



HAND-OUT MATAKULIAH

BIOKIMIA PANGAN

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PROGRAM STUDI TEKNOLOGI PANGAN
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BIOKIMIA: METABOLISME KIMIAWI DALAM TUBUH MAKHLUK HIDUP UNTUK PRODUKSI ENERGI

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METABOLISME

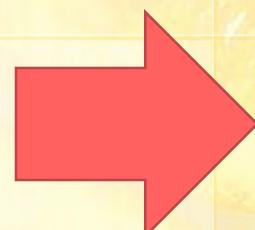
→ IBARAT PABRIK

- BAHAN BAKU:
- PATI → dirombak menjadi gula sederhana
→ glukosa
- PROTEIN → Asam amino
- LEMAK → Asam lemak

Glukosa

Asam amino

Asam lemak



Dirombak menjadi
cadangan energi (ATP)
melalui serangkaian
Proses BIOKIMIAWI

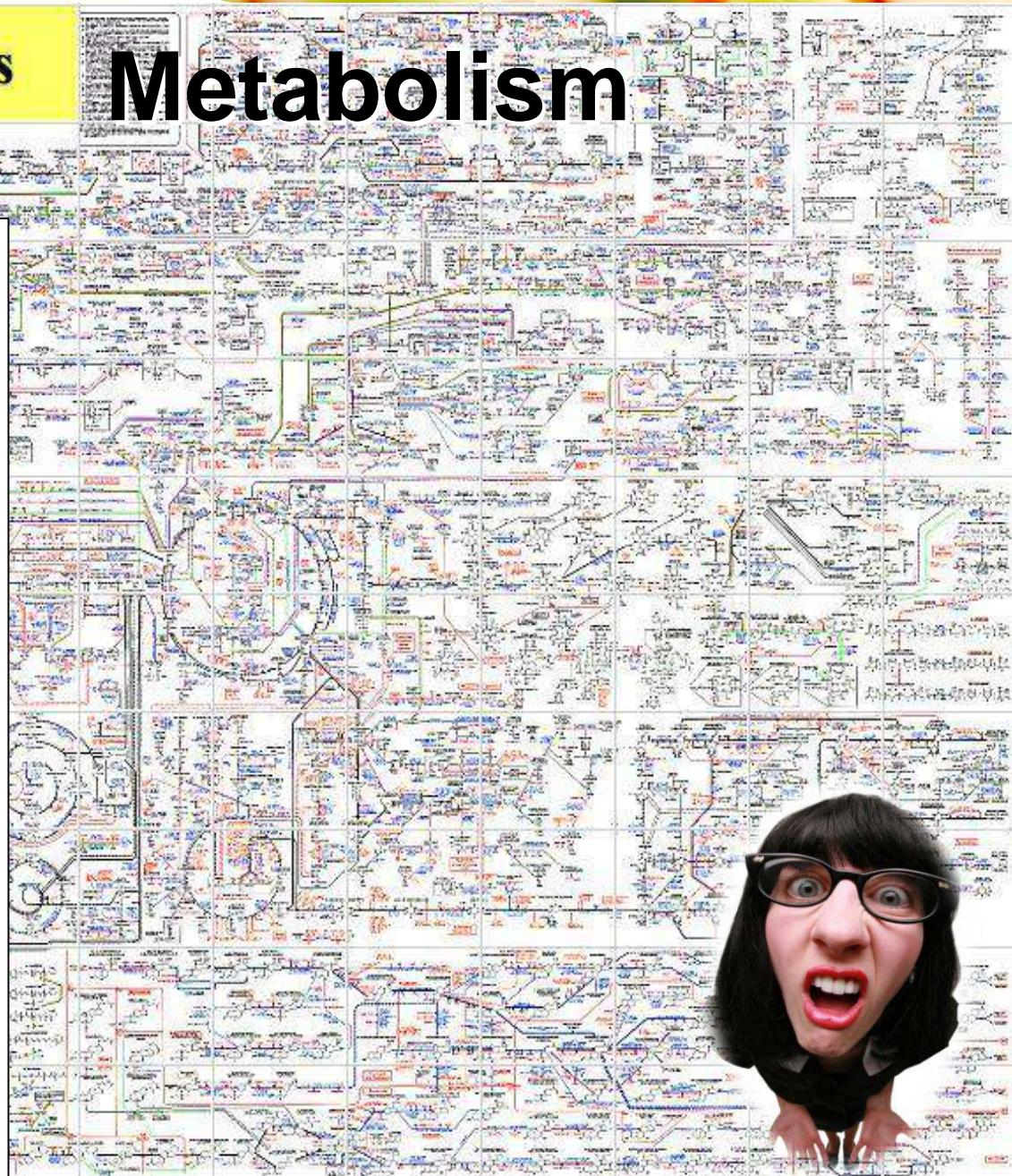


Biochemical Pathways

Metabolism

Metabolism is all chemical reactions within a cell (or whole organism), including energy-releasing breakdown of molecules (catabolism) and the synthesis of complex molecules (anabolism)

It is extraordinarily COMPLEX



PRODUKSI ENERGI DARI MAKANAN?

- PATI → dirombak menjadi gula sederhana (glukosa)
- Glukosa masuk ke usus → diserap di dinding usus halus → masuk pembuluh darah → dibawa ke sel-sel tubuh
- Masuk di sel otot → diubah menjadi energi

