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PSC311; Biochemistry

Friday, Nov 1st to Wed, Nov 6th, 2024

Metabolism-Glycolysis & Citric acid cycle

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ALBANY COLLEGE OF PHARMACY
AND HEALTH SCIENCES
PHARMACEUTICAL SCIENCES

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Friday, Nov 1st to Wed, Nov 6th, 2024

Metabolism-Glycolysis & Citric acid cycle

Learning objectives:

- Explain in a broad sense, what cellular respiration is and why we need it.
- Be familiar with the steps of glycolysis and citric acid cycle.
- Outline the key regulatory steps of glycolysis and citric acid cycle.
- Summarize the energy output of glycolysis and the citric acid cycle.

Corresponding chapters:

King, Part II, Chaps 10 and 16

3

Lectures 23-25: Metabolism-Glycolysis and Citric acid cycle

Topic	slides
I. Metabolism overview.	5
II. Overview of cellular respiration.	6-10
III. Role of glucose in human physiology.	13-15
IV. Glycolysis (part I).	16-36
V. The role of vitamins in humans (in glycolysis).	37-39
VI. Glycolysis (part II).	40-48
VII. Citric acid cycle (Oxidation of acetyl CoA).	49-72
VIII. Electron transfer and oxidative phosphorylation.	73-80

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Metabolism:

The chemical processes occurring within a living cell or organism that are necessary for the maintenance of life. In metabolism, some substances are broken down (catabolism) to yield energy for vital processes while other substances, necessary for life, are synthesized (anabolism).



5

How humans get energy:

Overview of Cellular Respiration

slides 7-12

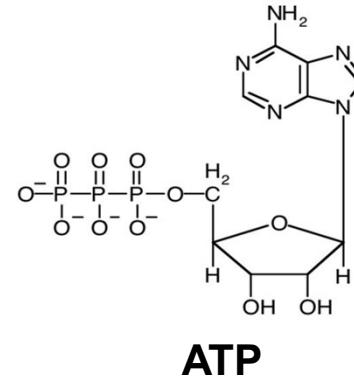
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All living entities require energy for survival

Where do we derive our energy from?

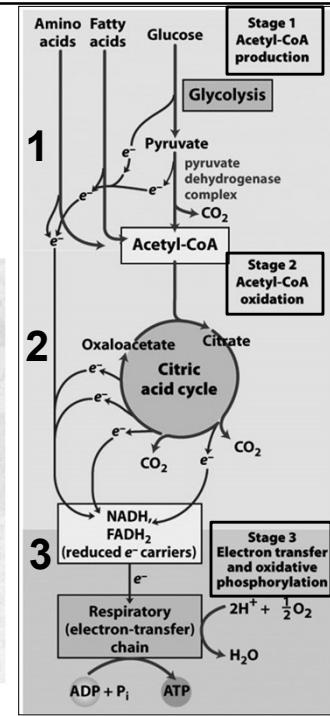
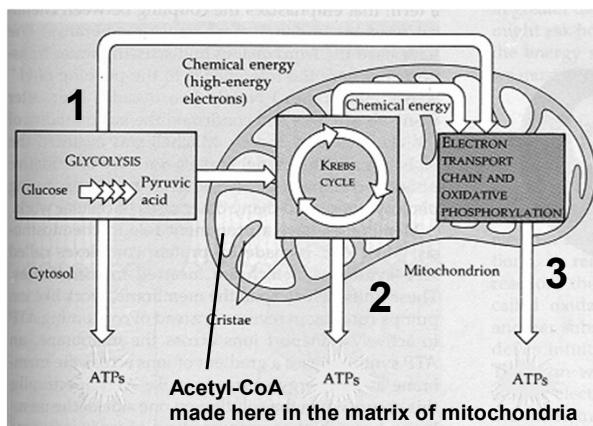
As we have seen, ATP is the major energy “currency” in our bodies

How is ATP produced?



7

Cellular respiration:
Molecular process by which cells produce energy (ATP) by consuming O₂ and producing CO₂. There are three stages of cellular respiration



8

- Oxidation is loss of electrons.
- Reduction is gain of electrons.

It is essential that you remember these definitions.

There is a very easy way to do this.

As long as you remember that you are talking about electron transfer:

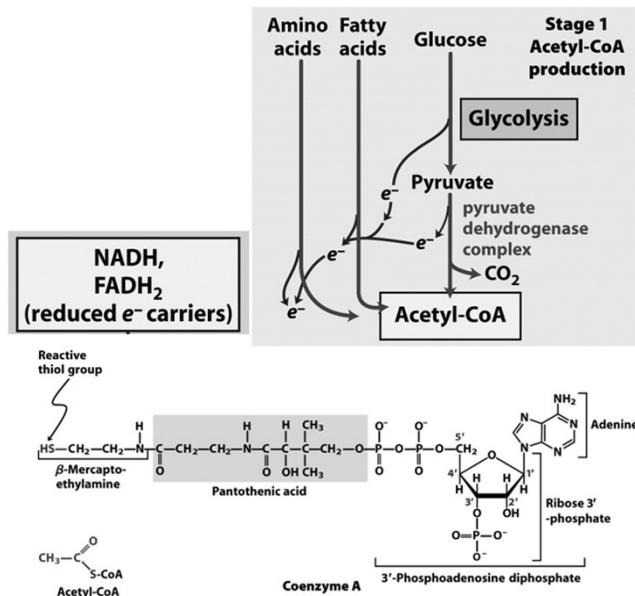
OIL RIG

oxidation is loss reduction is gain

As a general rule of thumb, if a carbon-containing molecule gains H atoms or loses O atoms during a reaction, it's likely been reduced (gained electrons). Conversely, if it loses H atoms or gains O atoms, it's probably been oxidized (lost electrons).

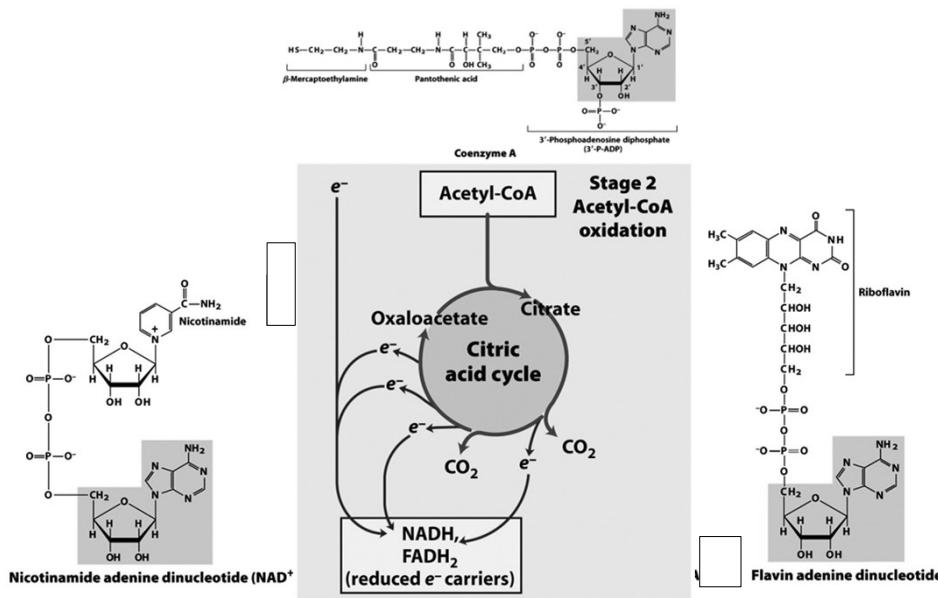
9

Stage 1: oxidation of fatty acids, glucose, and some amino acids to yield acetyl-CoA



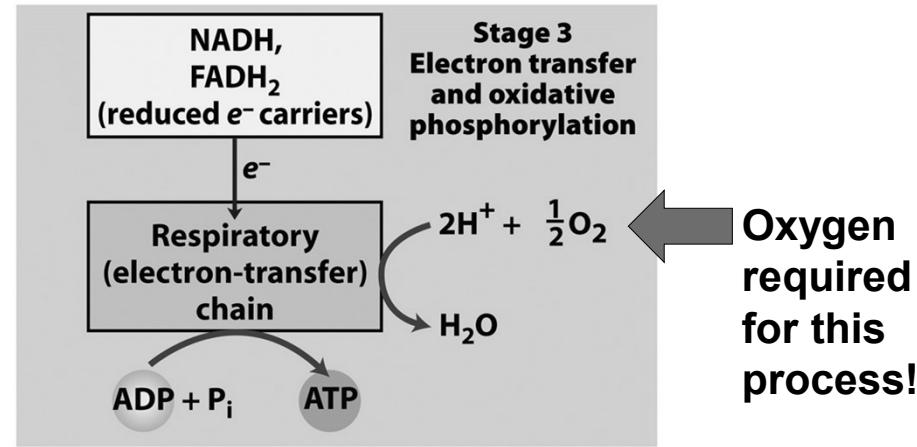
10

Stage 2: oxidation of acetyl groups in the citric acid cycle includes four steps in which electrons are transferred to electron carriers



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**Stage 3: electrons carried by NADH and FADH₂ are funneled into a chain of mitochondrial electron carriers
(Electron transfer and oxidative phosphorylation)**



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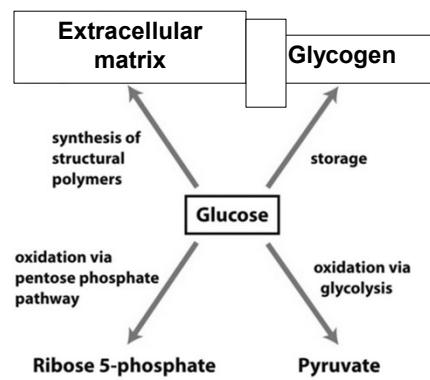
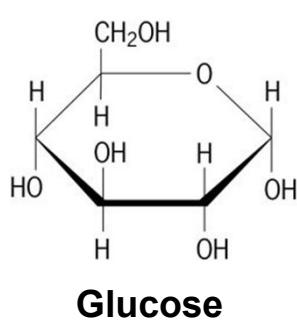
Role of glucose in human physiology

slides 14-15

13

Glucose plays a critical role in metabolism

- 1) Glucose is rich in potential energy (2840 kJ/mol released during glycolysis and citric acid cycle) MW=180.1559
- 2) Through the pentose phosphate pathway, can form precursors for nucleotides and nucleic acids and aromatic amino acids.
- 3) Can be polymerized for energy storage.
- 4) Can be incorporated into other macromolecules.



