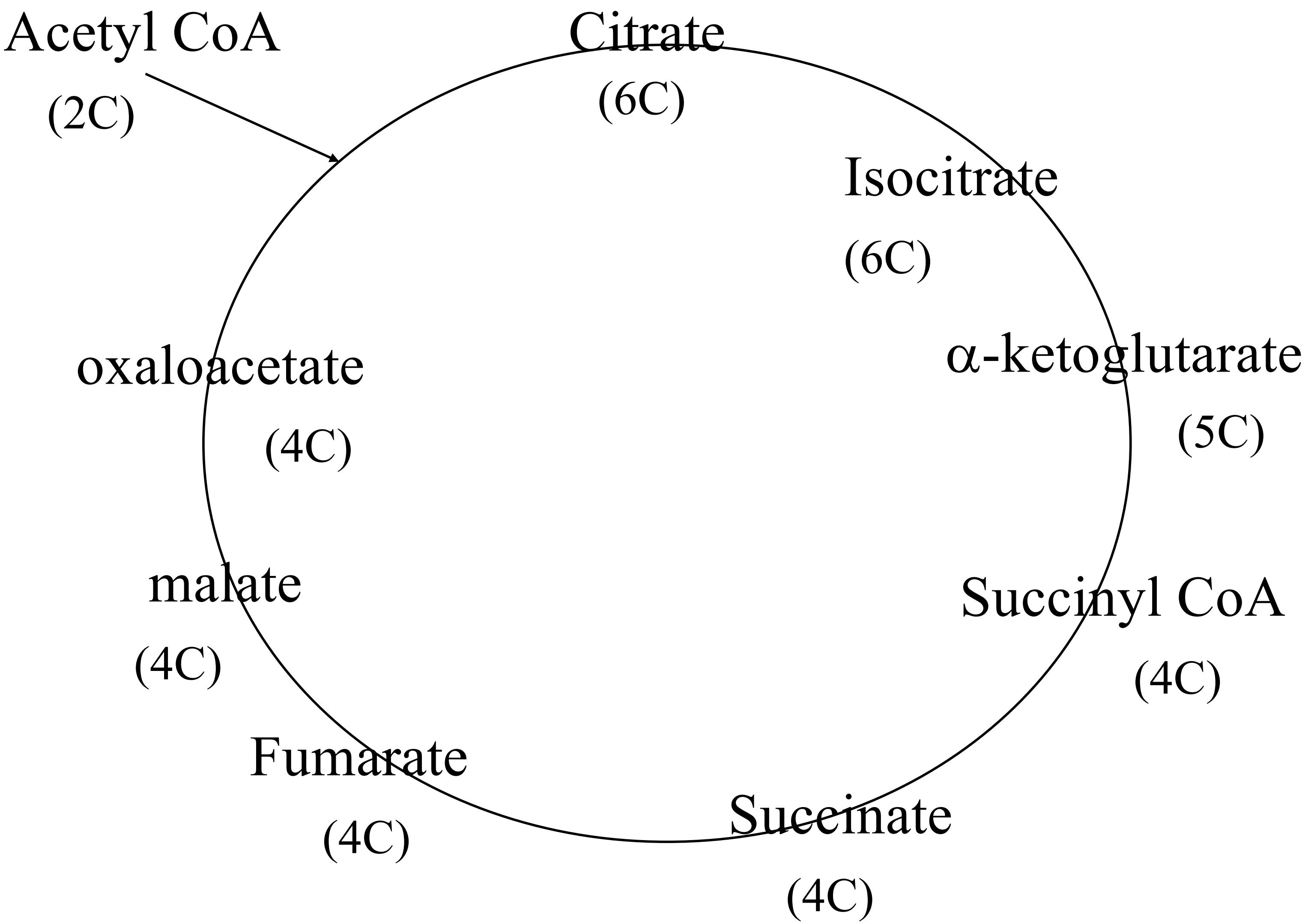
Glucose
Pyruvate
Acetyl CoA
CO_2
Lipids

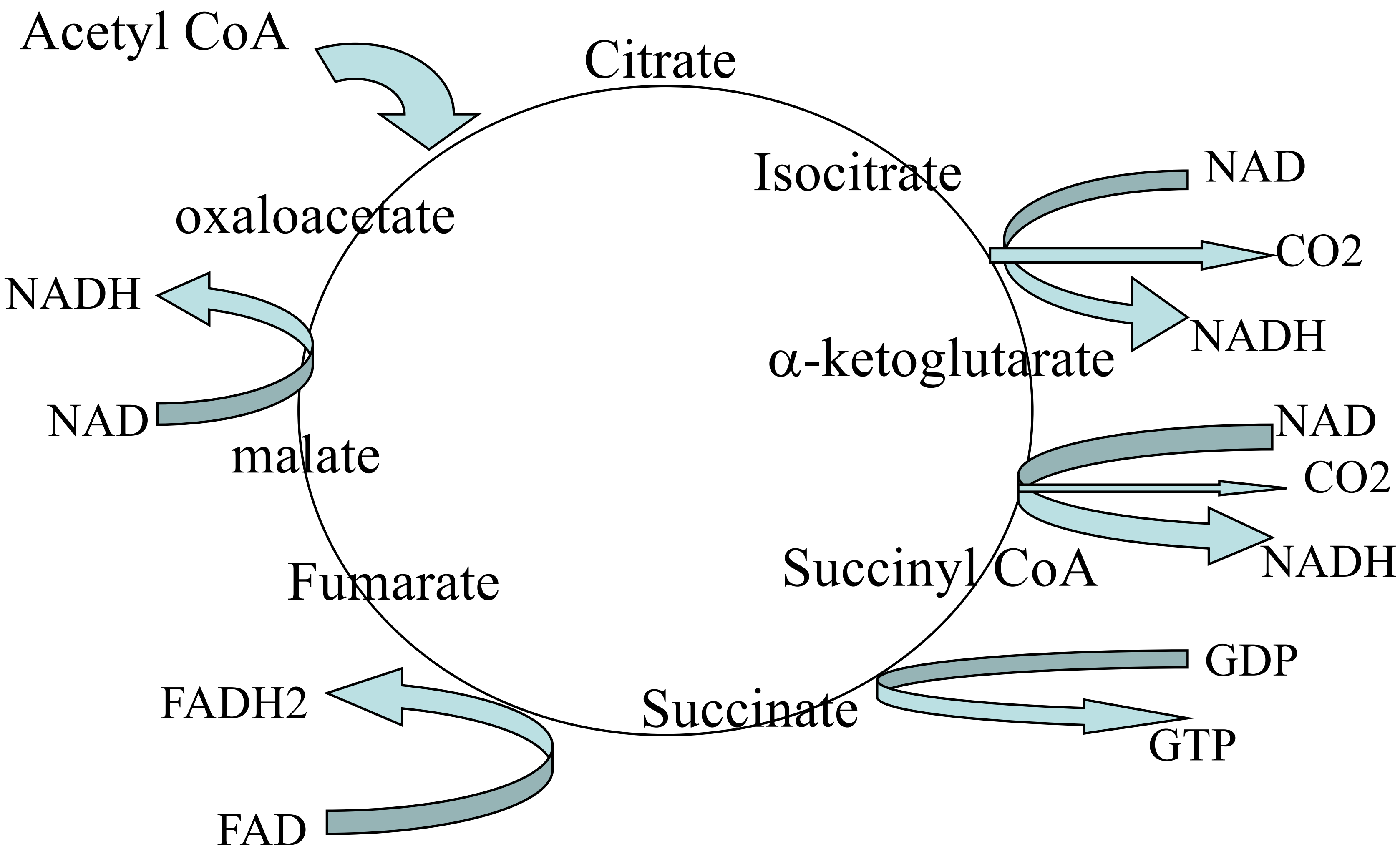
Overall rxn

- Acetyl CoA + $3NAD^+$ + FAD + GDP + Pi + $2H_2O$

$$\downarrow$$

- $2CO_2$ + CoA + 3NADH + $FADH_2$ + GTP + H^+


Acetyl CoA
(2C)
Citrate
(6C)
Isocitrate
(6C)
α-ketoglutarate
(5C)
Succinyl CoA
(4C)
Succinate
(4C)
Fumarate
(4C)
malate
(4C)
oxaloacetate
(4C)


Acetyl CoA
Citrate
Isocitrate
NAD
CO2
NADH
α-ketoglutarate
NAD
CO2
NADH
Succinyl CoA
GDP
GTP
Succinate
FADH2
FAD
Fumarate
malate
NAD
NADH
oxaloacetate

Regulation of Citric Acid Cycle

- 3 Control sites

Regulation of Citric Acid Cycle con't
Site 1 - rxn 1

Acetyl CoA + Oxaloacetate

↓

Citrate

- Enzyme: citrate synthase
- Inhibited by ATP

Regulation of Citric Acid Cycle con't Site 2 - rxn 3

- Isocitrate → α-Ketoglutarate

- Enzyme: isocitrate dehydrogenase
- Inhibited by ATP & NADH
- Stimulated by ADP & NAD^+

Regulation of Citric Acid Cycle con't
Site 3 - rxn 4

- α-Ketoglutarate → Succinyl CoA

- Enzyme: α-Ketoglutarate dehydrogenase
- Similar to PDH complex
- Inhibited by Succinyl CoA & NADH also high-energy charge.