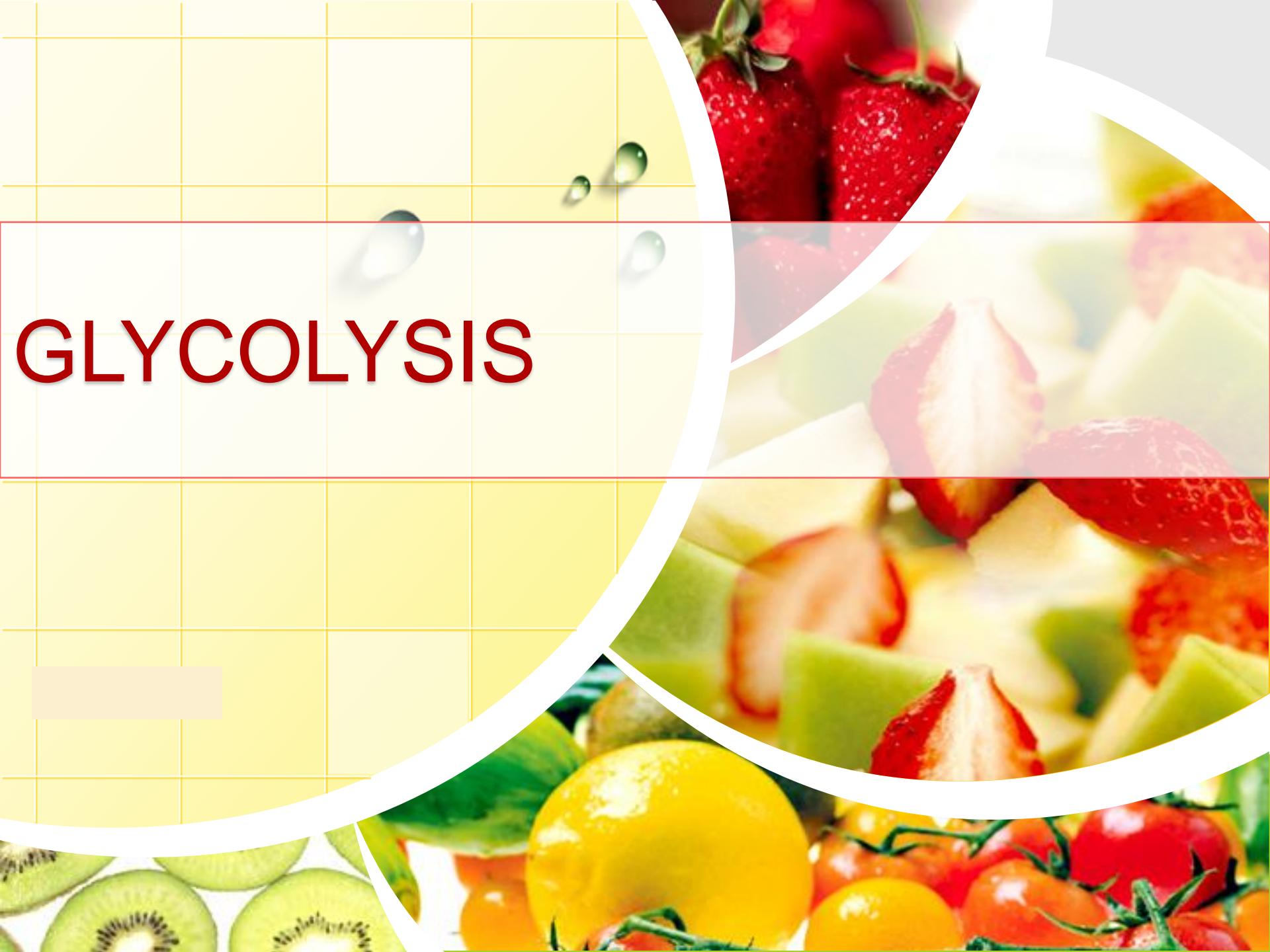


PRODUKSI ENERGI DARI GULA

UNTUK ORGANISME AEROB, JALUR UTAMA ADA 3 TAHAPAN:

1. GLIKOLISIS → lokasi: sitoplasma
2. SIKLUS TRI KARBOKSILAT / TCA CYCLE / SIKLUS KREB → lokasi: matriks mitokondria
3. TRANSPOR ELEKTRON → dinding mitokondria

GLYCOLYSIS



GLYCOLYSIS : A CENTRAL PATHWAY OF GLUCOSE CATABOLISM

- **GLYCOLYSIS** : the process by which the **GLUCOSE** molecule – which have 6 carbon atoms – **is enzymatically degraded in a sequence of 10 enzyme-catalyzed reactions** to yield 2 molecules of **PYRUVATE** – which have 3 carbon atoms
- During the sequential reactions of glycolysis, the free energy released from glucose is conserved in the form of ATP

The three important routes by PYRUVATE after glycolysis

- The pyruvate is oxidized, with loss of its carboxyl group as CO_2 , to form acetyl group of **acetyl-CoA**. Then the acetyl-CoA is oxidized to $\text{CO}_2 + \text{H}_2\text{O}$ by the **CITRIC ACID CYCLE**
- The pyruvate is reduced to **lactate**
- The pathway of the pyruvate leads to **ethanol** (alcoholic fermentation)

Glycolysis Reactions

Glyco – lysis :
breakdown of glucose to pyruvate

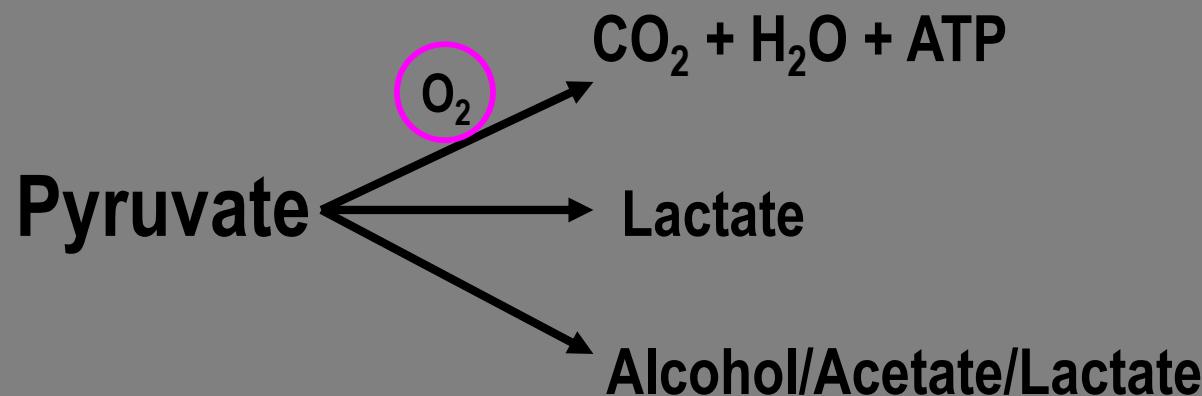
1.



Anaerobic (O_2 is not required)