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To get some sense of what a joule is:

1 joule: the energy required to lift a small apple (with a mass of approximately 100 g) vertically through one meter of air



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Glycolysis**slides 17-36**

16

Which of the following is/are used to transport electrons ?

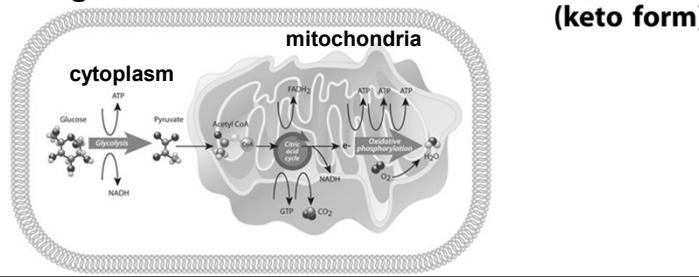
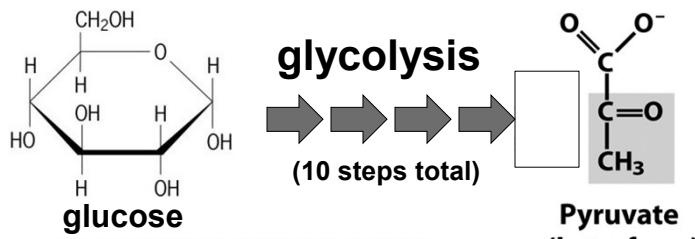
- NADH.
- FAD.
- NADPH.
- All of the above.
- None of the above

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The first stage of getting energy from glucose is glycolysis (from *glycose*, an older term for glucose plus; *lysis* - degradation) which is the metabolic pathway that converts glucose $C_6H_{12}O_6$, into pyruvate, $CH_3COCOO^- + H^+$

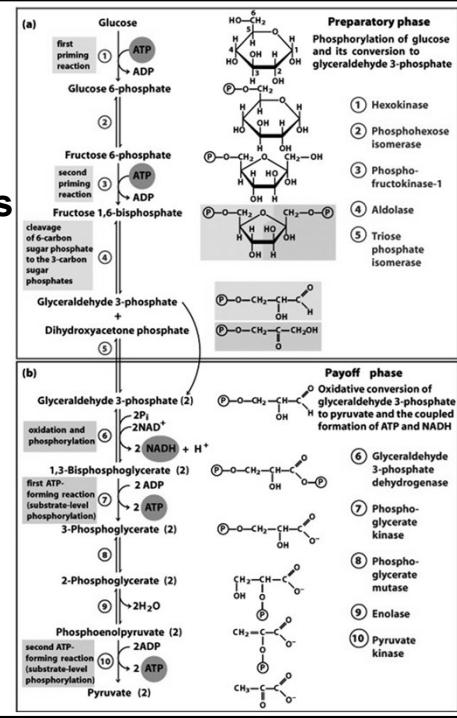


18

The two phases of glycolysis

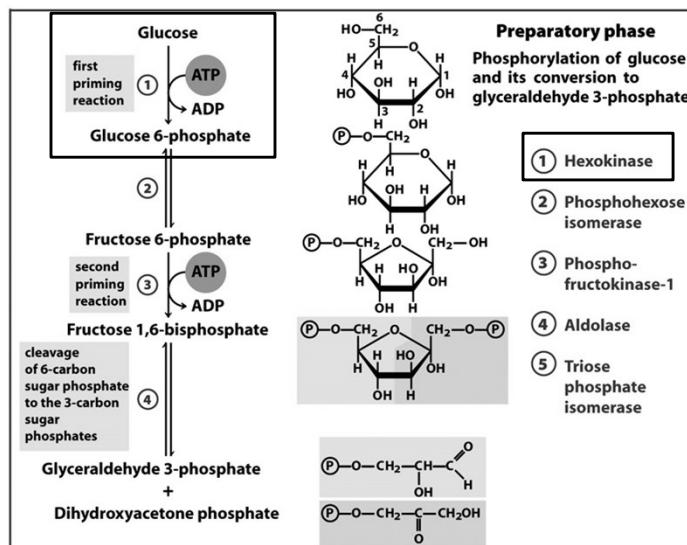
Preparatory phase: 5 steps

Payoff Phase: 5 steps



19

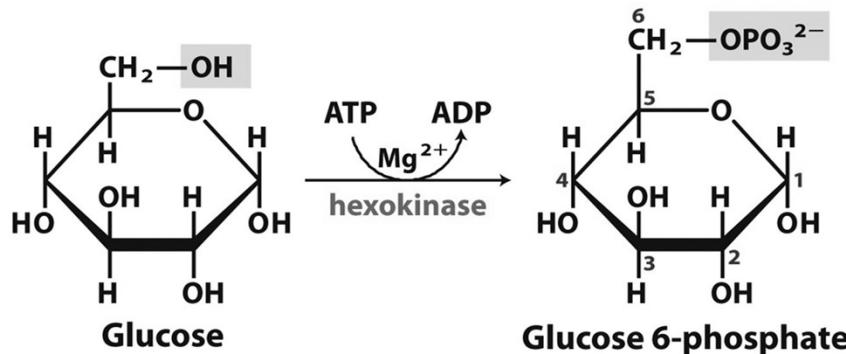
Preparatory Phase:



Isomerization is defined as the transformation of a molecule into a different isomer.
 Isomer: each of two or more compounds with the same formula but a different arrangement of atoms in the molecule and different properties

20

The first step in glycolysis is the addition of a phosphate group by hexokinase



$$\Delta G'^\circ = -16.7 \text{ kJ/mol}$$

The phosphorylation of glucose traps the glucose in the cell

21

Which of the following is/are used to transport electrons ?

NADH.

FAD.

NADPH.

All of the above.

None of the above

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Hexokinase isozymes

Isoenzymes (or isozymes) are a group of enzymes that catalyze the same reaction but have different enzyme forms and catalytic efficiencies. Coded by different genes.

There are four hexokinase isozymes (I, II, III, IV). Hexokinase type IV is also called Glucokinase.

Hexokinase vs Glucokinase

	Hexokinase	Glucokinase (Hexokinase type IV)
Location	All the tissues	Liver & pancreatic β cell
K_m for glucose	0.1 mM (1.8 mg/dL)	10 mM (180 mg/dL)
Relationship between glucose concentration & reaction rate	Hyperbolic curve Red curve above	Sigmoidal curve Blue curve above
Feedback inhibition by Glucose-6-Phosphate	Yes	No
Function	Basal metabolism of glucose	Glucose sensor -uses glucose only at high concentration.
Induction by Insulin	No	Yes

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Regulation of Glucose metabolism

HEXOKINASE

- Key Features**
- 1st of three regulated enzymes in glycolysis
- Catalyzes 1st glycolytic reaction: irreversible phosphorylation of glucose
- 4 isozymes in mammals —
 - Hexokinase I, II & III - (Hexokinase)
 - Hexokinase IV - (Glucokinase)
- Hexokinase vs. Glucokinase**
- Key differences —
 - Tissue distribution
 - Kinetics
 - Regulation

HEXOKINASE Skeletal muscle (Allosteric regulation)

GLUCOKINASE Liver (Hormonal regulation)

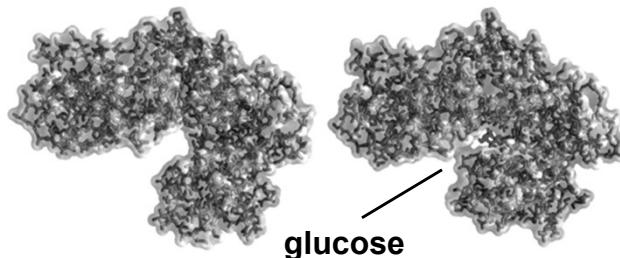
Enzyme activity graph

Diabetes mellitus Treat with insulin to lower pathologically high blood glucose

Pancreas (beta cells)

24

Induced fit in hexokinase



Inactive conformation Active conformation

Animation on induced fit:

http://web.chem.ucsb.edu/~molvisual/ABLE/induced_fit/index.html

Four hexokinase isozymes (I-IV) (different proteins having the same activity) in humans expressed in tissue specific manner)

25

Hexokinases I-III are regulated enzymes

Activity is inhibited by glucose-6 phosphate;

an example of allosteric regulation

Allosteric regulation; when modulators or effectors, which are generally small metabolites or co-factors, bind to sites other than the active sites and cause a conformational change to alter the activity of enzymes.

In this case, the type of allosteric regulation is feedback inhibition in which the product or a metabolite downstream of the reaction inhibits the enzyme that synthesizes it.

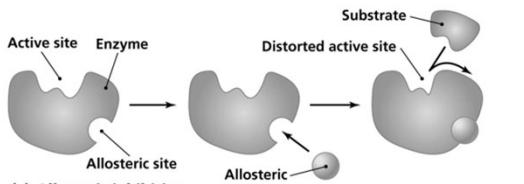
Very important!

26

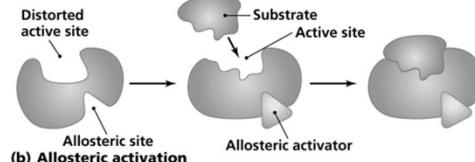
Allosteric regulation:

The control of the activity of an enzyme by small molecules binding to a site other than the substrate binding site

Allosteric Inhibition:



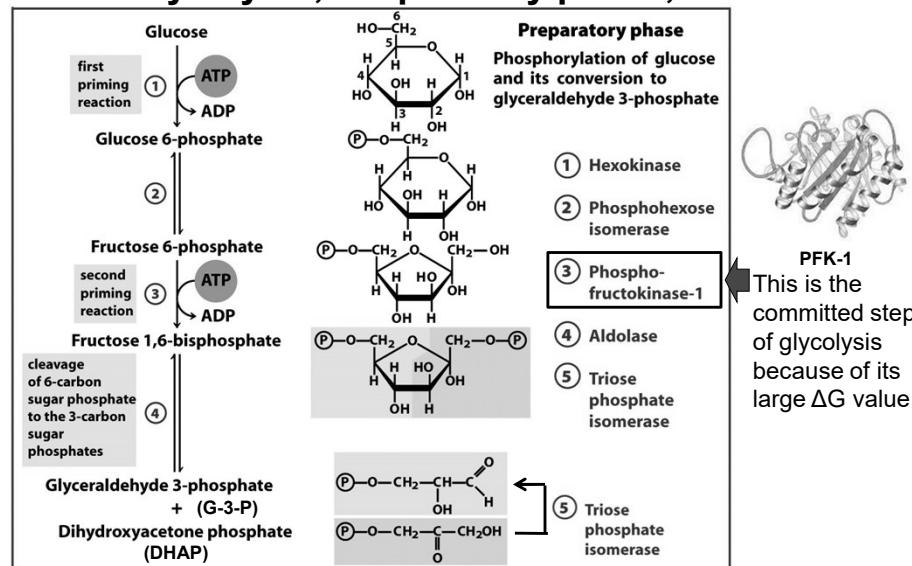
Allosteric Activation:



