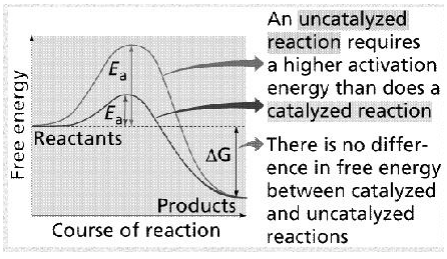
Metabolism

5.7.00:
- Enzymatic Reactions
- General Concepts of Metabolism
- Central Metabolism (Glycolysis, TCA, oxidative Phosphorylation)

12.7.00:
- Photosynthesis
- Metabolism of selected compounds
- Principles of Metabolic Engineering

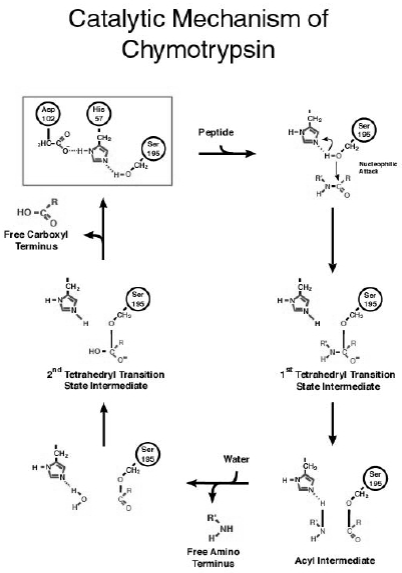
Principle of Enzymatic Catalysis I

- Enzymes are biocatalysts
- By decreasing the activation barrier enzymes enhance chemical reactions



Principle of Enzymatic Catalysis II

- Enzymes can be highly specific
- Most enzymes are regulated by activators and inhibitors

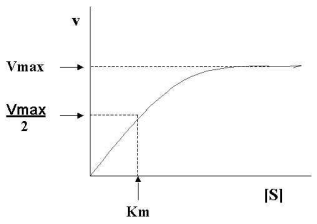


Principles of Enzymatic Catalysis III

- One enzymatic reaction really consists of many reactions
- The simplest example:

$$E + S \longrightarrow ES \longrightarrow E + P$$

- There are enzymatic reactions which involve dozens of reactions



Metabolic Pathways I

- There is not a clear definition of this term!
- Example for an abstract pathway:

  A ⟶ B ⟶ C ⟶ D ⟶ E
- Pathways are often regulated e.g. E inhibits the enzyme that converts A into B
- There are some myths about metabolism e.g. about rate-limiting steps and irreversible reactions even in widespread basic books

Metabolic Pathways II

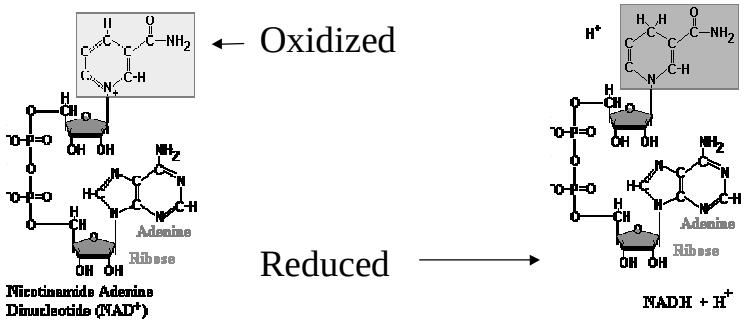
- Reactions that are thermodynamically not favorable are driven by a favorable reaction e.g. the hydrolysis of ATP:

  $ATP + H_2O \longrightarrow ADP + P_i + H^+$ (- 7.3 kcal/mol)

  $ADP + H_2O \longrightarrow AMP + P_i + H^+$ (- 7.3 kcal/mol)
- ATP hydrolysis shifts the equlibria of coupled reactions by a factor of up to 10^8