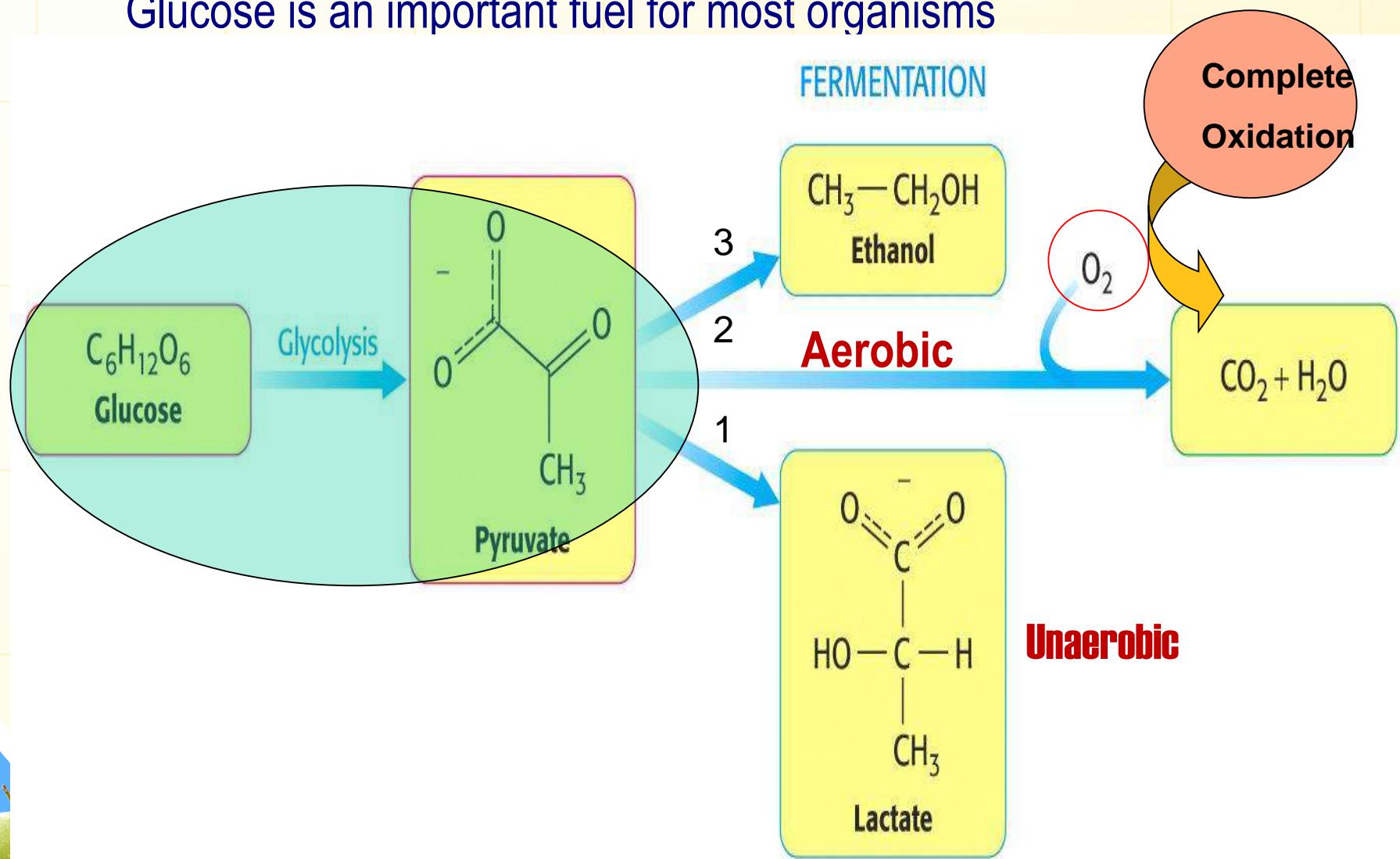
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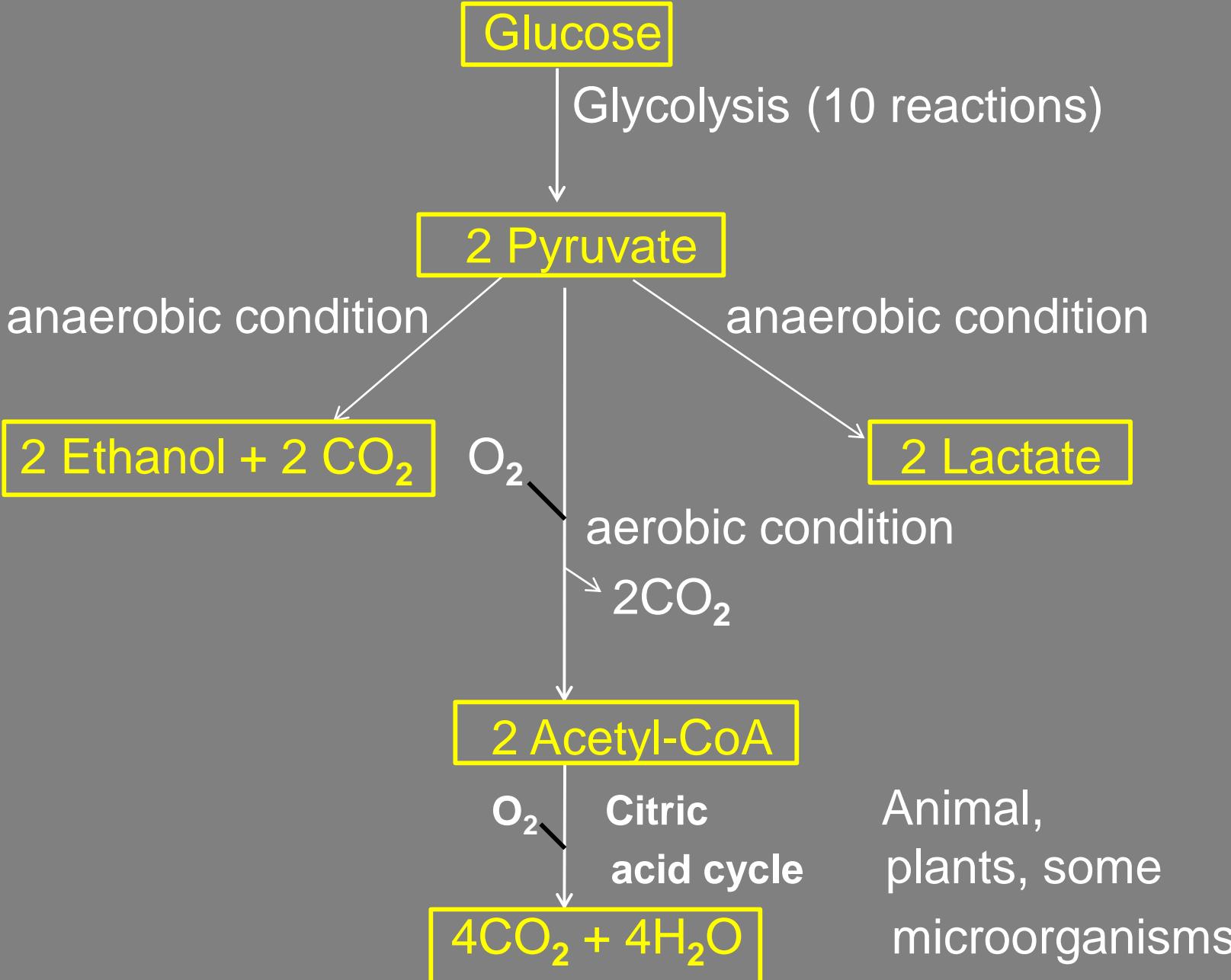
Further reaction of pyruvate can either:



Some Fates of Glucose

Glucose is an important fuel for most organisms





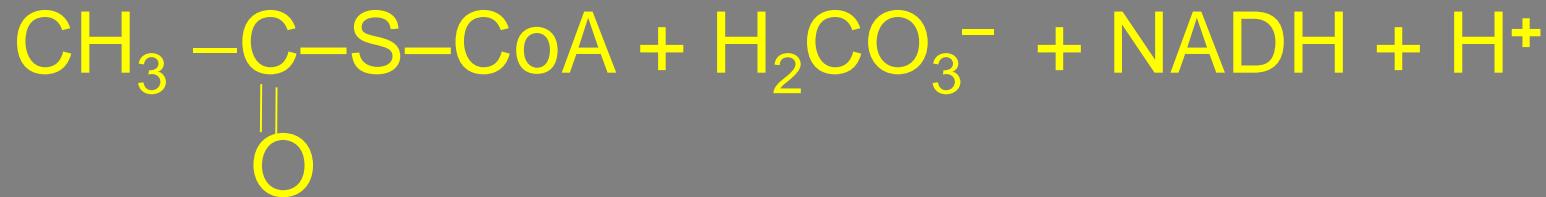
♣ Formation of acetyl-CoA from pyruvate



Pyruvate



pyruvate dehydrogenase



Acetyl-CoA

(Lehninger, p. 257)



Glycolysis Has Two Phases (Lehninger, p.400)

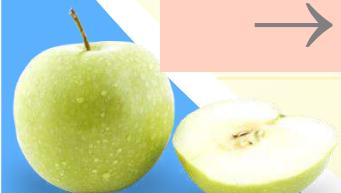
1. Preparatory phase : the first 5 steps of glycolysis

Glucose (1 molecule) → → → → →
glyceraldehyde 3-P (2 molecules)

2 ATP must be invested

2. The second phase of glycolysis : the remaining 5 reaction of glycolysis

Glyceraldehyde 3-P (2 mol.) → → → →
→ pyruvate (2 mol.)



- **Another reference** → glycolysis has 3 stages :

1. **Stage 1 : contains 4 steps**

Glucose (1 molecule) → → → → →
fructose 1,6-bisP (1 molecules)

2. **Stage 2 : contains 1 step**

Fructose 1,6-bisP (1 mol.) → → → → →
glyceraldehyde 3-P (2 mol.)