<http://highered.mheducation.com/olcweb/cgi/pluginpop.cgi?it=swf::535::535::sites/dl/free/0072437316/120070/bio10.swf::Feedback%20Inhibition%20of%20Biochemical%20Pathways>

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Glycolysis; Preparatory phase, cont

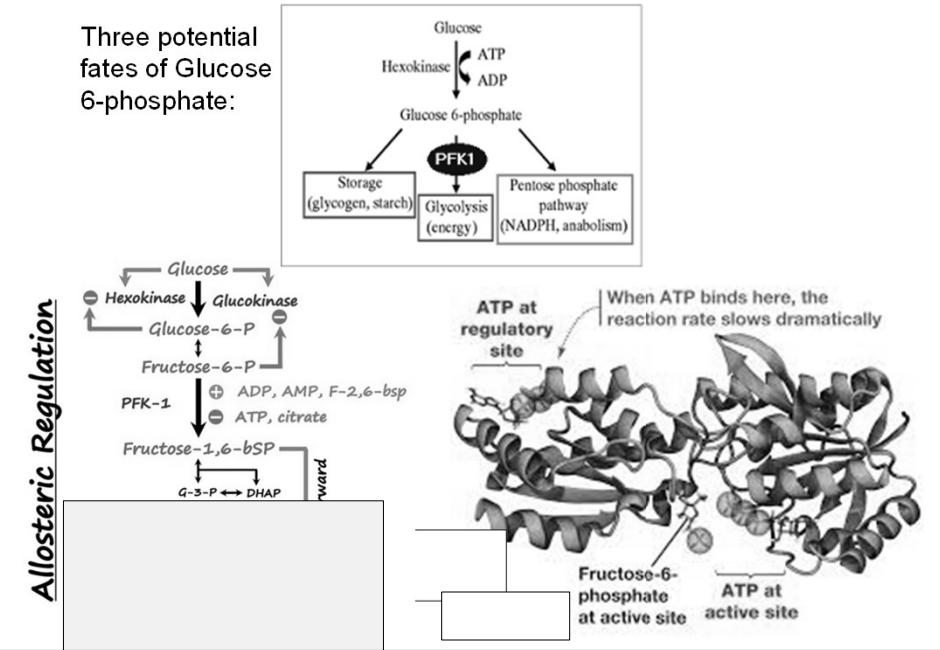


Isomerization is defined as the transformation of a molecule into a different isomer.
Isomer: each of two or more compounds with the same formula but a different arrangement of atoms in the molecule and different properties

28

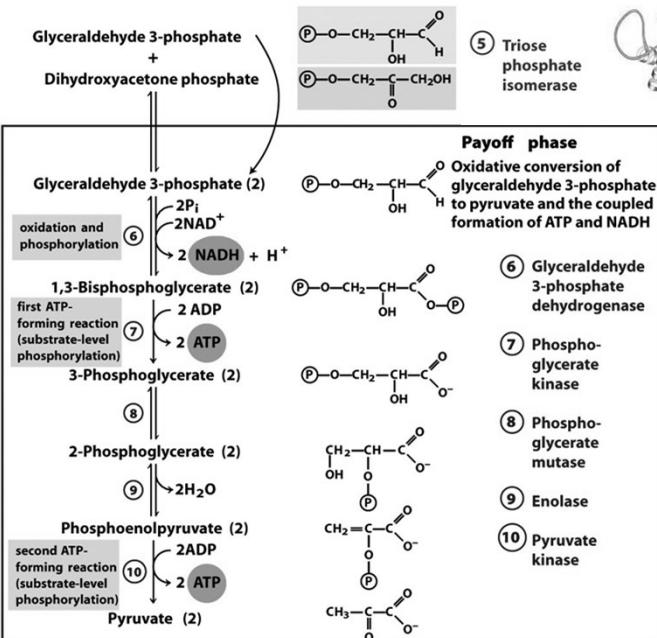
Allosteric Regulation of Glycolysis

Three potential fates of Glucose 6-phosphate:



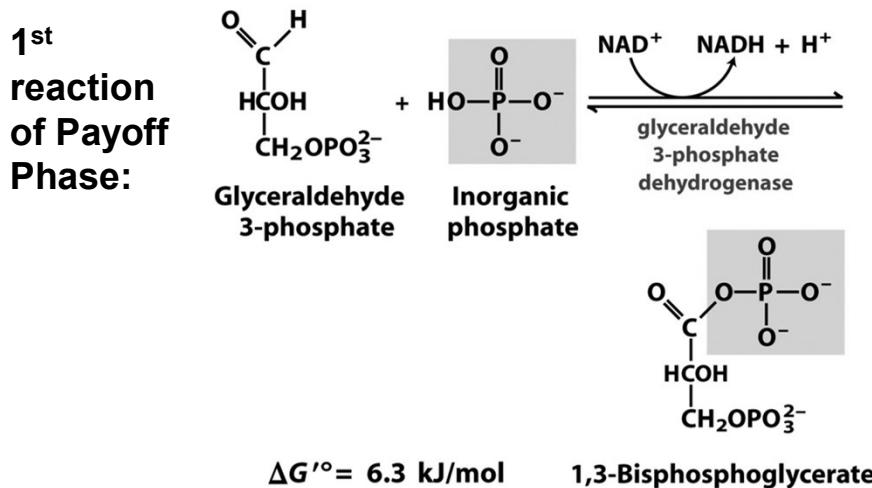
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Glycolysis; Payoff phase



30

Oxidative conversion of glyceraldehyde 3-phosphate to pyruvate begins with:



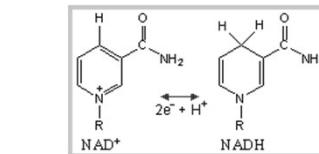
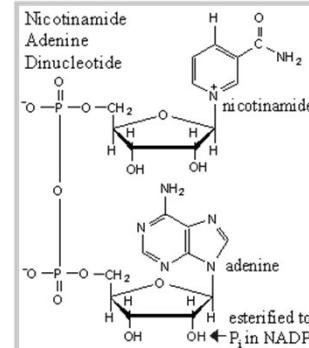
31

NAD⁺ and FAD

Two important electron carriers in metabolism are NAD⁺ and FAD. NAD⁺ (Nicotinamide Adenine Dinucleotide) functions as an electron acceptor in catabolic pathways.

The nicotinamide ring of NAD⁺, which is derived from the vitamin niacin, accepts 2 e⁻ and one H⁺ in going to the reduced state, as NAD⁺ becomes NADH.

NADH/NADPH is similar, except for an additional phosphate esterified to a hydroxyl group on the adenosine ribose. NADPH functions as an electron donor in synthetic pathways.

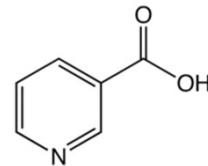


The electron transfer reaction may be summarized as: $\text{NAD}^+ + 2 \text{e}^- + \text{H}^+ \rightleftharpoons \text{NADH}$
It may also be written as:
 $\text{NAD}^+ + 2 \text{e}^- + 2\text{H}^+ \rightleftharpoons \text{NADH} + \text{H}^+$

32

Niacin (vitamin B₃)

Also known as vitamin B₃, is found in dairy products, poultry, fish, lean meats, nuts, and eggs. Legumes and enriched breads and cereals also supply some niacin



It is used with diet changes (restriction of cholesterol and fat intake) to reduce the amount of cholesterol and certain fatty substances in the blood. Niacin is also used to prevent and treat pellagra (niacin deficiency), a disease caused by inadequate diet and other medical problems.

The symptoms of pellagra are commonly referred to as the three "Ds": **sun-sensitive dermatitis, diarrhea, and dementia**. A fourth "D," death, occurs if pellagra is left untreated

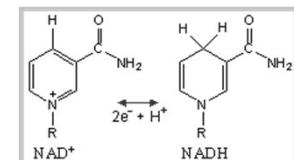
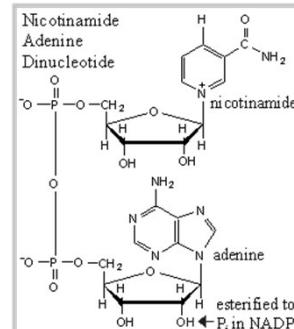
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 $\text{NAD}^+ + 2 \text{e}^- + 2\text{H}^+ \rightleftharpoons \text{NADH} + \text{H}_2\text{O}$

34

- **Oxidation is loss of electrons.**
- **Reduction is gain of electrons.**

It is essential that you remember these definitions.

There is a very easy way to do this.

As long as you remember that you are talking about electron transfer:

OIL RIG

oxidation is loss reduction is gain

As a general rule of thumb, if a carbon-containing molecule gains H atoms or loses O atoms during a reaction, it's likely been reduced (gained electrons). Conversely, if it loses H atoms or gains O atoms, it's probably been oxidized (lost electrons).

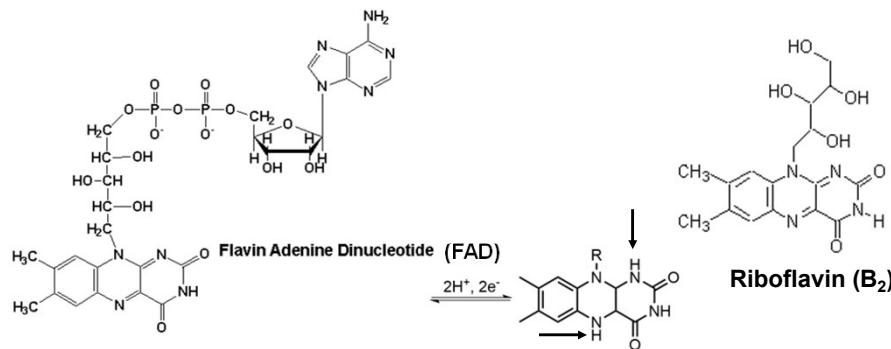
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FAD (Flavin Adenine Dinucleotide) also functions as an electron transporter. The portion of FAD that undergoes reduction/oxidation is the dimethylisoalloxazine ring, derived from the vitamin riboflavin.

FAD normally accepts 2 e⁻ and 2 H⁺ in going to its reduced state:

- FAD + 2 e⁻ + 2 H⁺ ⇌ FADH₂
- NAD⁺ is a coenzyme, that reversibly binds to enzymes.
 - FAD is a prosthetic group, that usually remains tightly bound at the active site of an enzyme.