Metabolic Pathways III

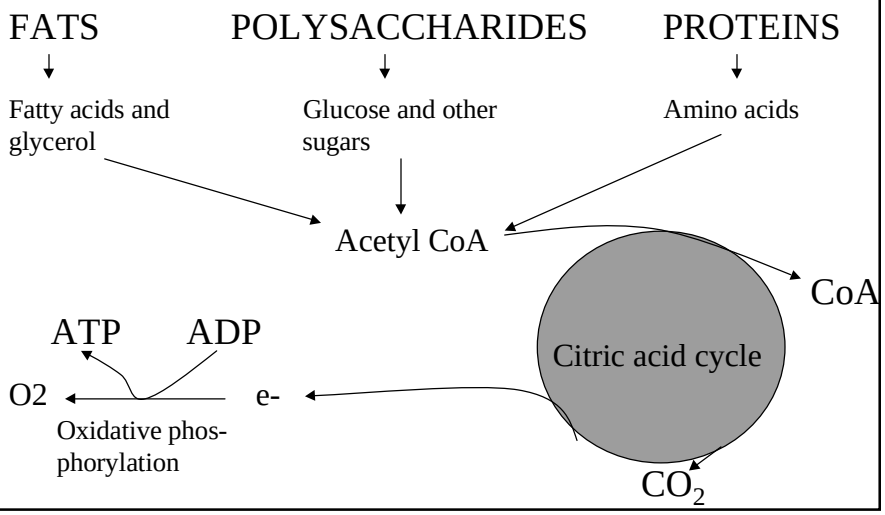
- The ultimate electron acceptor from fuel molecules is
- oxygen in aerobic organims
- Major electron carriers are NADH and flavins



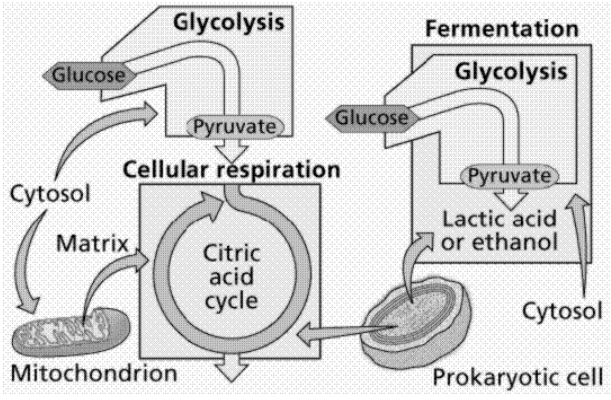
Metabolic Pathways IV

Carrier molecule	Group carried in activated form
ATP	Phosphoryl
NAD(P)H	Electrons
$FADH_2$	Electrons
Coenzyme A	Acyl
Biotin	CO_2
S-Adenosylmethionine	Methyl
……..	

Extracting Energy from Food



Metabolism is Organized in Compartments



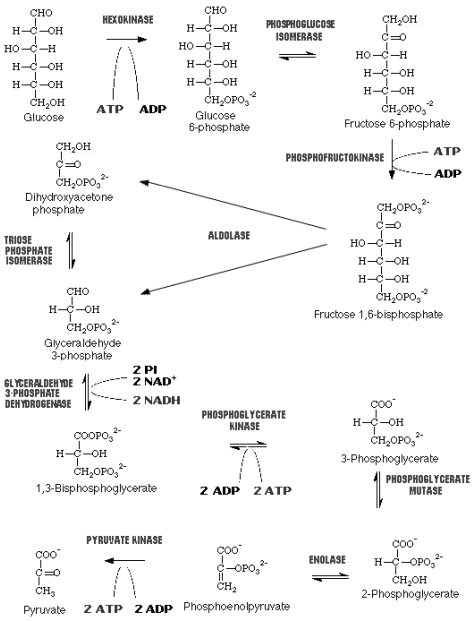
Glycolysis

- no regulatory inter-actions shown
- many of the enzymes occur in isoformes

glucose + 2 P_i + 2 ADP + 2 NAD^+

↓

2 pyruvate + 2 ATP + 2 NADH + 2 H^+ + 2 H_2O

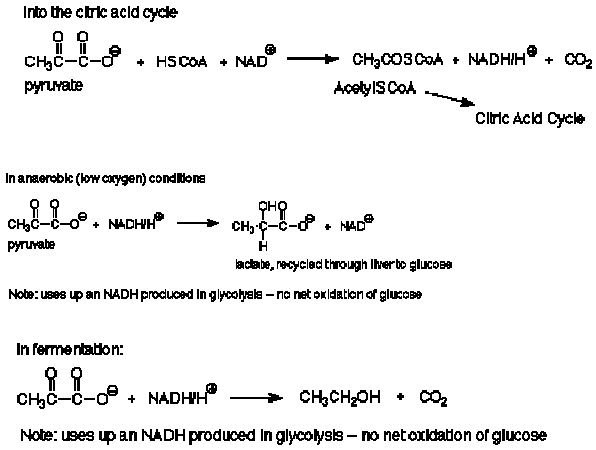


Phosphofructokinase

Fructose-6-phosphate ⟶ Fructose-1,6-bisphosphate

- inhibited by high levels of ATP
- activated by AMP
- inhibited by H^+
- inhibited by citrate
- activated by fructose-2,6-bisphosphate