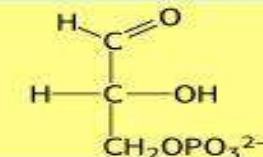
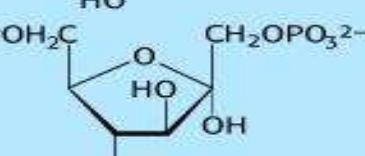
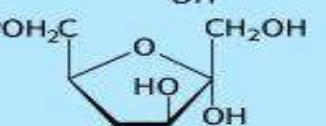
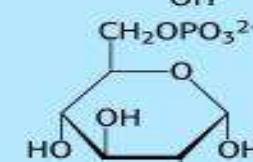
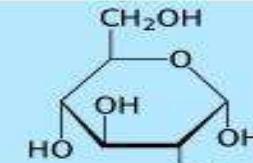
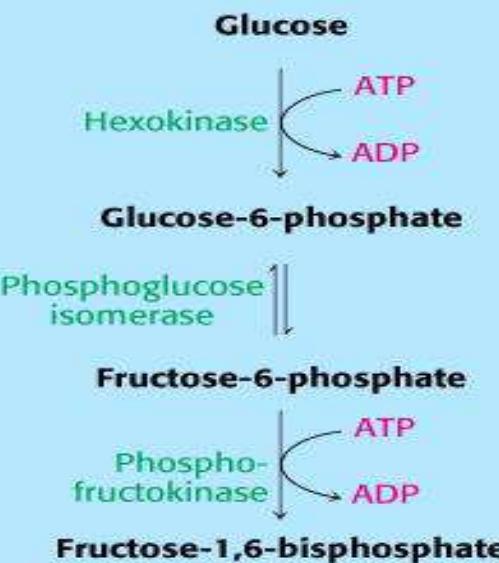
3. **Stage 3 : contain 5 steps**

Glyceraldehyde 3-P (2 mol.) → → → → →
pyruvate (2 mol.)

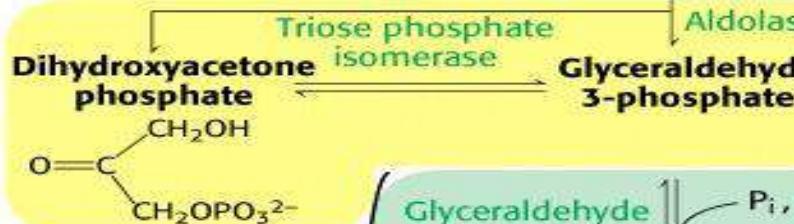
Glycolysis in 3 Stages

Stage 1: 4 steps
 Stage 2: 1 step
 Stage 3: 5 steps

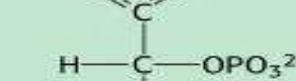
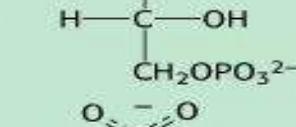
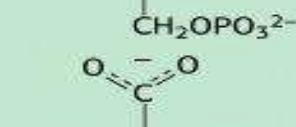
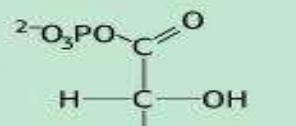
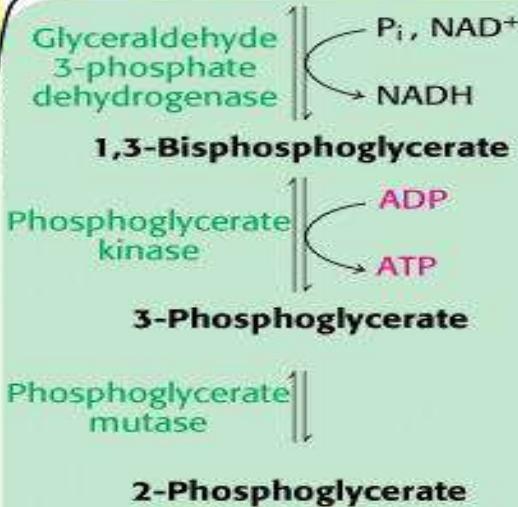
Stage 1



Stage 2

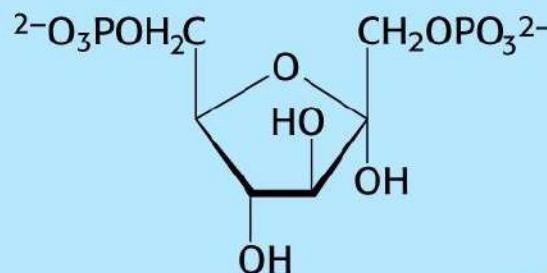
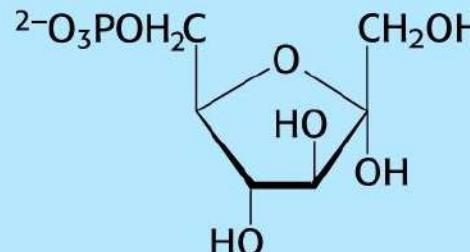
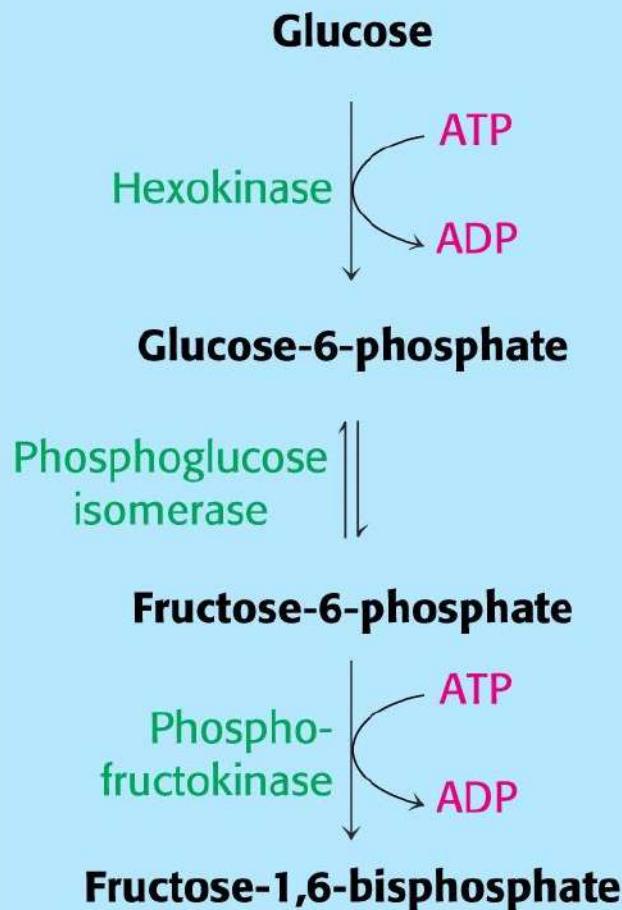


