Lecture 1: Biochemistry II
Carbohydrate digestion and Metabolism

3rd stage

Anbar University-College of Pharmacy-Clinical Laboratory Sciences Department
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- **Metabolism**: the chemical reactions that occur in a cell that produce energy and basic materials needed for important life processes

- A $\xrightarrow{1}$ [B] $\xrightarrow{2}$ [C] $\xrightarrow{3}$ D
- 1,2 and 3 = Metabolic pathways
- [B] and [C] = intermediates

✓ Thousands of enzymes
✓ Various conditions (fed, fasted, exercise, stress)

Metabolism consist of 2 parts:

- **Catabolism** : Degradation, pathways by which nutrients and cellular components are broken down for reuse or to generate energy for example, glycolysis and β-oxidation.
- **Anabolism** : Biosynthesis, building up of biomolecules from simpler components. Therefore, these processes require to energy and NADPH or NADH or FADH
- **Metabolism is regulated into three main stages:**
- Stage 1: large molecules are broken down into smaller molecules
- Stage 2: small molecules are degraded to a few simple molecules e.g. glycolysis, produce acetyl coA.
- Stage 3: Citric acid cycle and oxidative

Carbon sources and energy for cellular life

- **Autotrophic cells:** These cells are use Carbone dioxide (CO_2) as a carbon source and sunlight as an energy source and thus can make large biomolecules.

$$6\ CO_2 + 6\ H_2O + \text{energy (sun)} \longrightarrow C_6H_{12}O_6\ (\text{Glucose}) + 6\ O_2$$

- **Heterotrophic cells:** These cells do not use Carbone dioxide as the only carbon source, but depend on other organic compounds that get as a food. These cells are classified into two groups
  - **Aerobes:** They live in the air and use Oxygen to oxidize their food.
  - **Anaerobes:** These can live without Oxygen and can break down their nutrition by using oxidizing materials such as NAD+. Most cells can live aerobic and anaerobic at the same time and this is called **Facultative cells**

- **Photosynthesis:** Carbone dioxide + Water + energy (sunlight) + Chlorophyll ⟶ **Glucose**

Carbohydrate Metabolism

- Serve as primary source of energy in the cell.
- Digestible carbohydrates provide 4 - 4.5 kilocalories per gram
- Central to all metabolic processes
- **Carbohydrate Metabolism includes the following processes:**

1- Glycolysis

2- Glycogenesis

3- Glycogenolysis

4- Gluconeogenesis

5- Pentose phosphate pathway

6- Citric acid cycle (Kreb's cycle) or Tricarboxylic acid cycle (TCA)

7- Photosynthesis

Digestion of Carbohydrate

- Digestion is the breakdown of large insoluble molecules into smaller soluble molecules to make energy (ATP). The digestion process is carried out by an enzymes that are excreted from various parts of the body
- **In the Mouth**

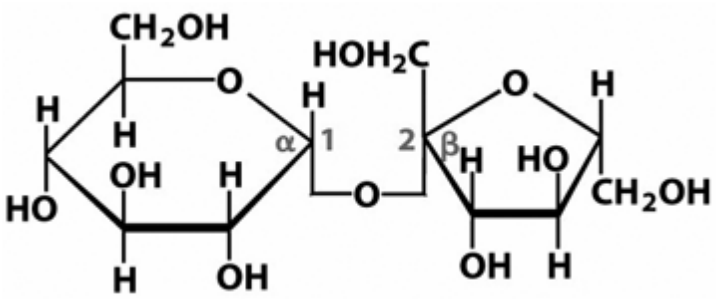
Glycogen
Starch
→ In the mouth (saliva), **α-amylase** → **Maltose, Isomaltose, starch dextrins**

- **α-amylase** is produced by salivary glands. Its optimum **pH is 6.7**
- It acts on cooked starch and glycogen breaking **α 1-4 glycosidic bonds**, converting them into **maltose**.
- The food remains for a short time in the mouth. Therefore, the digestion of glycogen and starch may be incomplete and gives a partial digestion products called **starch dextrins** (amylodextrin, erythrodextrin and achrodextrin).

Structures of common, di- and polysaccharides

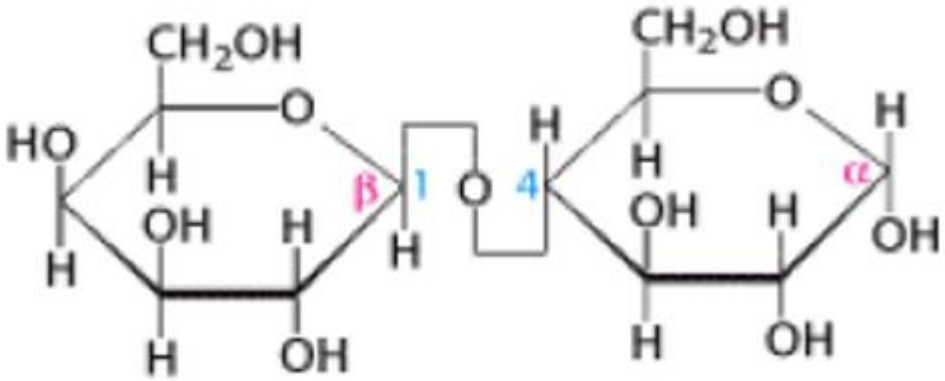
Sucrose: disaccharide containing glucose and fructose attached by **α- (1,2)** linkage

Glucose **Fructose**

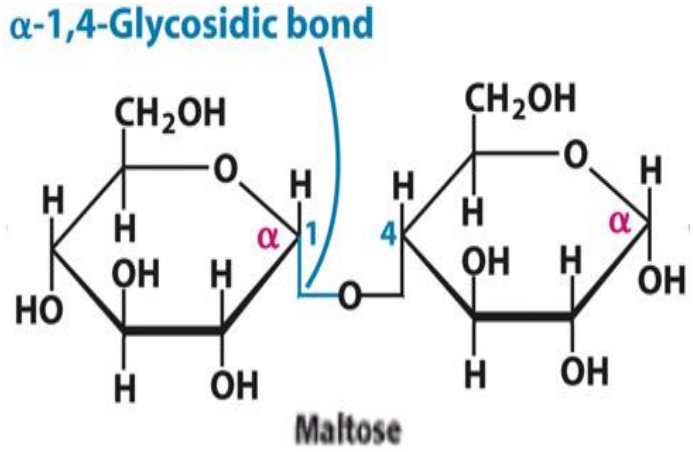


Lactose: disaccharide containing **glucose** and **galactose** attached by **β-(1,4)** linkage

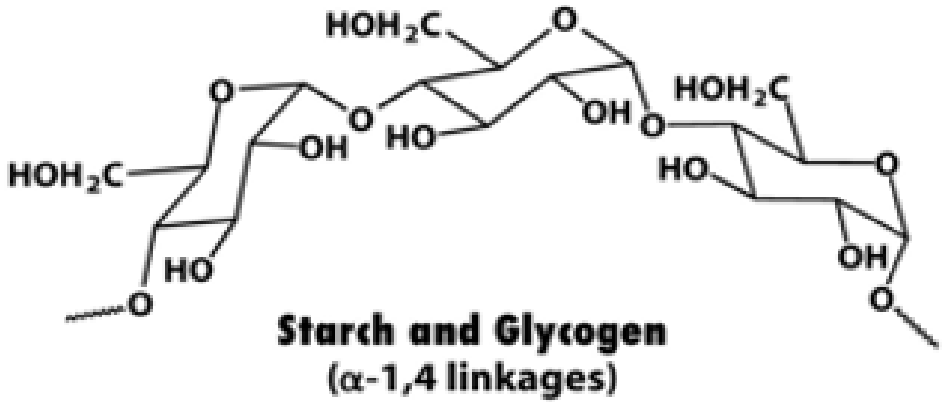
Galactose **Glucose**

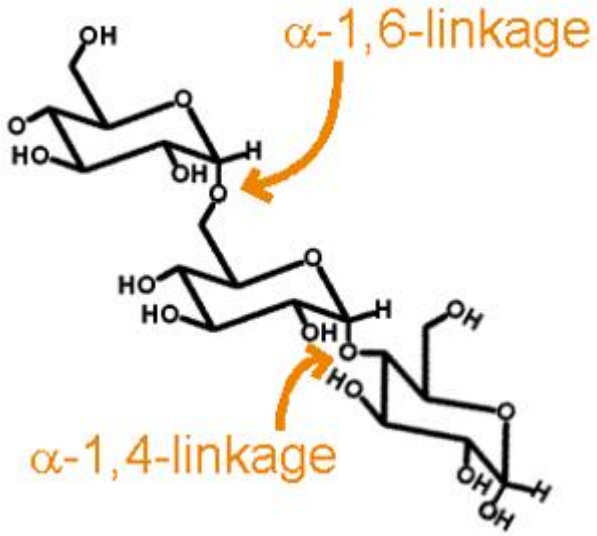


- **Maltose:** disaccharide containing **two glucose** molecules attached by **α-(1,4) linkage**. This bond is not attacked by **α-amylase**.



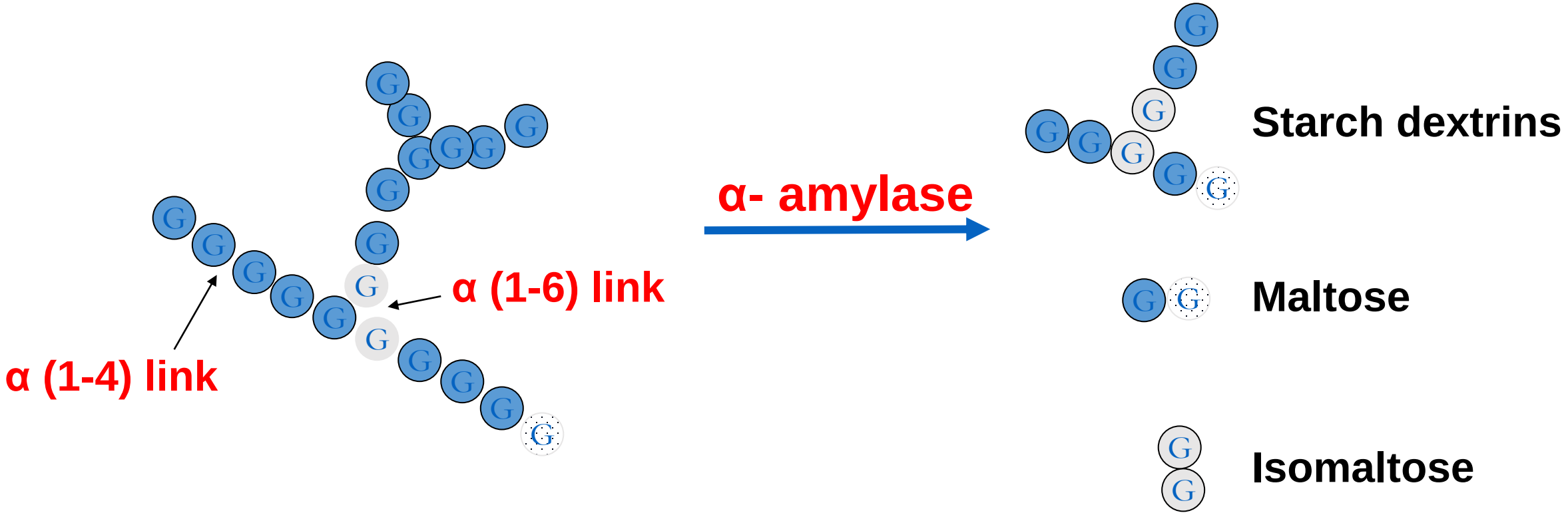
- **Glycogen:** Major storage carbohydrate in **animals**
- **Starch:** Major storage carbohydrate in **plants**





Starch and Glycogen
(**α-1,4 and α-1,6** linkages)

Digestion of carbohydrates



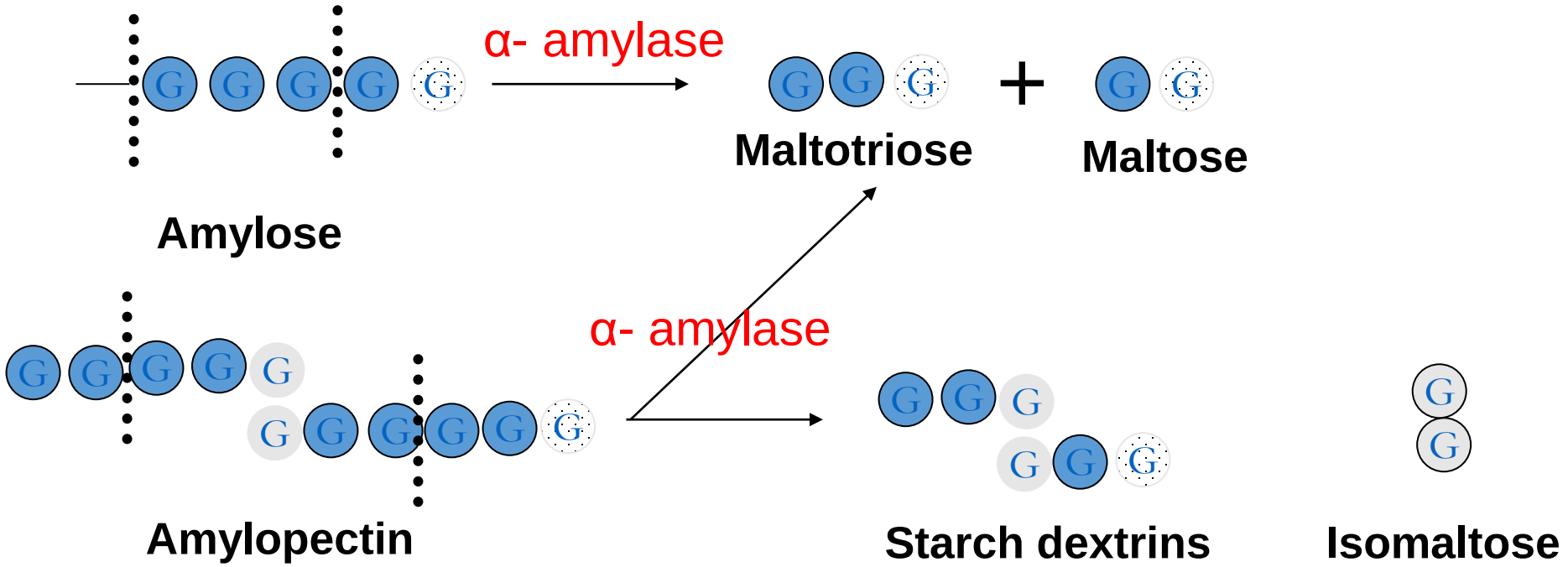
- **α- amylase** cannot attack α1-4 linkage close to α1-6 branch points.
- **Isomaltose:** Two glucose molecules are attached by α1-6 linkage

➢ Stomach:

Carbohydrate digestion stops temporarily due to the high acidity, where low pH in the stomach (1.5-3.5) inactivates the action of salivary amylase.

➢ Small intestine:

- The digestion of carbohydrate continues by the pancreatic enzyme (α-amylase) in the small intestine
- **α-amylase enzyme** is produced by pancreas and acts in small intestine. Its optimum pH is 7.1



Final carbohydrate digestion occurs at the **small intestine by intestinal enzymes** that secreted through intestinal epithelial cells. These enzymes include the action of several disaccharidases as shown below:

- Maltase enzyme hydrolyses α-(1,4) linkage Maltose into two molecules of glucose:

  Maltose $\xrightarrow{\text{Maltase}}$ Glucose + Glucose

- Lactase enzyme hydrolyses β-(1 ,4) linkage Lactose into Glucose and Galactose:

  Lactose $\xrightarrow{\text{Lactase}}$ Glucose + Galactose

- Sucrase enzyme hydrolyses α, β -(1 ,2) Sucrose into Glucose and Fructose

  Sucrose $\xrightarrow{\text{Sucrase}}$ Glucose + Fructose

- α-dextrinase enzyme hydrolyses (1 ,6) linkage of isomaltose into two molecules of glucose

  Isomaltose $\xrightarrow{\text{α-dextrinase}}$ Glucose + Glucose

- Cellulose contains β(1-4) glycosidic bonds. In humans, there is no **cellulase** enzyme that can break down these bonds between glucose molecules. Therefore, cellulose passes as such in stool.

- **Small intestine:**
  - Portal for transport of virtually all nutrients

- **Enzymes associated with intestinal surface membranes are:**
  - α- dextrinase
  - Maltase
  - Lactase
  - Sucrase
  - peptidase

Absorption of Carbohydrates

- After complete digestion, monosaccharides (Glucose, fructose, and galactose) are absorbed across the membrane of the small intestine and transported to the liver through bloodstream, where they are either used by the liver (Glycogenesis), or further distributed to the rest of the body (Oxidation)
- - Fructose and galactose are converted into glucose by liver cells
- - All cells can use glucose for energy production
- - Liver is central site for carbohydrate metabolism
- - Blood glucose is regulated by insulin
- - Glucose is the main energy source for most organisms

Fate of absorbed sugars

- **Glucose**
- **Fructose**
- **Galactose**

Liver

Glucose

Feeding state

Oxidation

- Glycolysis and Kreb's cycle for production of energy
- Pentose (Hexose) phosphate pathway

Storage

- glycogen in liver and muscle
- Fat

Conversion

- Ribose (RNA), deoxyribose (DNA)
- Lactose ⟶ Milk
- Fructose in semen
- Glucosamine

Lecture 2: Biochemistry II
Energy and Metabolism

3rd stage

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Learning outcomes

By the end of this lecture you will be able to:

- ✓ Understand the importance of energy in metabolism
- ✓ Describe different types of metabolic pathways, giving examples of each
- ✓ Explain the role of electron carriers in metabolism

What's important in Metabolism?

- **Energy ATP** – released from some molecules, needed to build others
- **Carbon skeletons** – building blocks for many different types of molecules
- **Reducing equivalents** – electrons are released from some reactions, needed for other reactions: NADH, NADPH

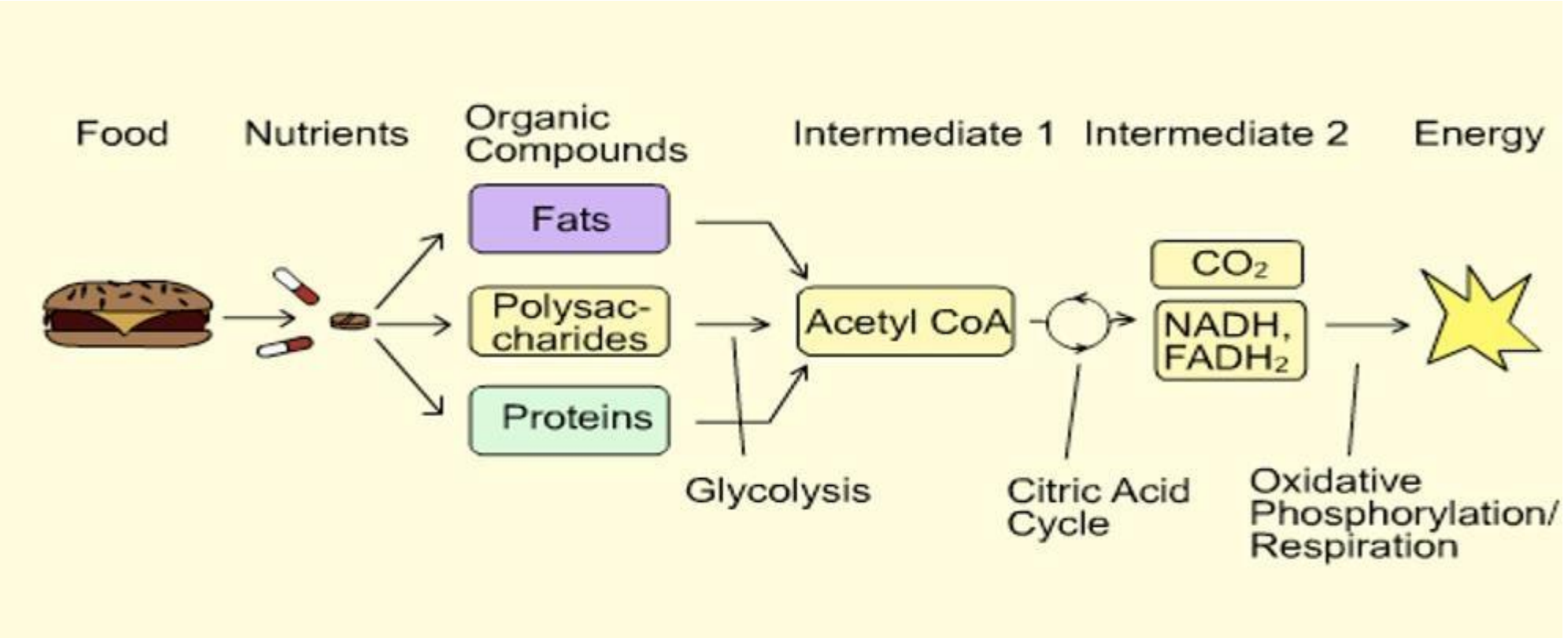
Energy is needed by the body for:

✓ Work 1/3

✓ Maintaining body functions, homeostasis and metabolic integrity 2/3

How can food supply an energy?

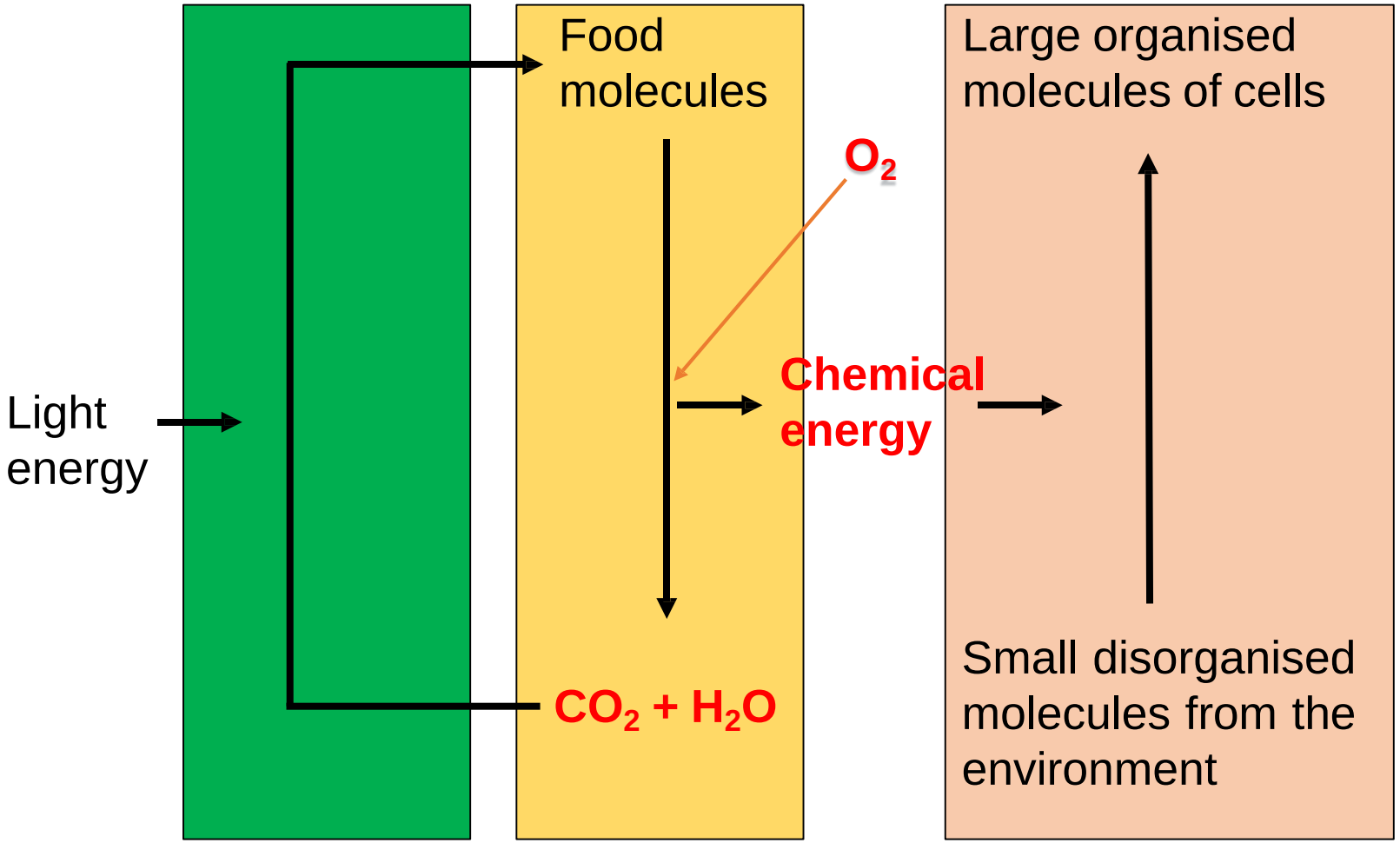
Food is broken down to release energy - **Catabolism**



Energy in food measured in kilocalories, (1 calorie = 4.184 joules):

- Protein = 4 kcal per gram
- Fat = 9 kcal per gram
- Carbohydrate = 4 kcal per gram

Energy cycle in Life



Basal Metabolic Rate (BMR)

Energy requirement in mammals is defined by the Basal Metabolic Rate which depends on:

1- Surface area (e.g weight):

- A short obese person has large surface area ⟶ large heat loss

2- Age:

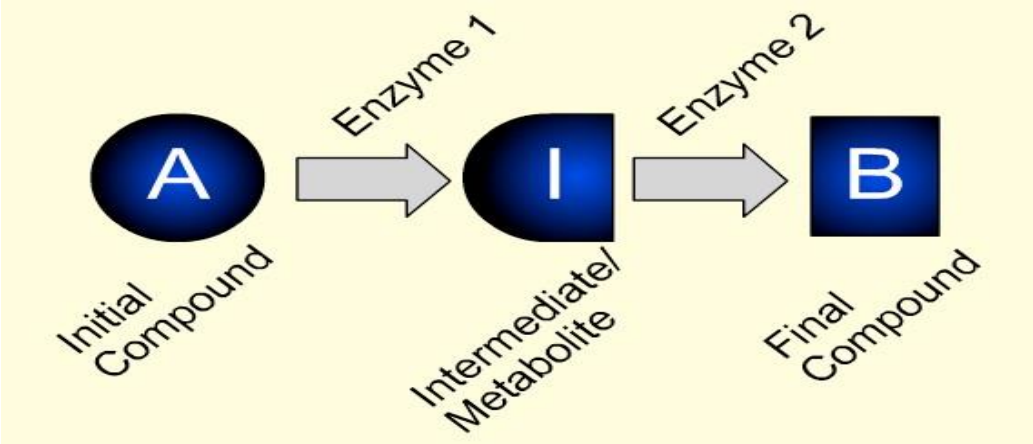
- Children require more energy for growth BMR ⟶ ↑
- Muscle tissue is replaced with fat and water as you age ⟶ BMR ↓

3- Gender:

- Women have a lower BMR than men due to:
  - Less muscle mass
  - Effect of hormones on metabolism

Metabolic Pathways

Breaking down compounds to release **energy** is done in steps helped by **enzymes**.