Fate of Pyruvate



Oxygen deficiency

Fermentation

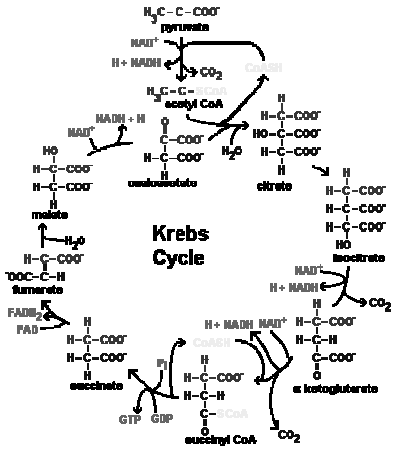
Dynamics of Glycolysis

- starving yeast
- mammalian muscle
- possibly in blood cells

- purpose is still a matter of debate
- involved in pulsatile production of insuline and therefore in diabetes

TCA- Tricarboxylic acid cycle

(Citric acid cycle/ Krebs cycle)



Citrate Synthase
Aconitase
Isocitrate Dehydrogenase
alpha-Ketoglutarate Dehydrogenase
Succinyl CoA Synthetase
Succinate Dehydrogenase
Fumarase
Malate Dehydrogenase

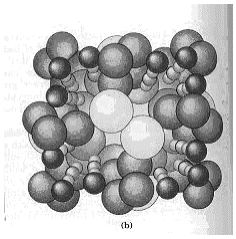
Acetyl CoA + $3NAD^+$ + FAD + GDP
$+P_i + 2\ H_2O$ ↓

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

Beriberi - originating in the malfunctioning of metabolism

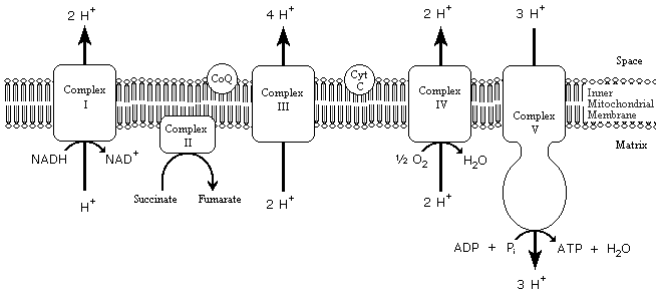
<u>Pyruvate dehydrogenase:</u>

The green cluster of spheres on the interior of the cubic arrangement are the 24 E2 (dihydrolipoamide acetyltransferase) catalytic domains. The red spheres projecting out from these are the lipoyllysyl domains of the E2s. The orange spheres on the "edges" of the cube represent the 24 dimeric E1s (pyruvatedehydrogenase). The yellow spheres in the center of the "cube face" represent the 6 dimeric E3s (dihydrolipoamide dehydrogenase).



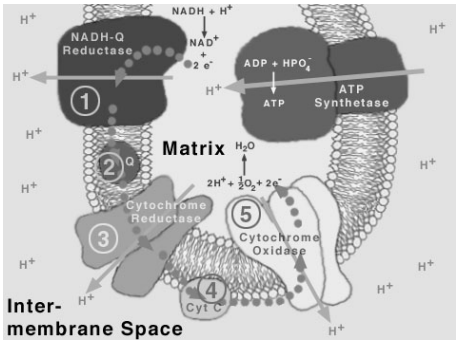
E1: Oxidative decarboxylation of Pyruvate (Thiamine Pyrophosphate)
E2: Transfer of the acetyl group to CoA (Lipoamide)
E3: Regeneration of the oxidized form of lipoamide (FAD)

Oxidative Phosphorylation



The general principle is the creation of a proton gradient which drives the synthesis of ATP

Enzymes in the Respiratory Chain



- Electron carrying groups are flavins, iron-sulfur-clusters, hemes, copper ions
- Electrons from $FADH_2$ are carried by Ubiquinone

How the electrons of cytosolic NADH enter mitochondria