Stage 3



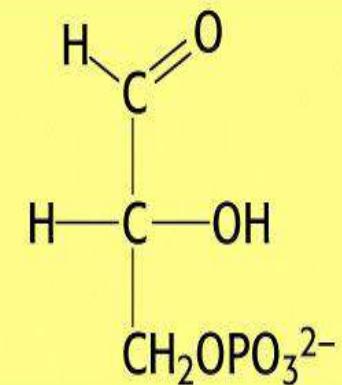
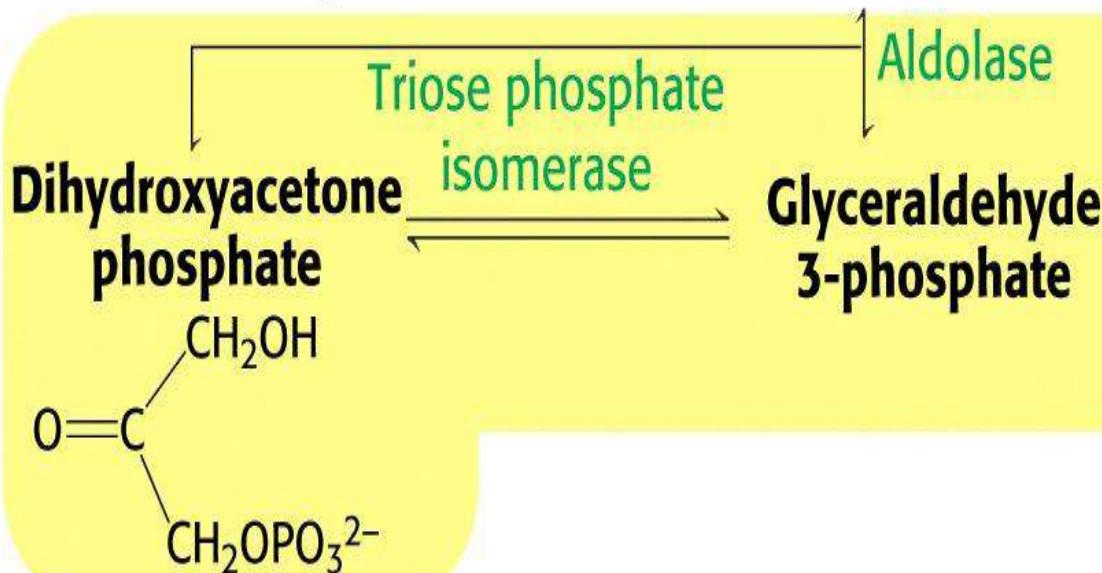
Glycolysis: 1

Stage 1



Glycolysis: 2

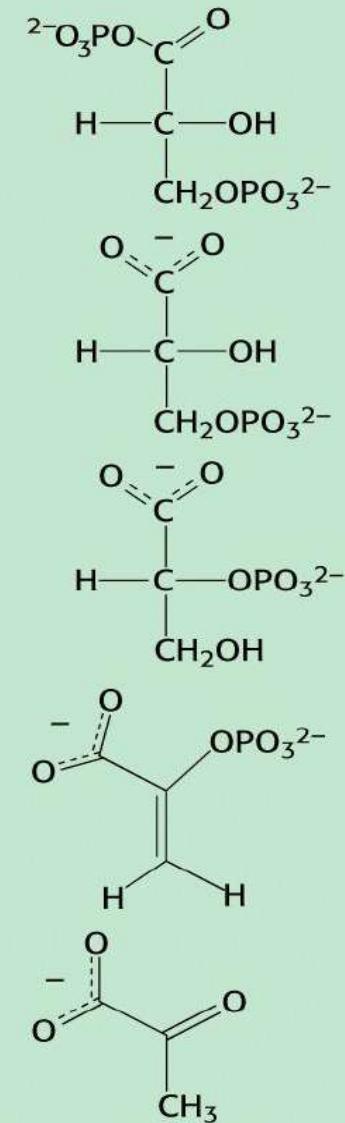
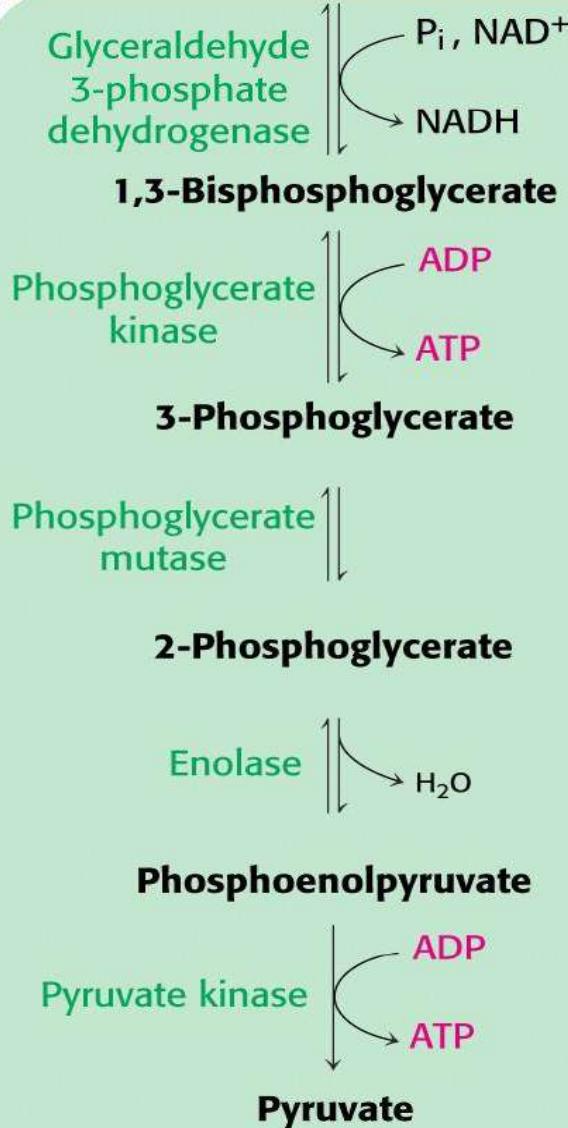
Stage 2