Different types of pathways

M⇨N⇨O

- **linear pathway**

A⇨B⇨C⇨D

- **branched pathway**

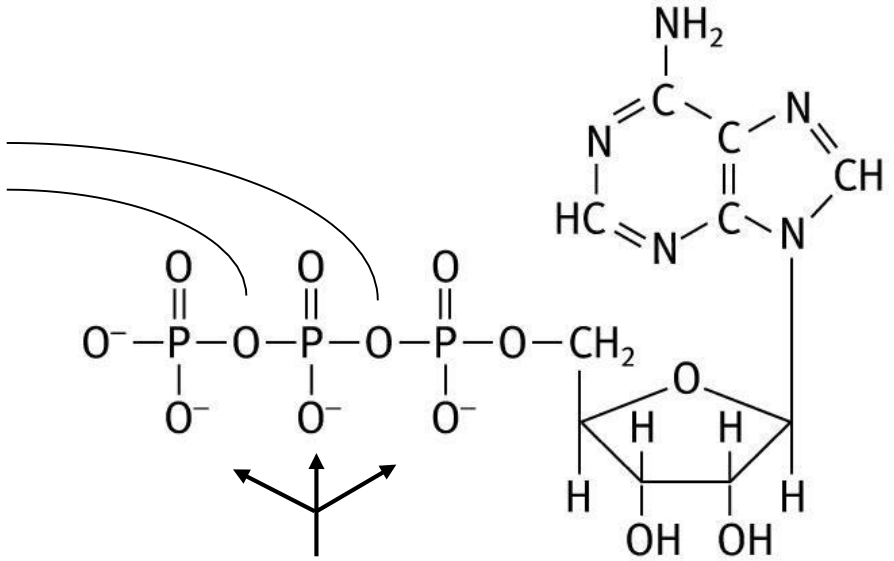
X⇨Y⇨Z

- **Cyclic pathways** (Kreb's cycle)
- **Repeating pathways (**β-oxidation)

ATP: Universal energy intermediate in all life

Adenosine triphosphate (ATP)

phosphoric anhydride linkages

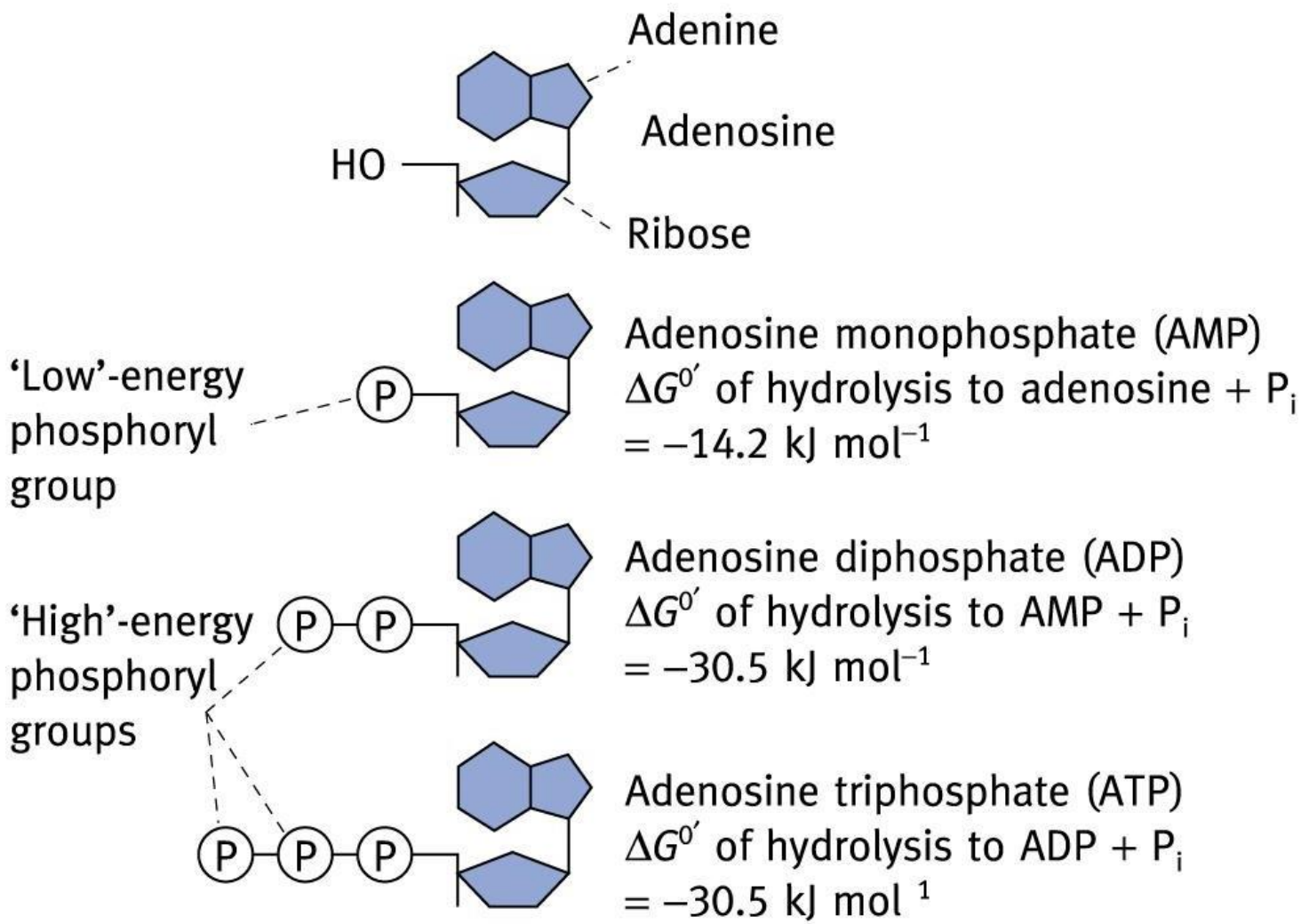


Adenine

Ribose

triphosphate

AMP, ADP, and ATP



Oxidation of food molecules

- The most common type of reaction in food breakdown is oxidation
  - Oxidation is the loss of electrons
  - Reduction is the gain of electrons

The major coenzymes

coenzyme		precursor	functions
CoA	coenzyme A	pantothenate	acyl transfer
NAD	nicotinamide adenine dinucleotide	niacin	redox
FAD	flavin adenine dinucleotide	vitamin B2	redox
FMN	flavin mononucleotide	vitamin B2	redox
PLP	pyridoxal phosphate	vitamin B2	amino acid metabolism

Coenzymes: NAD^+ and $NADP^+$

- **NAD^+ :** Nicotinamide adenine dinucleotide
- **$NADP^+$** : Nicotinamide adenine dinucleotide phosphate
- Both used as intermediates to carry electrons

$$NAD^+ + 2[H] \rightarrow NADH + H^+$$

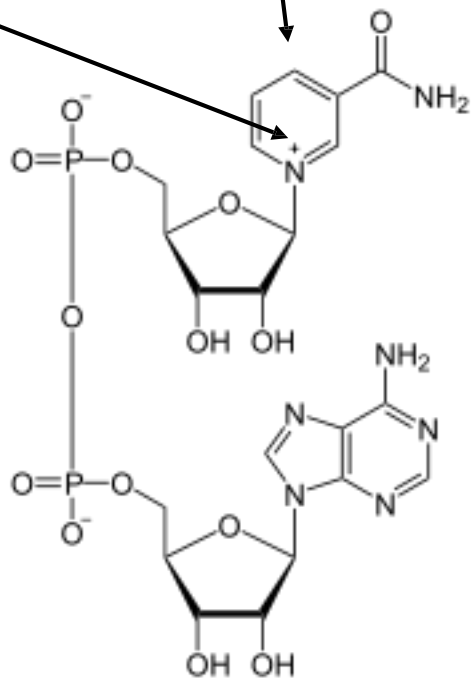
Oxidized **Reduced**

- **NAD^+** takes **two electrons** and **one proton H^+** from the molecules it is oxidizing.
- **NAD^+** is a critical coenzyme found in all living cells, and it's involved in hundreds of metabolic processes. But **NAD^+** levels decline with age

Nicotinamide adenine dinucleotide (NAD^+)

- The nicotinamide ring can take the **2 electrons** because of the electron deficient **N^+**
- It can subsequently release the electrons to another molecule

The **proton** is added on



Lecture 3: Biochemistry II
Respiratory chain and oxidative phosphorylation

3rd stage

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Learning Outcomes

By the end of this lecture you will be able to understand:

- ✓ What is oxidative phosphorylation and its role.
- ✓ Where oxidative phosphorylation takes place.
- ✓ The complexes involved in the electron transport chain.

Oxidative Phosphorylation

- Oxidative phosphorylation is the **synthesis of ATP** by phosphorylation of ADP for which energy is obtained by electron transport and which takes place in the mitochondria during aerobic respiration.

$$ADP + P_i \longrightarrow ATP + H_2O$$

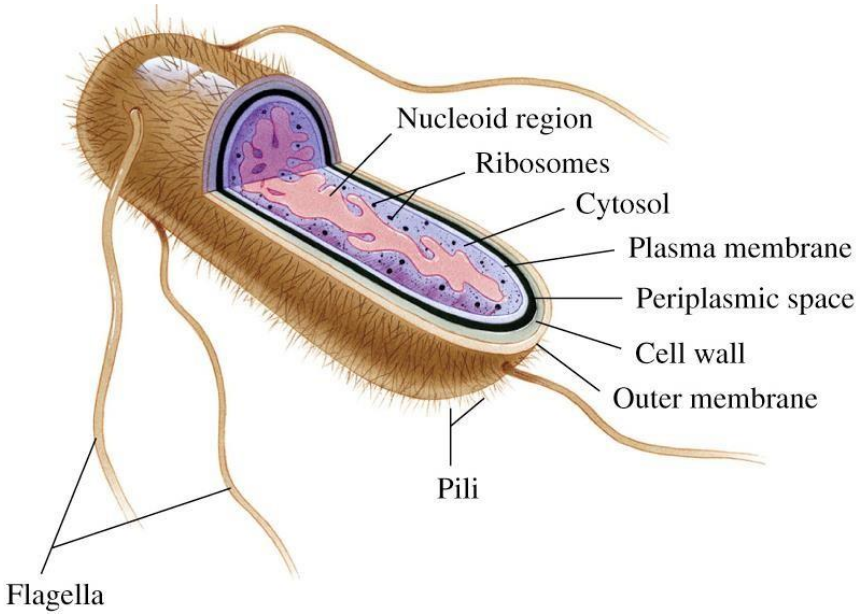
- The oxidative phosphorylation generating **26 ATP** out of **30 (or 32) ATP** obtainable by oxidation of one molecule of glucose to CO2 + H2O.
- Aerobic organisms are able to capture the free energy more than anaerobic organisms through generation of **ATP** by oxidative phosphorylation.

Oxidative Phosphorylation

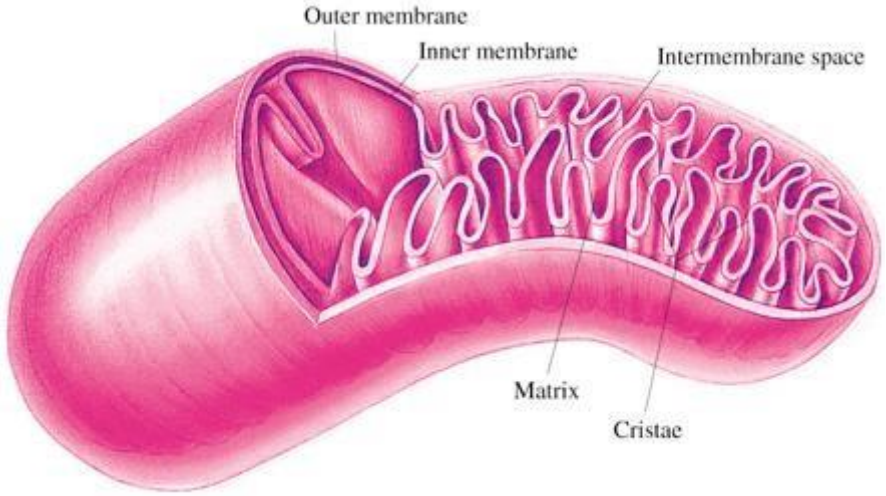
- Electrons from tricarboxylic acid cycle (TCA cycle) reducing equivalents (NADH, FADH2) are transferred to **oxygen** by a series of electron carriers, releasing energy to form **ATP**.
- The flow of electrons through the respiratory chain generates **ATP** by the process of **oxidative phosphorylation**
- A number of drugs (eg, amobarbital) and poisons (eg, cyanide, carbon monoxide) inhibit oxidative phosphorylation, usually with fatal consequences.

Location of Oxidative Phosphorylation

Prokaryotes (bacteria): Plasma membrane



Eukaryotes: Mitochondria, inner membrane



The Concept of Oxidative Phosphorylation

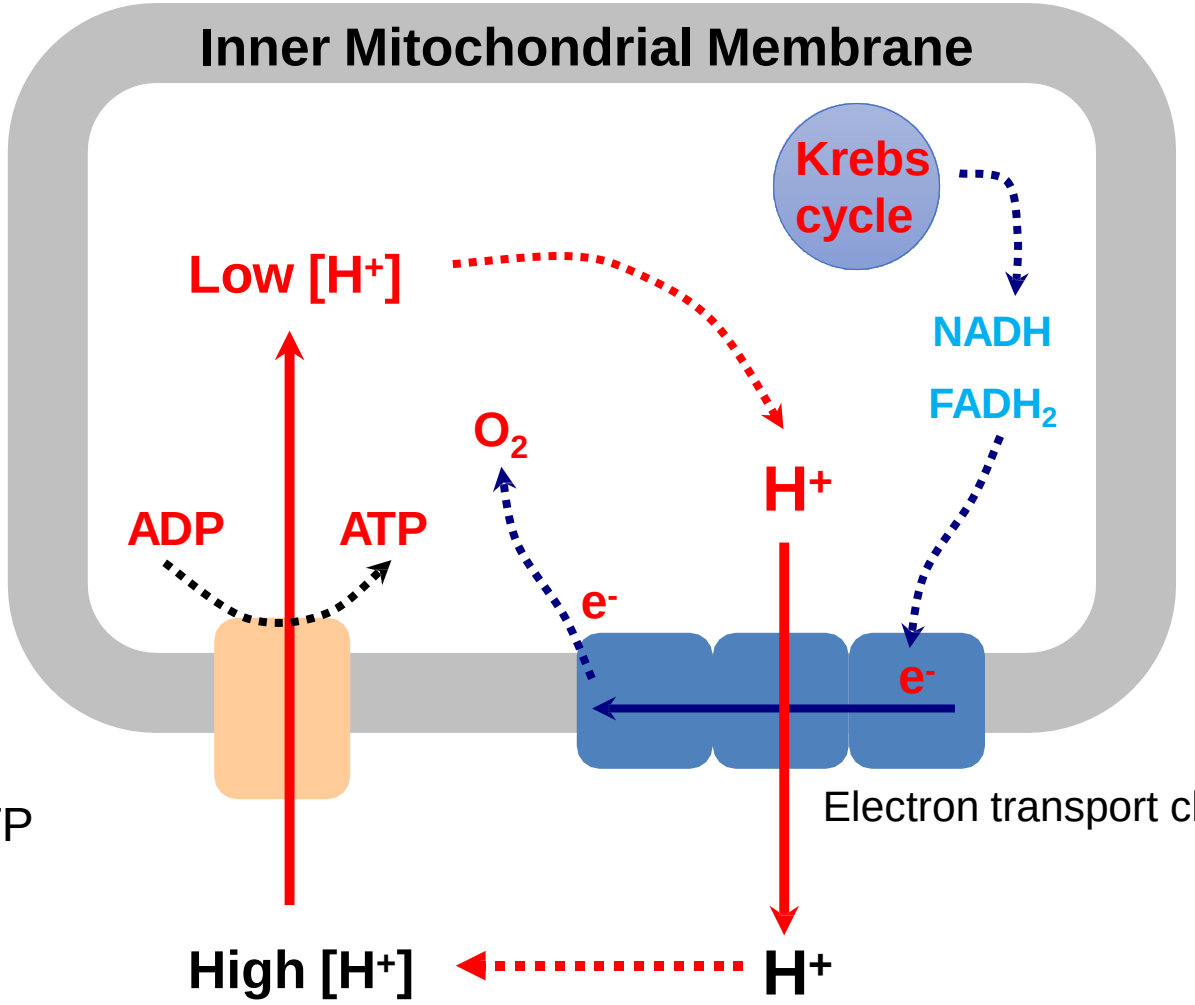
1 Electrons from **NADH** and **FADH2** flow through **complexes** in the inner mitochondrial membrane

2This drives export of protons **(H^+)** to the intermembrane space to result in a proton gradient

3 The **H^+** gradient is used by ATP synthase to make ATP

This is called the Chemiosmotic theory

Diagram of the Chemiosmotic Theory



The H+ gradient is used by ATP synthase to make ATP

Electron transport chain (ETC)

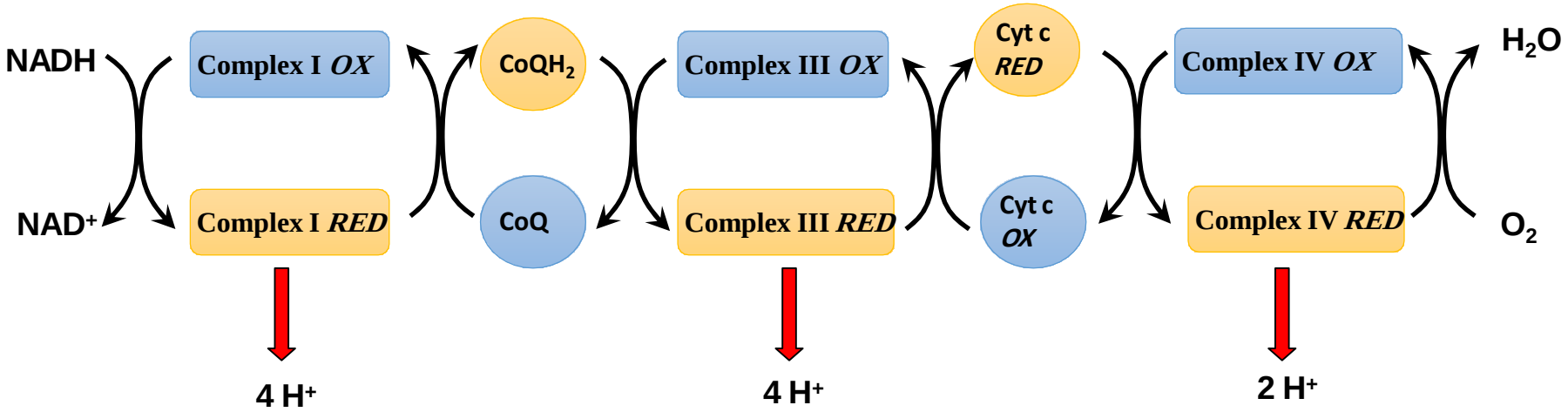
- ETC – a bucket carrying electrons
- Proton export is driven by e^- transfer along the ETC
- Energy is used to transport protons across the membrane

Four complexes in the electron transport chain (ETC)

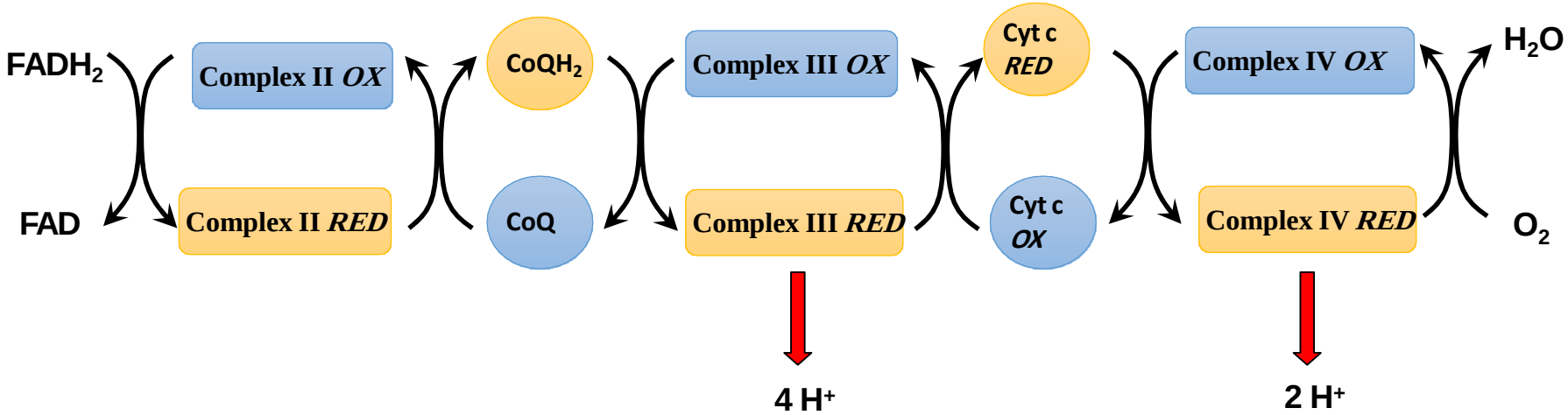
	Complex Name	H^+ Pumped / $2e^-$	Size (kD)	inhibitor
Complex I	NADH-CoQ Reductase	4	>900	Rotenone
Complex II	Succinate-CoQ Reductase	None	140	
Complex III	CoQ-Cytochrome c Oxidoreductase	4	250	Antimycin A
Complex IV	Cytochrome c Oxidase	2	160	Cyanide (CN-), Carbon monoxide (CO)

Electrons pass through the electron transport chain (ETC) by cycles of redox reactions

NADH passes e^- to Complex I:

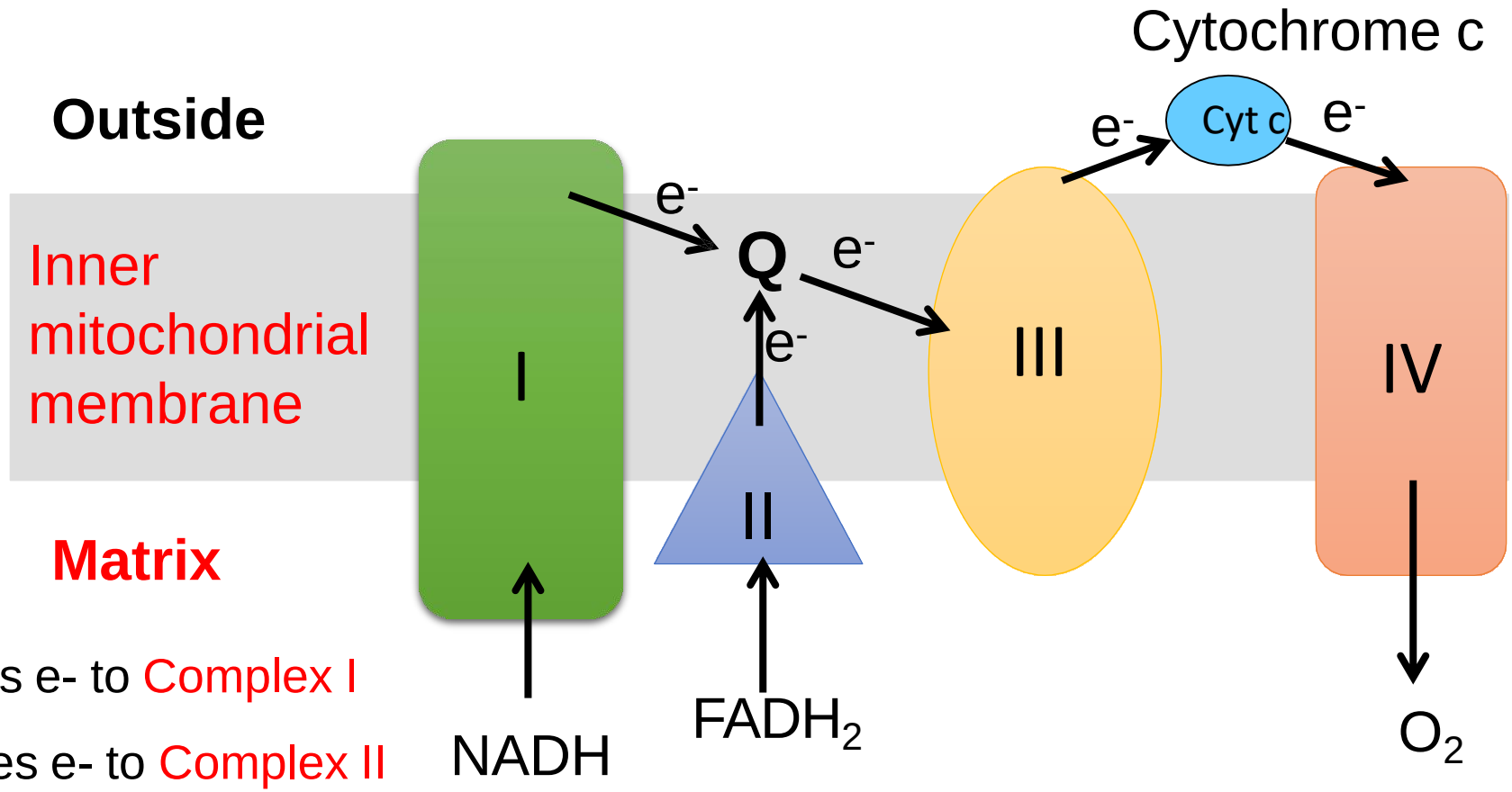


$FADH_2$ passes e^- to Complex II:



- For each **NADH**: 10 **H^+** are pumped from matrix to intermembrane space. **Each H^+ = 2.5 ATP**
- For each **FADH2**: 6 **H^+** are pumped from matrix to intermembrane space. **Each H^+ = 1.5 ATP**

Electron Transport Chain (ETC)



- NADH passes e- to Complex I
- FADH2 passes e- to Complex II

- Q – Ubiquinone (CoQ): A small lipid soluble electron carrier. It accepts electrons from complexes I and II and diffuses through the membrane to deliver them to complex III
- Cyt c is a small water-soluble heme-containing protein. It diffuses in the intermembrane space between complex III and complex IV

Lecture 4: Biochemistry II
Glycolysis 2

3rd stage

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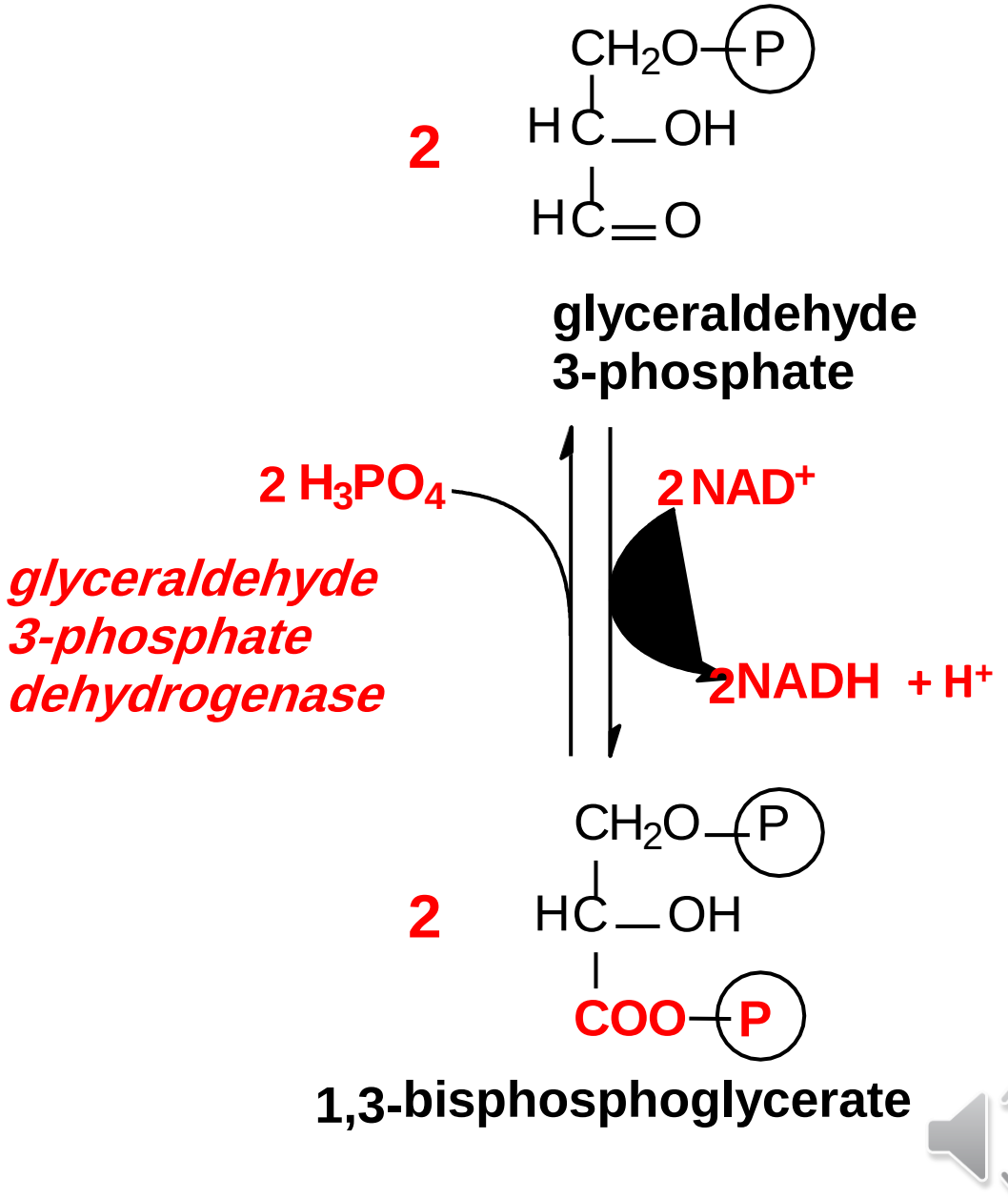
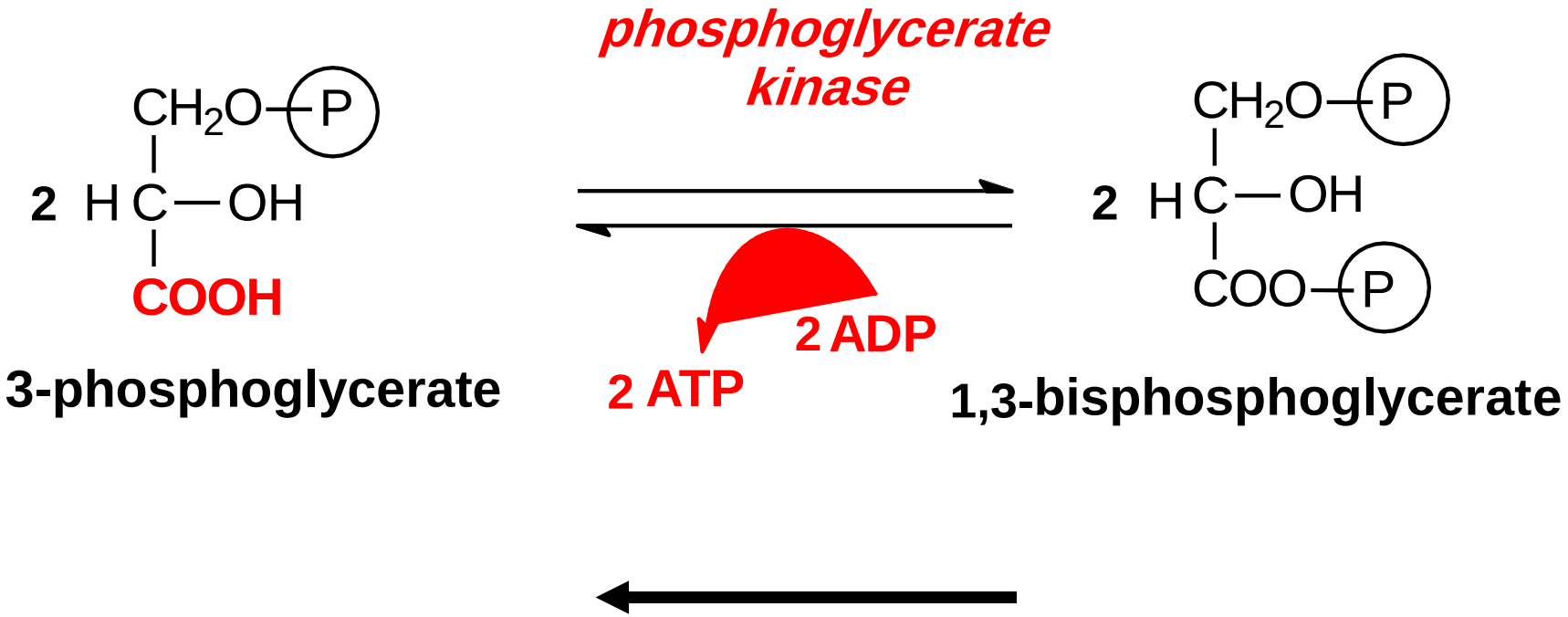
Glycolysis: (6) oxidation of glyceraldehyde 3-phosphate

- Two molecules of glyceraldehyde-3-phosphate are oxidised and phosphorylated
- Oxidation and phosphorylation using NAD^+ and inorganic phosphate
- NAD^+ serving as the electron acceptor.
- So far, **2 ATP** molecules have been invested **(stage 1)** without any energy being extracted.
- 1,3 bisphosphoglycerate has a high phosphoryl-transfer potential



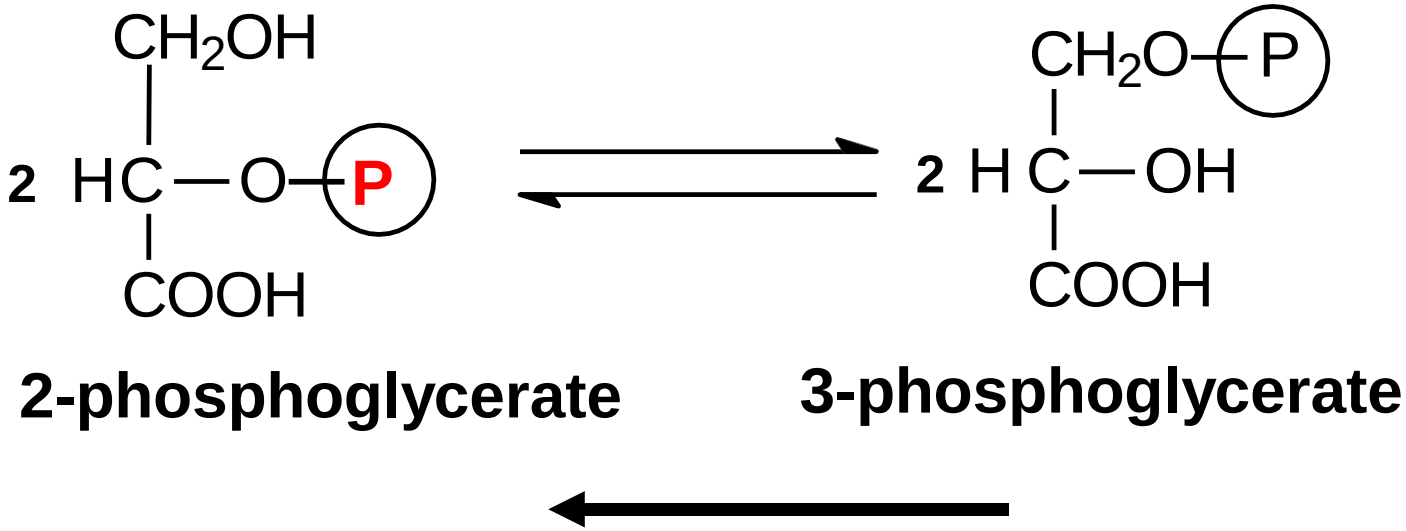
Glycolysis: (7) substrate-level phosphorylation