Riboflavin is a B vitamin (B₂). It can be found in certain foods such as milk, meat, eggs, nuts, enriched flour, and green vegetables.



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Vitamins and their role in human biology including glycolysis

slides 38-39

37

Vitamins:

Organic substances required in small quantities in the diet. Generally functions as a component of a coenzyme.

Vitamins include: A, C, D, E, K, Thiamine (B_1), Riboflavin (B_2), Niacin (B_3), Pantothenic acid (B_5), Pyridoxine (B_6), Biotin (B_7), Folic acid (B_9), Cobalamins (B_{12}).

Vitamins are distinguished from minerals, such as calcium, iron, and magnesium, which are also essential for optimum health (these are elements). Vitamins are organic and can be broken down by heat, air, or acid. Minerals are inorganic and hold on to their chemical structure

The vitamins in red are fat-soluble



38

Natural Medicines Comprehensive Database rates effectiveness based on scientific evidence according to the following scale: *Effective, Likely Effective, Possibly Effective, Possibly Ineffective, Likely Ineffective, Ineffective, and Insufficient Evidence to Rate*.

The effectiveness ratings for RIBOFLAVIN (VITAMIN B2) are as follows:

Effective for...

Preventing and treating riboflavin deficiency and conditions related to riboflavin deficiency.

Possibly effective for...

Preventing migraine headaches. Taking high-dose riboflavin (400 mg/day) seems to significantly reduce the number of migraine headache attacks. However, taking riboflavin does not appear to reduce the amount of pain or the amount of time a migraine headache lasts.

Preventing cataracts, an eye disorder.

Insufficient evidence to rate effectiveness for...

Lactic acidosis (a serious blood-acid imbalance) in people with acquired immunodeficiency syndrome (AIDS). There is preliminary clinical evidence that riboflavin may be useful for treating lactic acidosis in patients with acquired immunodeficiency syndrome (AIDS) caused by drugs called nucleoside analog reverse transcriptase inhibitors (NRTI).

Preventing cervical cancer. There is evidence that increasing riboflavin intake from dietary and supplement sources, along with thiamine, folic acid, and vitamin B12, might decrease the risk of developing precancerous spots on the cervix.

Acne.

Muscle cramps.

Boosting the immune system.

Aging.

Maintaining healthy skin and hair.

Canker sores.

Memory loss including Alzheimer's disease.

Other conditions.

More evidence is needed to rate the effectiveness of riboflavin for these uses.

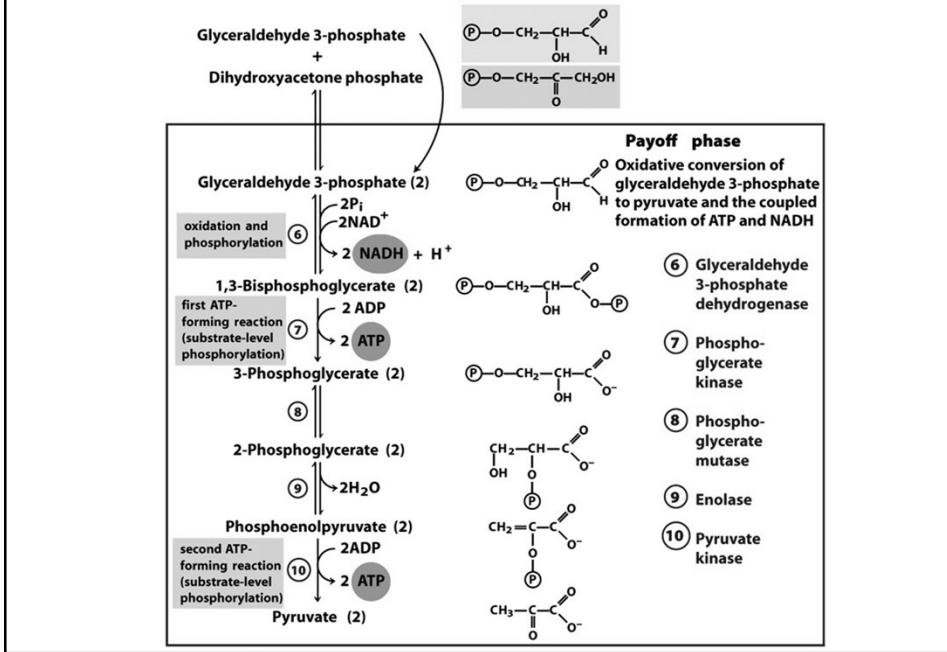
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Back to Glycolysis

slides 41-48

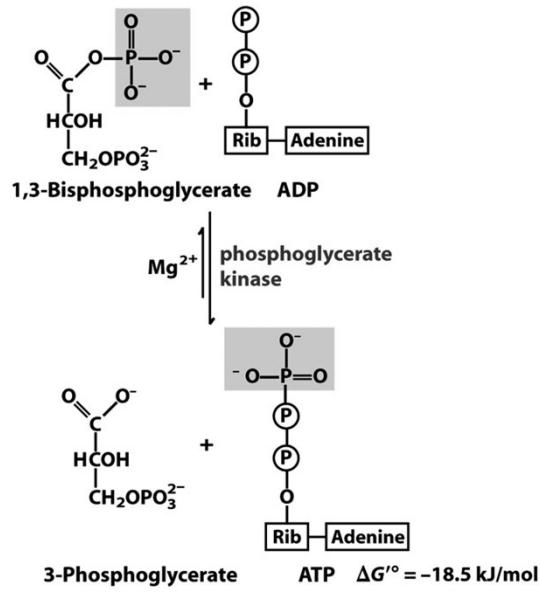
40

The payoff cycle of glycolysis



41

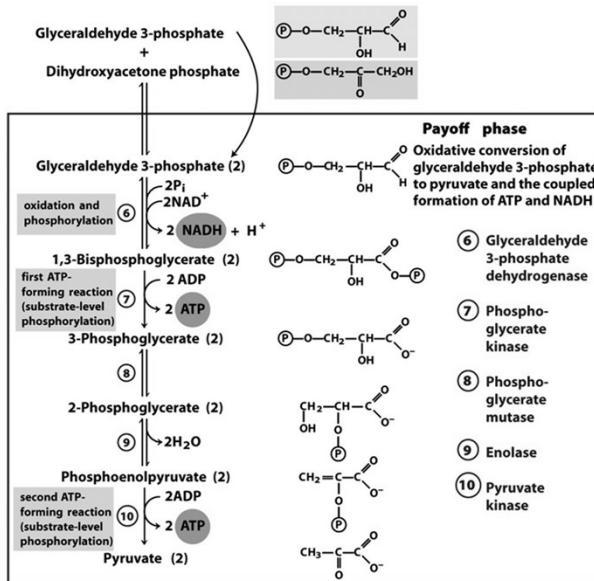
The second reaction of the payoff phase of glycolysis



Substrate level phosphorylation:
the formation of ATP by phosphoryl group transfer from a substrate. The name is to distinguish this mechanism from oxidative phosphorylation which occurs in the mitochondria

42

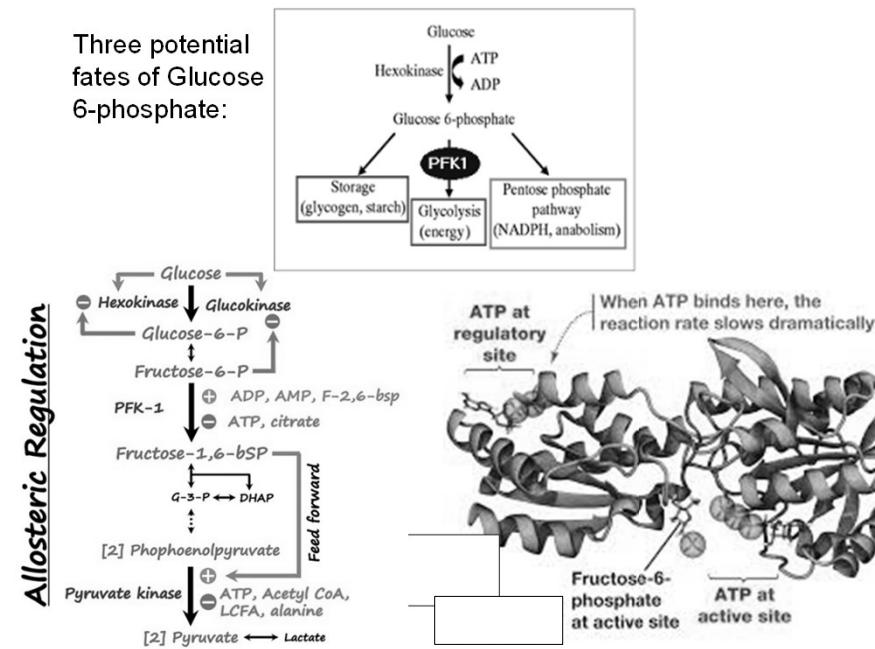
The rest of the payoff cycle of glycolysis



In the final reaction of glycolysis, the high-energy phosphate of phosphoenolpyruvate is transferred to ADP, yielding pyruvate plus ATP

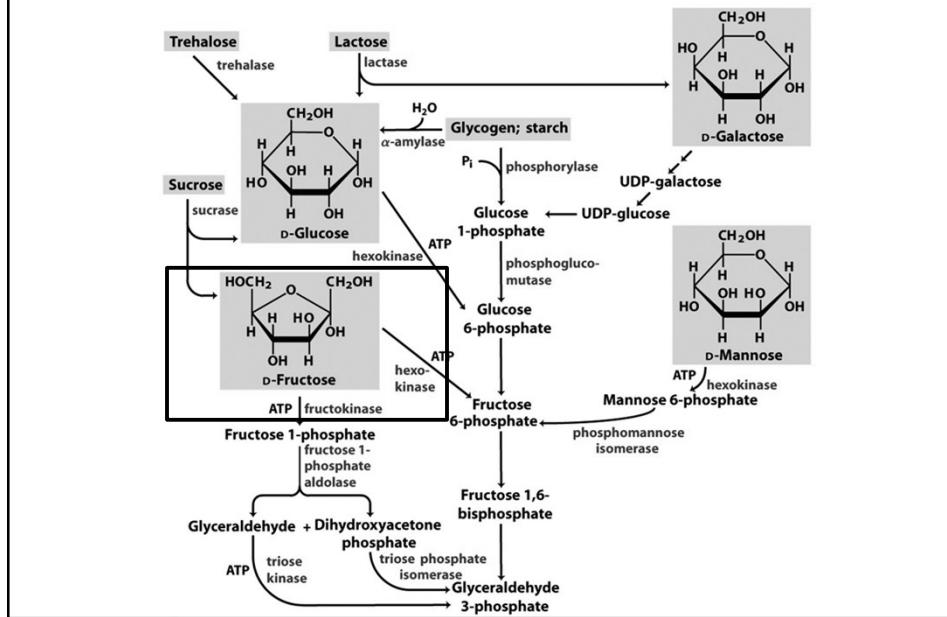
43

Allosteric Regulation of Glycolysis



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Entry of dietary glycogen, starch, disaccharides, and hexoses into the preparatory stage of glycolysis