Glycolysis:3

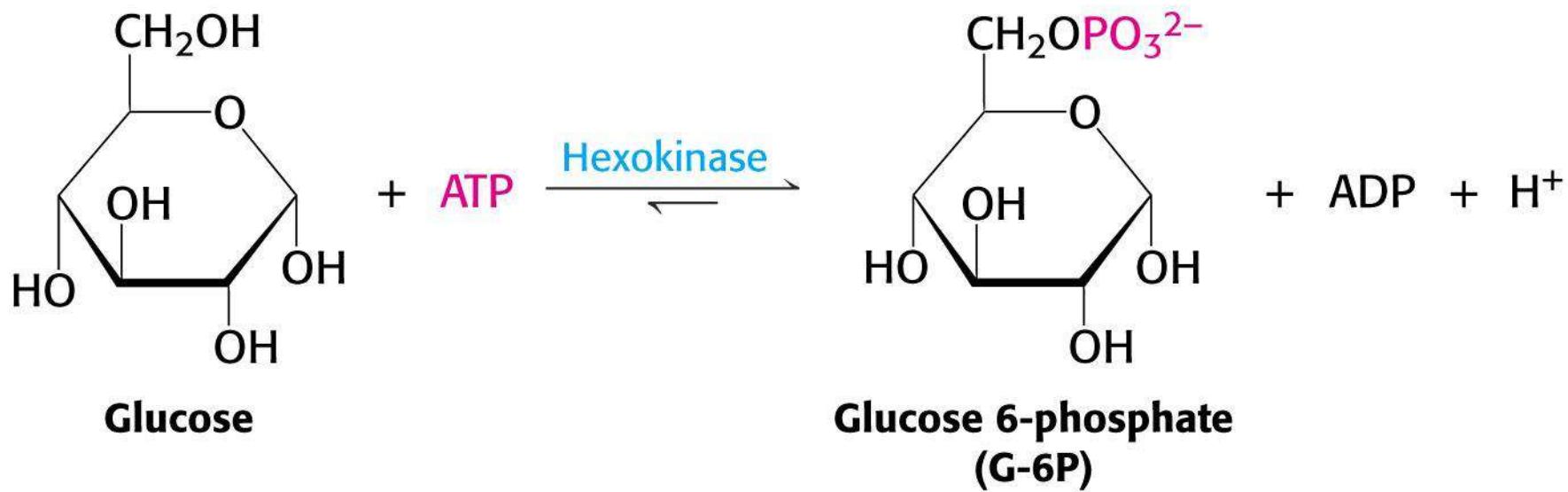
Stage 3

2 X



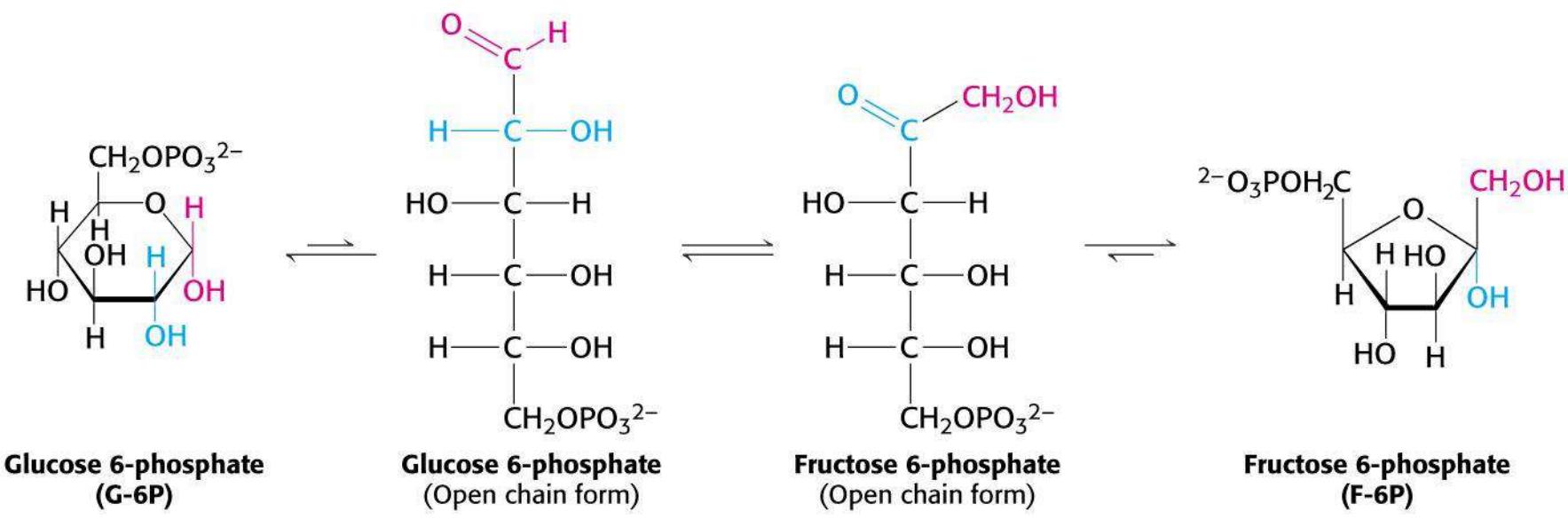
STAGE 1

Glucose phosphorylation (by hexokinase)



STAGE 1

Formation of fructose-6-phosphate (by phosphogluucose isomerase)

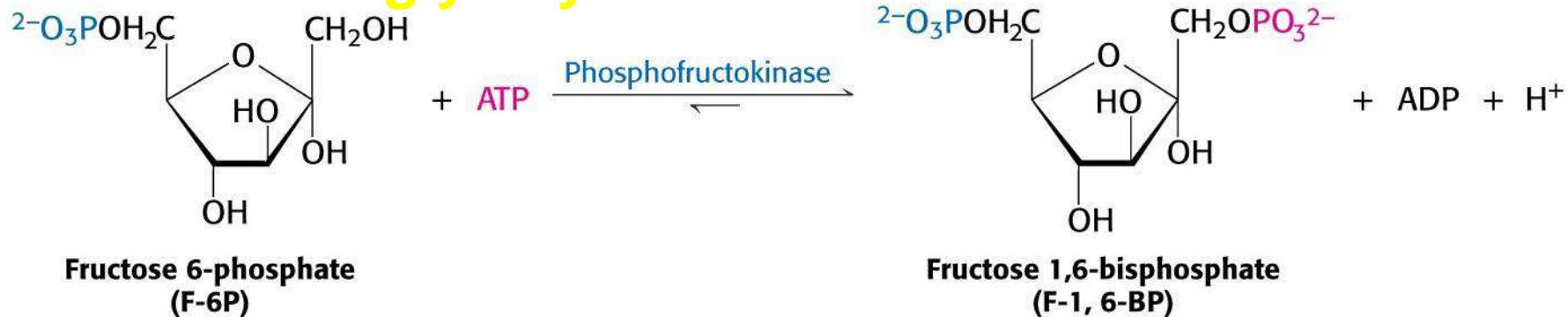


Conversion of an aldose to a ketose

STAGE 1

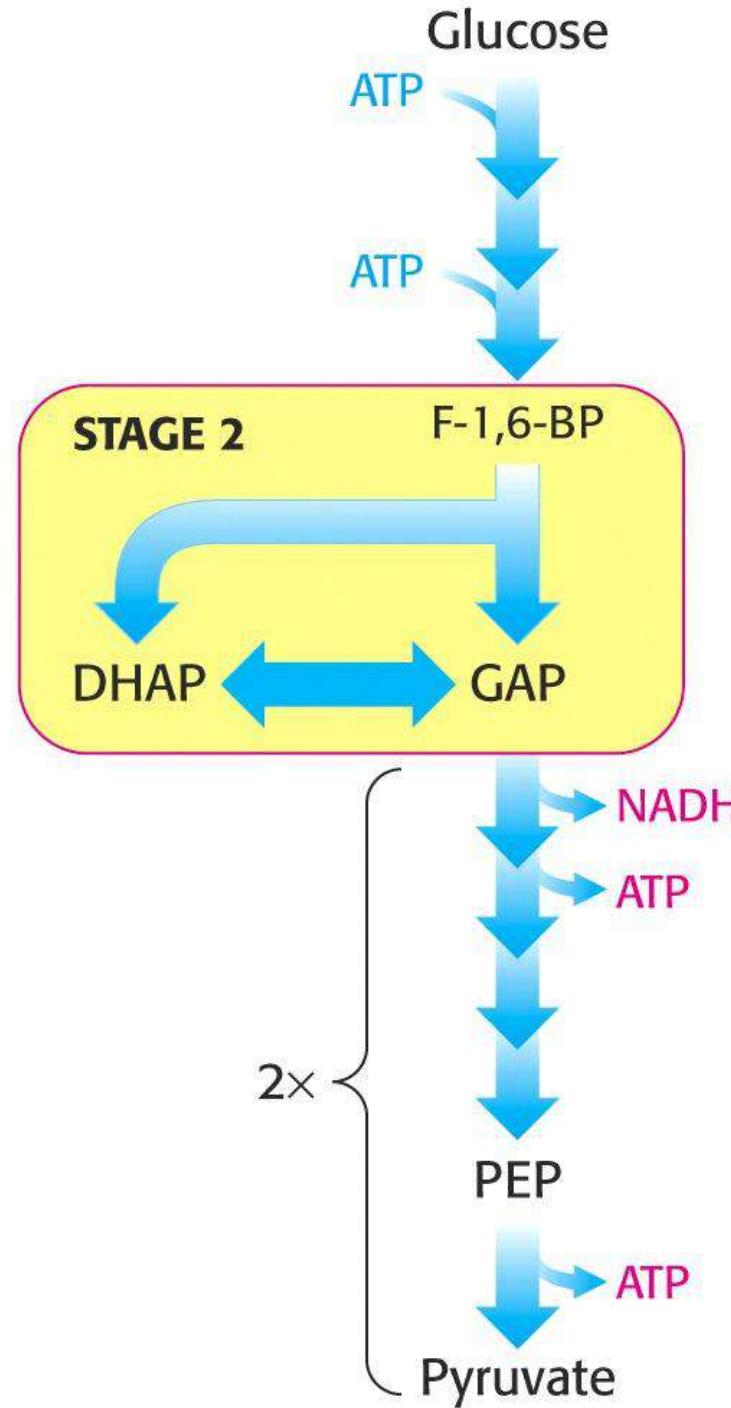
Step 3: Formation of fructose 1,6-bisphosphate