- High phosphoryl transfer potential in bisphosphoglycerate is used to form **2 ATP**
- **2 molecules of ATP used in the beginning are regained**

Glycolysis: (8) isomerisation (phosphoryl shift) of 3-phosphoglycerate to 2-phosphoglycerate

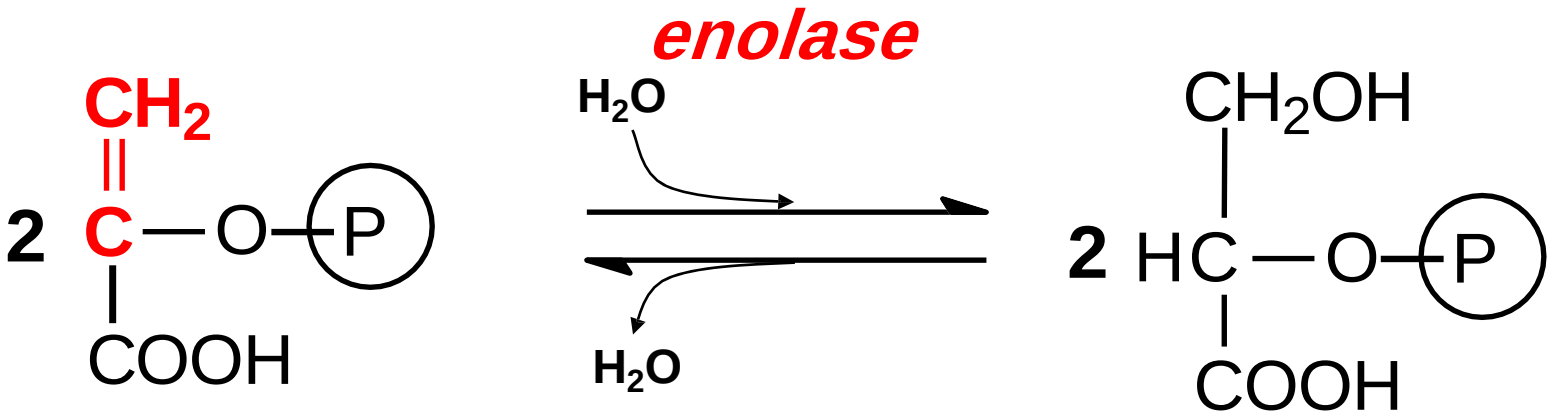
phosphoglyceromutase



2-phosphoglycerate **3-phosphoglycerate**

- Mutase catalyses the intramolecular shift of a chemical group
- Preparation for the next energy production step

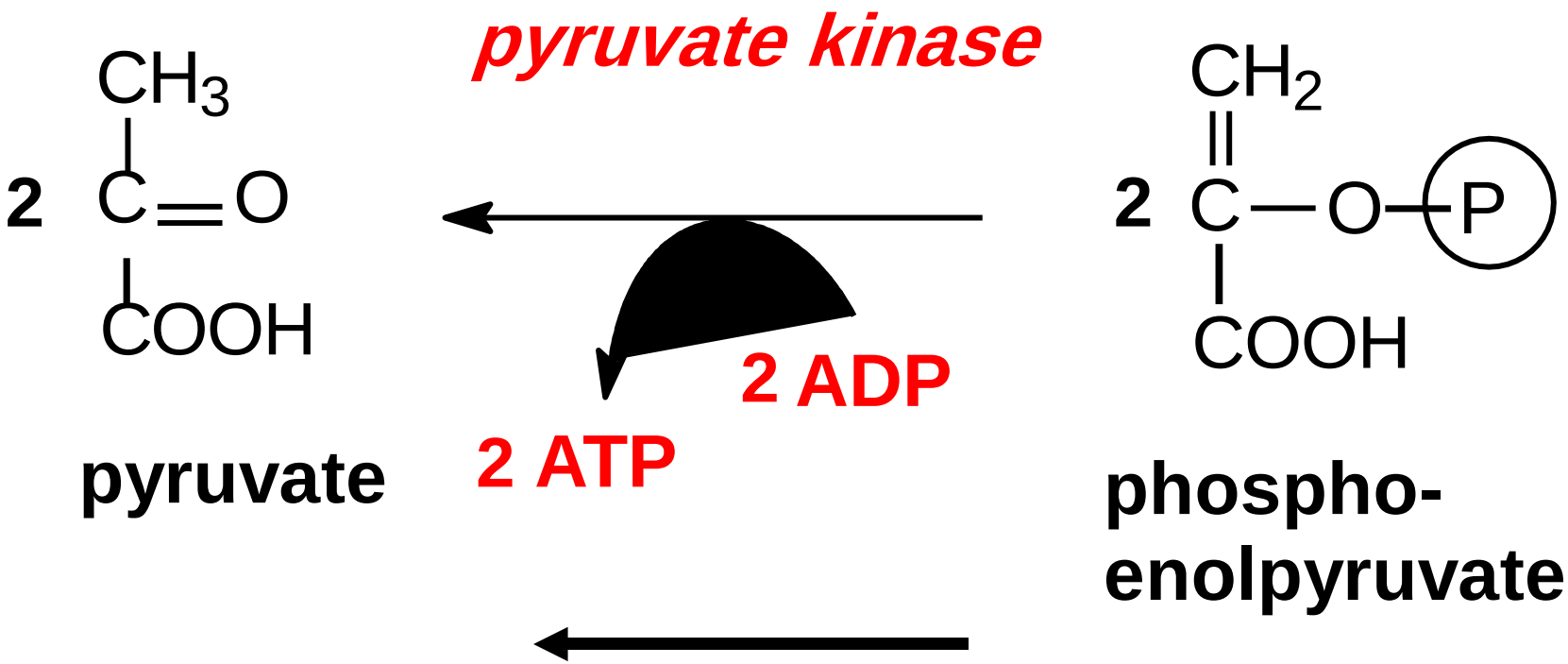
Glycolysis: (9) dehydration of 2-phosphoglycerate to phosphoenolpyruvate (PEP)



phosphoenolpyruvate **2-phosphoglycerate**

- Dehydration of 2-phosphoglycerate to form **phosphoenolpyruvate** where unstable enol form favours donation of the phosphoryl group

Glycolysis: (10) substrate-level phosphorylation



- Converting the enolpyruvate into pyruvate is spontaneous and irreversible reaction
- Useful control point near the end of the pathway
- Gain 2 molecules of ATP
- Result (the second stage of glycolysis): 2 NADH + H^+ + 4 ATP (produced)
- The fiest stage of glycolysis = 2 ATP (required)
- Net energy produced is 4 ATP – 2 ATP = 2 ATP
- Net reaction in glycolysis (total pathway):

Glucose + 2 NAD^+ + 2 ADP + 2 P_i → 2 pyruvate + 2 ATP + 2 NADH + 2 H^+ + 2 H_2O

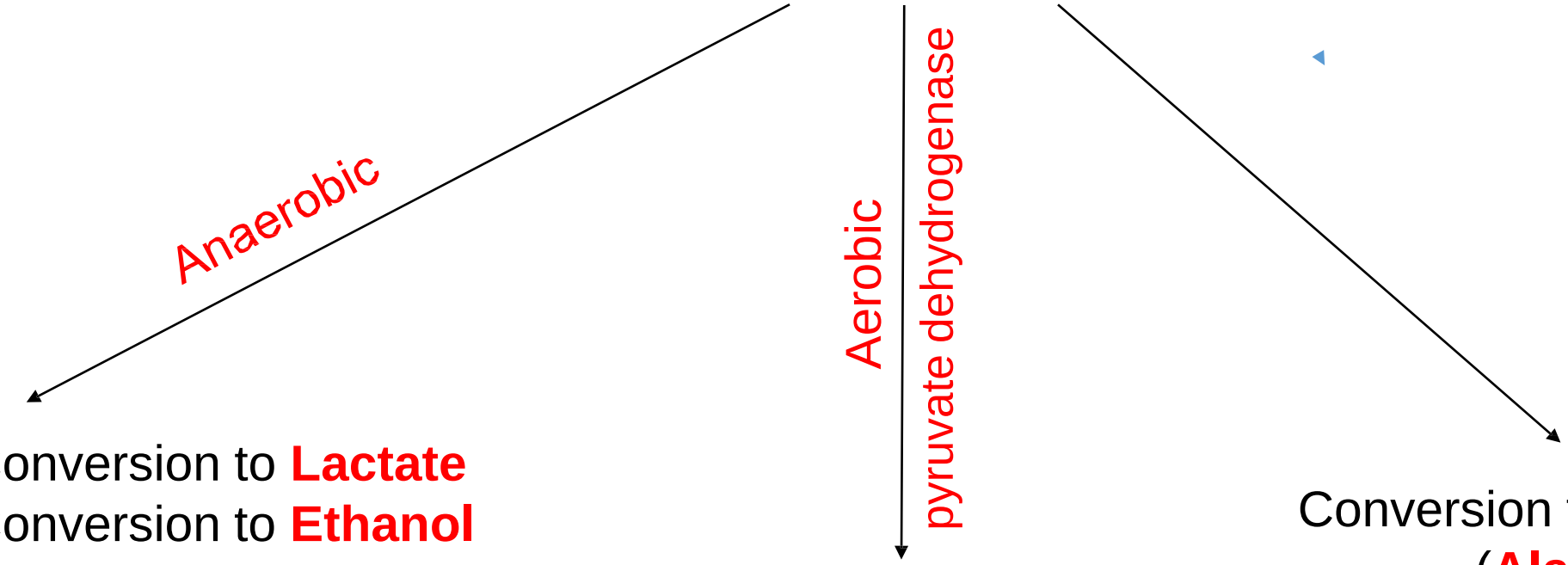
Summary of Glycolysis

Enzyme	Reaction type
Hexokinase	Phosphoryl transfer
Phosphoglucose isomerase	Isomerization
Phosphofructokinase	Phosphoryl transfer
Aldolase	Aldol cleavage
Triose phosphate isomerase	Isomerization
Glyceraldehyde 3-phosphate dehydrogenase	Phosphorylation coupled to oxidation
Phosphoglycerate kinase	Phosphoryl transfer
Phosphoglycerate mutase	Phosphoryl shift
Enolase	Dehydration
Pyruvate kinase	Phosphoryl transfer

Step	Reaction
1	Glucose + ATP $\rightarrow$ glucose 6-phosphate + ADP + H^+
2	Glucose 6-phosphate $\rightleftharpoons$ fructose 6-phosphate
3	Fructose 6-phosphate + ATP $\rightarrow$ fructose 1,6-bisphosphate + ADP + H^+
4	Fructose 1,6-bisphosphate $\rightleftharpoons$ dihydroxyacetone phosphate + glyceraldehyde 3-phosphate
5	Dihydroxyacetone phosphate $\rightleftharpoons$ glyceraldehyde 3-phosphate
6	Glyceraldehyde 3-phosphate + P_i + NAD^+ $\rightleftharpoons$ 1,3-bisphosphoglycerate + NADH + H^+
7	1,3-Bisphosphoglycerate + ADP $\rightleftharpoons$ 3-phosphoglycerate + ATP
8	3-Phosphoglycerate $\rightleftharpoons$ 2-phosphoglycerate
9	2-Phosphoglycerate $\rightleftharpoons$ phosphoenolpyruvate + H_2O
10	Phosphoenolpyruvate + ADP + H^+ $\rightarrow$ pyruvate + ATP

Fate of Pyruvate

Pyruvate



- Conversion to **Lactate**
- Conversion to **Ethanol**

Conversion to amino acid (**Alanine**)

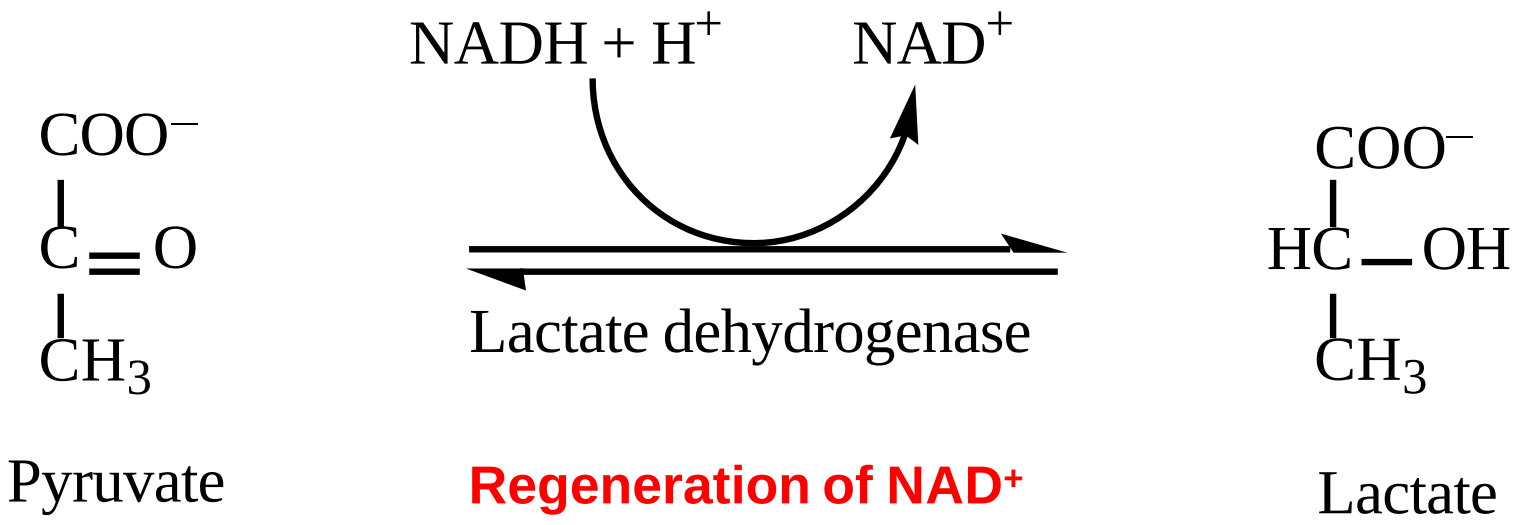
Entry into the **TCA** via acetyl-CoA

- Glycolysis (**anaerobic**): **2 ATP** are produced and pyruvate is converted to **lactate.**
- Glycolysis (**aerobic)**: pyruvate is converted to **acetyl-CoA**, that can be aerobically oxidized to CO2 in the **Krebs cycle (TCA)** and much larger amounts of ATP are produced (**32 ATP**)

In anaerobic conditions → Lactic acid fermentation

- Respiratory chain doesn't work.
- NADH ⟶ NAD^+ ?
- NADH produced in glycolysis must be reoxidised to NAD^+ due to NAD^+ is needed for the reaction **No 6** of glycolysis, where without regeneration of NAD^+ glycolysis will stop

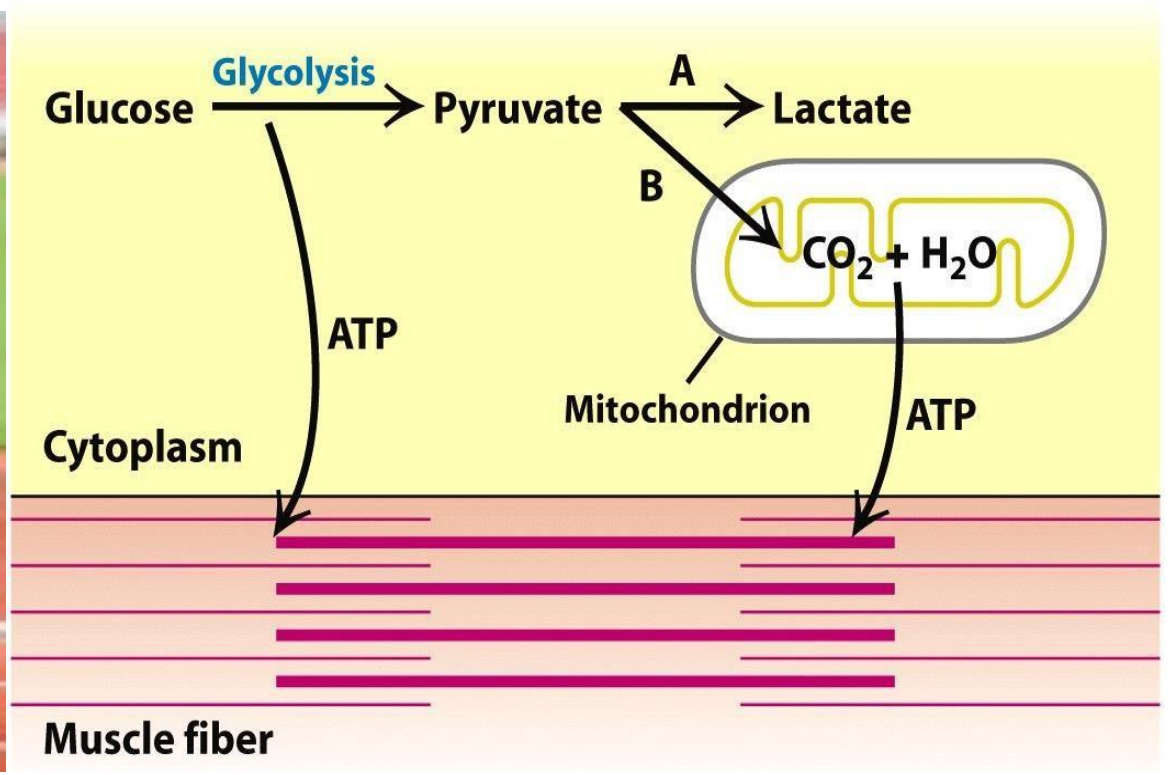
- NAD^+ needs to be regenerated by transferring the hydrogen to pyruvate, yielding lactate



Pyruvate

Regeneration of NAD^+

Lactate



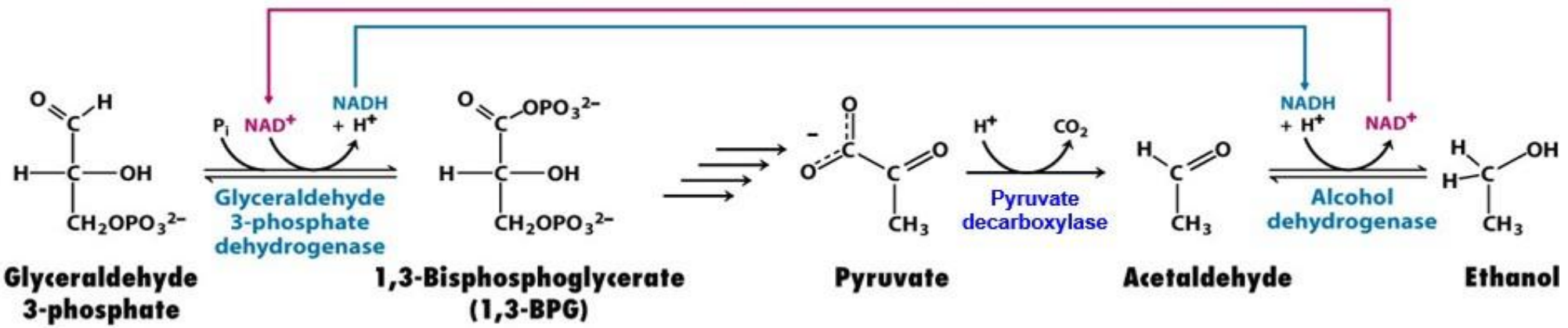
A. Low O_2
(last seconds of a sprint)

B. Normal
(long slow run)

In anaerobic conditions → Ethanol fermentation

Used by anaerobic bacteria and yeast

Regeneration of NAD^+



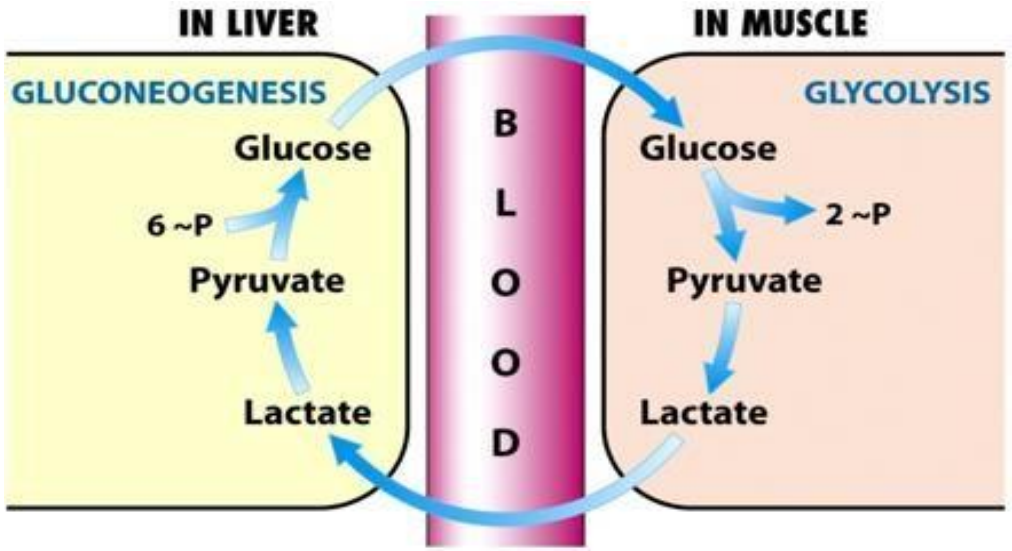
Decarboxylation

Reduction

Cori cycle (lactic acid cycle)

- Lactate is produced by muscles when the body can‘t supply enough oxygen
- Body must take in extra oxygen to oxidise lactate
- Lactate must be converted back into pyruvate
- Lactate produced by anaerobic glycolysis in the muscles moves to the liver and is converted to glucose, which then returns to the muscles (Cori cycle)
- Liver cells convert lactate into pyruvate followed by gluconeogenesis to produce glucose (Cori cycle)

Carl Cori



Cori cycle

Gerty Cori

(Home work)

Control of the glycolytic pathway

- Enzymes catalysing irreversible reactions are potential sites of control.
- What are the control sites in glycolysis ?

Next time on Class..

- TCA-cycle
- Gluconeogenesis

Lecture 5: Biochemistry II
Glycolysis

3rd stage

Anbar University-College of Pharmacy-Clinical Laboratory Sciences Department
2020-2021

Dr. Yousif H. Khalaf

References

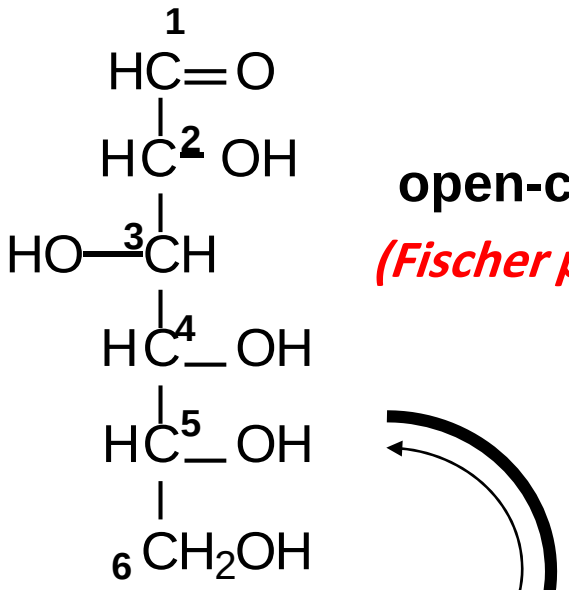
- ✓ Harper’s Illustrated biochemistry, 26th edition
- ✓ Biochemistry – Berg, Tymoczko and Stryer, 6th edition
- ✓ Lippincott’s Illustrated Reviews: Biochemistry 5th edition

Learning Outcomes

By the end of this lecture you will be able to:

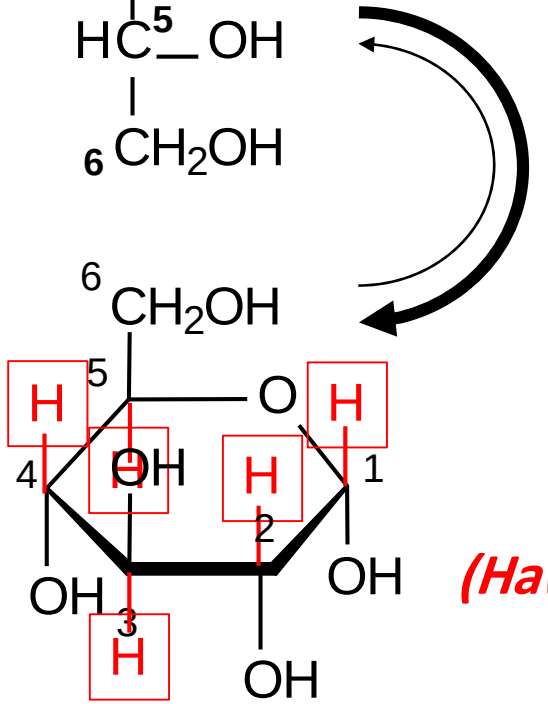
- know the reactions in glycolysis
- Understand the Cori cycle
- Understand the control of glycolysis

Glucose



open-chain form

(Fischer projection)



ring-form

(Haworth projection)

glucose

- After digestion and absorption the principal monosaccharides present in the blood and internal tissues are: glucose, fructose, and galactose.
- Fructose and galactose are converted into glucose by liver cells
- Glucose in solution exists mostly in the ring form at equilibrium, with less than 0.1% of the molecules in the open-chain form.

Glycolysis

- **Glycolysis** (oxidation of glucose) is the sequence of reactions that converts one molecule of glucose to two molecules of pyruvate.

D-glucose + 2 NAD^+ + **2 ADP** + 2 P_i → **2 pyruvate** + **2 ATP** + 2 NADH + 2 H^+ + 2 H_2O

Glucose → 2 Pyruvate → 2 Acetyl-CoA (TCA cycle)-(in the presence of oxygen)

Glucose → 2 Pyruvate → 2 Lactate (in the absence of oxygen)

- **Does not** require oxygen
- Stage 1 (non-oxidative) - requires energy
- Stage 2 (oxidative) - produces energy
- Glycolysis reactions occur in cytoplasm
- Small amount of energy produced

Anaerobic Glucose Utilization

- **Glucose → 2 Pyruvate → 2 Lactate**
- **2 ATP** are generated in glycolysis per one mole of glucose
- **2 NADH** are formed but cannot be used for energy in the absence of oxygen - recycled by lactate dehydrogenase (LDH)
- ADP + P + Energy ⟷ ATP (Rechargeable Battery)
- ATP "molecular currency" is using for intracellular energy transfer
- Glycolysis provides building blocks for synthetic reactions, e.g. formation of fatty acids

Glycolysis: the (anaerobic) metabolism of glucose

A- Stage one (non-oxidative stage): Reactions 1 to 5 (requires energy):

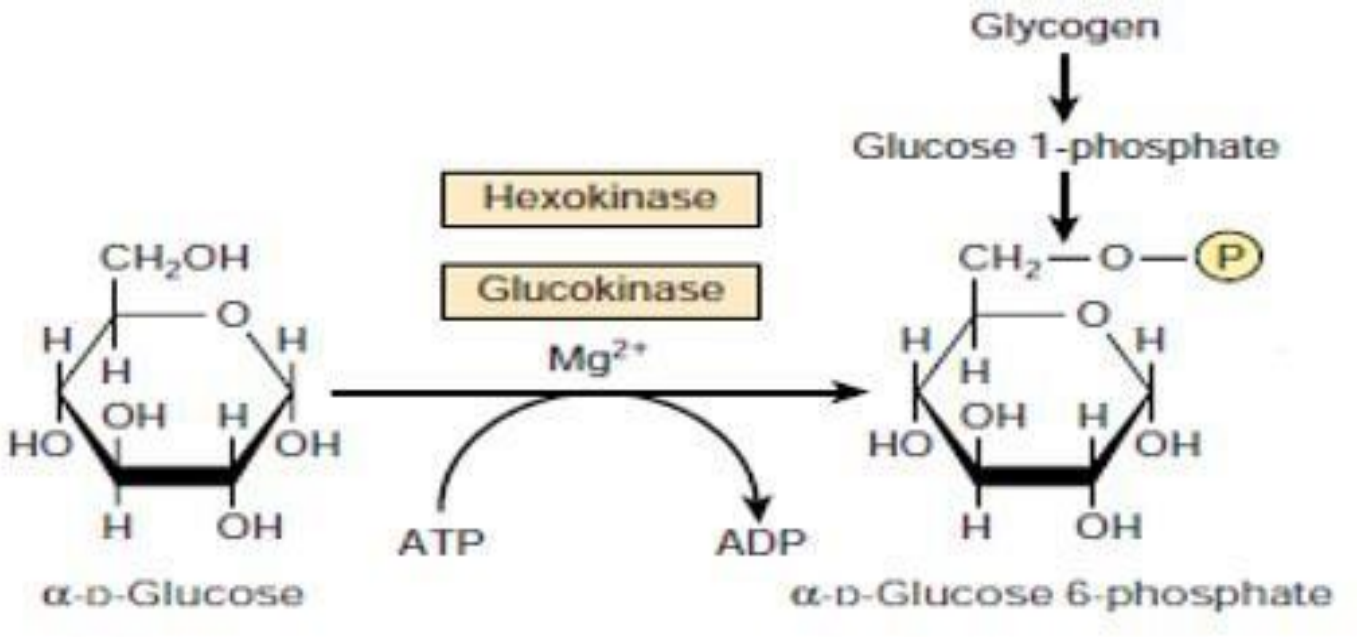
One molecule of **glucose** is converted into **two** molecules of **glycerosldhyde-3-phosphate**.These steps requires **2 ATP** molecules.