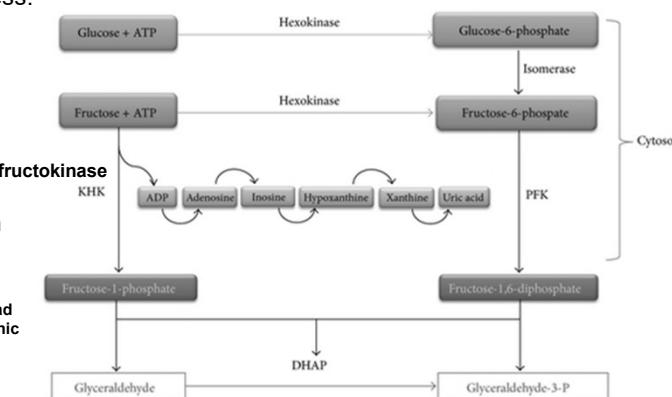
45

Fructose metabolism

In the liver, fructose bypasses the two highly regulated steps of glycolysis, catalyzed by **hexokinase** and **phosphofructokinase (PFK-1)**, both of which are inhibited by increasing concentrations of their byproducts. Instead, fructose enters the pathway at a level that is not regulated and is metabolized to fructose-1-phosphate primarily by **fructokinase** or **ketohexokinase (KHK)**. Fructose may also be metabolized by hexokinase; however, the K_m for fructose is much higher than glucose, and hence minimal amounts of fructose are metabolized via this pathway. **Fructokinase** has no negative feedback system, and ATP is used for the phosphorylation process.

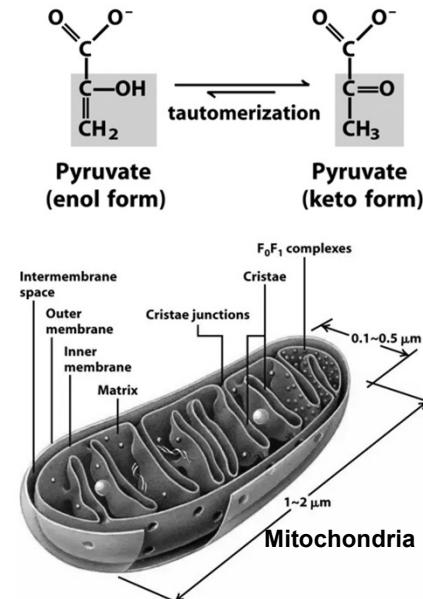
As a result, continued fructose metabolism results in intracellular phosphate depletion, activation of AMP deaminase, and **uric acid** generation which is harmful at the cellular level.

High levels of uric acid can lead to: Gout, Kidney stones, Chronic kidney disease, High blood pressure and heart failure, Metabolic syndrome



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What happens to the pyruvate produced by glycolysis?

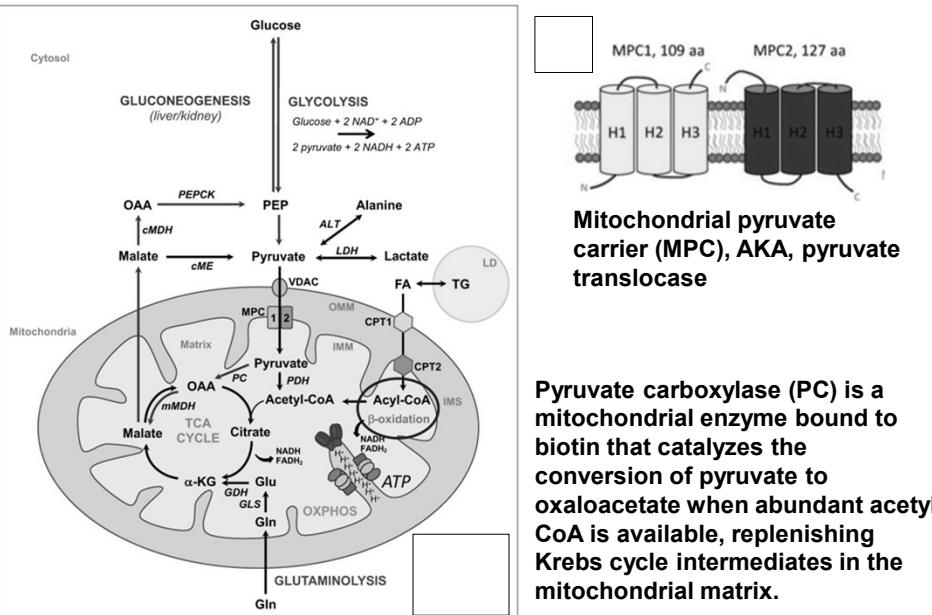


tautomerism, the existence of two or more chemical compounds that are capable of facile interconversion, in many cases merely exchanging a hydrogen atom between two other atoms, to either of which it forms a covalent bond.

Unlike other classes of isomers, tautomeric compounds exist in mobile equilibrium with each other, so that attempts to prepare the separate substances usually result in the formation of a mixture that shows all the chemical and physical properties to be expected on the basis of the structures of the components.

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Pyruvate metabolism and transport into mitochondrial matrix



Pyruvate carboxylase (PC) is a mitochondrial enzyme bound to biotin that catalyzes the conversion of pyruvate to oxaloacetate when abundant acetyl CoA is available, replenishing Krebs cycle intermediates in the mitochondrial matrix.

48

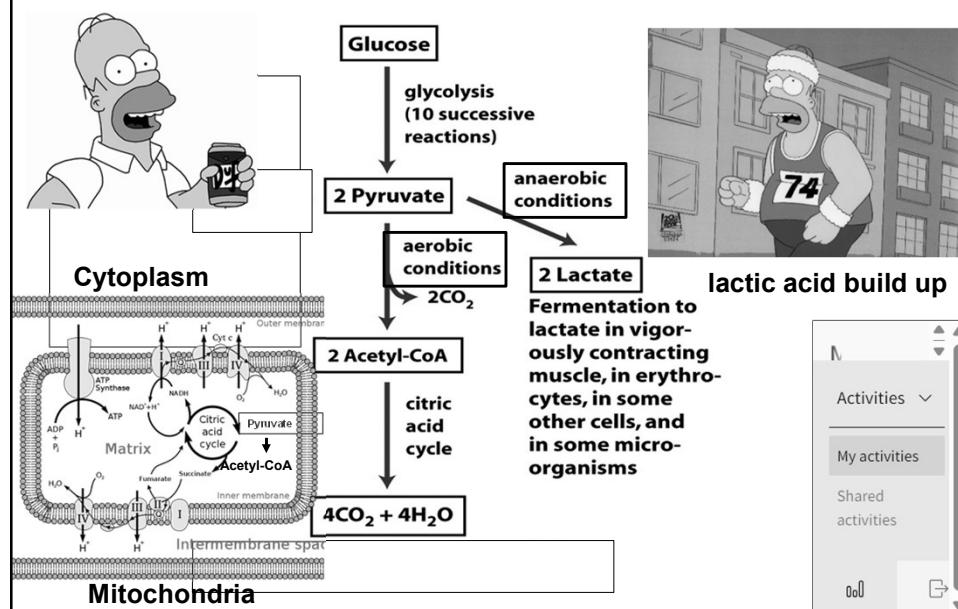
The second phase of respiration:

Formation of acetyl CoA

slides 50-58

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Fermentation process in humans

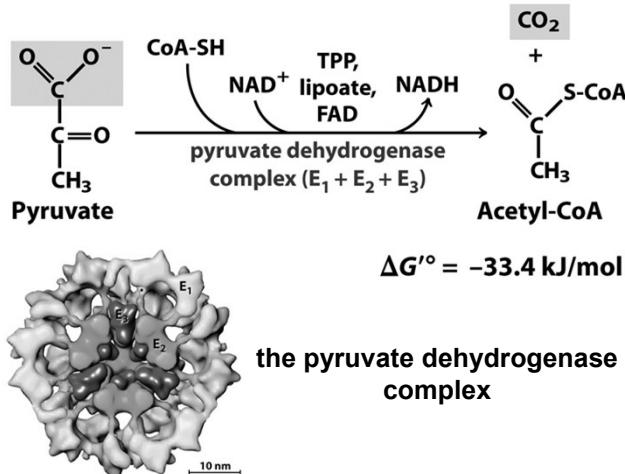


50

Pyruvate can get converted to acetyl-CoA. The reactions are catalyzed by the pyruvate dehydrogenase complex

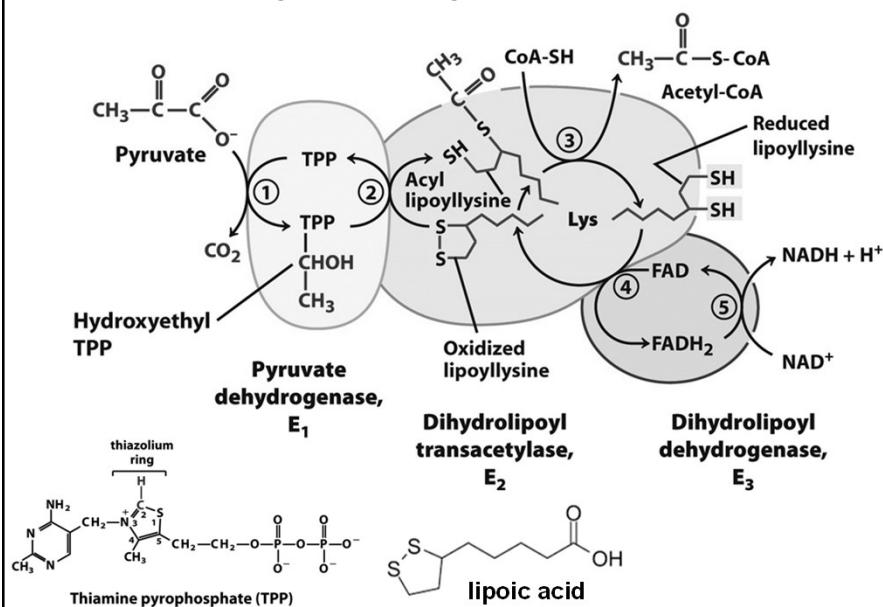
For energy synthesis, pyruvate enters the mitochondria by active transport with the help of MPC, aka, pyruvate translocase, a transport protein.