by phosphofructokinase (PFK): an allosteric enzyme that regulates the pace of glycolysis.



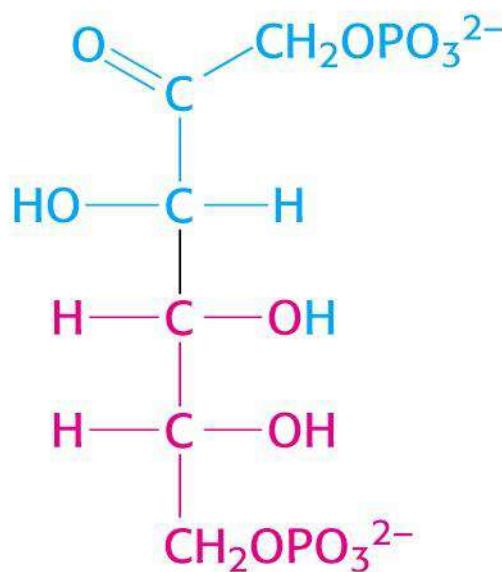
Glycolysis: STAGE 2

Two 3-carbon
fragments are
produced from one
6-carbon sugar

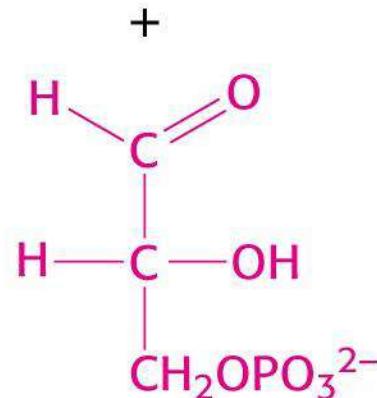
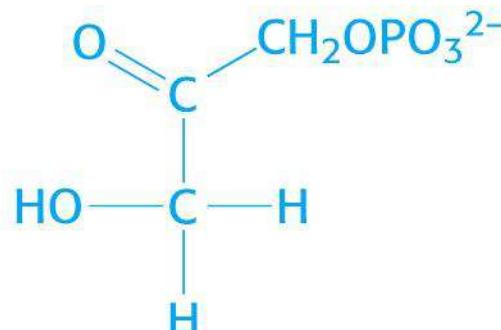