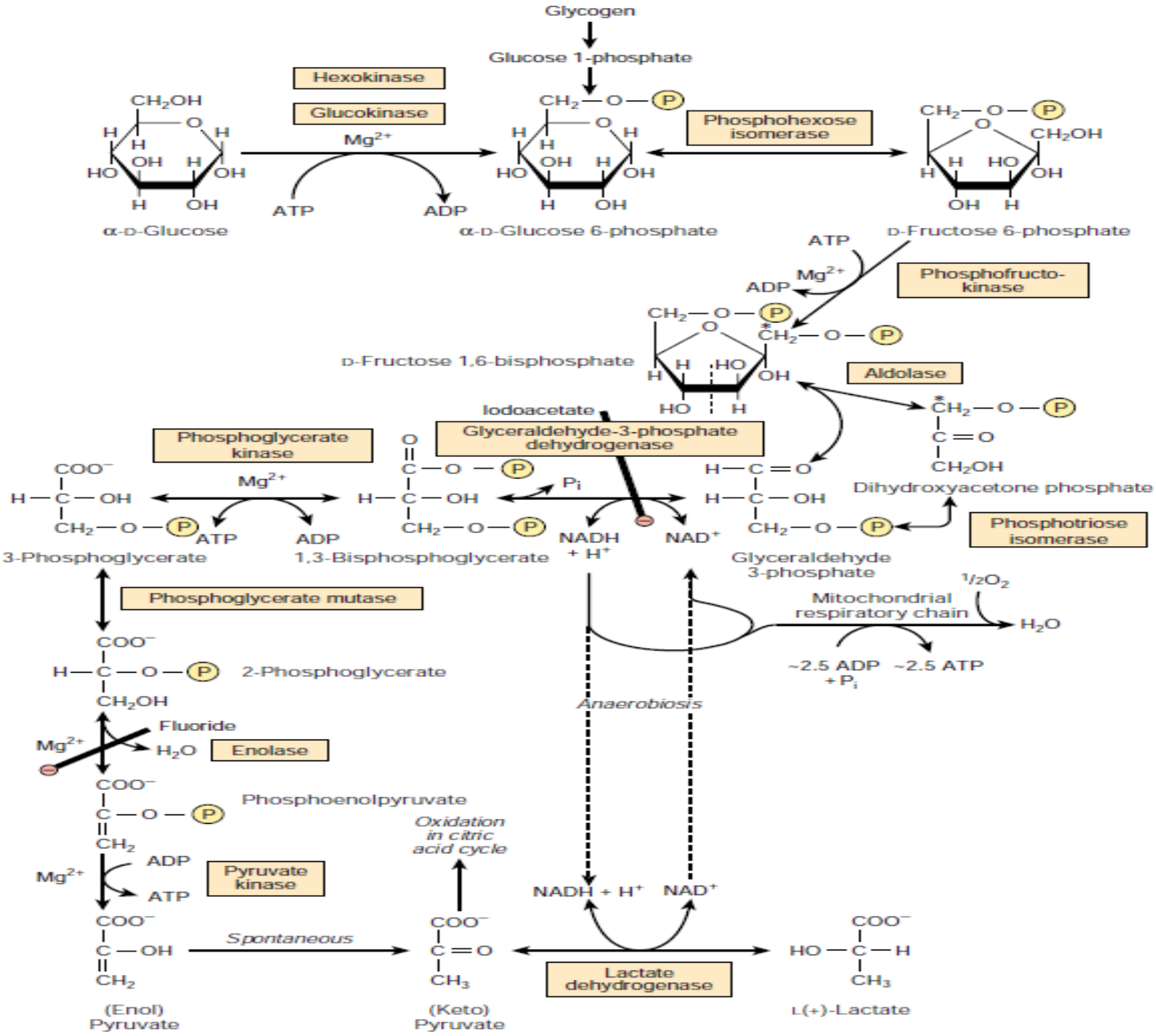
B- Stage two (oxidative stage): Reactions 6 to 10 (produces energy):

The **two** molecules of **glyceroaldehyde-3-phosphate** are converted into **2 pyruvate**. These steps produce **4 ATP** molecules.

Glycolysis: the (anaerobic) metabolism of glucose

- The first substrate for glycolysis is glucose 6-phosphate
- In the **feeding state** glucose 6-phosphate is formed by phosphorylation of glucose by **hexokinase or glucokinase**
- In the **fasting state** liver and muscle form glucose 6-phosphate **from glycogen**





Glycolysis Reactions

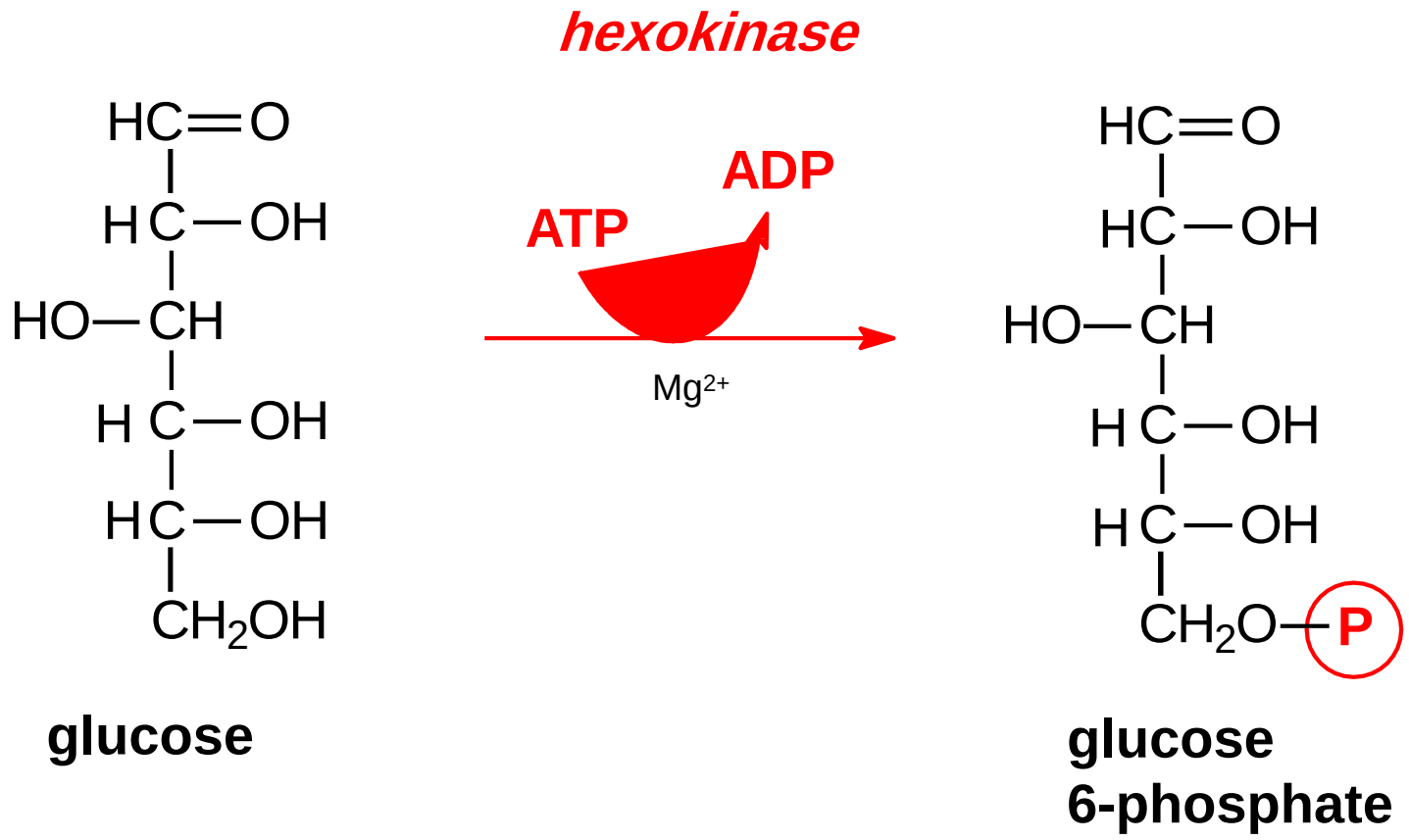
(anaerobic)

Glycolysis Reactions

Five important types of enzymes that present in glycolysis:

- **Kinase (Phosphoryl transfer)**: phosphoryl group transferred from ATP to a glycolytic intermediate, or from the intermediate to ADP.
- **Isomerase (Aldose-ketose isomerization)**: the conversion of a ketose to an aldose, or vice versa.
- **Aldolase (Aldol cleavage)**: the splitting of a carbon-carbon bond.
- Dehydrogenase: the removal of hydrogen.
- **Mutase (Phosphoryl shift)**: phosphoryl group is shifted from one oxygen atom to another within a molecule.

Glycolysis: (1) phosphorylation of glucose to glucose 6-phosphate



glucose

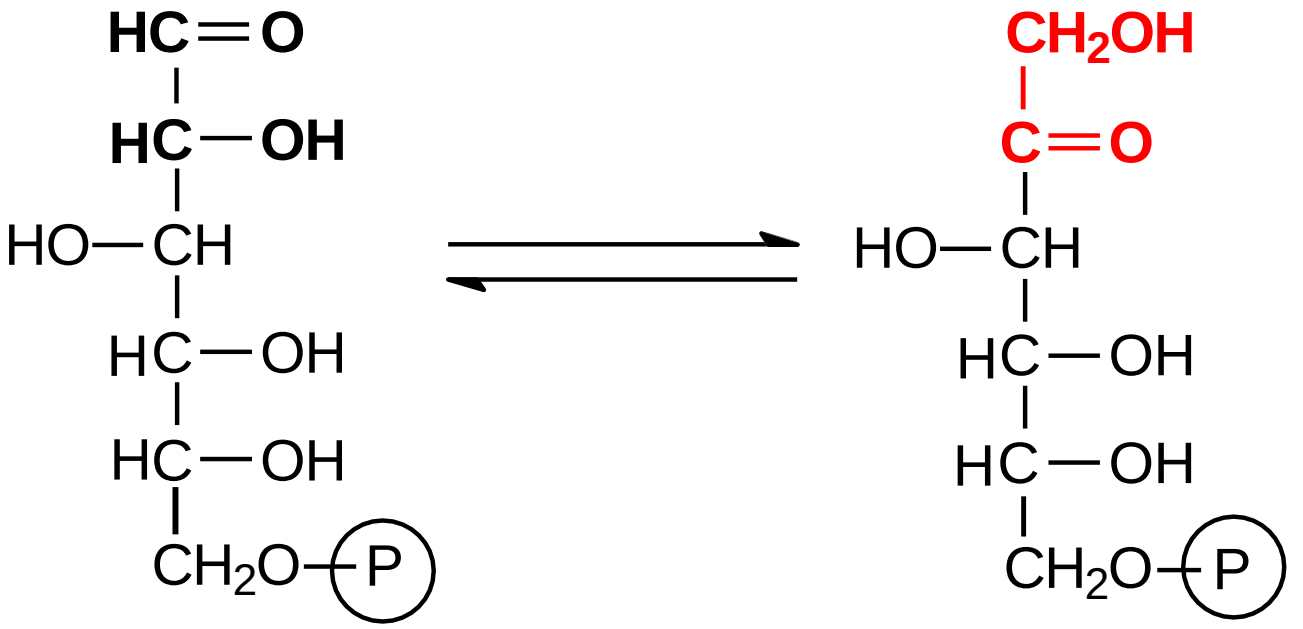
glucose 6-phosphate

- Glucose enters to cells through specific transport proteins
- Phosphorylation **traps** glucose within the cell
- Phosphorylation is an **irreversible step**
- **One** molecule of **ATP** has been spent
- Phosphorylation **destabilises** glucose facilitating its further metabolism

Glycolysis: (2) isomerisation of glucose 6-phosphate to fructose 6-phosphate

phosphohexose isomerase

aldose

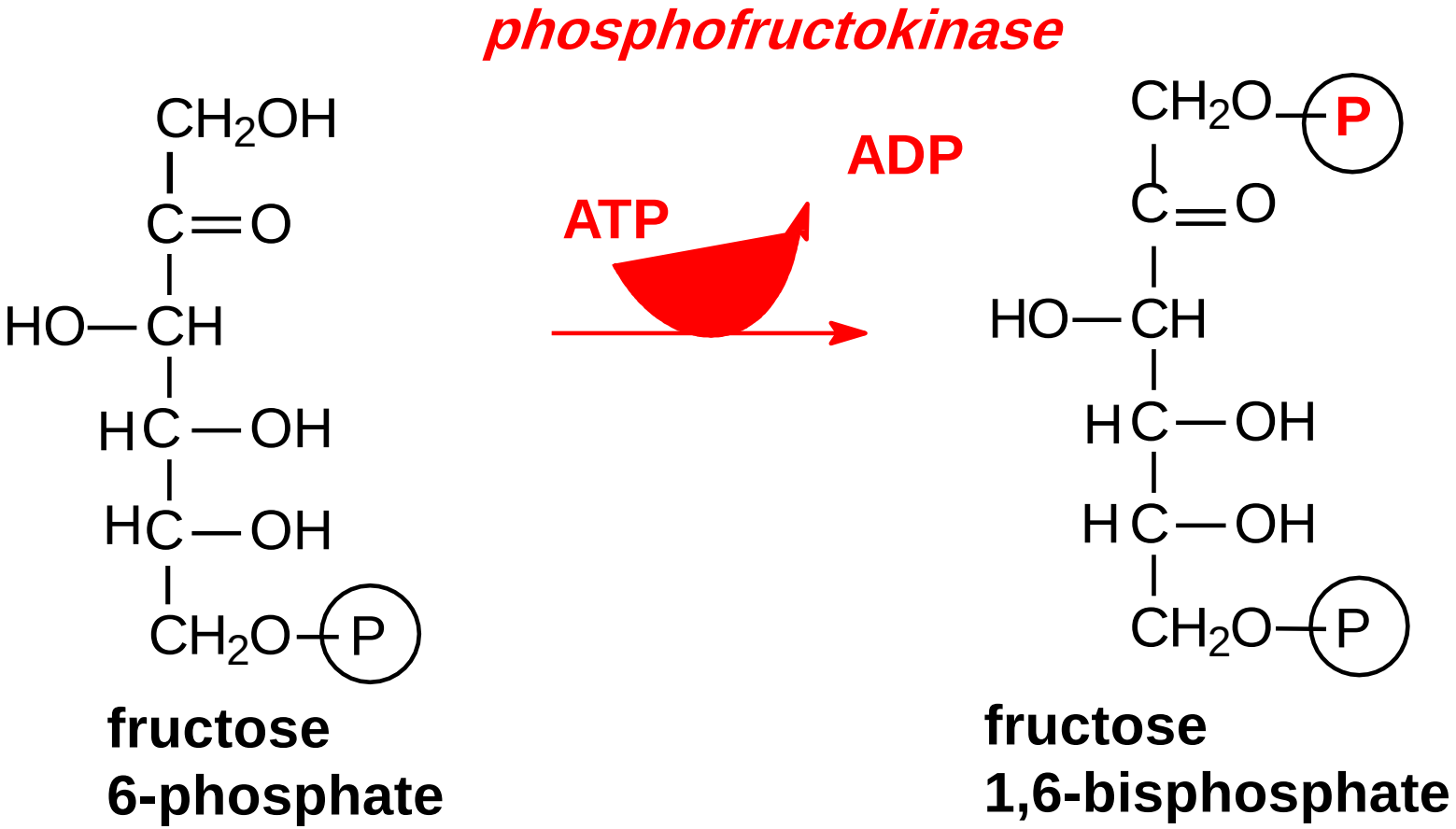


ketose

glucose 6-phosphate

fructose 6-phosphate

Glycolysis: (3) phosphorylation of fructose 6-phosphate to fructose 1,6-bisphosphate

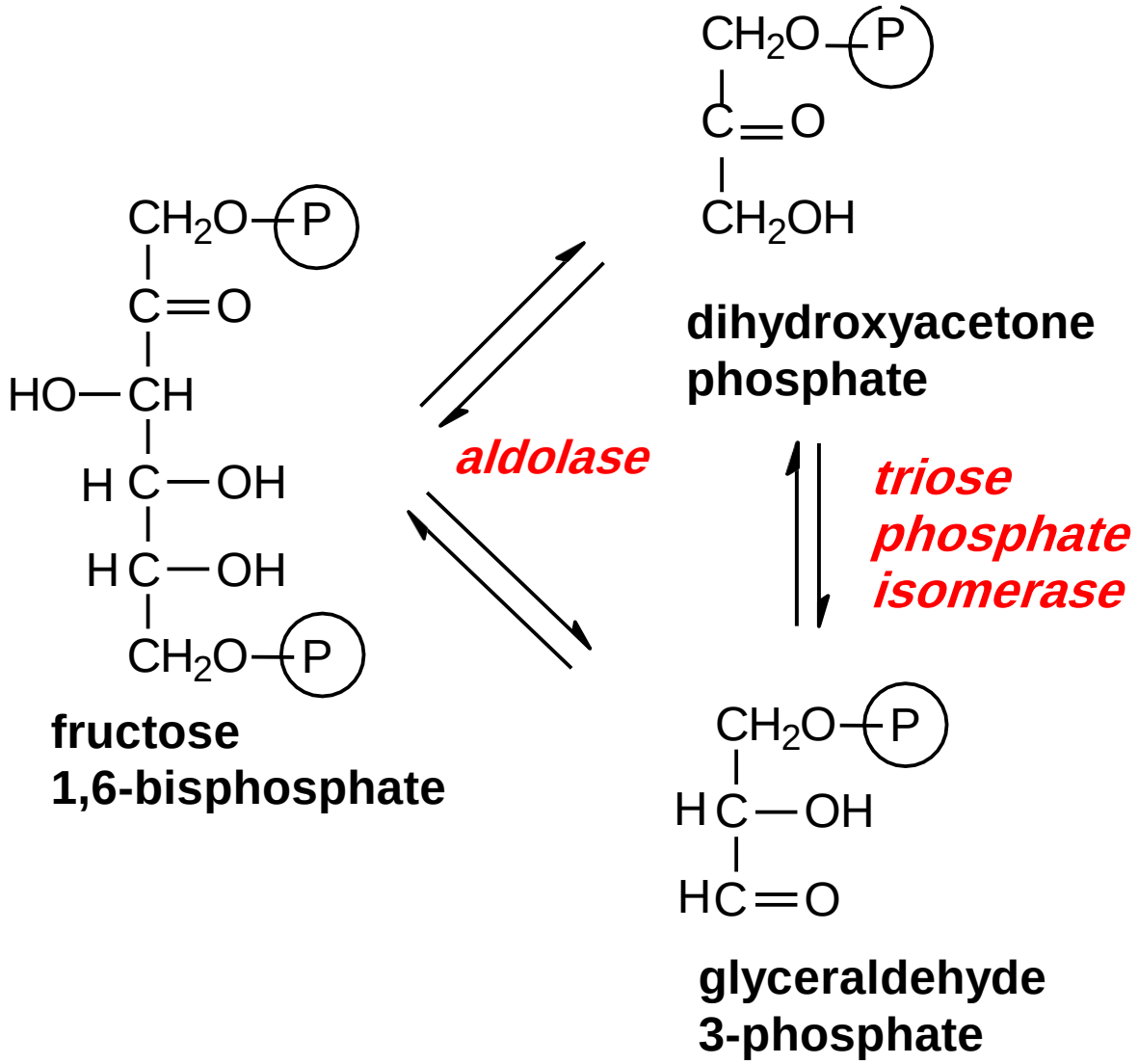


fructose 6-phosphate

fructose 1,6-bisphosphate

- **phosphate group** has been added at each **end** of the molecule
- molecule is ready to be split into **two 3C**-structure
- **One** molecule of **ATP** has been spent

Glycolysis: (4 & 5) cleavage of fructose 1,6-bisphosphate to dihydroxyacetone phosphate & glyceraldehyde 3-phosphate (two triose phosphates). But only glyceraldehyde-3-phosphate can proceed through glycolysis



- Dihydroxyacetone-phosphate is isomerized to form glyceraldehyde-3-phosphate

Lecture 6: Biochemistry II
The TCA Cycle

3rd stage

Anbar University-College of Pharmacy-Clinical Laboratory Sciences Department
2020-2021

Dr. Yousif H. Khalaf

Learning outcomes

By the end of this lecture you should be able to:

- Define the term oxidative decarboxylation
- To understand the components of the TCA cycle
- To understand the regulation of the TCA cycle
- Distinguish between substrate level phosphorylation and oxidative phosphorylation

The TCA Cycle

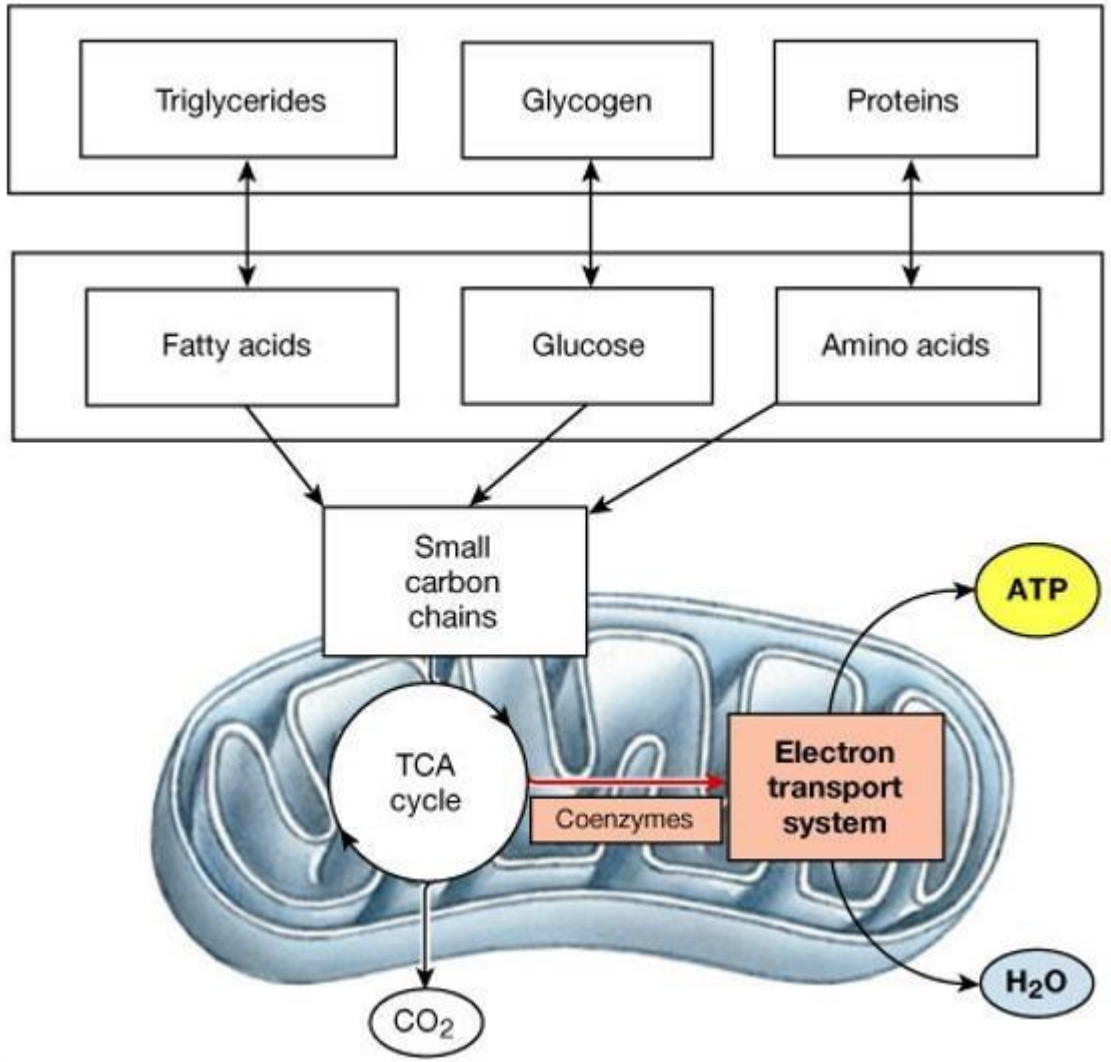
- In **glycolysis**, the energy yield is **2 ATP** (low)
- How can we get **more ATP from glucose**?

- The **TCA cycle** (**T**ri**c**arboxylic **A**cid Cycle)**.** Also known as:
- The **Citric Acid Cycle**
- The **Krebs Cycle** (After being discovered by Hans Krebs, Nobel Prize 1953, who first described it in 1937)

- In **eukaryotes** the TCA cycle takes place in the **mitochondrial matrix**
- The **Krebs Cycle** has both **catabolic** (Degradation) and **anabolic** (Biosynthetic) functions **(amphibolic)**

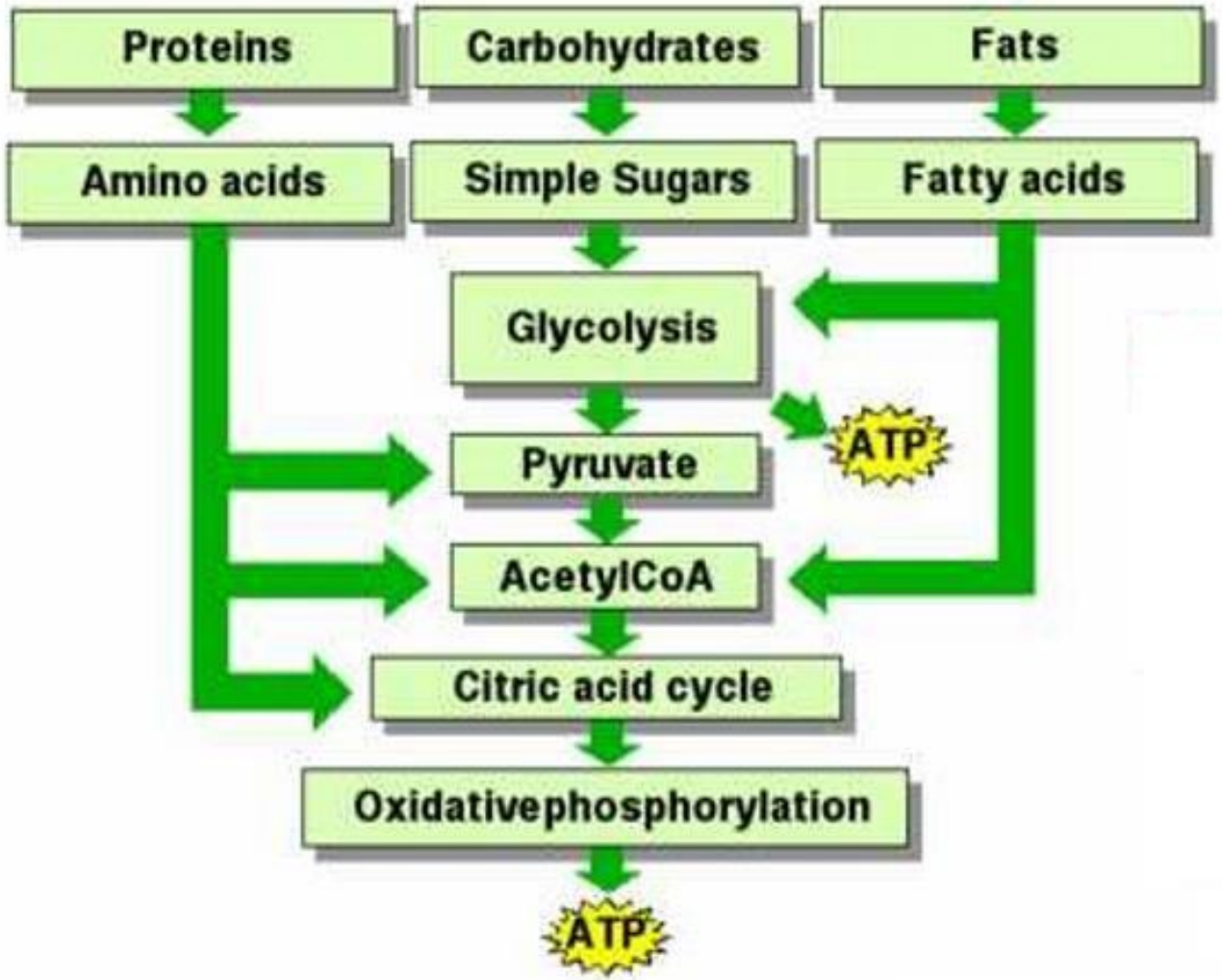
The Krebs Cycle has a central role in metabolism

- Degradation products of carbohydrates, lipids and proteins are fed into the **TCA** for oxidative metabolism to release energy.



- **Metabolites** from the **TCA** cycle can also be used to synthesise glucose, lipids and amino acids

Overview of catabolic processes



Stage I

Breakdown of macromolecules into their building blocks.
No useful energy.

Stage II

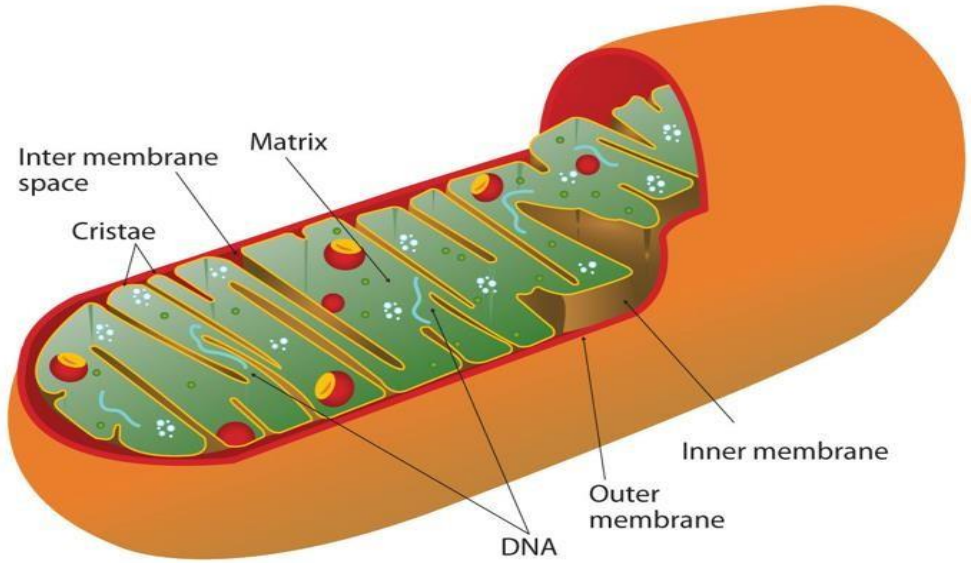
Oxidation of Stage I products to acetylCoA.
Limited energy production.

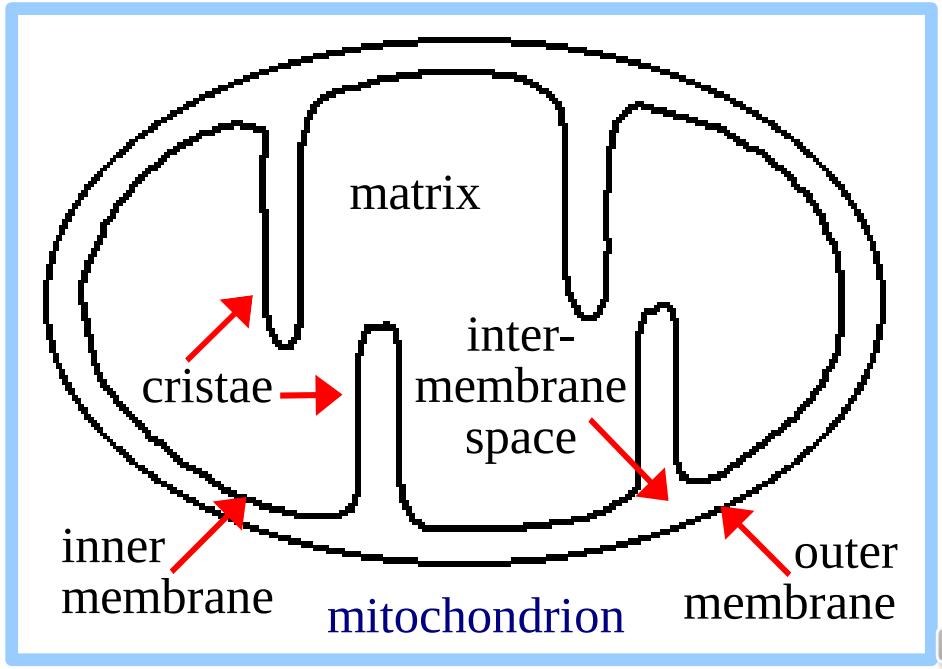
Stage III

Oxidation of acetyl CoA to CO_2 and H_2O and energy.