Regulation of Citric Acid Cycle Summary

- IN GENERAL THE TCA CYCLE IS INHIBITED BY A HIGH ENERGY CHARGE AND STIMULATED BY LOW ENERGY CHARGE

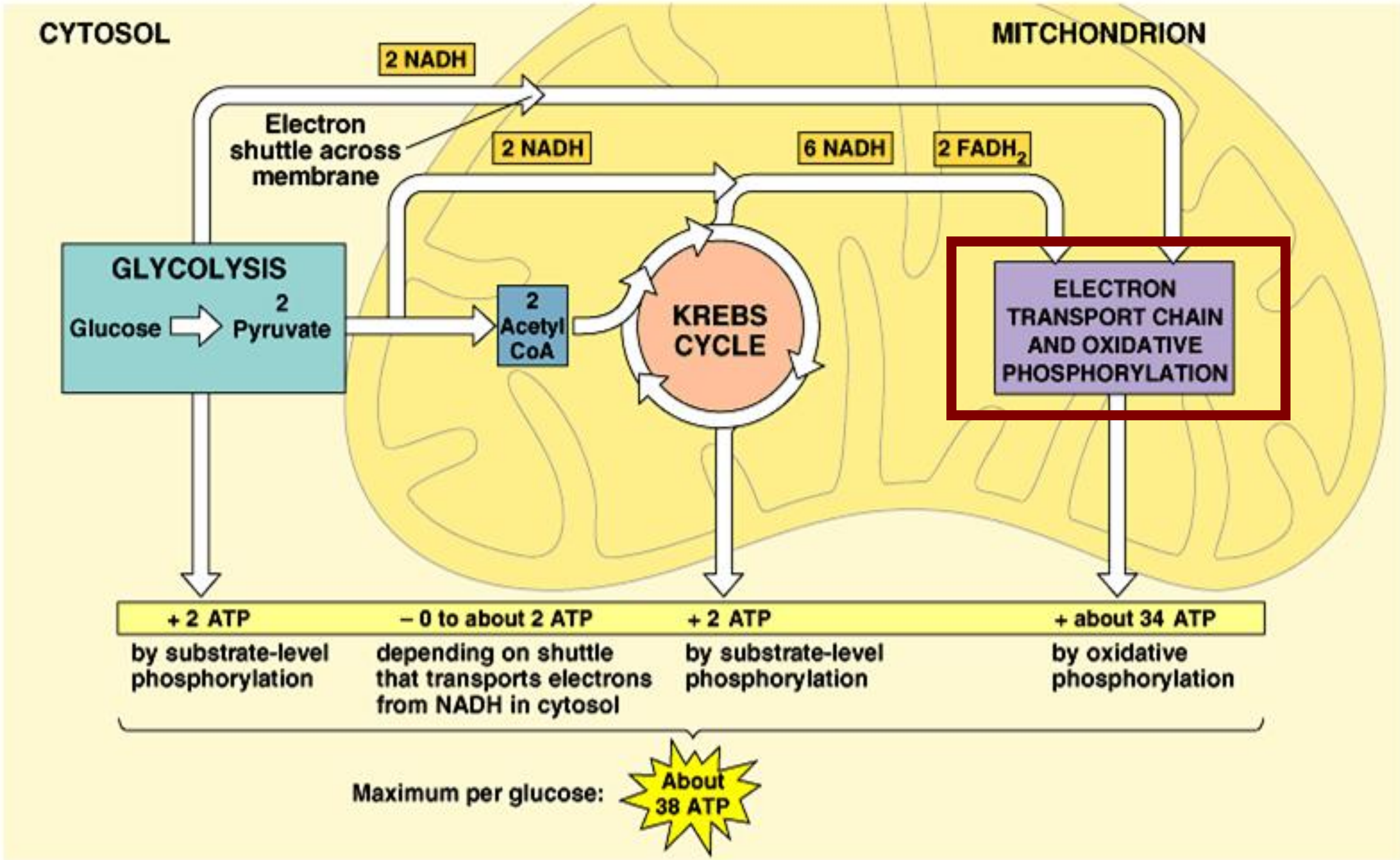
Study Questions

- What’s the importance of the TCA cycle?
- Where is this process carried out?
- By the aid of diagrams explain the reactions of the TCA cycle.
- Write down the overall stoichiometric equation for the TCA cycle.
- What are the points of regulation in TCA cycle?
- How is Pyruvate dehydrogenase regulated?
- How are amino acid, carbohydrates and fatty acids metabolism related to the TCA cycle?
- How does the TCA cycle function as biosynthetic precursors?
- What is the committed step in TCA cycle?
- Why is it that Glycolysis can take place under either aerobic or anaerobic conditions but the citric acid cycle proceeds strictly under aerobic conditions?