Within the mitochondrial matrix:



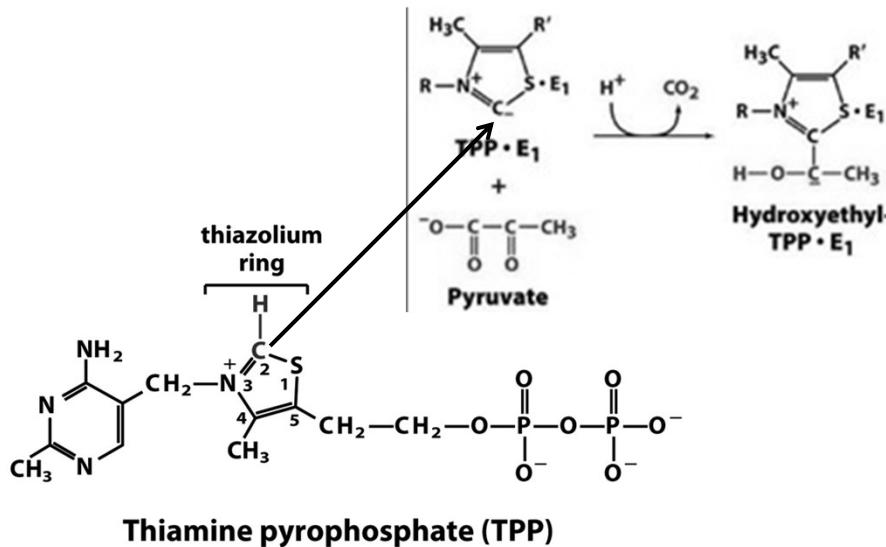
51

Oxidative decarboxylation of pyruvate to acetyl-CoA by the PDH complex



52

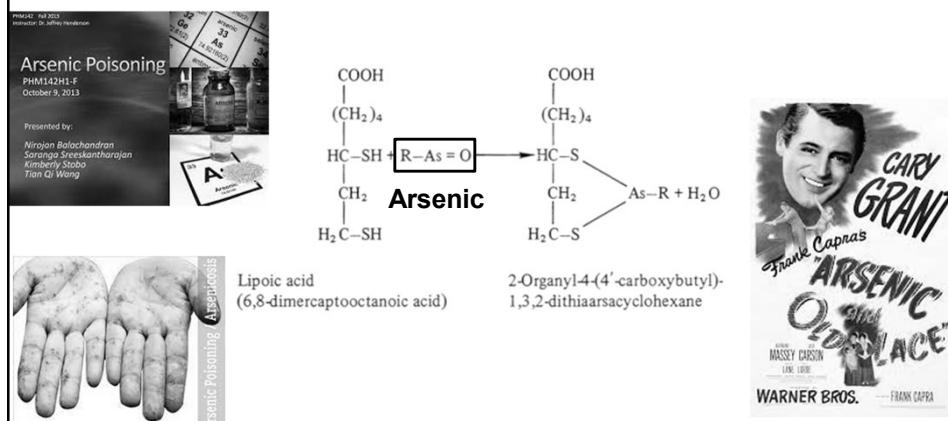
Coenzyme form of vitamin B₁ (thiamine)



53

A mechanism of toxicity by Arsenic

A small molecule that can easily get into cells, arsenic can cause cell injury and death by multiple mechanisms. Interference with cellular respiration (specifically during the formation of acetyl CoA) seems to contribute to the potent toxicity of arsenic. The immediate symptoms of acute arsenic poisoning include vomiting, abdominal pain and diarrhea. These are followed by numbness and tingling of the extremities, muscle cramping and death, in extreme cases.



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Beriberi

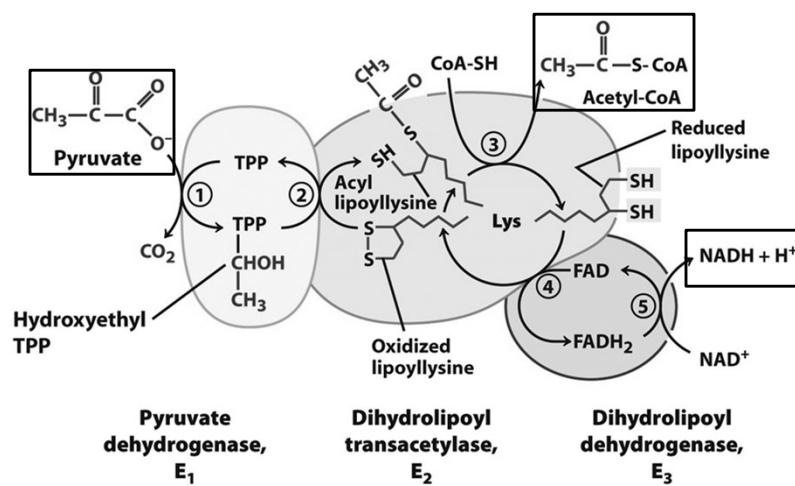
Beriberi is a disease that results from thiamine (vitamin B₁) deficiency. Beriberi is rare in developed countries because most foods are now vitamin enriched.

These days, beriberi occurs mostly in patients who abuse alcohol. Drinking heavily can lead to poor nutrition, and excess alcohol makes it harder for the body to absorb and store thiamine.

Symptoms of beriberi include: severe lethargy, difficulty walking, loss of feeling (sensation) in hands and feet, loss of muscle function or paralysis of the lower legs, mental confusion/speech difficulties, pain, etc.

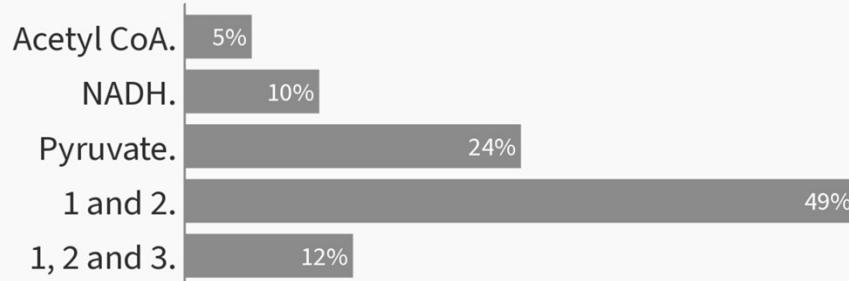
55

Oxidative decarboxylation of pyruvate to acetyl-CoA by the PDH complex



56

Now that you know what allosteric regulation and feedback inhibition is, which of the following would you expect to inhibit the PDH complex via feedback inhibition?



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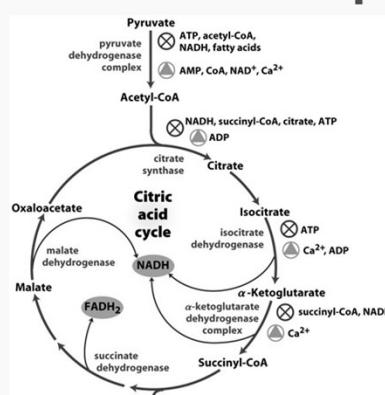
When poll is active, respond at pollev.com/insonglee217

In continuing with the previous question, do you think ATP may inhibit the PDH complex?

Unlikely.

Likely.

Don't know.



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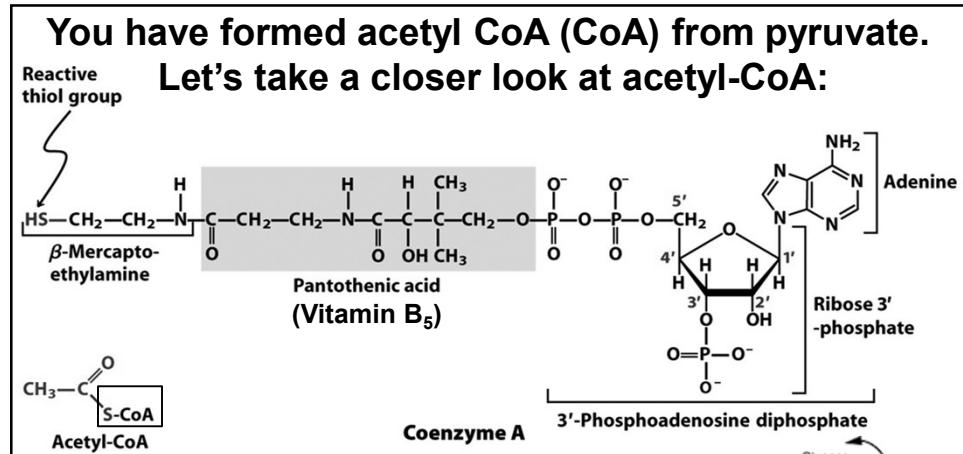
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The second phase of respiration:
Oxidation of acetyl CoA (Citric acid cycle)
slides 60-72

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You have formed acetyl CoA (CoA) from pyruvate.
 Let's take a closer look at acetyl-CoA:



Reactive thiol group

β -Mercaptethylamine

Pantothenic acid (Vitamin B₅)

Adenine

Ribose 3'-phosphate

3'-Phosphoadenosine diphosphate

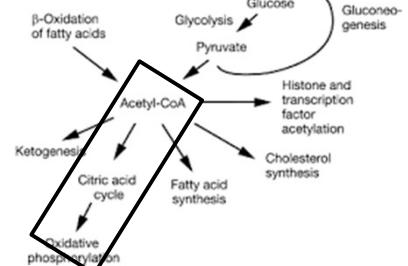
Acetyl-CoA

Coenzyme A

Now, what happens to acetyl-CoA?