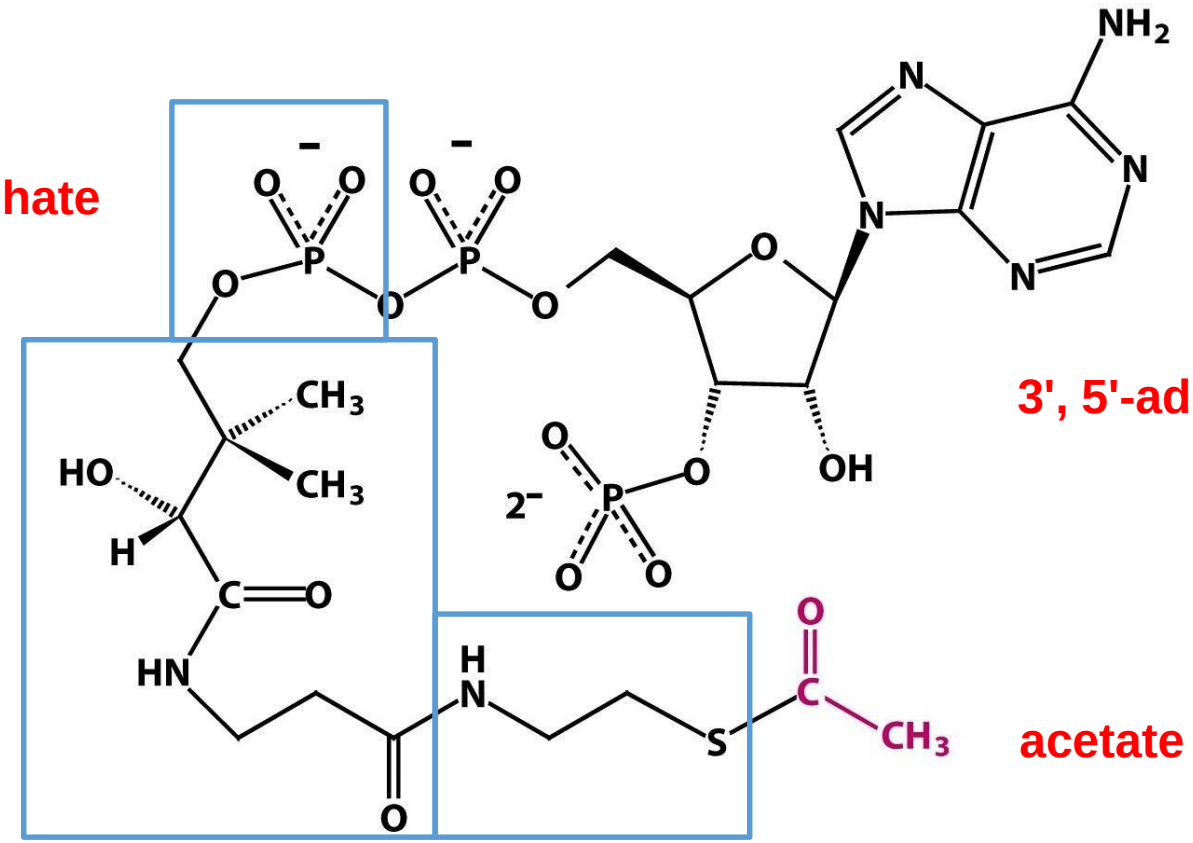
Mitochondrial Compartments

- **Matrix** – internal space containing enzymes of the **TCA** cycle and oxidative decarboxylation of pyruvate
- **Inner membrane** – large surface by invaginations (cristae); proteins of the electron transport chain, transport proteins; electrochemical gradient of H^+, and ATP synthase
- **Outer membrane** – channel protein, molecules up to 5 kDa can enter the intermembrane space





Acetyl coenzyme A (Acetyl CoA)



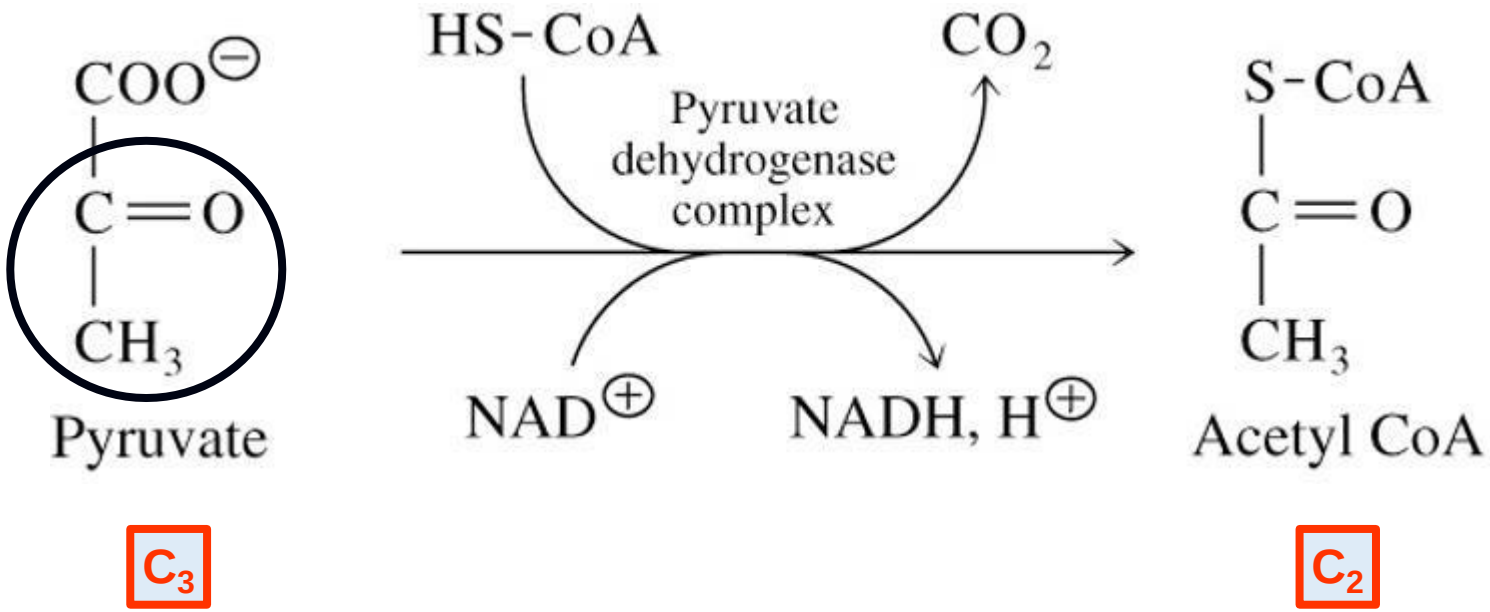
Oxidative decarboxylation of pyruvate

Before the cycle can begin:

- The **irreversible** link from **glycolysis** to the **TCA** cycle is Pyruvate Dehydrogenase complex which occurs in the mitochondrium.
- Pyruvate is oxidized and a carbon group (CO_2) is lost (Decarboxylation), **C3** ⟹ **C2**
- The **acetate unit** (**C2**) within pyruvate is activated by linking it to **Coenzyme A** through a thioester bond (esterification).
- Commits the carbon atoms of carbohydrates and amino acids to **oxidation** via the **TCA cycle** or to the synthesis of lipids.
- The reaction only occurs if **ATP** is needed or two-carbon fragments are required for lipid biosynthesis

Oxidative decarboxylation of pyruvate

acetate unit



C_3 C_2

- Catalyzed by enzymes in the **pyruvate dehydrogenase complex**
- This is a **REDOX** reaction, this type of reaction is called an **oxidative decarboxylation**.

Pyruvate oxidative decarboxylation components

Pyruvate Dehydrogenase complex is a Multi-Enzyme Complex:
Three enzymes:

Enzyme	Abbreviated	Prosthetic Group
Pyruvate dehydrogenase	E_1	Thiamine pyrophosphate (TPP)
Dihydrolipoamide acetyltransferase	E_2	Lipoamide
Dihydrolipoamide dehydrogenase	E_3	FAD

Pyruvate Dehydrogenase complex requires several cofactors:

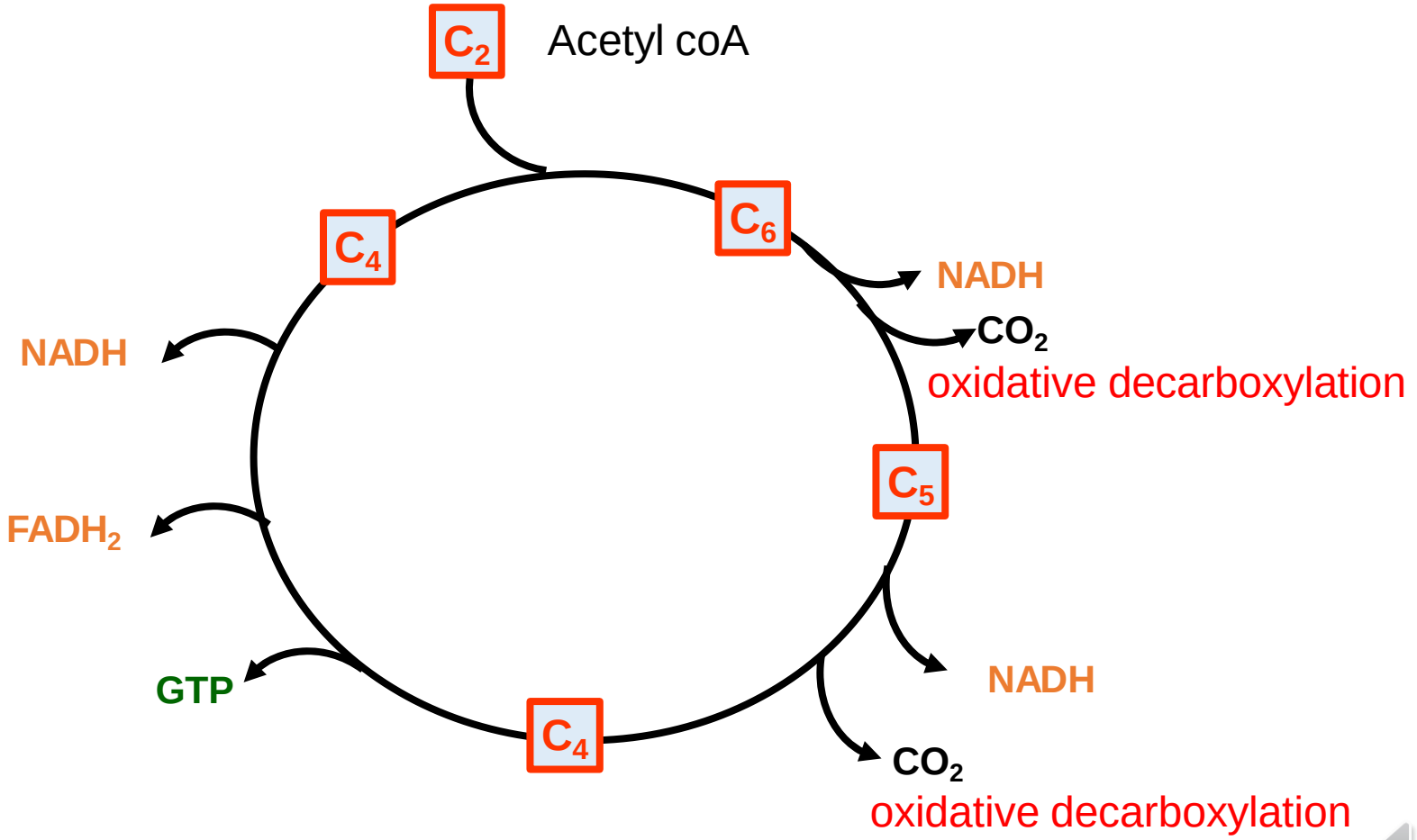
- **TPP** attached to E_1
- **Lipoamide** attached to E_2
- **FAD** attached to E_3
- **NAD^+** and **Coenzyme A-** free coenzymes

TCA cycle overview

- Acetyl CoA (**2 C**) feeds into the cycle by joining with Oxaloacetate (**4 C**)

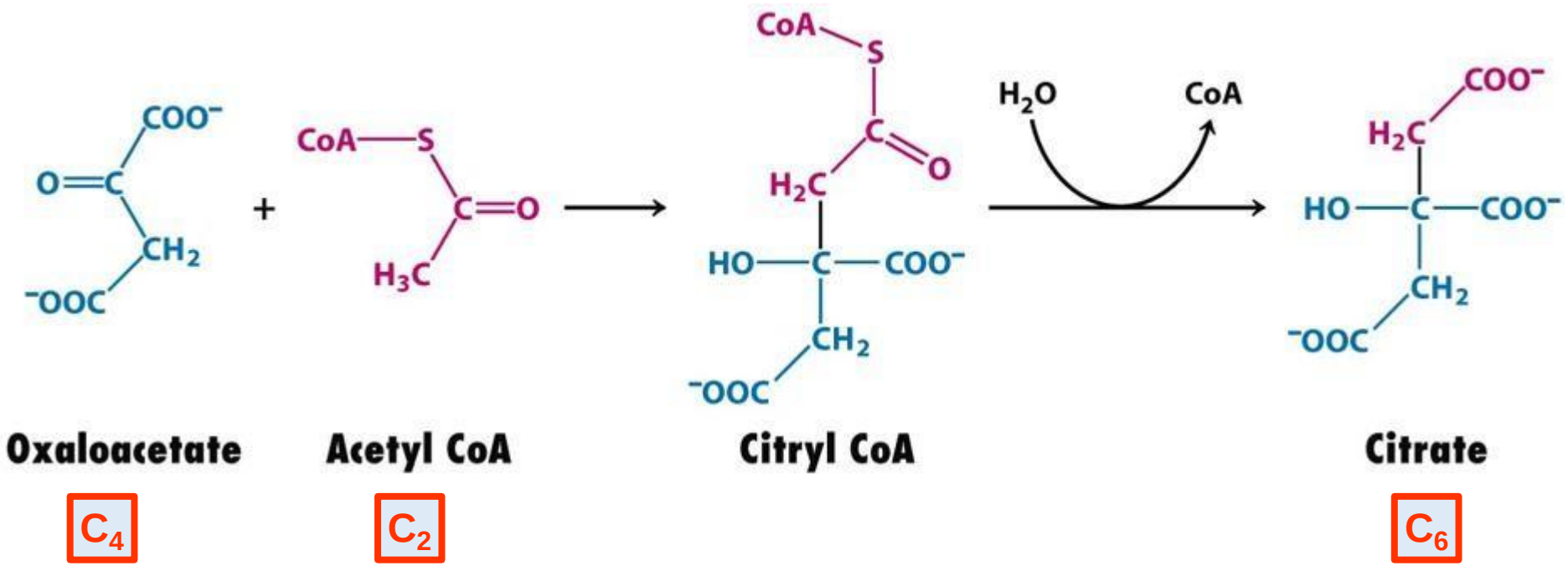
- **8 steps**

- The cycle can only work if there is sufficient oxidizing capability in the cell (oxygen)



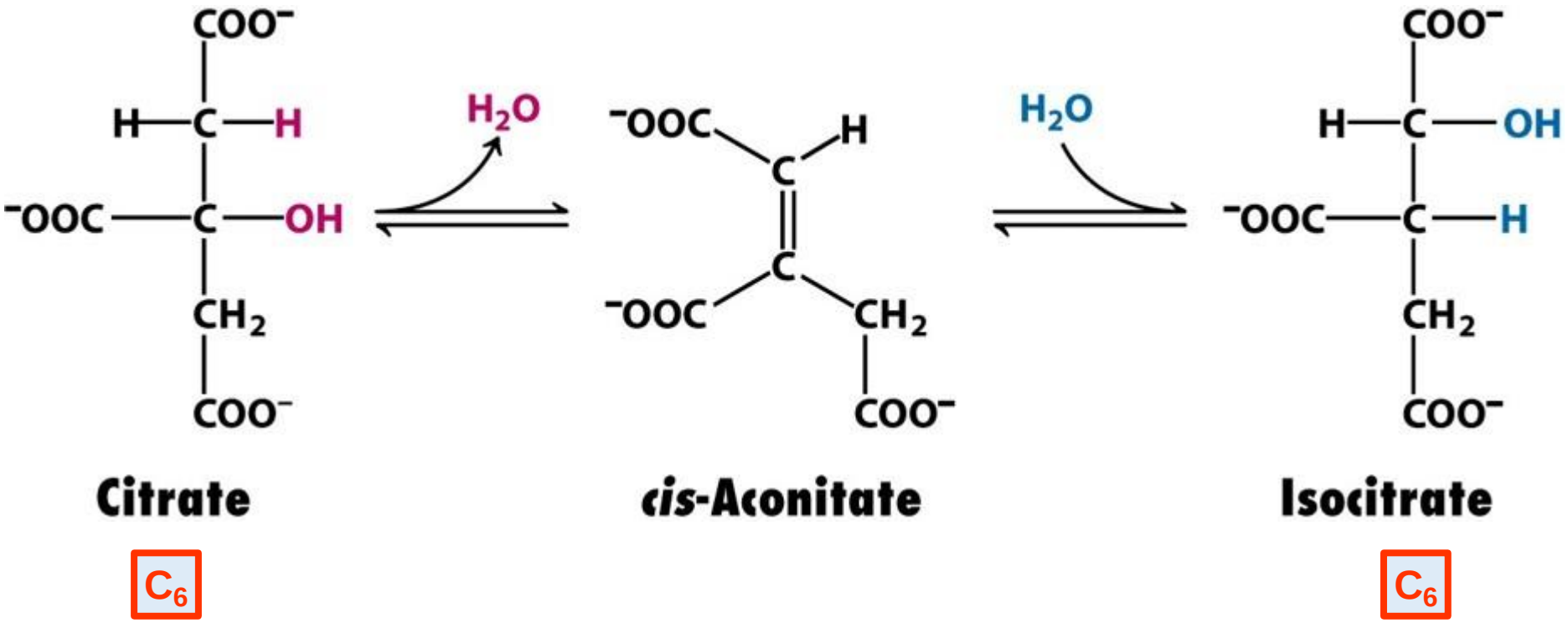
Steps of the TCA cycle

Step 1: Citrate synthase



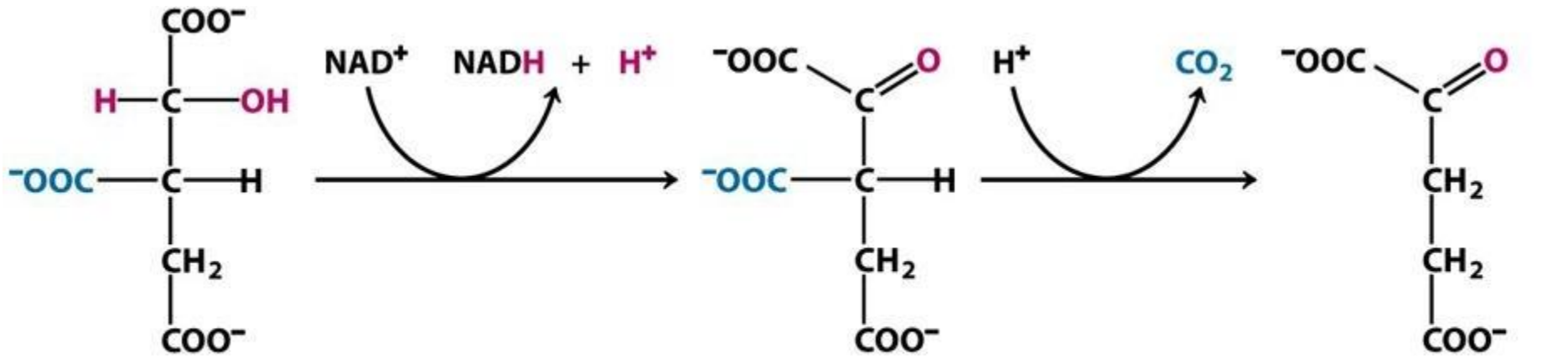
- Oxaloacetate bind to acetyl CoA to form citryl CoA (Condensation)
- Citryl CoA is hydrolysed by water which releasing **CoA and citrate**.
- Accumulation of citrate → moves to cytoplasm and inhibits phosphofructokinase (**PFK)** which **stops glycolysis**

Step 2: Aconitase



- **Dehydration** of citrate followed by **hydration** of cis-Aconitate to form **isocitrate** (isomerisation)

Step 3: Isocitrate dehydrogenase

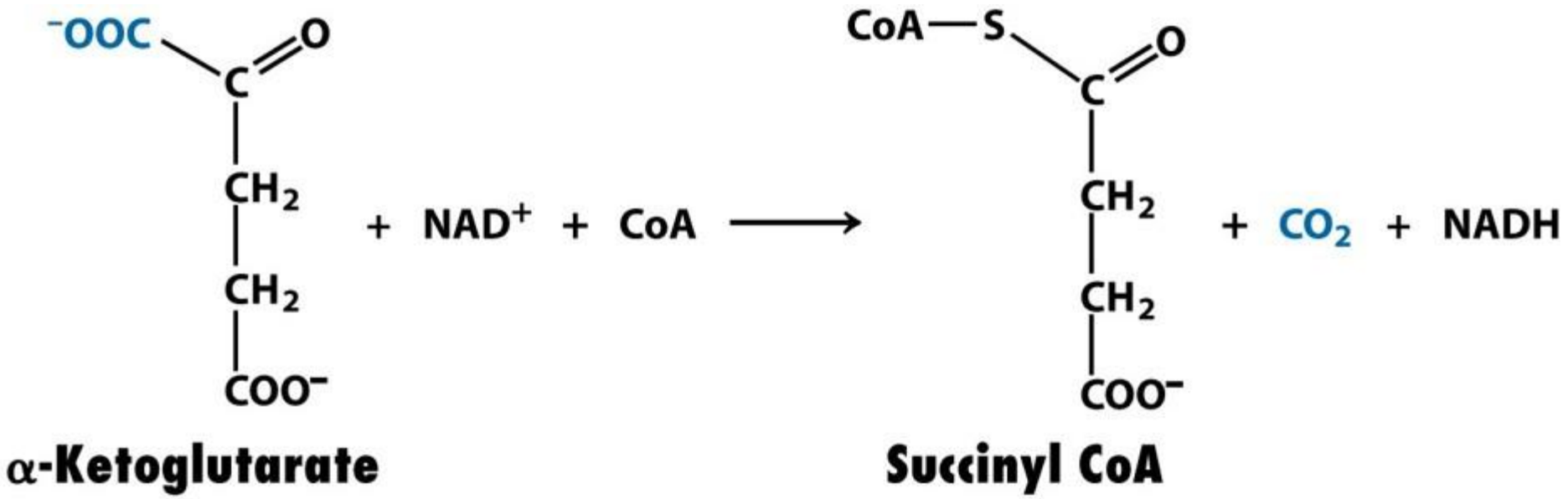


Unstable intermediate

Oxidative decarboxylation

- The **oxidation of isocitrate** results in unstable intermediate (oxalosuccinate) that converted to **α-ketoglutarate**

Step 4: α-Ketoglutarate dehydrogenase

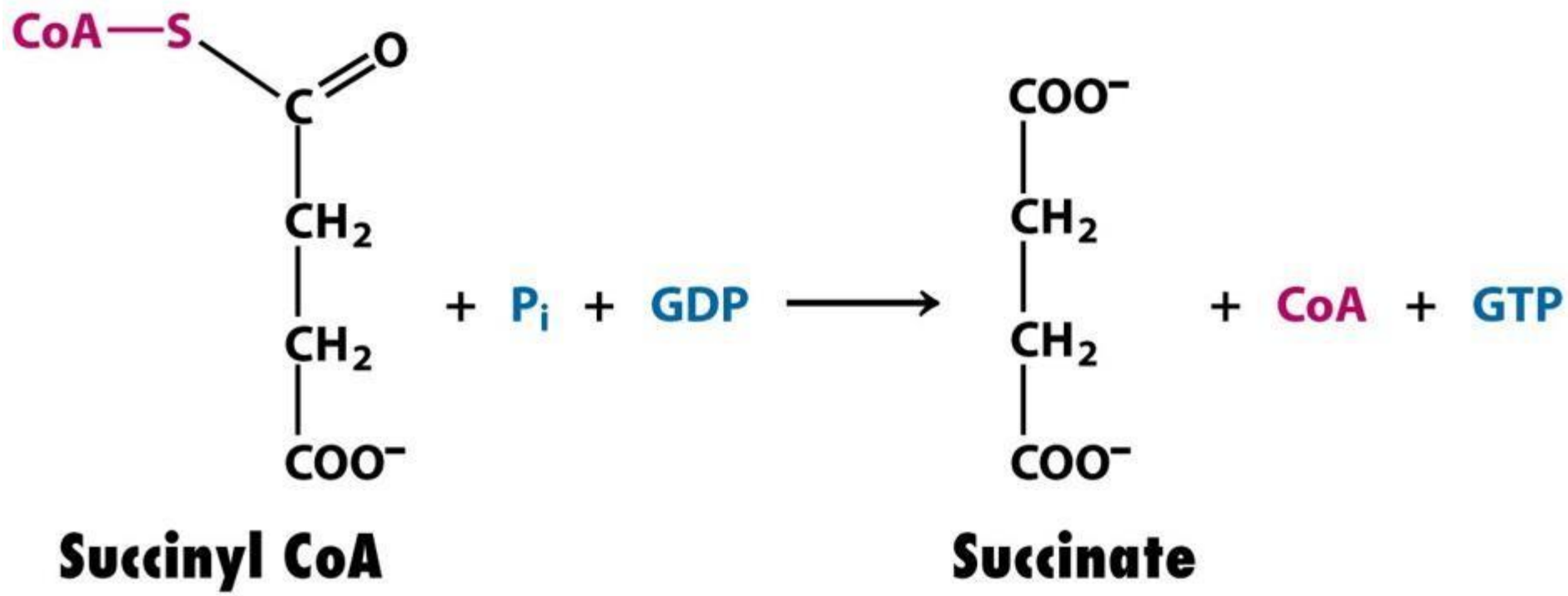


C_5 C_4

Similar reaction mechanism to pyruvate dehydrogenase

Oxidative decarboxylation

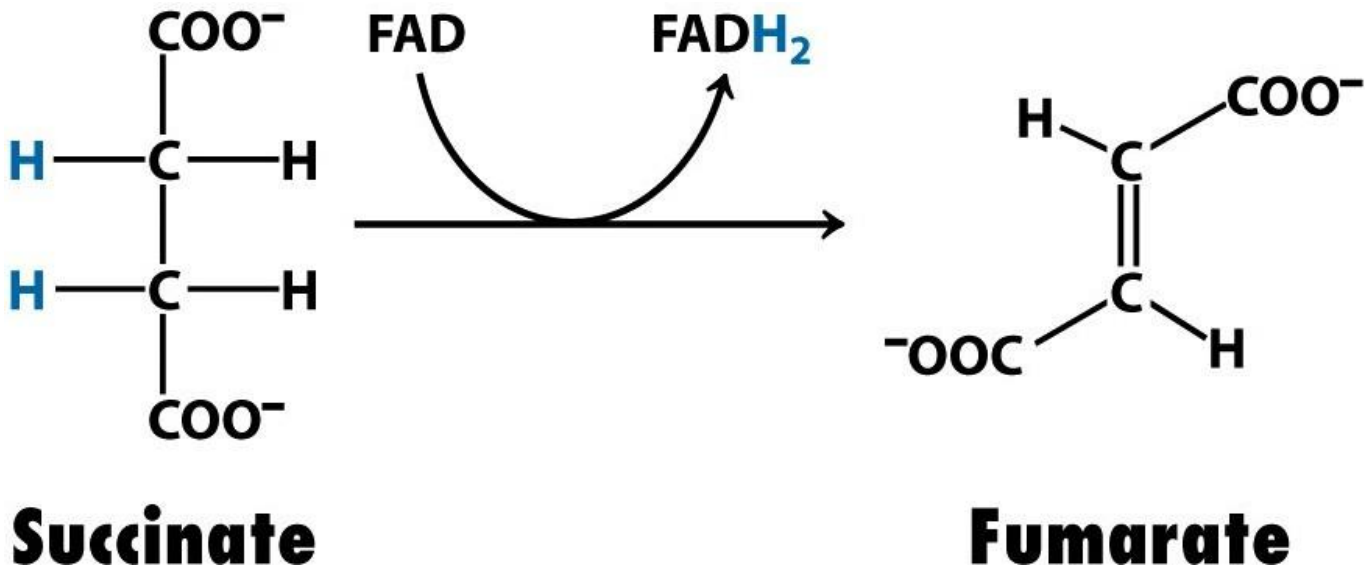
Step 5: Succinyl CoA synthetase



(succinyl phosphate intermediate)

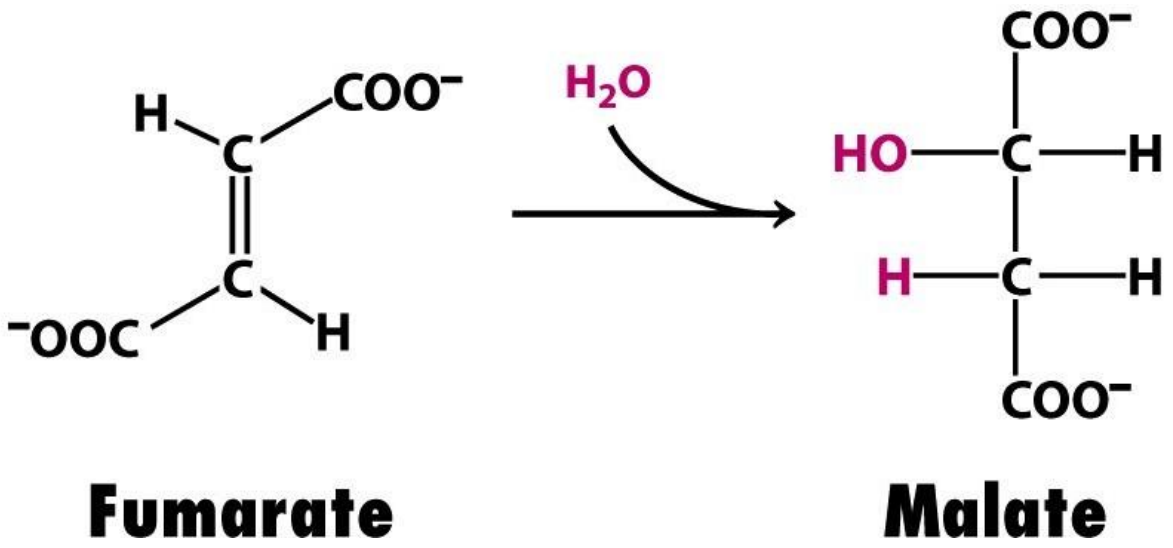
- **Energy of the thioester is transferred into phosphoryl-group transfer potential.**
- **Substrate level phosphorylation is the formation of GTP at the expense of succinyl CoA.**