Overview

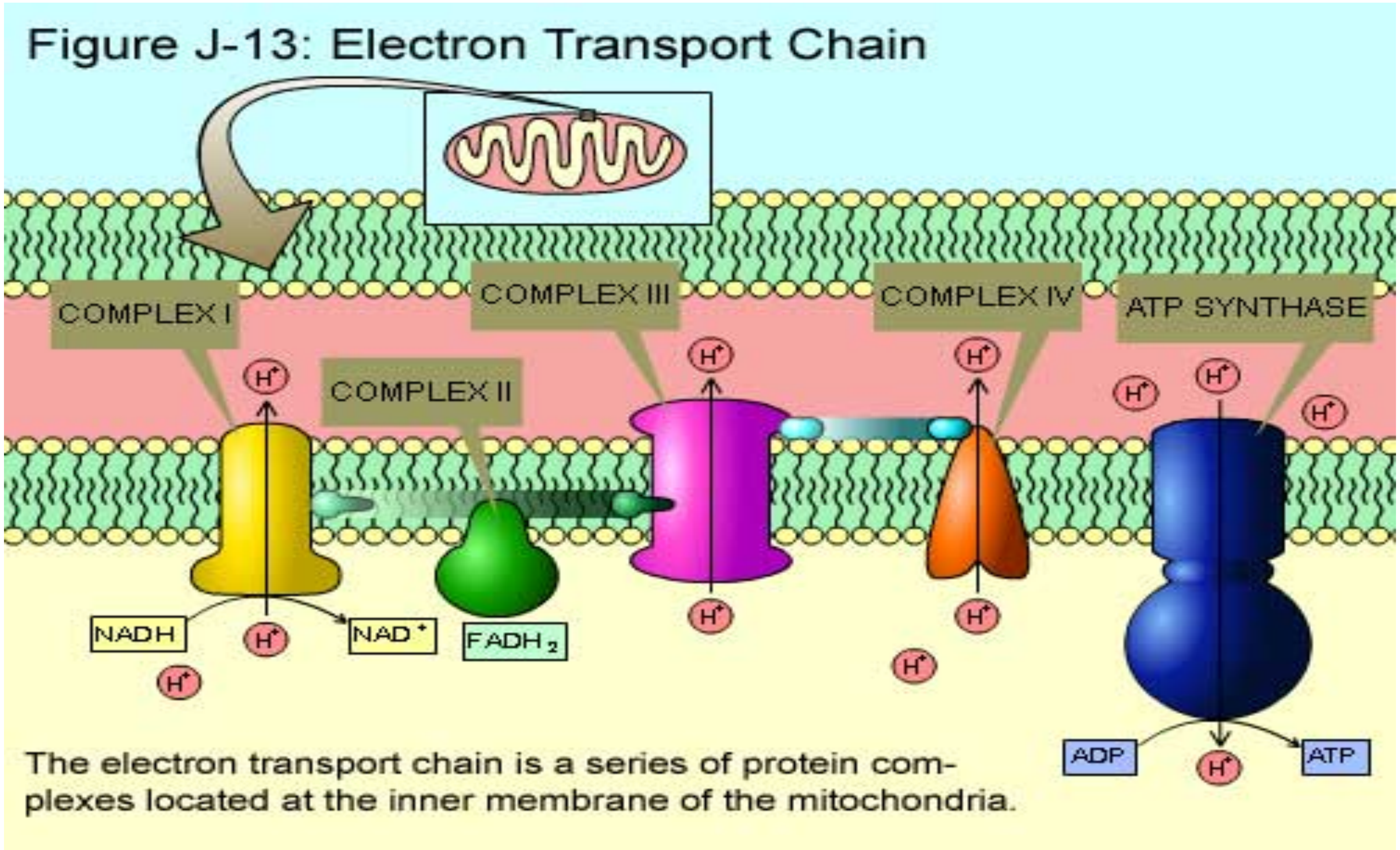
- Glycolysis produces pyruvate by oxidation of glucose
- The pyruvate is than oxidized to A.CoA in the mitochondria
- The acetly units are oxidized to CO_2 by TCA cycle in the mitochondrial matrix
- Energy released during both the oxidation rxns are collected by NAD^+ and FAD
- So NADH and $FADH_2$ carry energy in the form of electrons