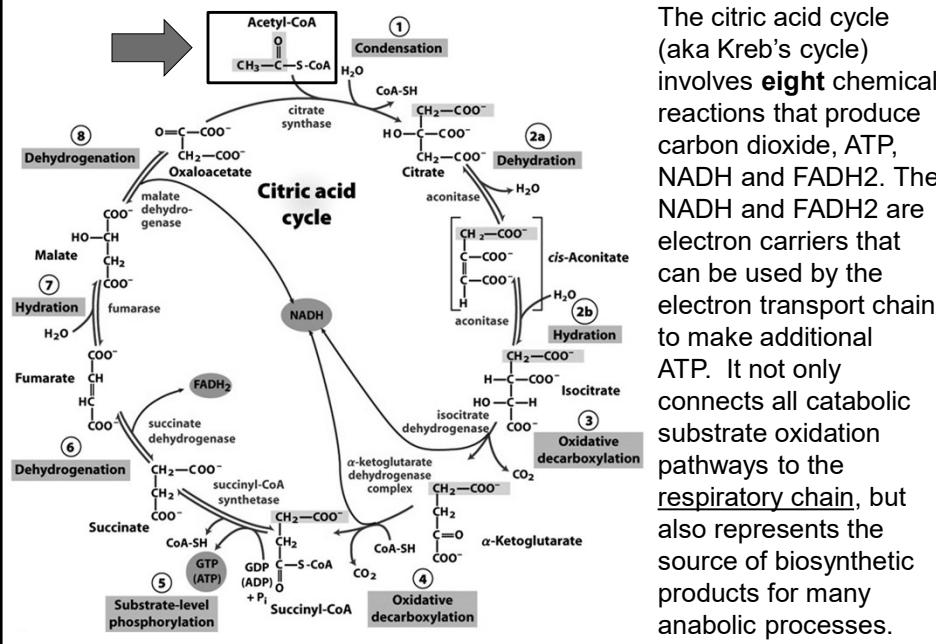
Acetyl-CoA can have many fates:

We will focus on the Citric acid cycle Process for now.



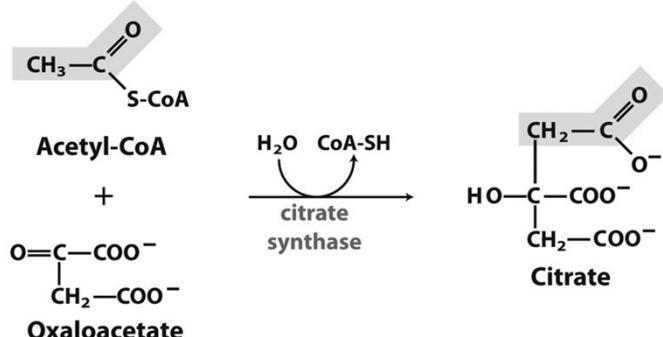
60

Acetyl-CoA feeds into the citric acid cycle



61

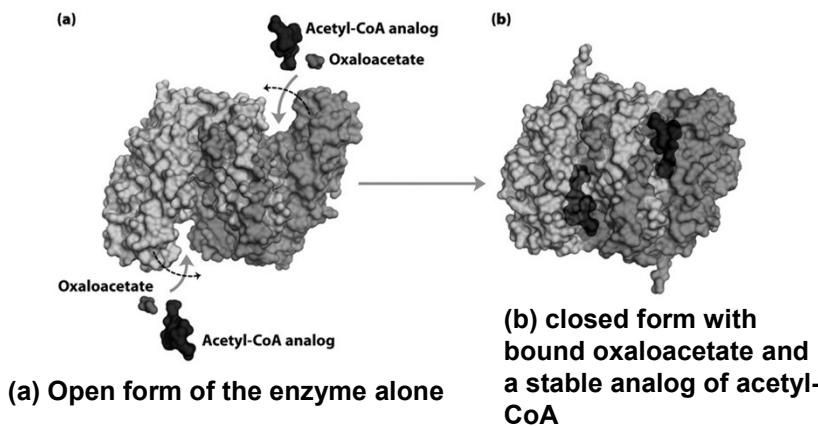
First step in Citric acid cycle: condensation of acetyl-CoA with oxaloacetate to form citrate



$$\Delta G'^\circ = -32.2 \text{ kJ/mol}$$

62

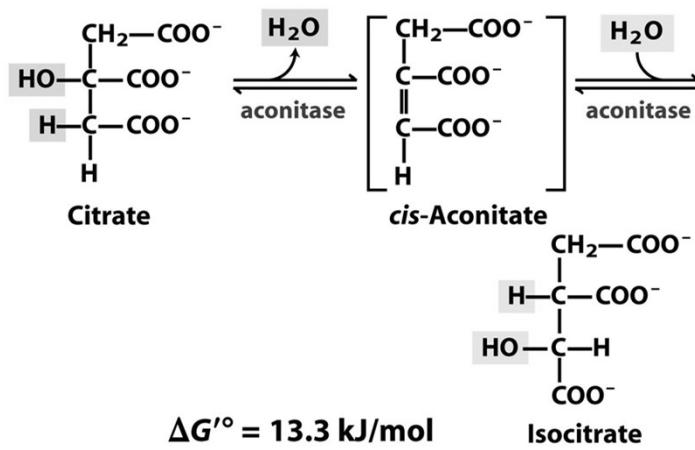
Structure of citrate synthase



The flexible domain of each subunit undergoes a large conformational change on binding oxaloacetate, creating a binding site for acetyl-CoA

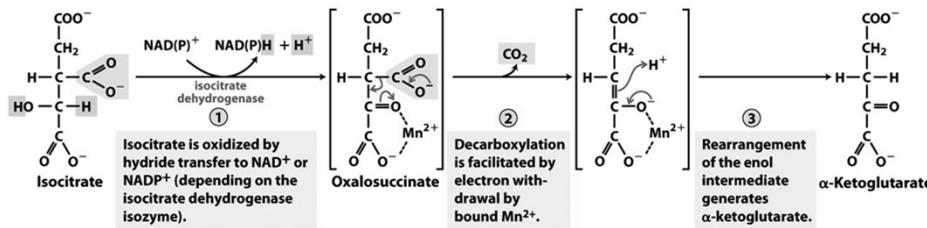
63

Second steps in citric acid cycle: dehydration of citrate and hydration of cis-aconitate to form isocitrate



64

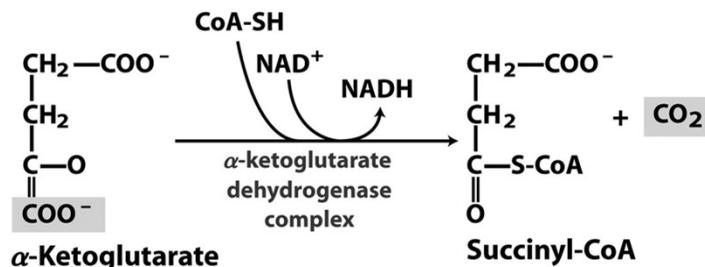
Third step in citric acid cycle: isocitrate is converted to α -ketoglutarate via multiple steps



Hydride is formally the anion of hydrogen (H⁻), a hydrogen atom with two electrons.

65

Fourth step in citric acid cycle: oxidation of α -ketoglutarate to form succinyl-CoA

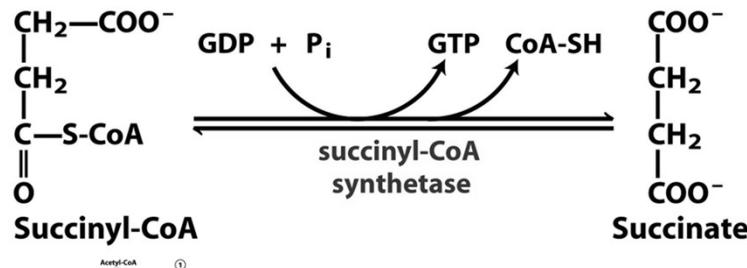


$$\Delta G'^\circ = -33.5 \text{ kJ/mol}$$

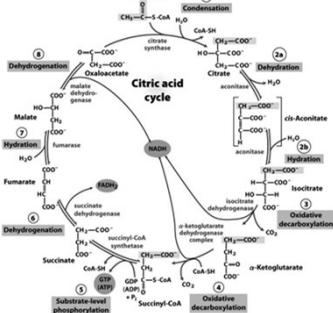
This reaction is very similar to the pyruvate dehydrogenase reaction

66

Fifth step in citric acid cycle: oxidation of succinyl-CoA to form succinate

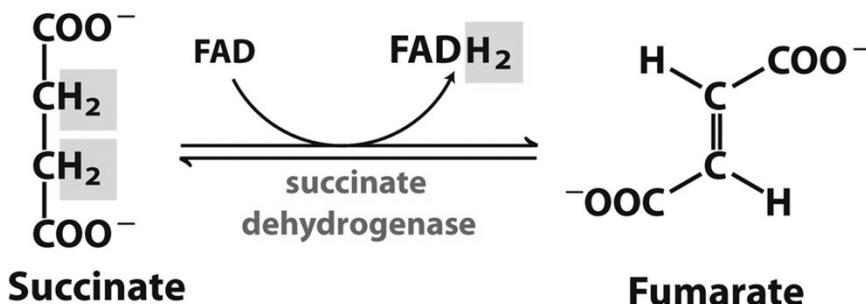


$$\Delta G'^\circ = -2.9 \text{ kJ/mol}$$



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Sixth step in citric acid cycle: dehydration of succinate to form fumarate

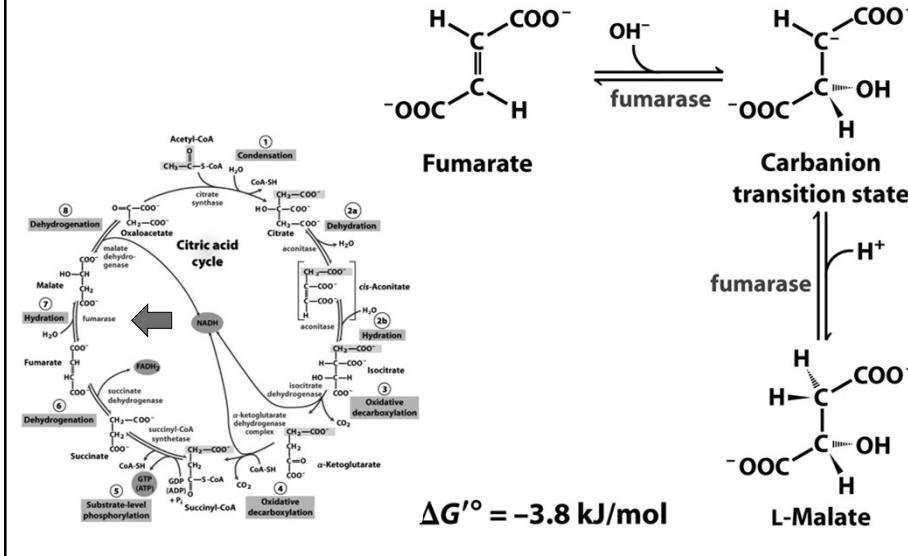


$$\Delta G'^\circ = 0 \text{ kJ/mol}$$

Succinate dehydrogenase (SDH) is part of both the citric acid cycle and respiratory electron transfer chain (we will cover later in the lecture). SDH is the only enzyme of the citric acid cycle that is membrane bound