Step 6: Succinate dehydrogenase



- **Oxidation** of succinate and reduction of **FAD**
- **C = C** is formed by oxidation

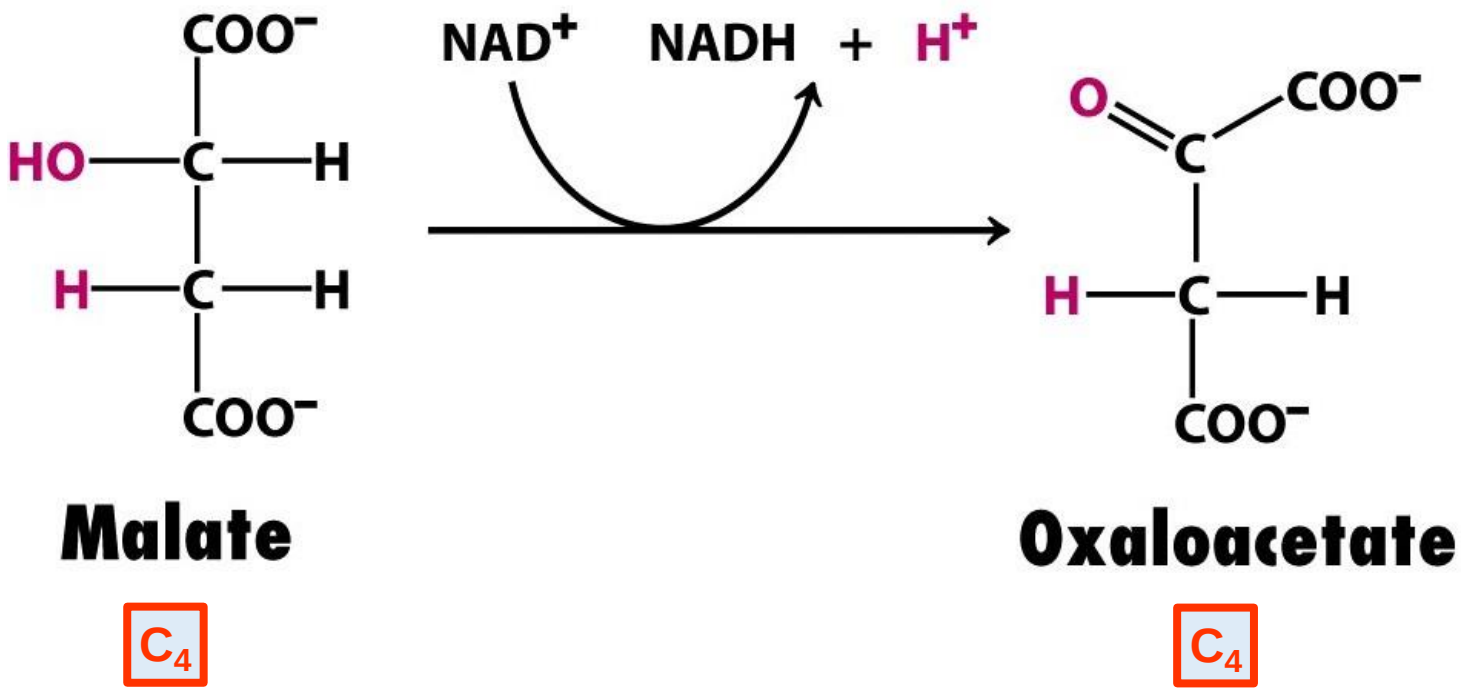
Step 7: Fumarase



Fumarate **Malate**

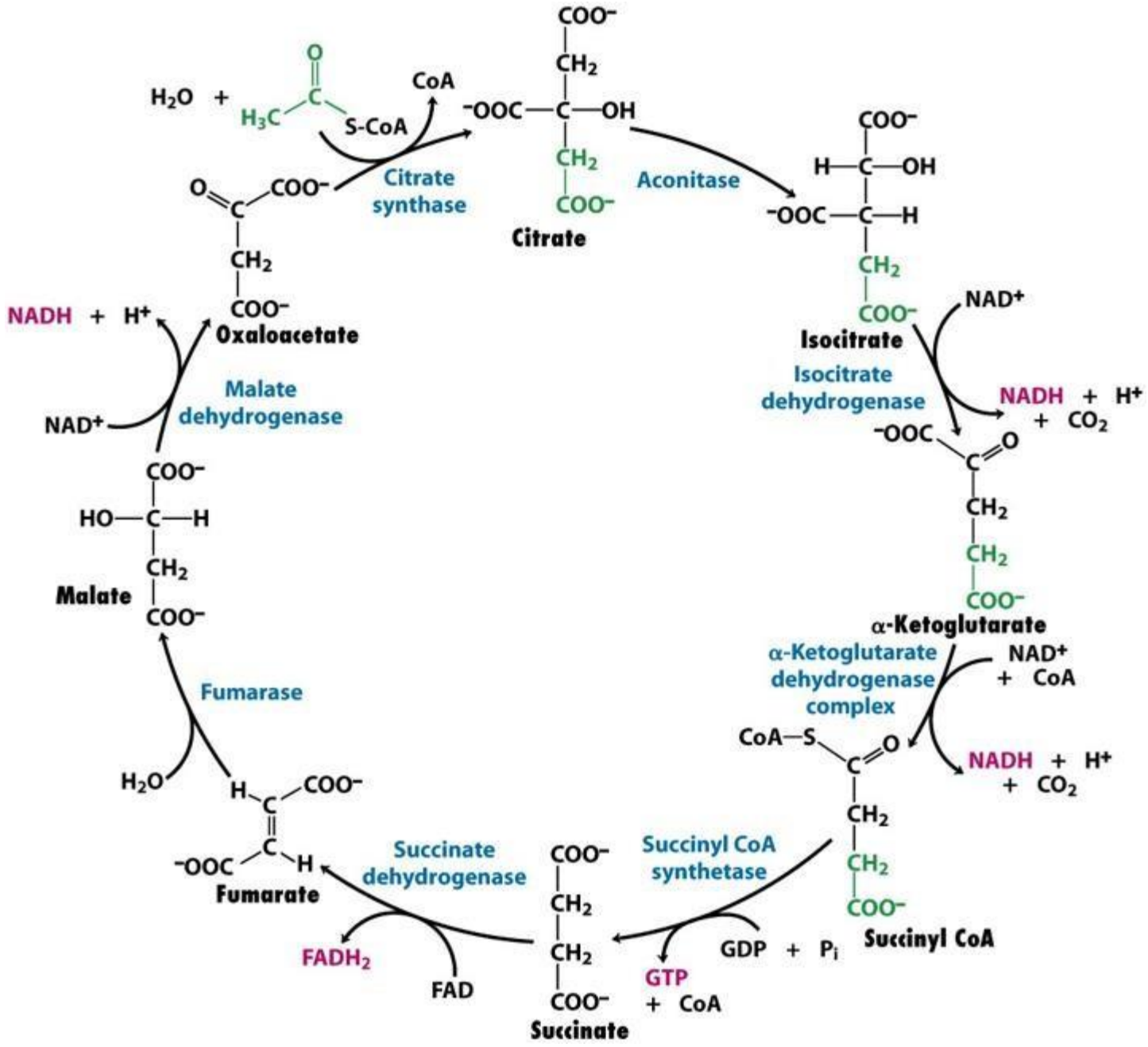
Hydration of Fumarate to form Malate

Step 8: Malate dehydrogenase



- Oxidation of Malate to form Oxaloacetate
- Oxaloacetate is now ready to react with another acetyl CoA

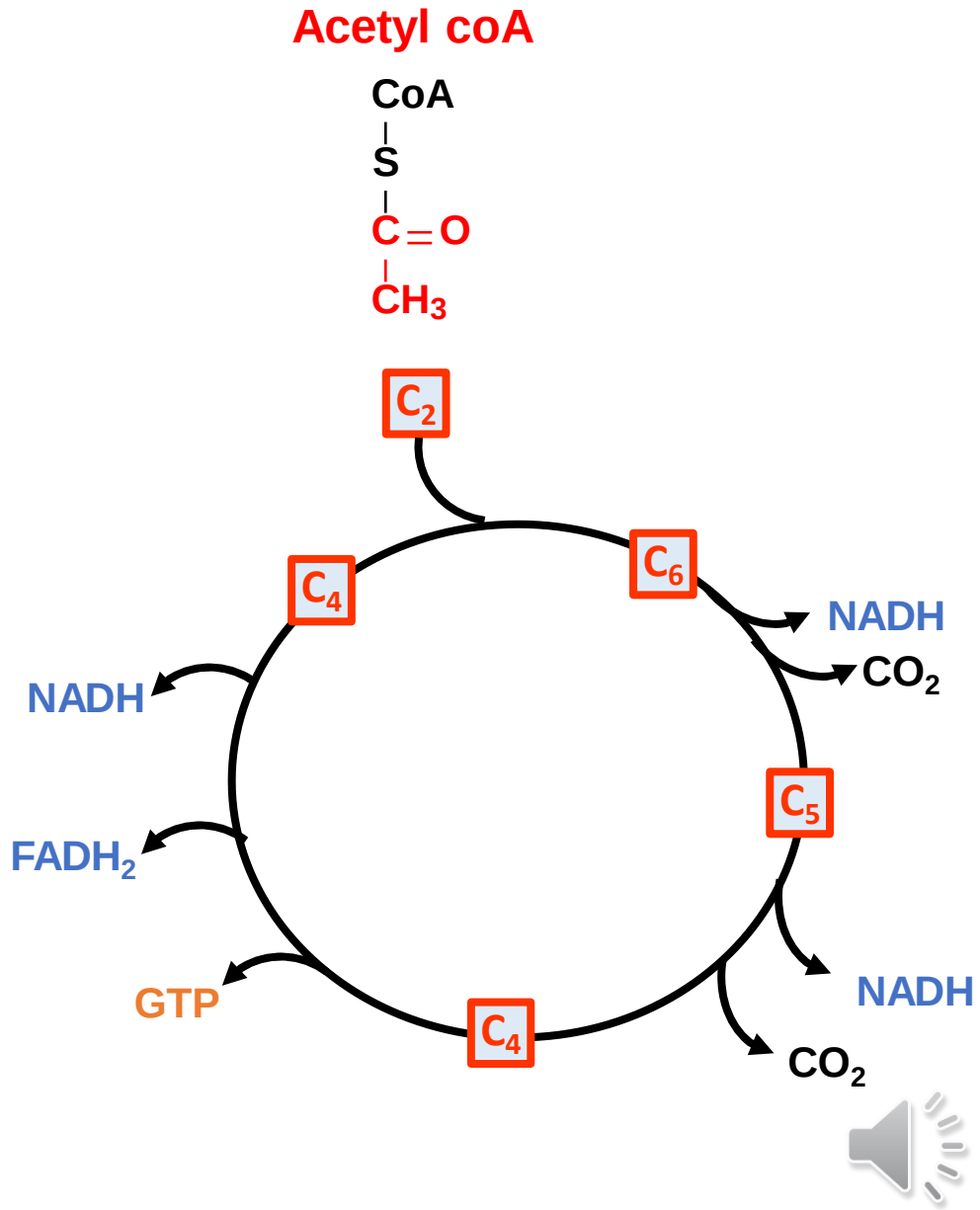
Structures of the TCA cycle metabolites



The TCA Cycle oxidises Acetyl CoA (summary)

For each acetyl CoA which enters the cycle:

- **Acetyl CoA** feeds into the cycle by joining the acetate portion (**2 C**) with oxaloacetate (**4 C**)
- **8 steps** (catalyzed by an enzymes) that take the acetate from acetyl CoA and converts it to **2** molecules of **CO_2**.
- **3** molecules of coenzyme **NAD^+** and **one** molecule of **FAD** are reduced to **NADH** and **$FADH_2$**
- **1 GDP** (= 1 ADP) is phosphorylated
- The initial acceptor molecule (oxaloacetate) is reformed and then reused-cyclic



Overall reaction: For each turn of the cycle

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

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

ATP

Energy output per acetyl CoA:

- **3 NADH**
- **1 $FADH_2$**
- **1 GTP**

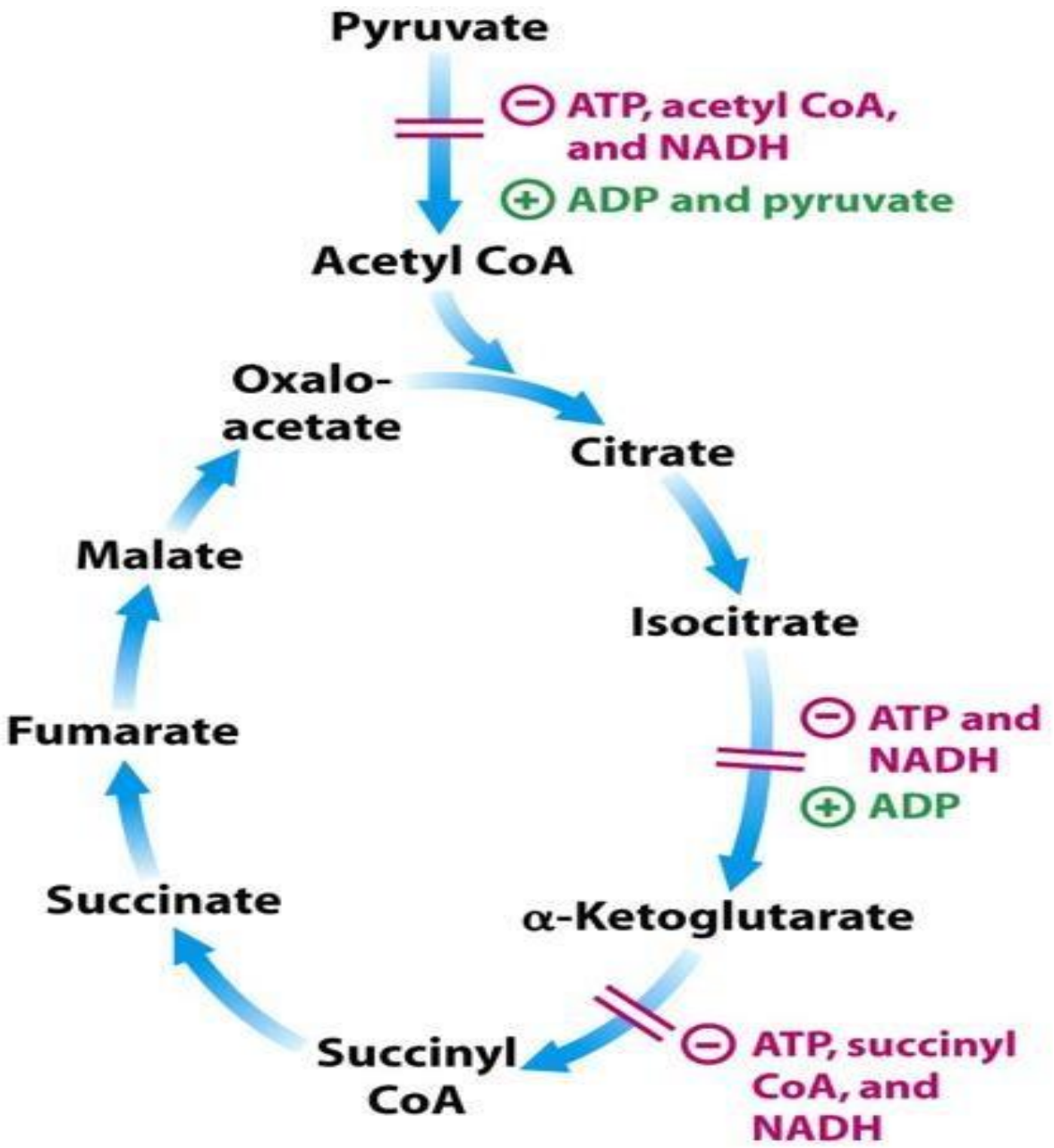
Remember that each molecule of glucose gives 2 pyruvate, hence 2 Acetyl coA

- **2 × 3 NADH = 6 NADH**
- **2 × $FADH_2$ = 2 $FADH_2$**
- **2 × GTP = 2 GTP**

❑ Before the cycle can begin:

- **2 NADH** is yield from converted **2** Pyruvate to **2** Acetyl coA

Regulation of the TCA cycle



The TCA is regulated primarily by **ATP and NADH** concentrations

❑ **Regulation of the entry to the TCA cycle:**

- **Pyruvate dehydrogenase:**
  - Inhibited by acetyl CoA, **ATP and NADH**
  - Activated by NAD^+, CoA-SH, ADP and pyruvate

❑ **Control points (Regulatory points)**

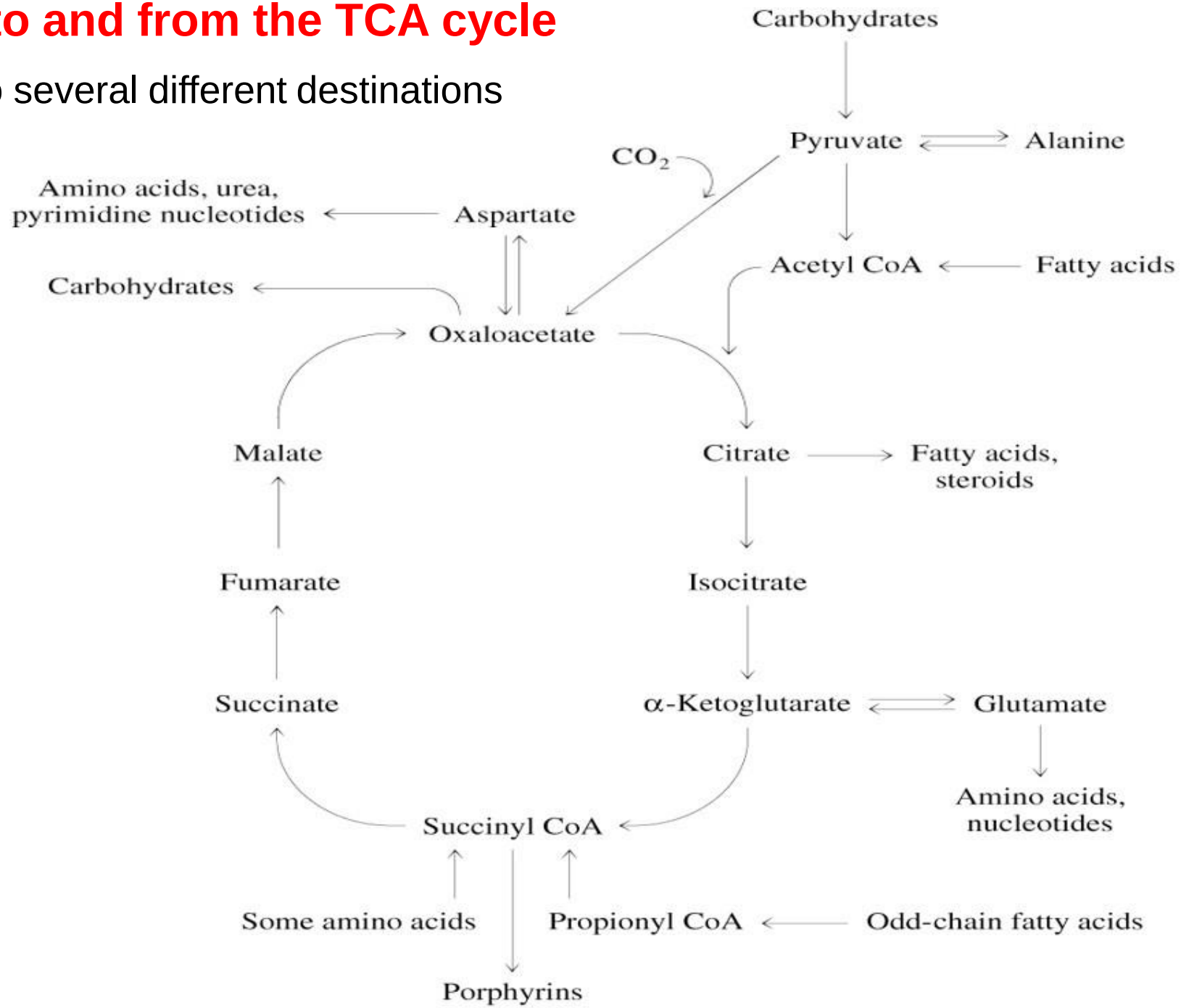
- **Isocitrate dehydrogenase:**
  - Inhibited by **ATP and NADH**
  - Activated by ADP

- **α-Ketoglutarate dehydrogenase:**
  - Inhibition by succinyl CoA, **ATP and NADH**

- **Citrate synthase in bacteria:**
  - inhibited by **ATP**

Pathways leading to and from the TCA cycle

- Metabolites can go to several different destinations



Complete oxidation of glucose

- 2 ATP from glycolysis
- 2 NADH from glycolysis (But some energy lost on transport into mitochondria)
- 2 NADH from Pyruvate dehydrogenase
- 6 NADH from TCA cycle
- 2 FADH2 from TCA cycle
- 2 GTP (ATP) from TCA cycle

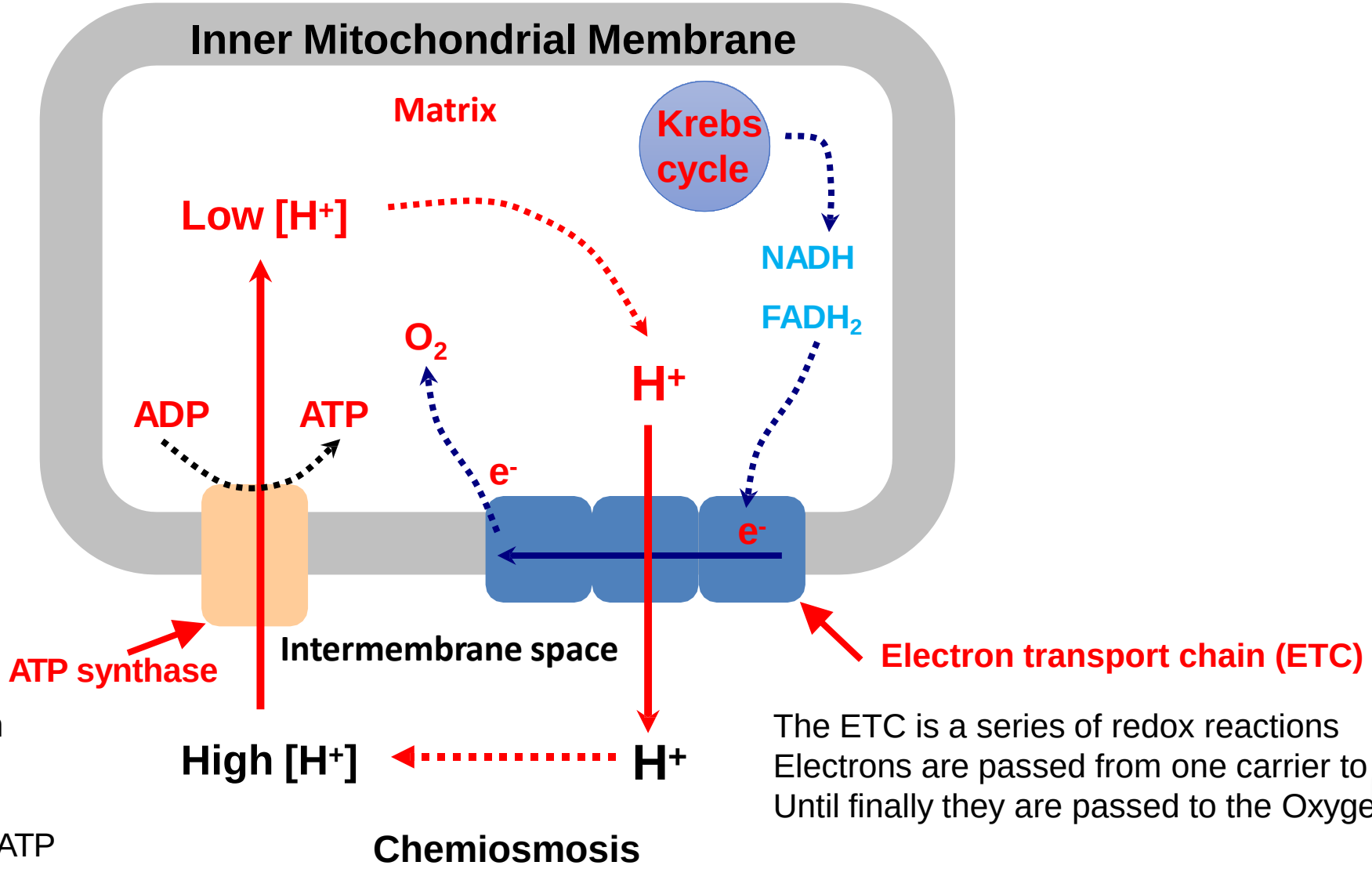
✓ 2 + (2 × 1.5) + (2 × 2.5) + (6 × 2.5) + (2 × 1.5) + 2 = 30 ATP / glucose

✓ 2 + (2 × 2.5) + (2 × 2.5) + (6 × 2.5) + (2 × 1.5) + 2 = 32 ATP / glucose

Why? Home work

- 2 NADH from glycolysis

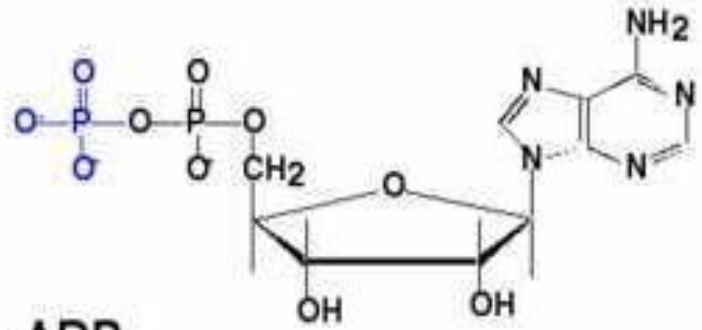
- In eukaryotes **ETC** and **ATP synthase** are located in the **mitochondrial inner membrane**
- In the **TCA cycle** reactions: **NAD^+** gains **2** electrons and so is **reduced**
- In the **ETC**: **NADH** loses electrons to other electron carriers so is **oxidized**
- **ATP synthase** is an enzyme that makes **ATP**



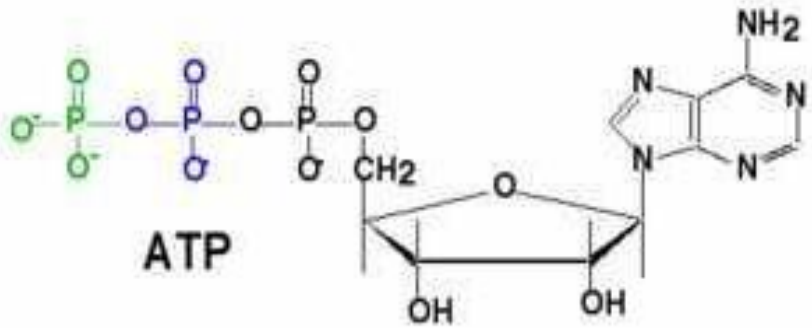
- ATP synthase uses the proton gradient to make ATP
- Protons flow back into the mitochondrial matrix to make ATP

The ETC is a series of redox reactions
Electrons are passed from one carrier to another
Until finally they are passed to the Oxygen

ATP and ADP



ADP



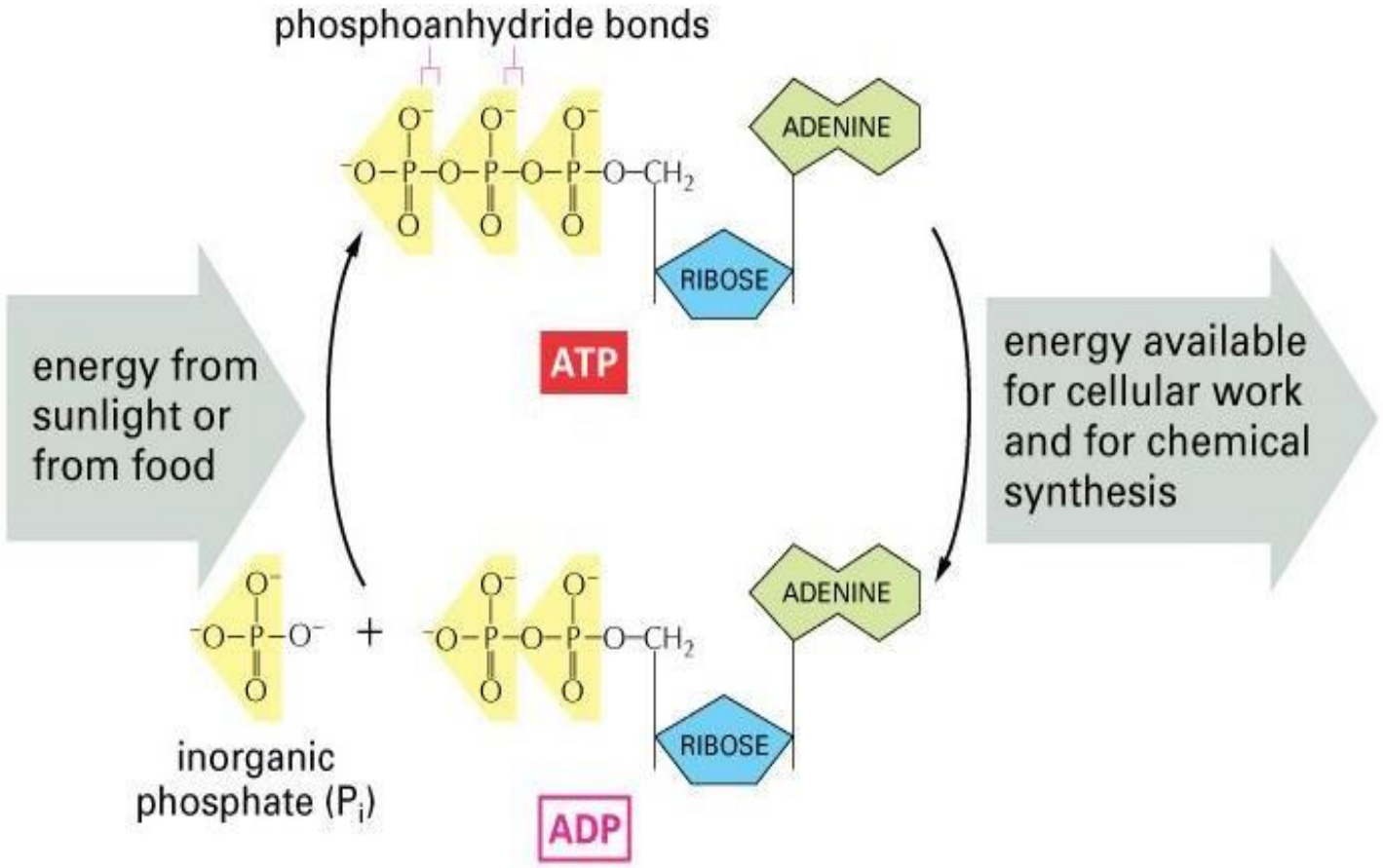
ATP

It takes energy to put on the third phosphate.