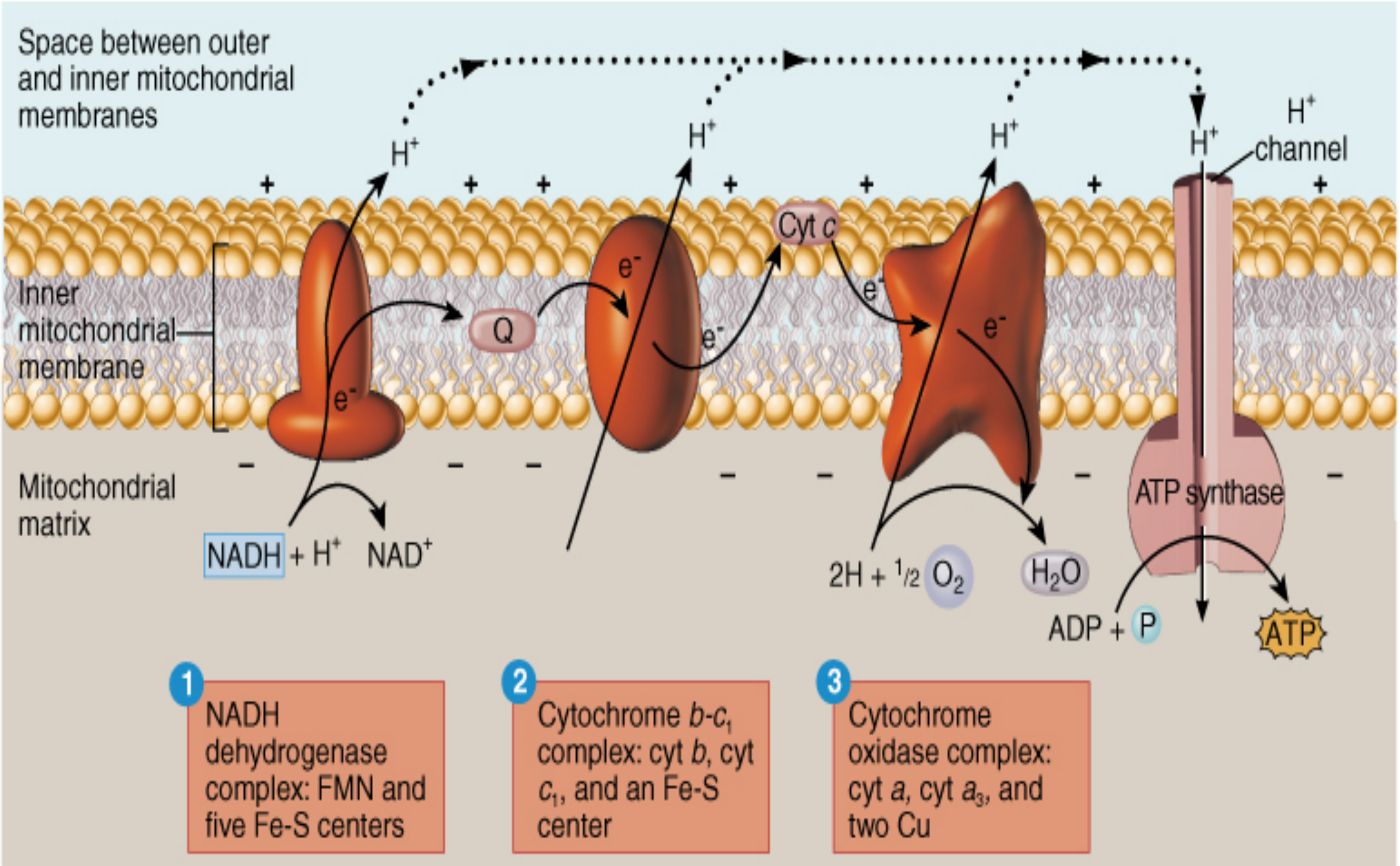
Where do all the NADH's and FADH2's Go

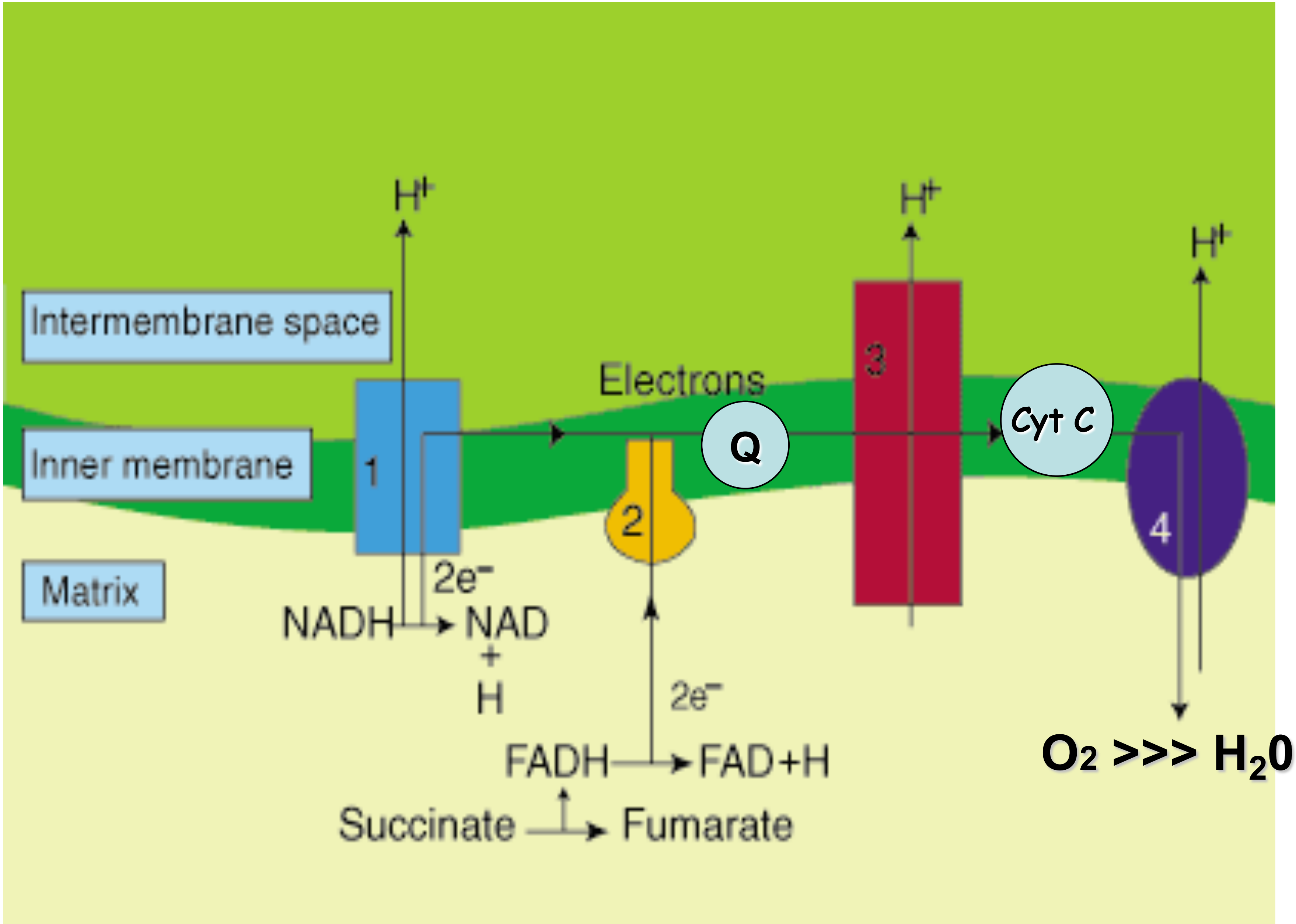


Electron Transport Chain

- Series of electron carriers embedded in the inner membrane of the mitochondria.