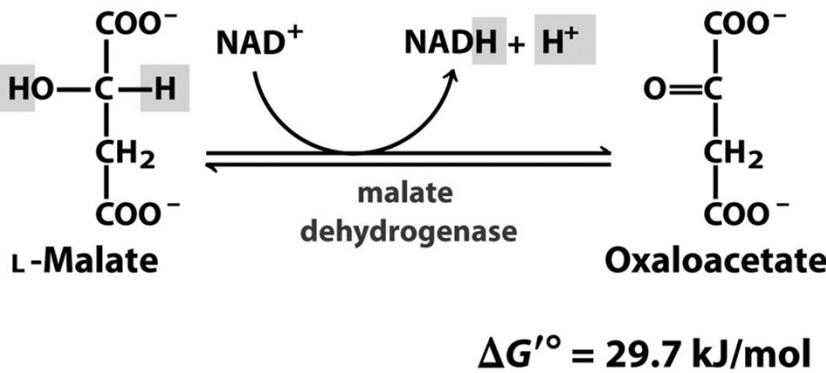
68

Seventh step in citric acid cycle: hydration of fumarate to form malate



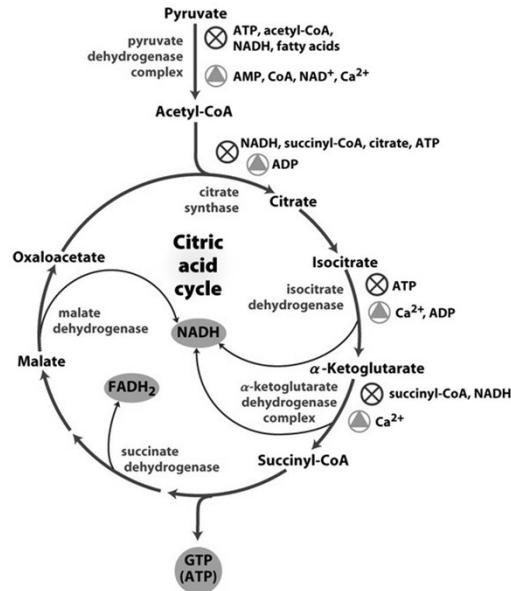
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Eighth step in citric acid cycle: dehydrogenation of malate to form oxaloacetate



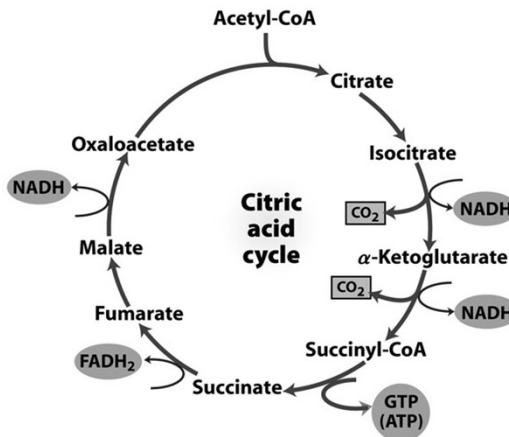
70

Regulation of metabolite flow from the PDH complex through the citric acid cycle



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Products of one turn of the citric acid cycle



At each turn of the cycle, three NADH, one FADH₂, one GTP (or ATP), and two CO₂ are released in oxidative decarboxylation reactions

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The third phase of respiration:

**Electron transfer and
Oxidative phosphorylation**

slides 74-80

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**Which of the following is/are used to
transport electrons ?**

NADH.

FAD.

NADPH.

All of the above.

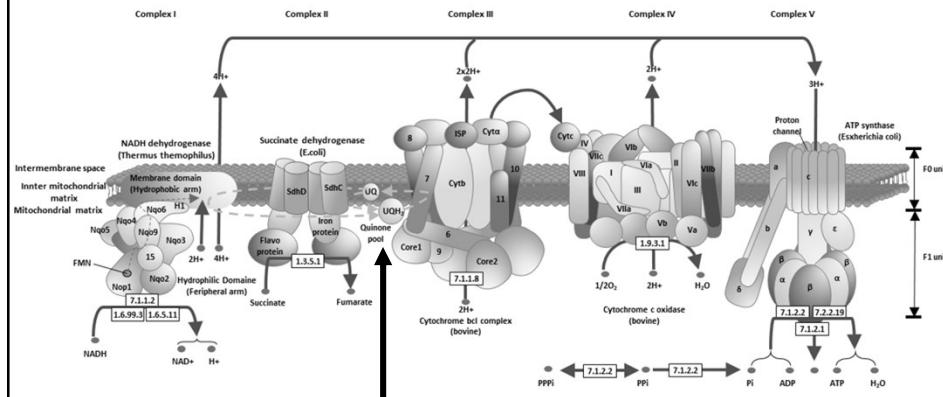
None of the above

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Protein complexes involved in electron transport & oxidative phosphorylation



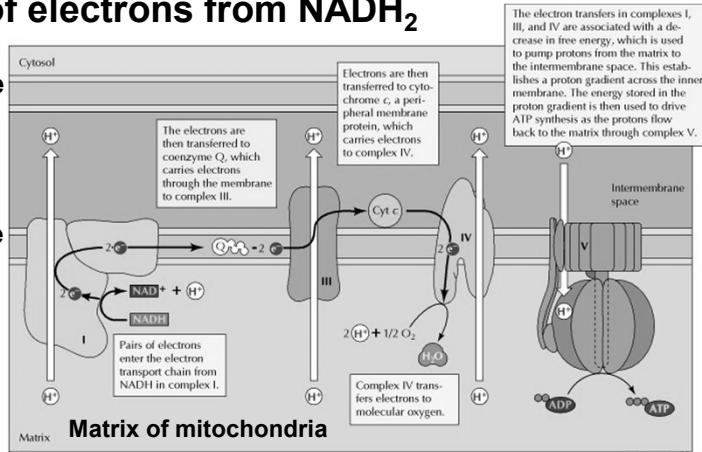
Complex I: Comprised of nearly 40 polypeptide chains

Coenzyme Q (also called ubiquinone (UQ)) is a small, lipid-soluble molecule that carries electrons from complex I through the membrane to complex III

75

Transport of electrons from NADH₂

Outer membrane of mitochondria



Inner membrane of mitochondria

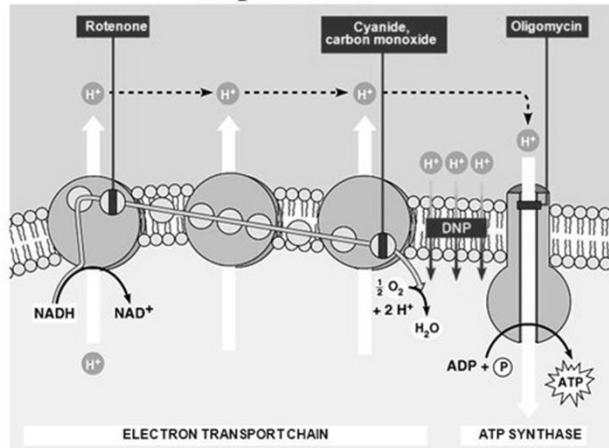


In complex III, electrons are transferred from cytochrome b to cytochrome c - an energy-yielding reaction with $\Delta G'' = -10.1 \text{ kcal/mol}$.

Cytochrome c, a peripheral membrane protein bound to the outer face of the inner membrane, then carries electrons to complex IV (cytochrome oxidase), where they are finally transferred to O₂ ($\Delta G'' = -25.8 \text{ kcal/mol}$).

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Poisons interrupt critical events in cellular respiration



Rotenone is a naturally occurring chemical found in the roots, seeds, and leaves of several subtropical plants and has been commonly used as a piscicide or fish killer.

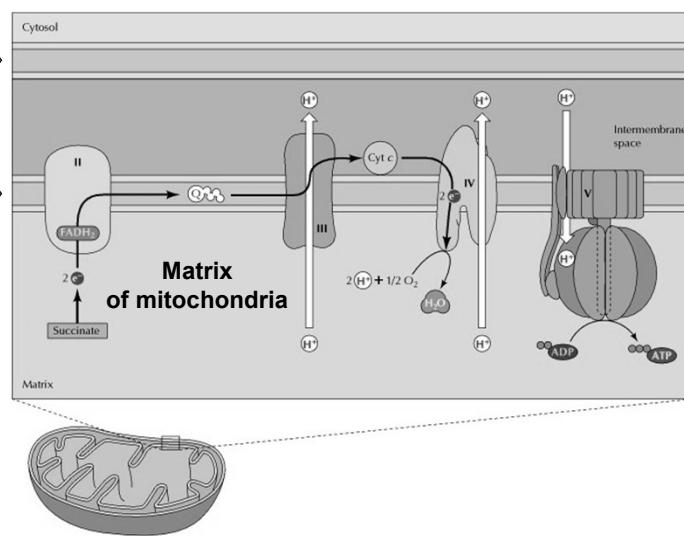
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Transport of electrons from FADH₂

Outer membrane of mitochondria

Inner membrane of mitochondria

Coenzyme Q (also called ubiquinone (UQ)) also carries electrons from complex II through the membrane to complex III



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Video about electron transfer (oxidative phosphorylation):

<https://www.youtube.com/watch?v=vZz-KLK-X40>

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ATP stoichiometry during glycolysis and citric acid cycle

TABLE 16-1

Stoichiometry of Coenzyme Reduction and ATP Formation in the Aerobic Oxidation of Glucose via Glycolysis, the Pyruvate Dehydrogenase Complex Reaction, the Citric Acid Cycle, and Oxidative Phosphorylation

Reaction	Number of ATP or reduced coenzyme directly formed	Number of ATP ultimately formed*
Glucose → glucose 6-phosphate	-1 ATP	-1
Fructose 6-phosphate → fructose 1,6-bisphosphate	-1 ATP	-1
2 Glyceraldehyde 3-phosphate → 2 1,3-bisphosphoglycerate	2 NADH	3 or 5†
2 1,3-Bisphosphoglycerate → 2 3-phosphoglycerate	2 ATP	2
2 Phosphoenolpyruvate → 2 pyruvate	2 ATP	2
2 Pyruvate → 2 acetyl-CoA	2 NADH	5
2 Isocitrate → 2 α-ketoglutarate	2 NADH	5
2 α-Ketoglutarate → 2 succinyl-CoA	2 NADH	5
2 Succinyl-CoA → 2 succinate	2 ATP (or 2 GTP)	2
2 Succinate → 2 fumarate	2 FADH ₂	3
2 Malate → 2 oxaloacetate	2 NADH	5
Total		30–32

*This is calculated as 2.5 ATP per NADH and 1.5 ATP per FADH₂. A negative value indicates consumption.

†This number is either 3 or 5, depending on the mechanism used to shuttle NADH equivalents from the cytosol to the mitochondrial matrix; see Figures 19–30 and 19–31.

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