Energy is released when it is removed.

ADP - ATP conversions act as a major method of transferring energy.

ATP – ADP cycle



ATP production is a phosphorylation event

ADP is phosphorylated by the addition of a **phosphate group**

We have two types of phosphorylation:

- **Substrate-level phosphorylation: energy is released directly**
  - Phosphate and energy comes from another molecule or substrate (e.g. in glycolysis)

Phosphoenolpyruvate + ADP ⟶ pyruvate + **ATP**

- **Oxidative phosphorylation**
  - Phosphate comes from solution (Pi) and requires a huge amount of energy input (e.g. from the proton gradient)

ADP + **Pi** ⟶ **ATP**

Lecture 7: Biochemistry II
Gluconeogenesis

3rd stage

Anbar University-College of Pharmacy-Clinical Laboratory Sciences Department

2020-2021

Dr. Yousif H. Khalaf

Learning outcomes

By the end of this lecture you should be able:

- To understand gluconeogenesis
- To know which types of molecules can be used to synthesise glucose
- To understand the Cori- and Glucose-Alanine cycles

Gluconeogenesis

- **During fasting, gluconeogenesis:** synthesis of **glucose** from **non-carbohydrate** sources.
- Conversion of **pyruvate** into **glucose**
- Formation of glucose from **pyruvate** or other molecules that can be converted into pyruvate, oxaloacetate or dihydroxyacetone phosphate.

Major non-carbohydrate precursors are:

lactate, propionate, glycerol and some amino acids

Where do they come from ?

- Rate of glycolysis exceeds the rate of oxidative metabolism → **Lactate**
- Breakdown of proteins → **Amino acids**
- Hydrolysis of triacylglycerols → **Propionate**, **Glycerol**

For a typical adult human:

160 g glucose is needed daily by the **whole body**.

120 g glucose is needed daily by the **brain**

Gluconeogenesis is important during a longer period of starvation or fasting.

when does the gluconeogenesis begin?

- inhibition of fructose 1,6-bisphosphatase is released and there is no phosphofructokinase (PFK) stimulation
- Glycolysis is **shut down**, gluconeogenesis **can occur**

- The **liver** is the major site for glucose synthesis in animals.
- small amount is formed in the **kidney**

Gluconeogenesis is required for survival

Gluconeogenesis is necessary process for some tissues that use glucose as their primary substrate, even after all dietary glucose has been used

- Brain
- Red Blood Cells (RBCs)
- Cornea
- Lens
- Testis
- Kidney medulla

Gluconeogenesis versus Glycolysis

- Reversible reaction means that the same enzyme can catalyses the reaction in both directions
- All reactions of glycolysis -except 3- are reversible
- The **three irreversible steps** in glycolysis are those catalyzed by kinase enzymes

➢ Hexokinase

➢ Phosphofructokinase

➢ Pyruvate kinase

- These steps can be reversed through **irreversible steps** by using other enzymes in the Gluconeogenesis pathway

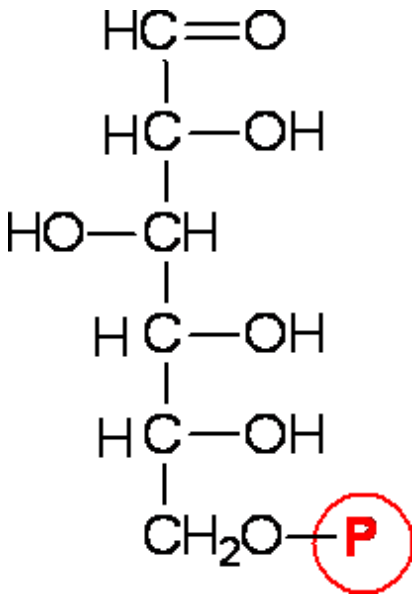
➢ Glucose 6-phosphatase

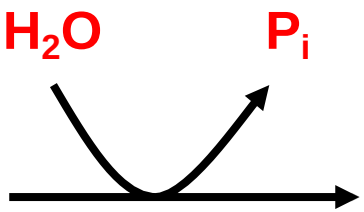
➢ Fructose 1,6-bisphosphatase

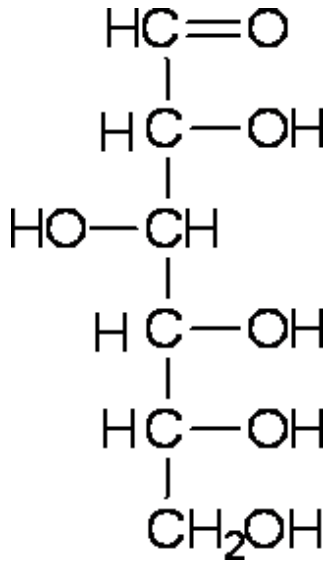
➢ Pyruvate carboxylase + Phosphoenolpyruvate carboxykinase

Is gluconeogenesis a reversal of glycolysis ?

Glucose 6-phosphatase





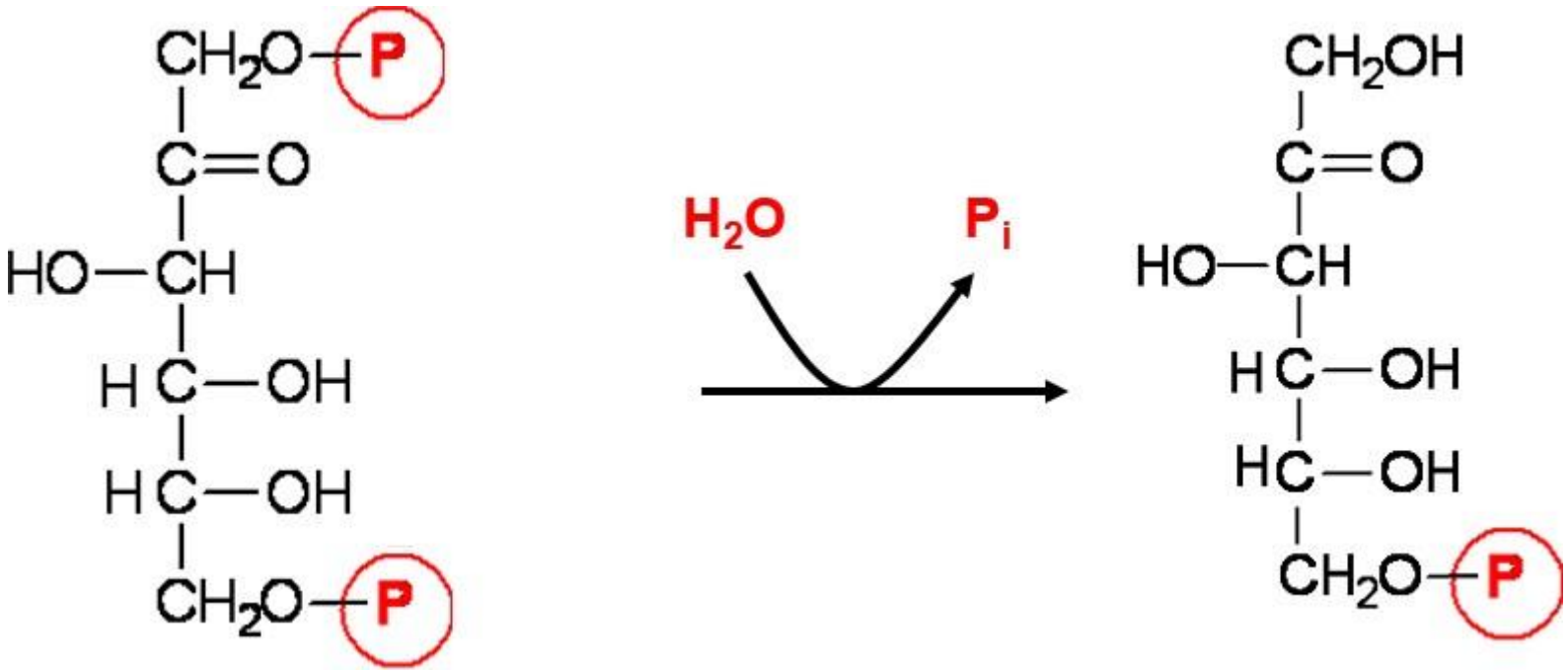


Glucose 6-phosphate

Glucose

- **Glucose 6-phosphatase:** Only present in **liver** and **kidney** (tissues that maintain blood glucose levels)
- Glucose 6-phosphate is **hydrolysed**
- Glucose and Pi are transported into the **cytosol**

Fructose 1,6-bisphosphatase

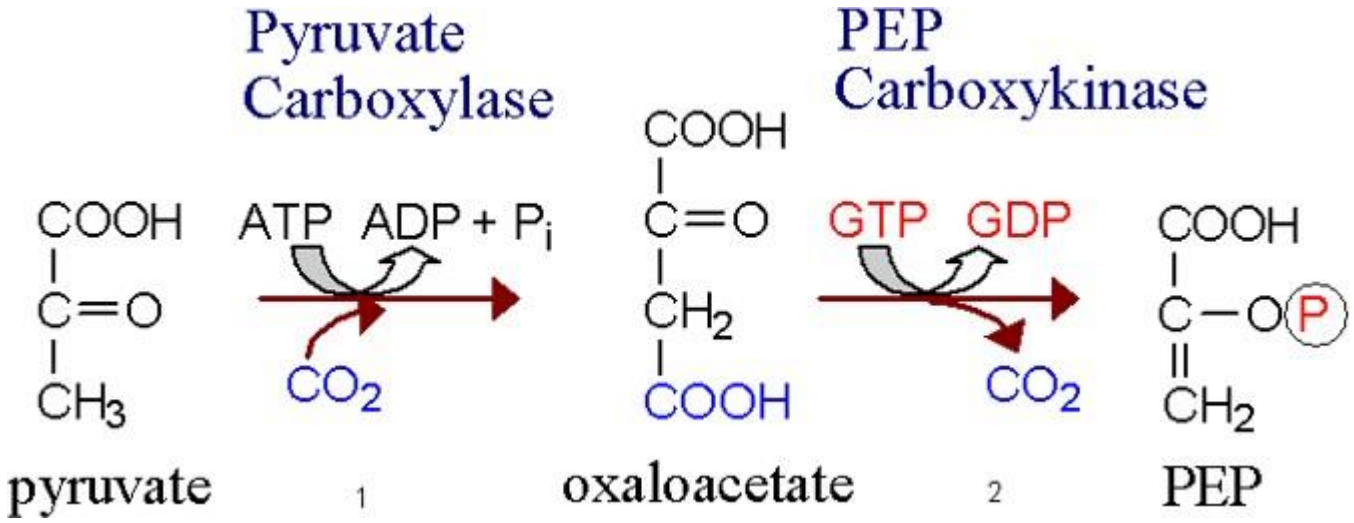


Fructose 1,6-bisphosphate **Fructose 6-phosphate**

- Fructose 1,6-bisphosphate is **hydrolysed**

- Under intracellular conditions, **pyruvate** can not be converted to **phosphoenolpyruvate (PEP)** by **pyruvate kinase** because the reaction is **irreversible.**
- Conversion of pyruvate to PEP requires two reactions and **two enzymes:**

1) **Pyruvate carboxylase**
2) **Phosphoenolpyruvate carboxykinase**



Pyruvate carboxylase

- Localised in **mitochondrium**
- Carries a **biotin** as a prosthetic group which acts as a carrier for activated **CO_2**
- The activated **carboxyl group** is transferred to **pyruvate** to form **oxaloacetate**
- **Requires ATP**, **ADP** inhibits the enzyme
- Active only in the presence of **acetyl CoA**

Phosphoenolpyruvate carboxykinase

- Oxaloacetate is simultaneously decarboxylated and phosphorylated
- **Requires GTP**, **ADP** inhibits the enzyme

Summary of Gluconeogenesis Pathway:

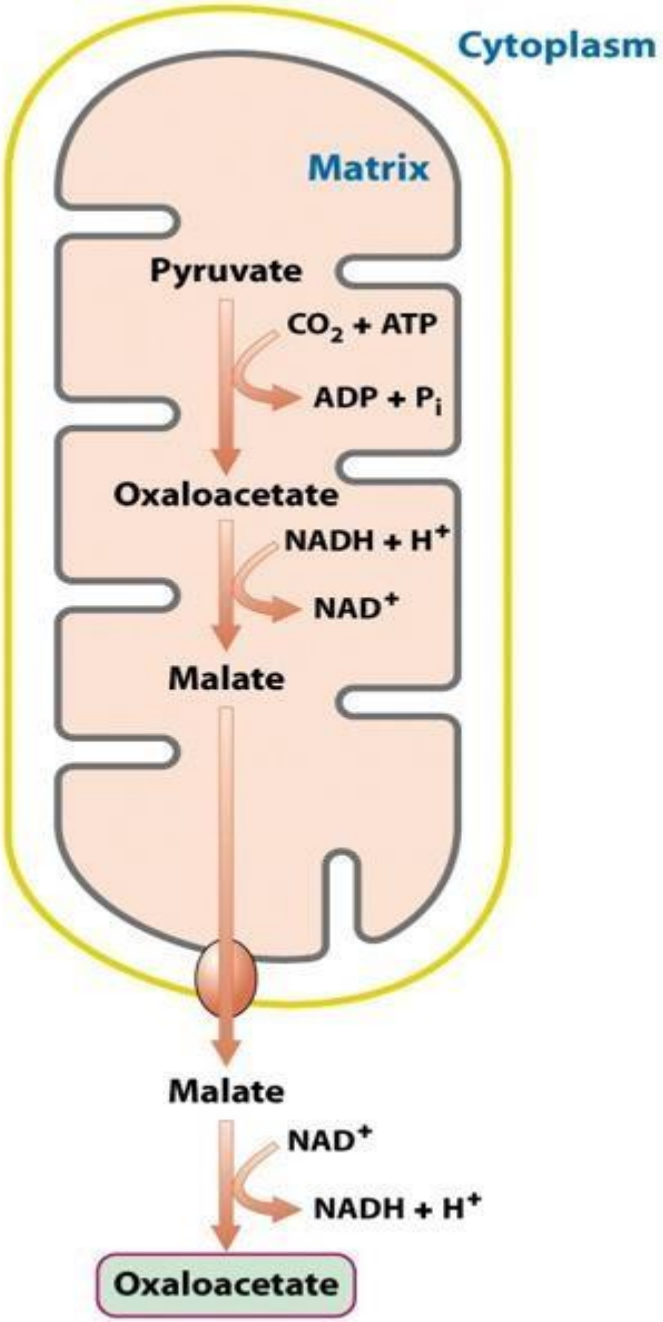
Progression of Gluconeogenesis

- For gluconeogenesis to proceed, the oxaloacetate produced by pyruvate carboxylase in the **mitochondrium** needs to be transported to the **cytosol**.

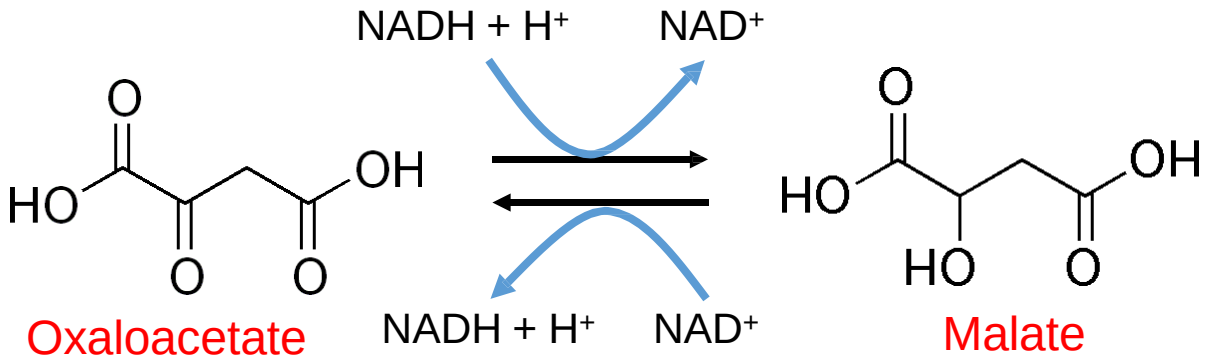
- Mitochondrial oxaloacetate can be transported to the cytosol via **three pathways:**

  - Reduction to malate
  - Transamination to aspartate
  - Conversion to phosphoenolpyruvate PEP (mitochondrial PEPCK)

Mitochondrium

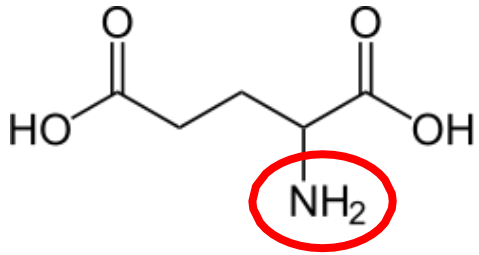


- **Oxaloacetate** formed from pyruvate cannot leave the **mitochondrium**
- **Oxaloacetate** is reduced to malate by **malate dehydrogenase** linked to **NADH**
- **Malate** is transported across the **mitochondrial membrane**
- **Malate** is oxidised by **cytosolic NAD^+-linked malate dehydrogenase**

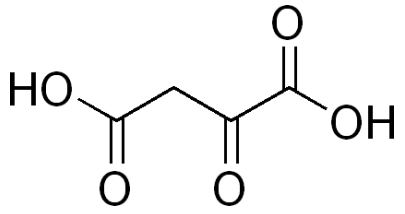


Oxaloacetate is transaminated to aspartate (Transamination)

- Oxaloacetate can be converted to aspartate if there is a lot of NADH in the cytoplasm
- Transamination is the transfer of the amino group of an amino acid to an α-ketoacid
- Requires continuous transport of glutamate into, and α-ketoglutarate out of, the mitochondrion.

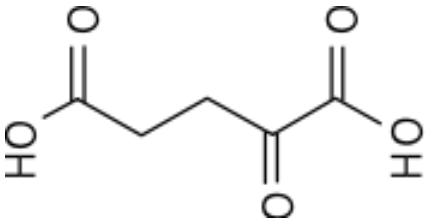


Glutamate

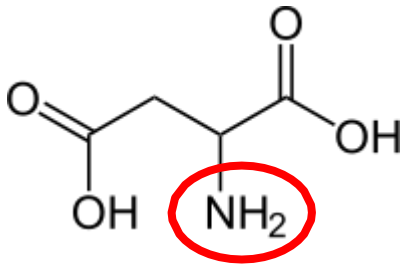


Oxaloacetate

Aminotransferase



α-Ketoglutarate



Aspartate

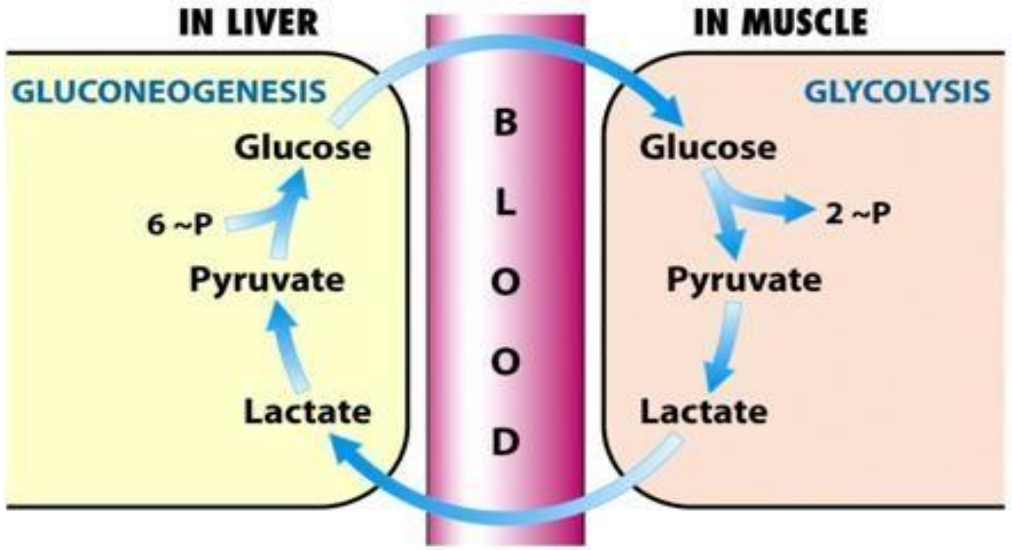
The Cori and Glucose-Alanine Cycles

- The Cori and Glucose-Alanine Cycles are two important cycles in tissues that involve gluconeogenesis.
- Both cycles provide a mechanism for continuous energy supply of tissues that require glucose as their primary energy source.
- Tissues must release either **lactate** as the end product of glucose metabolism or **alanine** and not oxidise glucose completely to CO_2 and H_2O.
- Glucose is synthesised from amino acids. All amino acids, **except leucine and lysine**, can supply carbon skeletons for **gluconeogenesis**

The Cori cycle (lactic acid cycle)

- Lactate is produced by muscles when the body can‘t supply enough oxygen
- Body must take in extra oxygen to oxidise lactate
- Lactate must be converted back into pyruvate
- **Lactate** produced by anaerobic glycolysis in the muscles moves to the liver and is **converted to glucose**, which then returns to the muscles (Cori cycle)
- **Liver** cells convert **lactate into pyruvate** followed by **gluconeogenesis** to produce glucose (Cori cycle)

Carl Cori



Cori cycle

Gerty Cori

The Cori cycle

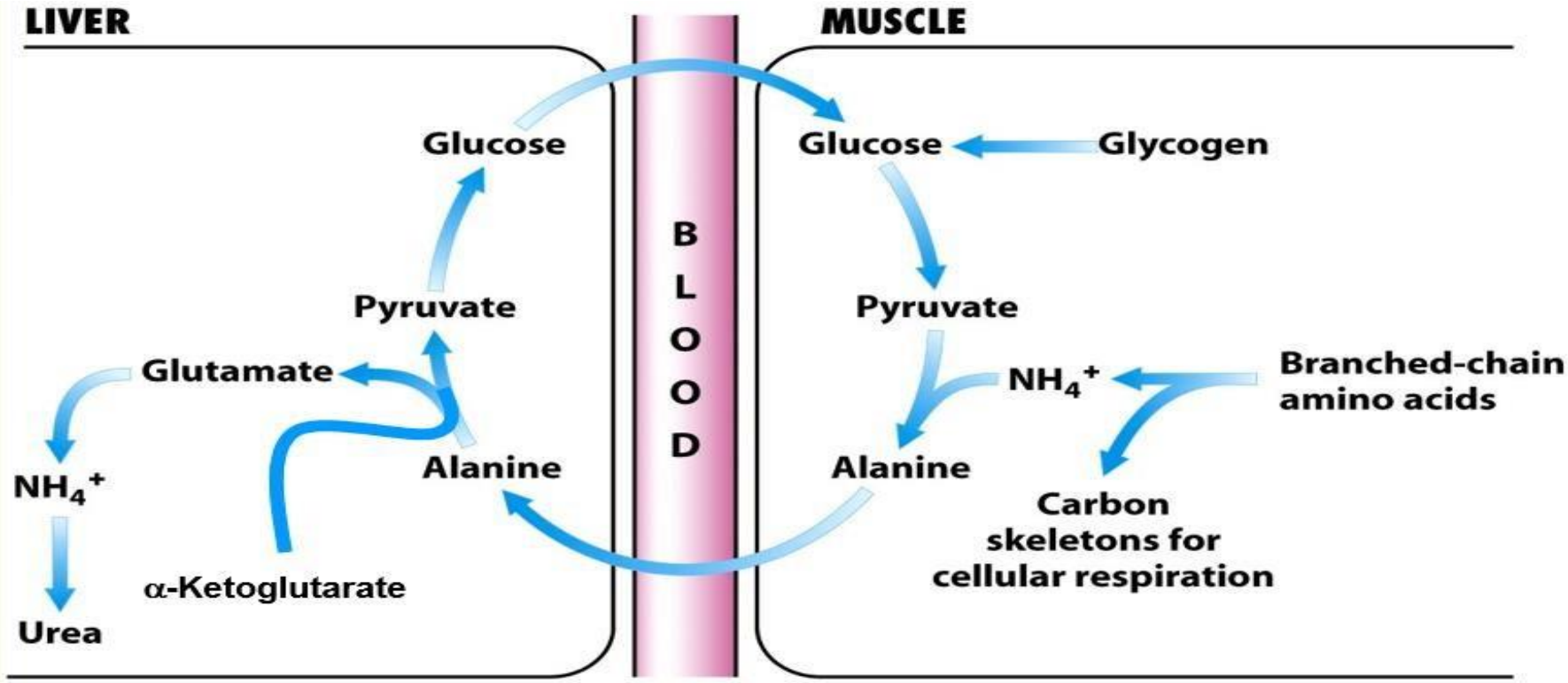
- **Gluconeogenesis** from lactate requires **6 molecules of ATP:**

- **2 Lactate** ⟶ 2 Pyruvate + **6 ATP** ⟶ **glucose** + 6 ADP + 6 P_i + 4 H^+

- **Only 2 molecules of ATP** are gained during **anaerobic glycolysis**
- The Cori cycle is costing the body **4 ATP** more than are produced during glycolysis
- **ATP** needed by **liver cells** for gluconeogenesis is provided by **fatty acid oxidation**.

The Glucose-Alanine cycle

- Glucose is synthesised from **amino acids**
- All amino acids **(Glucogenic),** except **leucine and lysine (Ketogenic)**, can supply carbon skeletons for **gluconeogenesis**
- Pyruvate, generated in muscle and other peripheral tissues, can be **transaminated to alanine (Alanine transaminase, ALT)** which then is returned to the liver for gluconeogenesis



Lecture 8: Biochemistry II

- Glycogen synthesis
- The pentose phosphate pathway (PPP)

3rd stage

Anbar University-College of Pharmacy-Clinical Laboratory Sciences Department
2020-2021

Dr. Yousif H. Khalaf

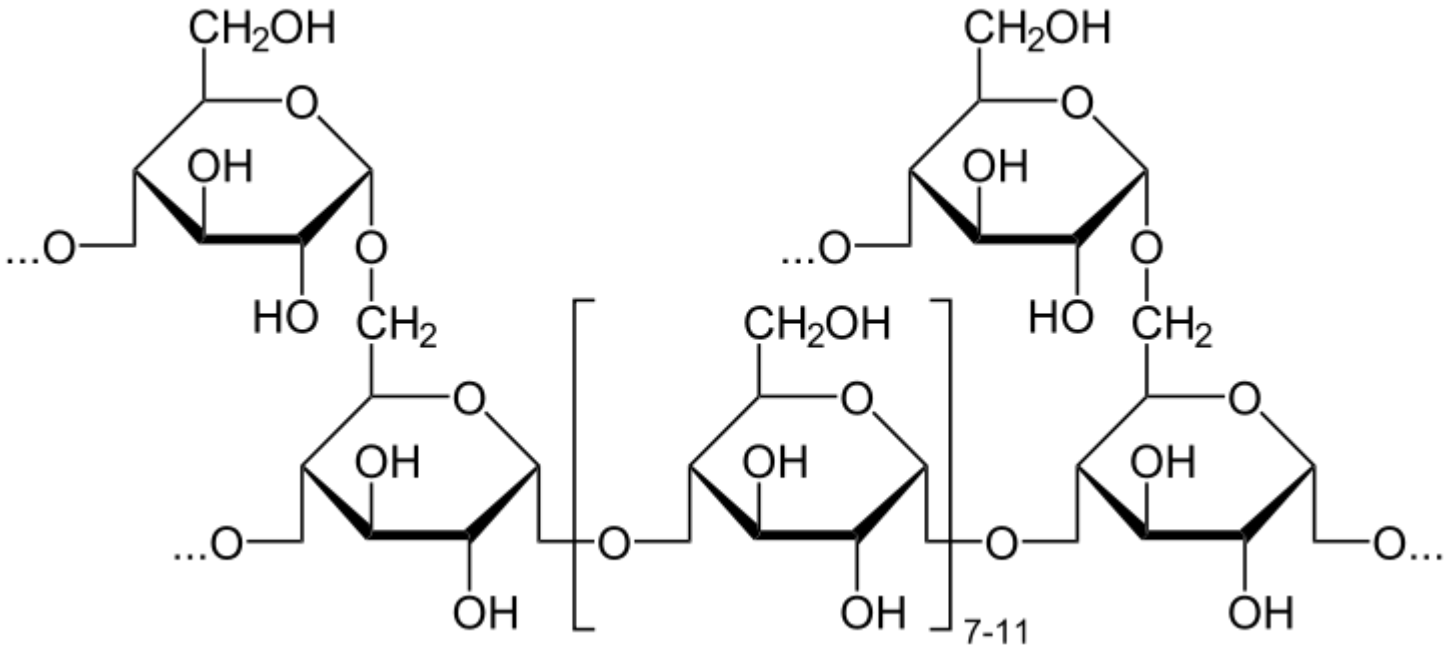
Learning outcomes

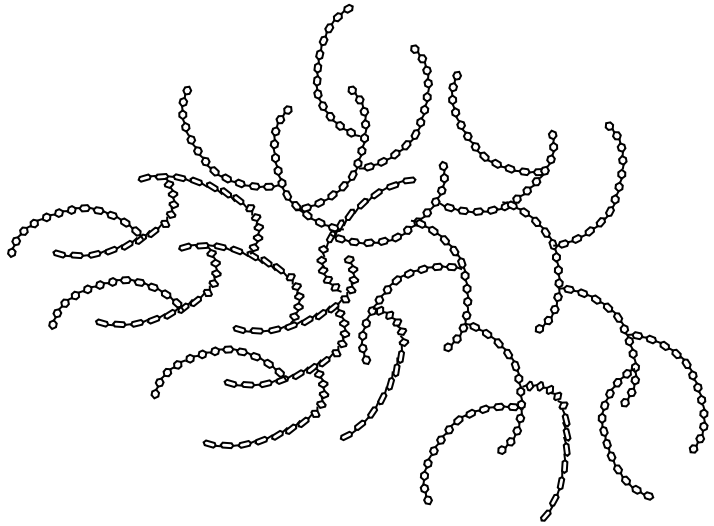
By the end of this lecture you should be able:

- To understand the function of glycogenin and glycogen synthase
- To know the difference between NAD(H) and NADP(H)
- To understand the importance of maintaining reduced glutathione and how this is affected in G6PDH deficiency and malaria.

Glycogen

- Having a similar structure to amylopectin of starch, but more branches. and is commonly referred to as animal starch.
- Glycogen does not possess a **reducing end**.
- The „reducing end“ glucose residue is not free but is covalently bound to a protein termed glycogenin
- Main storage of glucose in **liver and skeletal muscle.**
- The glycogen granules contain both glycogen and the enzymes of glycogen synthesis (**Glycogenesis**) and degradation (**Glycogenolysis**).