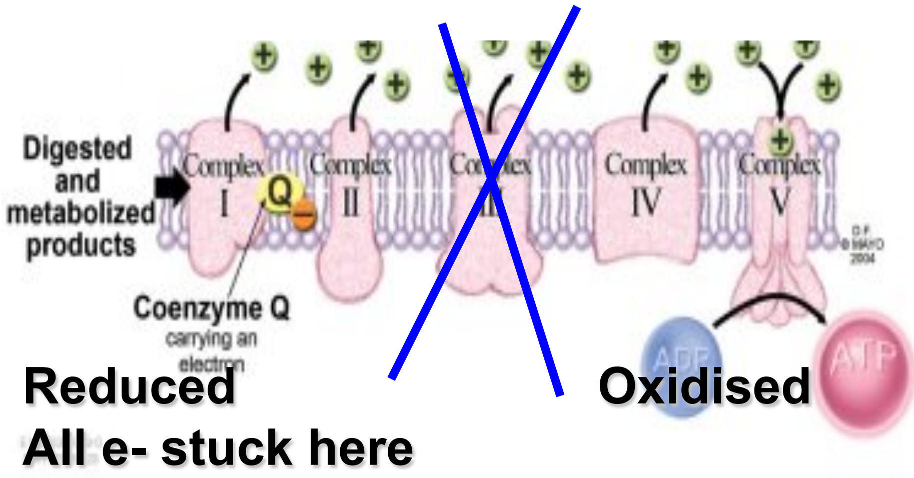

Space between outer and inner mitochondrial membranes
H+
H+
H+
H+
H+ channel
Cyt c
Inner mitochondrial membrane
Q
e-
e-
e-
e-
e-
e-
Mitochondrial matrix
NADH + H+
NAD+
2H + 1/2 O2
H2O
ATP synthase
ADP + P
ATP
1
NADH dehydrogenase complex: FMN and five Fe-S centers
2
Cytochrome b-c1 complex: cyt b, cyt c1, and an Fe-S center
3
Cytochrome oxidase complex: cyt a, cyt a3, and two Cu



H+
H+
H+
Intermembrane space
Electrons
3
Cyt C
Inner membrane
1
Q
2
4
Matrix
2e-
NADH
NAD
+
H
2e-
FADH
FAD+H
Succinate
Fumarate
O2 >>> H20

Inhibitors of ETC

- Inhibitors bind to the components of the electron transport chain and block electron transfer. All components before the block are stuck in a reduced state and all components after in an oxidized state.



Example

1. **Cyanide, carbon monoxide** **Blocks complex IV**
2. **rotenone, amytal** **Blocks complex I**
3. **antimycin** **Blocks complex III**

Inhibitors of ATP synthesis

They specially dissipates (destroys) the proton gradient

1. **Uncouplers**

- collapse the proton gradient by equalizing the proton concentration on both sides of membrane
- They diffuse across the membrane and pick up protons from one side and release then on the other side

2. Ionophores

- Hydrophobic molecules that disspate osmotic gradients by inserting them selves into the membrane and form a channel