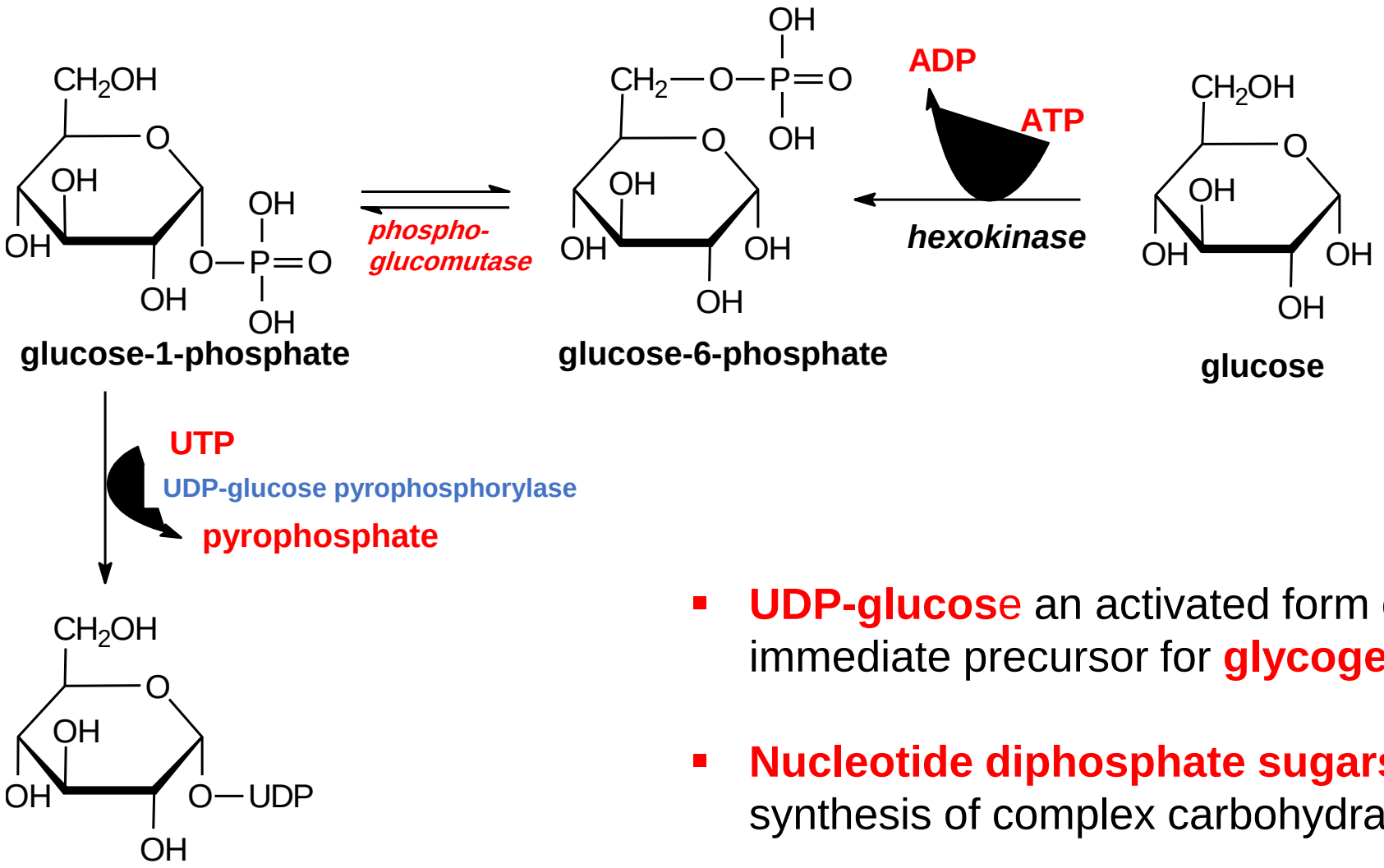
Glycogen metabolism

- Readily mobilised storage form of **glucose**
- Main storage in **liver** and **skeletal** muscle
- In the liver hepatocytes, glycogen can compose up to 8-10% of the fresh weight (100–120 g in an adult)
- 1-2% of the **muscle mass** can be glycogen
- Controlled release of glucose from glycogen **maintains blood glucose level.**
- The **uterus** also stores glycogen during pregnancy to nourish the **embryo**

Glycogen synthesis

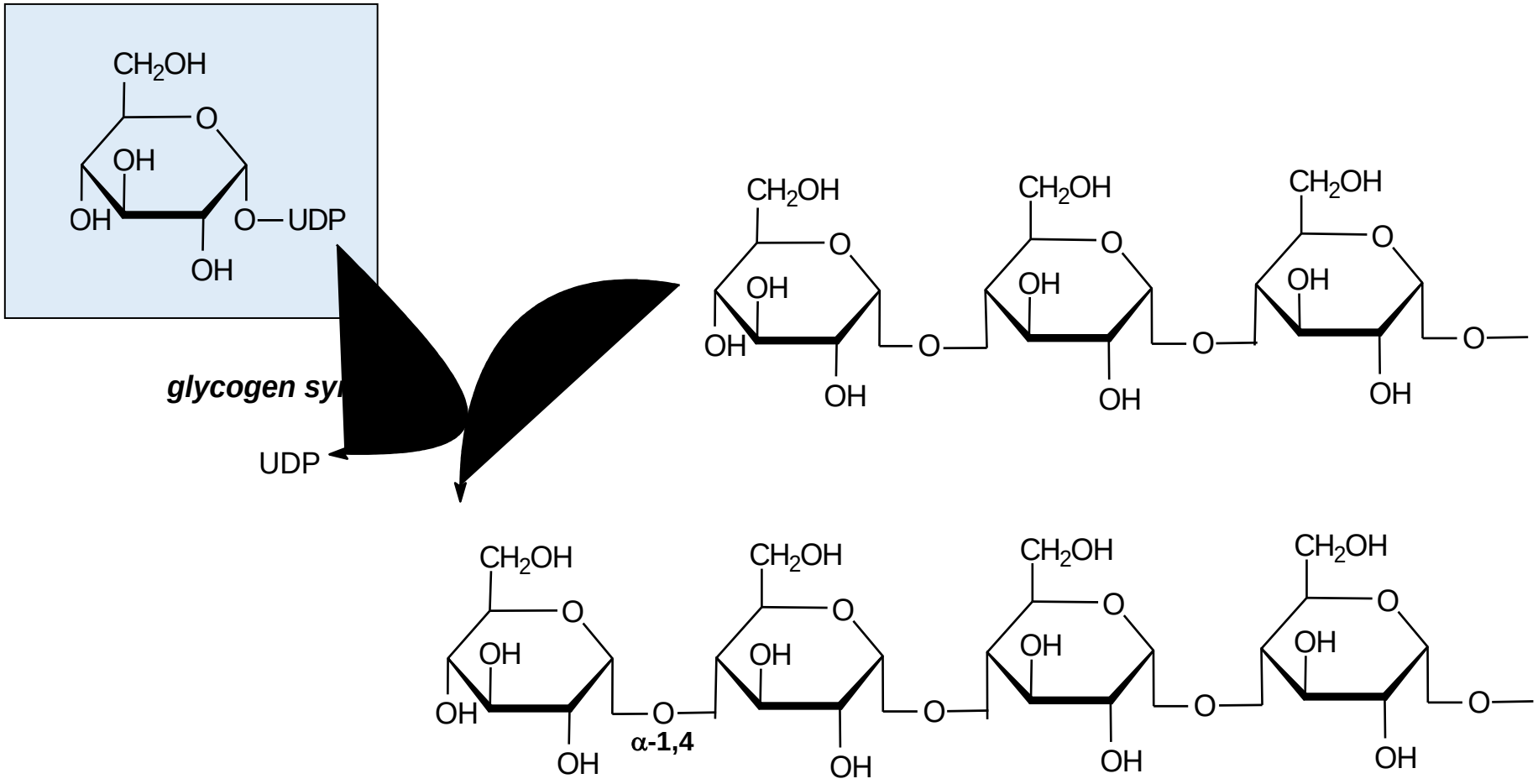
- Glycogen synthesis has distinct **initiation** and **elongation** stages:
- The initiation stage of glycogen synthesis is catalysed in an autocatalytic manner by **glycogenin.**
- The elongation stage of glycogen synthesis is catalysed by **glycogen synthase** in concert with the branching enzyme
- Each subunit of the **glycogenin** homodimer catalyses the addition of **eight glucosyl units** to the other subunit
- Once eight residues have been added, **glycogen synthase** takes over **extending the chain**.
- Uridine diphosphate glucose **(UDP-glucose),** an activated form of glucose is the immediate precursor for glycogen synthesis.

Uridine diphosphate glucose formation



- **UDP-glucose** an activated form of glucose is the immediate precursor for **glycogen synthesis**.
- **Nucleotide diphosphate sugars** are precursors for synthesis of complex carbohydrates

Glycogen synthesis



- As glucose residues are added to the non-reducing terminal residues of glycogen.
- UDP-glucose is the substrate and UDP is released as a reaction product.
- Formation of an **α-1,4-glycosidic linkage**.

Branch formation

- A block of typically **7 residues** from the non-reducing end of the chain is transferred to a more **interior site**
- the block must include the **non-reducing terminus**
- attaches them by an **α-(1,6) linkage** at least 4 residues from the nearest branch point
- It **increases** the **solubility** of glycogen
- It **creates** a large number of **terminal residues**
- **Terminal residues** are the sites of action of **glycogen phosphorylase** and **glycogen synthase**
- **Branching increases** the rate of **glycogen synthesis** and **Glycogenolysis** (**Degradation)**

Pentose Phosphate Pathway (PPP)

- The pentose phosphate pathway is an anabolic pathway that starts with glucose-6-phosphate (6C)
  - From **glucose**
  - From **gluconeogenesis**
  - From **glycogenolysis**
- Generates **NADPH** and **pentose sugars (5 carbons)**
- Both have important roles in **biosynthesis**, so it is a **biosynthetic pathway**
- Under certain conditions, pentose phosphate pathway oxidizes glucose can be **completely oxidized** to **CO_2** and **H_2O**.

Pentose Phosphate Pathway

- The **Pentose Phosphate Pathway** occurs in the **cytoplasm** of eukaryotic cells
- The **Pentose Phosphate Pathway** can be divided into different types of reactions:

➢ **stage I: Oxidative reactions (generate NADPH)**

➢ **Stage II: Non-oxidative reactions (carbon shuffling)**

- Both are important in cell function

Major functions of the Pentose Phosphate Pathway (PPP)

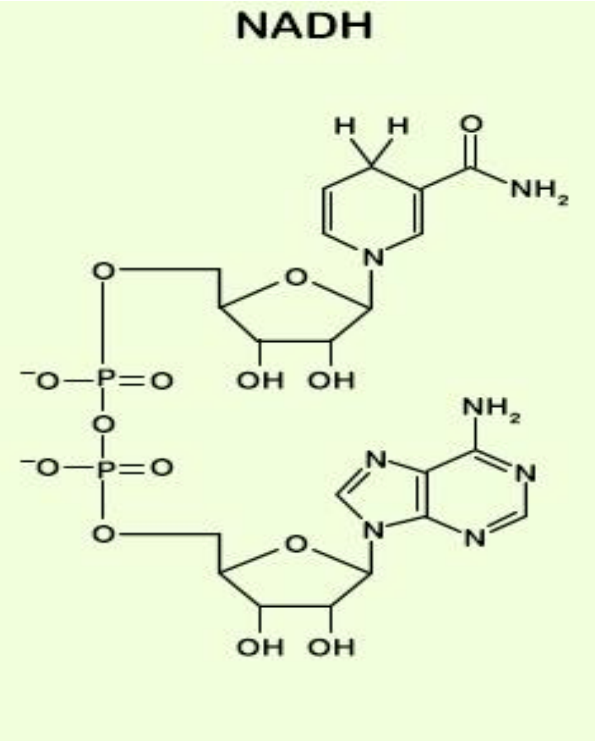
- To generate reducing equivalents, in the form of **NADPH**, for **reductive biosynthesis reactions** within cells, e.g., **fatty acid synthesis.**
- To provide the cell with **ribose-5-phosphate** for the synthesis of the **nucleotides and nucleic acids.**
- To **rearrange the carbon skeletons** of dietary carbohydrates into glycolytic/gluconeogenic intermediates (non-oxidative).
- To **maintain reducing conditions** within cell via **glutathione** – protects against oxidants.

The difference between NADH and NADPH

Nicotinamide adenine dinucleotide (NADH)

- Involved as a coenzyme in catabolic redox reactions
- NADH is used to supply reducing power in the Electron Transport Chain

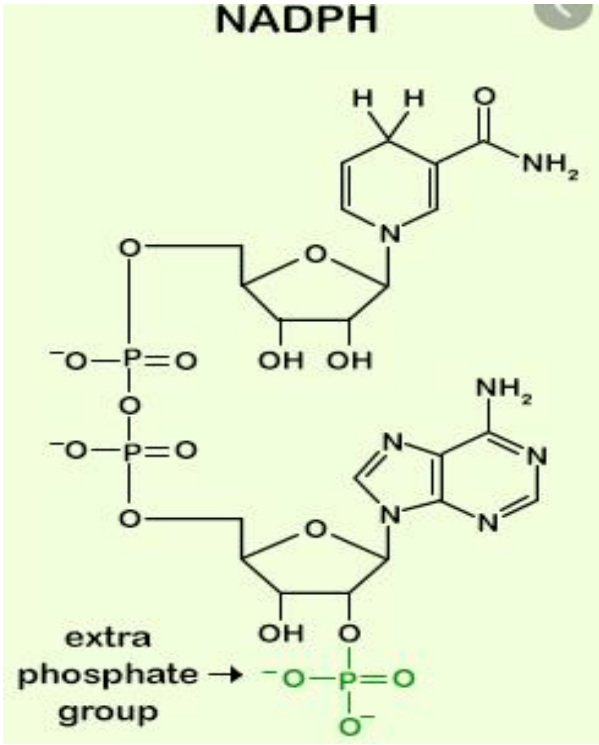
Reduce form



Nicotinamide adenine dinucleotide phosphate (NADPH)

- Involved as a coenzyme in biosynthetic redox reactions (anabolism).
- NADPH is used in synthesis of DNA, fatty acids, proteins, steroids, etc

Reduce form

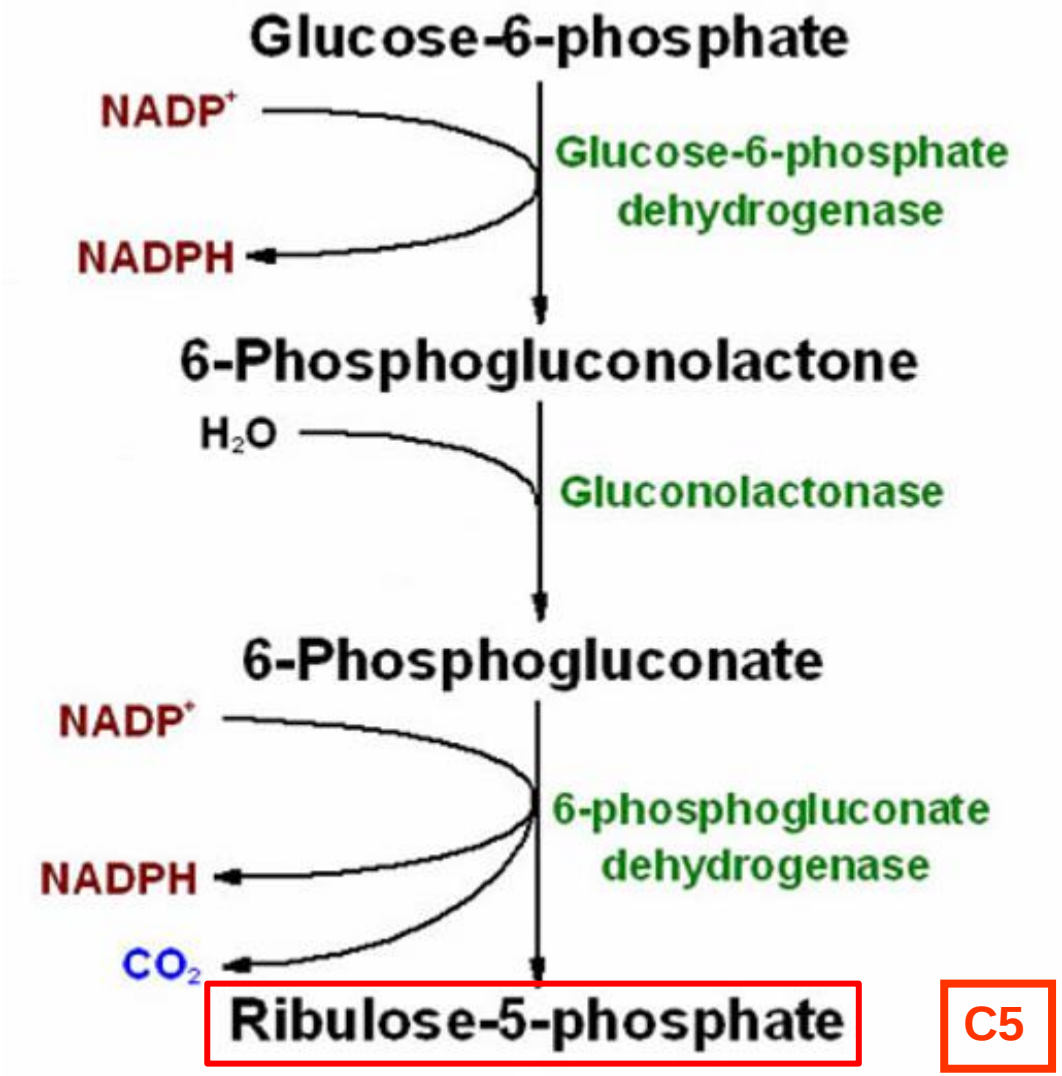


Oxidative reactions of PPP

Oxidation

Hydrolysis

Oxidative decarboxylation



C5

- **$NADP^+$** serves as electron acceptor

Overall

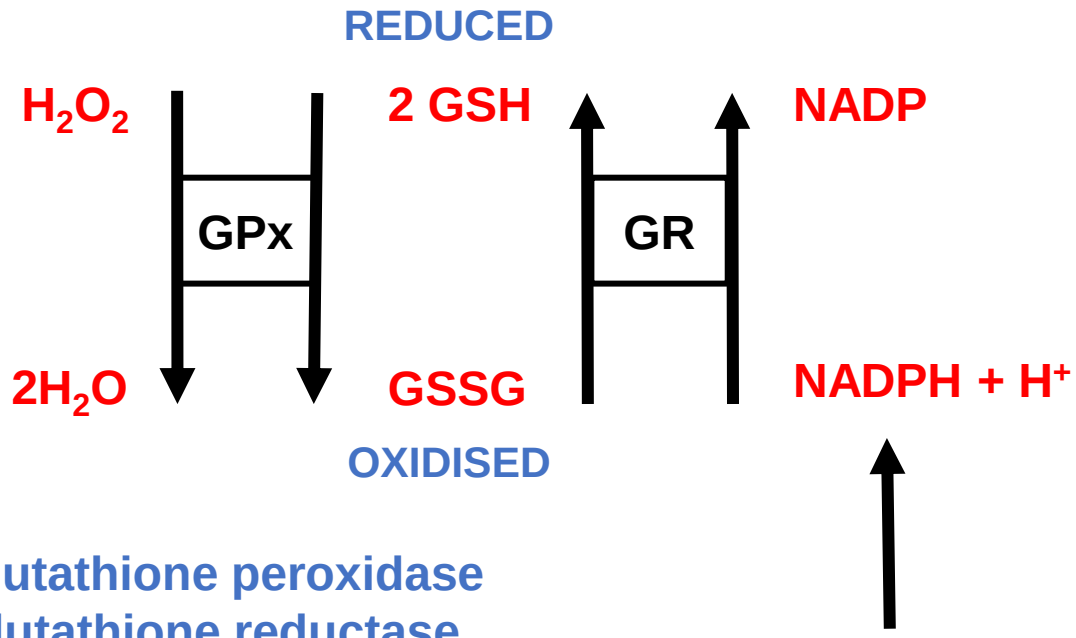
Glucose-6-phosphate + $2NADP^+$ + H_2O ⟶ Ribulose-5-P + $2NADPH + 2H^+ + CO_2$

NADP(H) as a Redox Cofactor

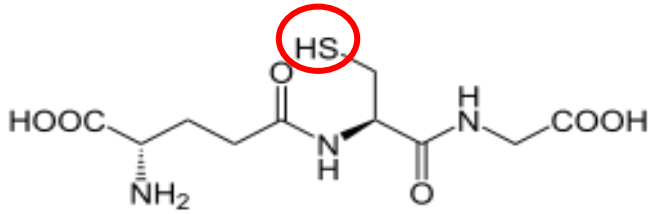
Oxidative reactions of PPP

$NADP^+$ (Oxidized) ⟷ **$NADPH + H^+$ (Reduced)**

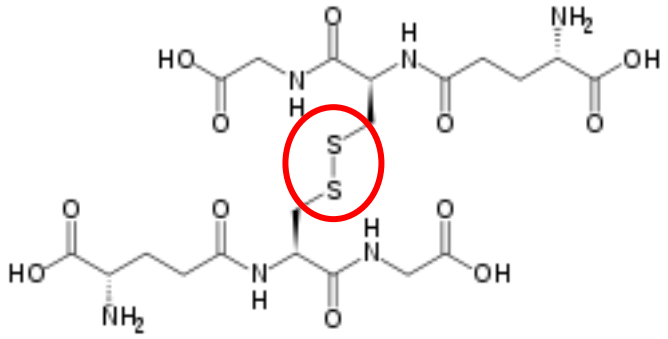
Glutathione Redox Cycle



GPx = Glutathione peroxidase
GR = Glutathione reductase



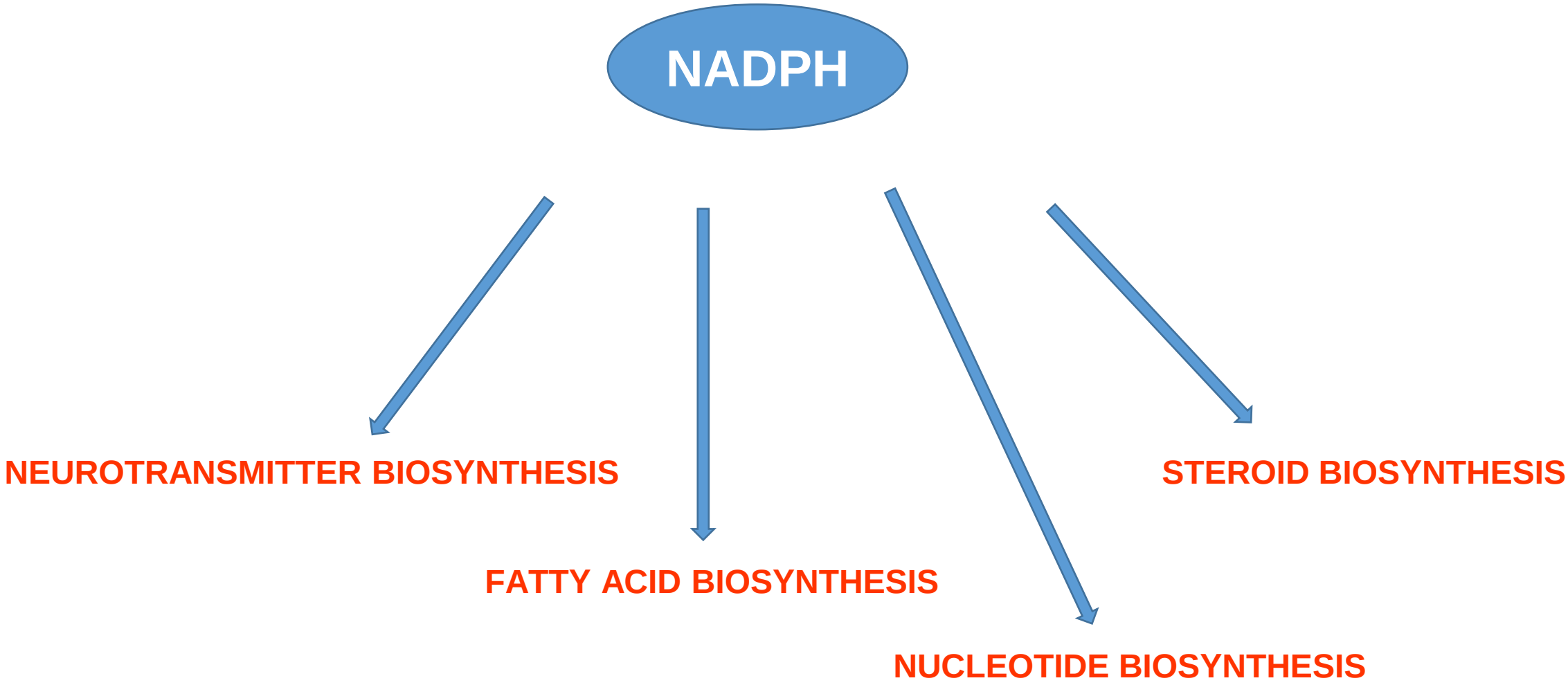
Glutathione (GSH)



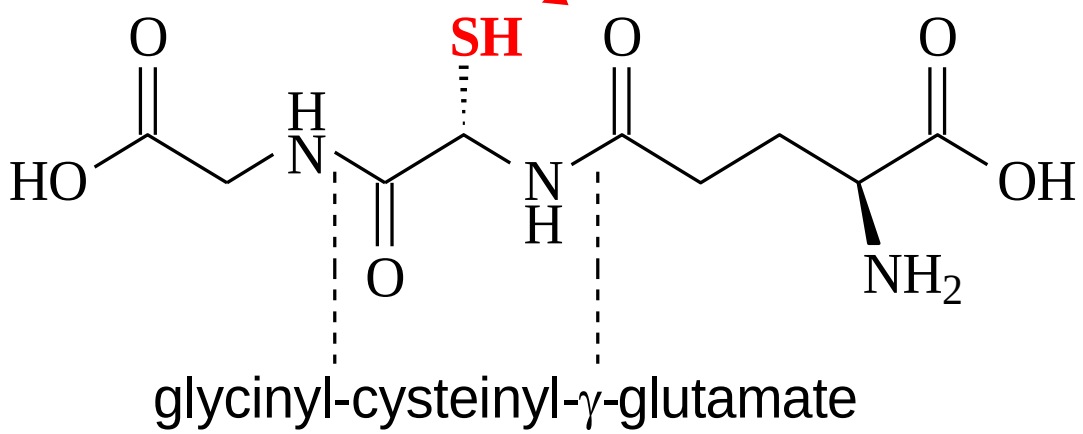
Glutathione disulfide (GSSG)

pentose phosphate pathway (PPP)

NADPH is then used for reductive biosynthesis



The thiol (-SH) is the active antioxidant group



glycinyl-cysteinyl-γ-glutamate

or γ-glutamyl-cysteinyl-glycine

- **GSH is a tripeptide of 3 amino acids: glycine, cysteine, glutamate**
- **GSH** is a natural antioxidant that protects against **oxidants**
- **NADPH** is needed to maintain **reduced glutathione (GSH)**

PPP and malaria

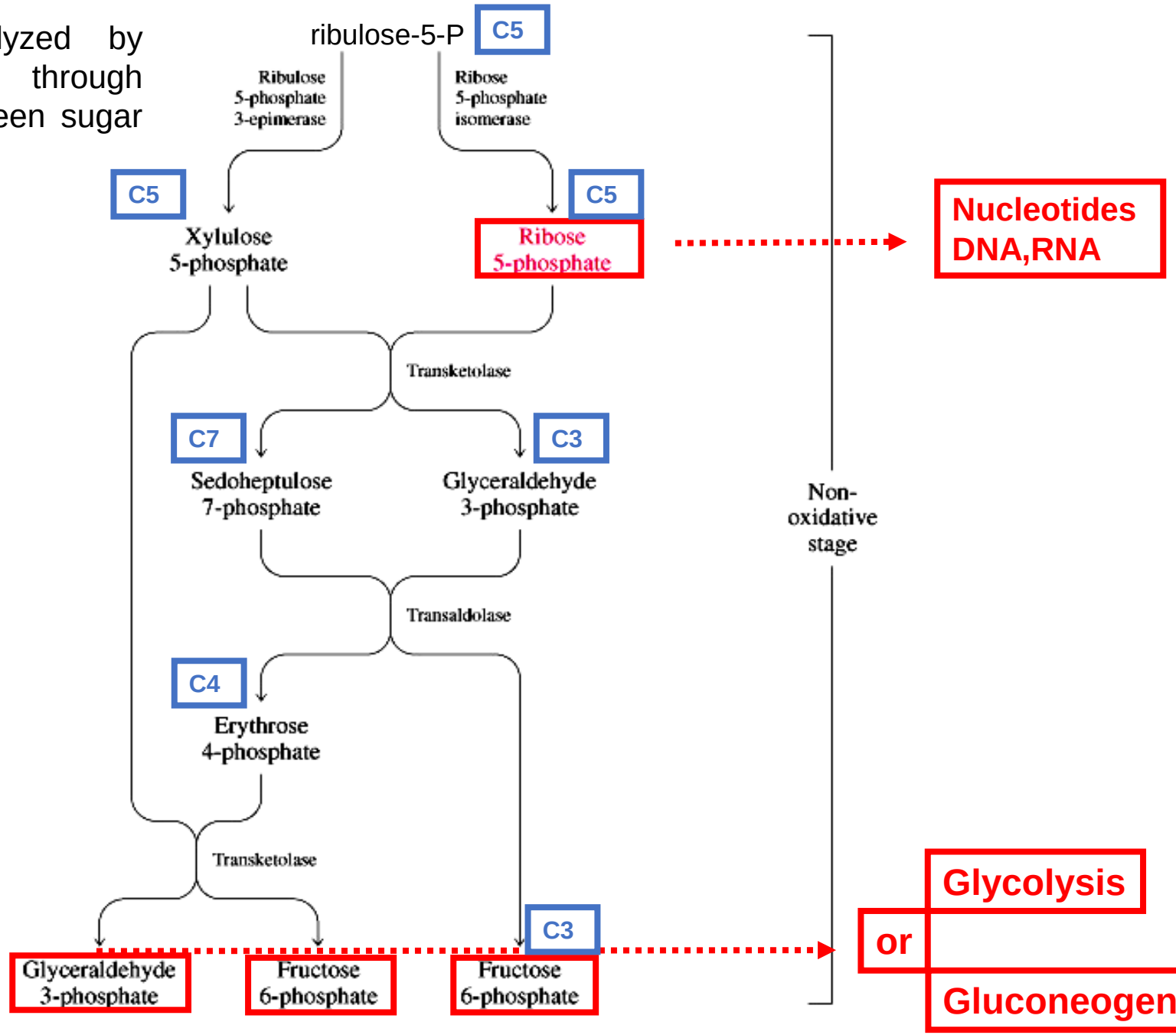
- Glucose-6-phosphate dehydrogenase catalyzes the first step in the oxidative stage of PPP
- Deficiency of this enzyme causes low NADPH and glutathione in red blood cells.
- RBC membrane is more susceptible to damage, causing **haemolytic anaemia** when oxidative stress occurs.
- The malarial parasite cannot survive without high NADPH levels.

PPP, erythrocytes and drugs

- Deficiency of G-6-PDH gives a benefit in terms of protection against malaria
- However, people with G6PDH deficiency are more susceptible to the effects of some drugs that cause redox cycling and oxidative stress.
- Treatment with these drugs causes increased haemolytic anaemia.

Non-oxidative reactions of PPP

These Interconversions are catalyzed by **Transketolase** & **Transaldolase** through exchange of carbon fragments between sugar phosphates



Energy metabolism of glucose