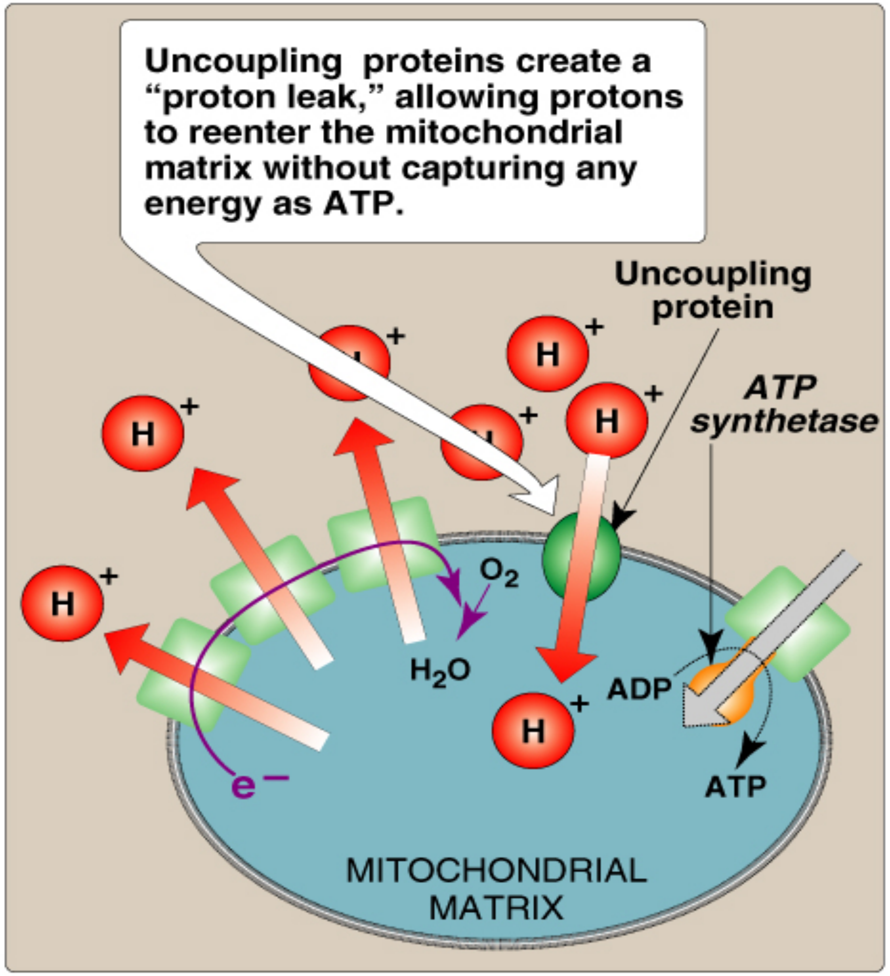
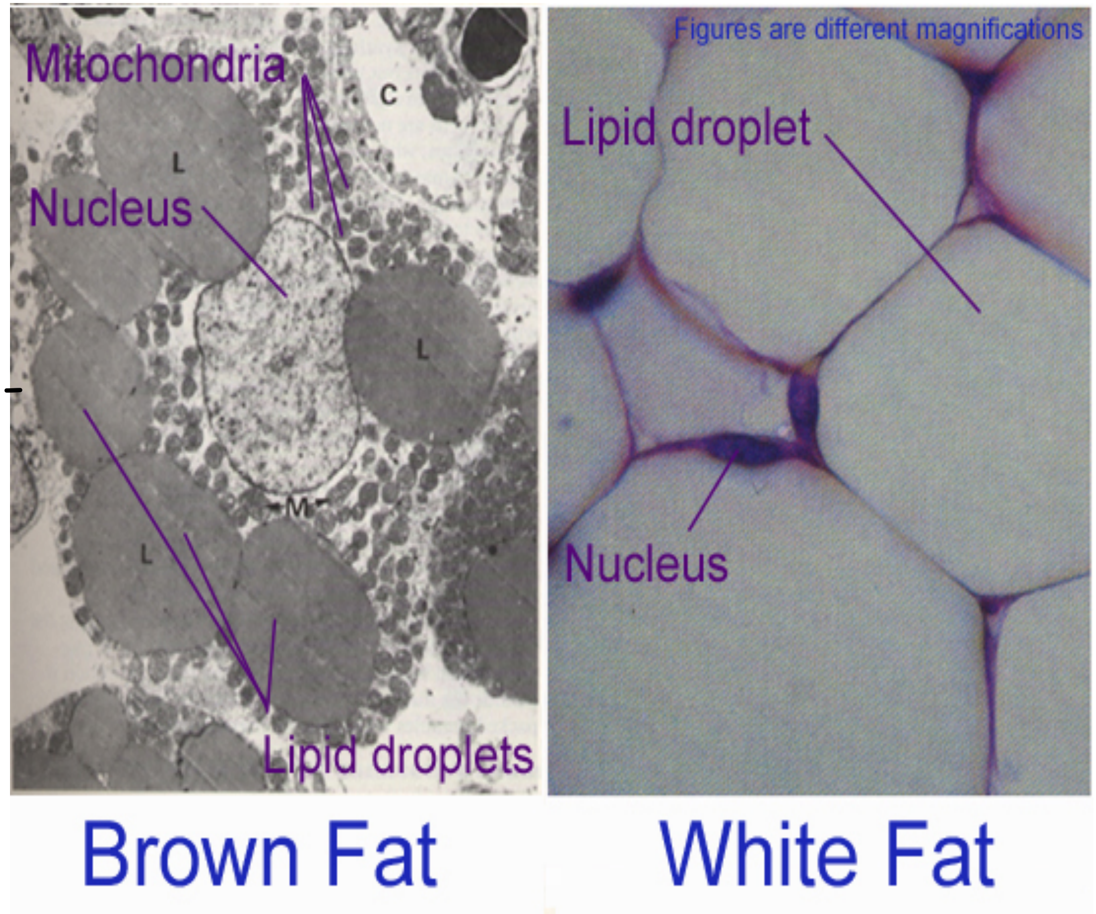


Figure 6.14

Transport of H^+ across mitochondrial membrane by 2,4-dinitrophenol.

Ever wondered how these keep warm?

Brown Fat



A dark-colored, mitochondrion-rich adipose tissue in many mammals that generates heat (not energy) to regulate body temperature, especially in hibernating animals.

- White adipocytes (fat cells) contain a single, large fat vacuole

- brown adipocytes contain several smaller vacuoles and a much higher number of mitochondria.

- Brown fat also contains more capillaries since it has a greater need for oxygen than most tissues

Study Questions

1. How do the enzyme complexes that make up the respiratory chain work?
2. How are the TCA cycle and glycolysis linked to ETC?
3. Differentiate between the effects of: -
   -Electron transport chain inhibitors
   -Uncouplers
1. Describe thermogenesis.
2. Apart from ATP synthesis what else is the proton gradient utilized for?
3. What is brown fat
4. How do babies and hibernating animals keep warm?