STAGE 2

Cleavage of six-carbon sugar

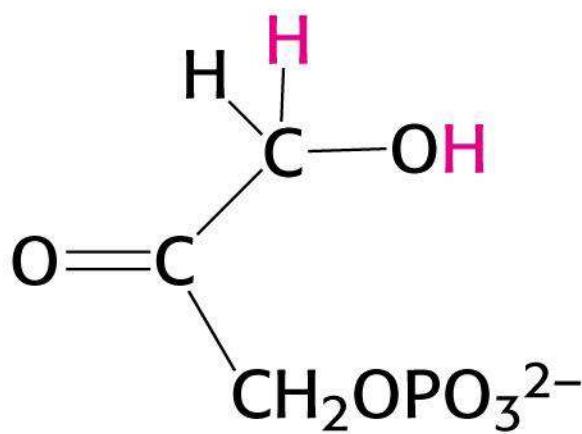


Aldolase

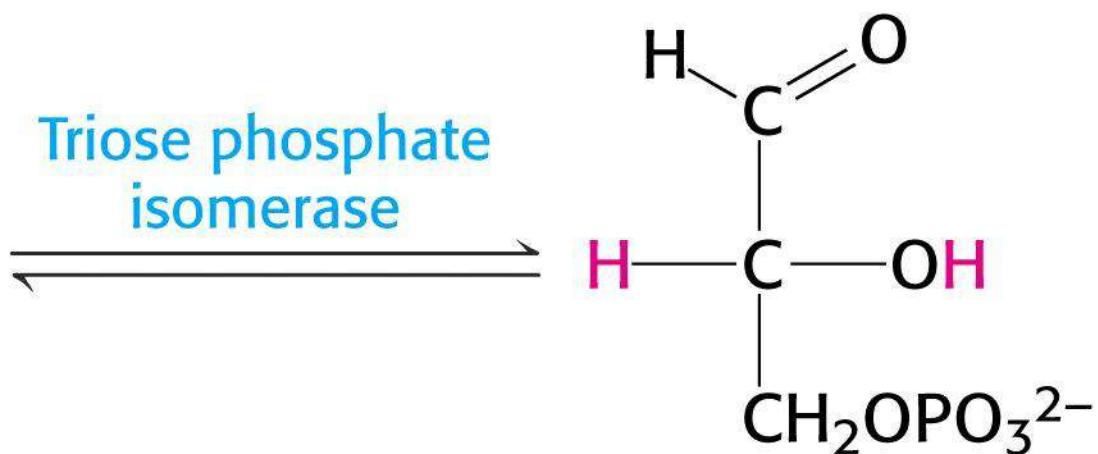


STAGE 2

Step 3 Salvage of three-carbon fragment



Dihydroxyacetone phosphate

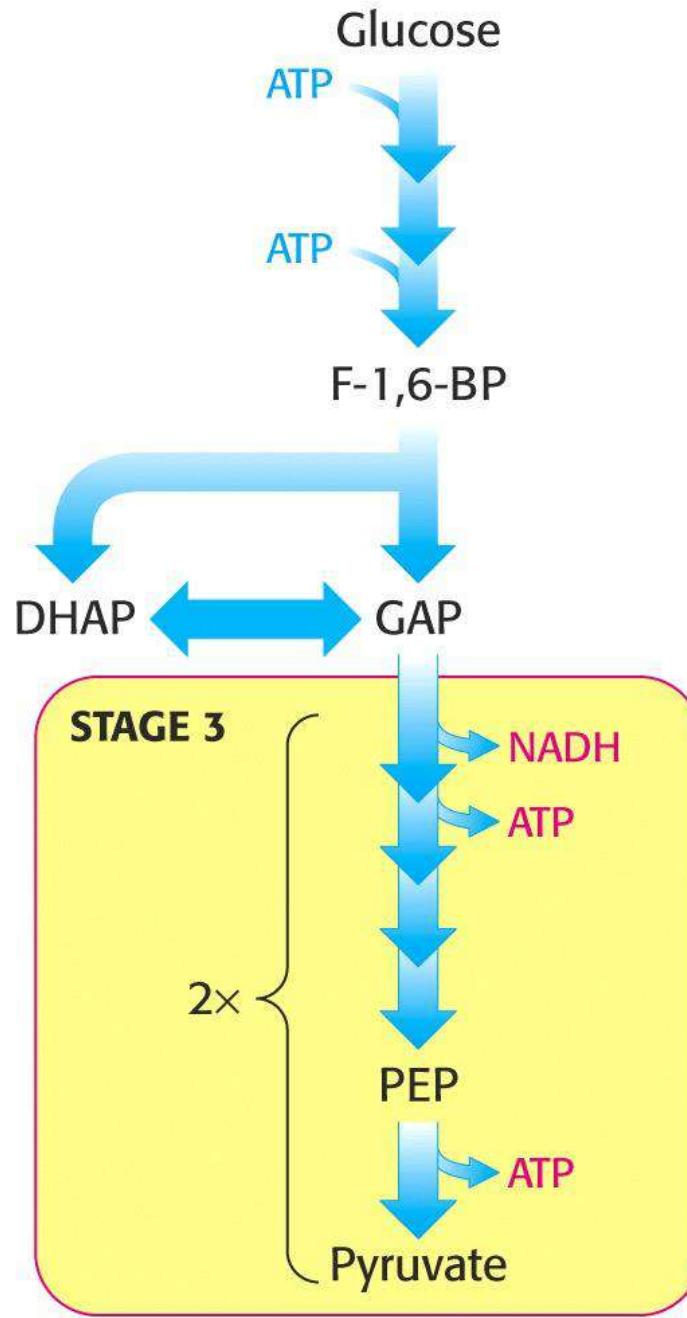


Glyceraldehyde 3-phosphate

Triose phosphate
isomerase

Glycolysis: STAGE 3

The oxidation
of three-
carbon
fragments
yields ATP

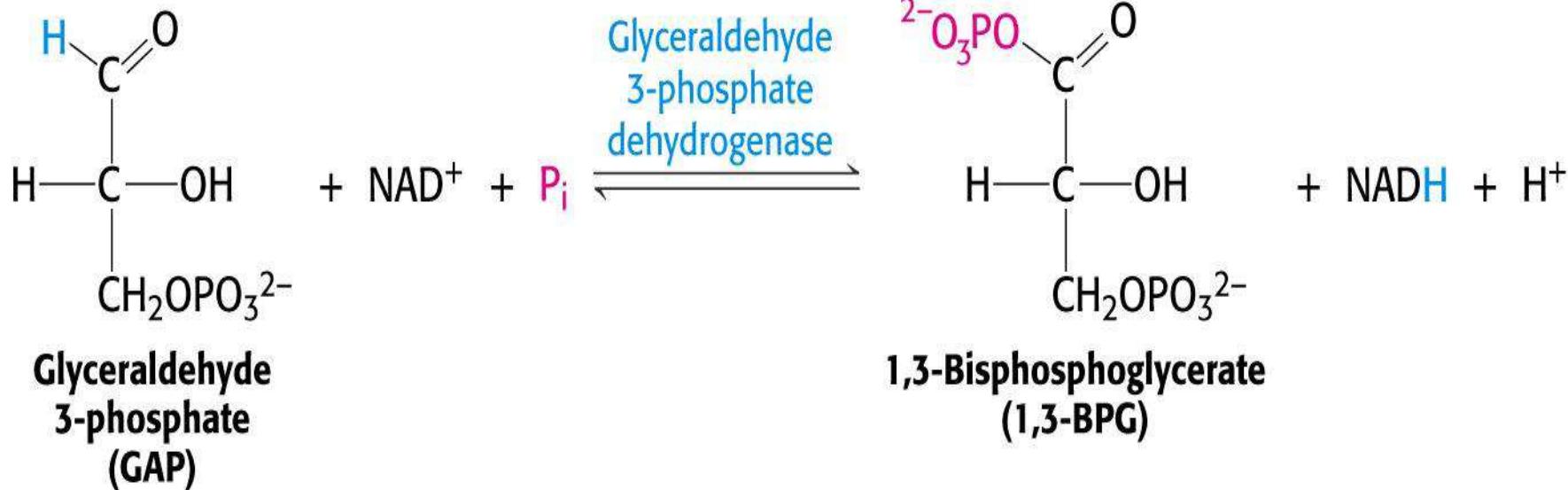


Energy
extracted,
2x2 ATP

STAGE 3

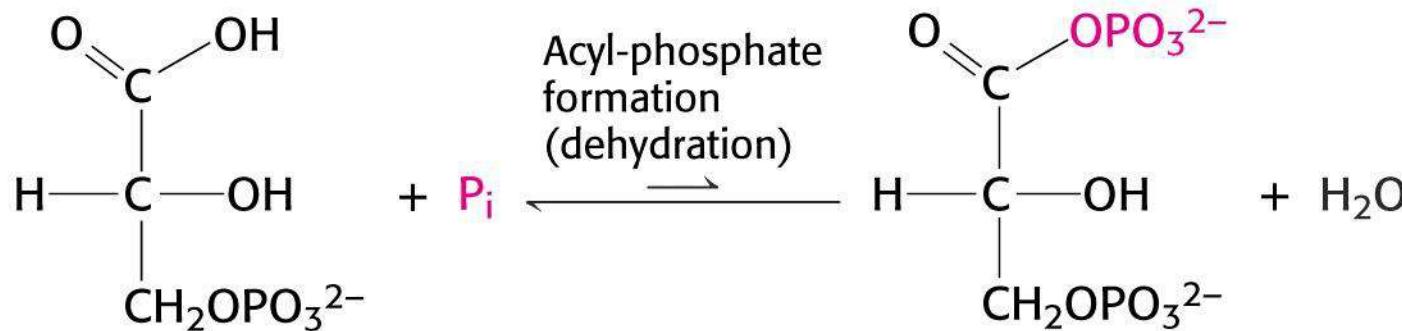
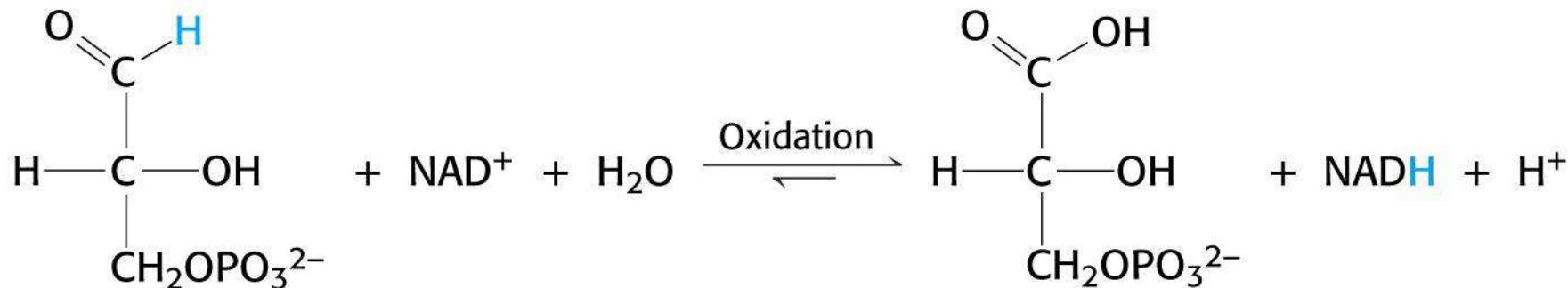
Formation of 1,3-Bisphosphoglycerate

Done in two steps



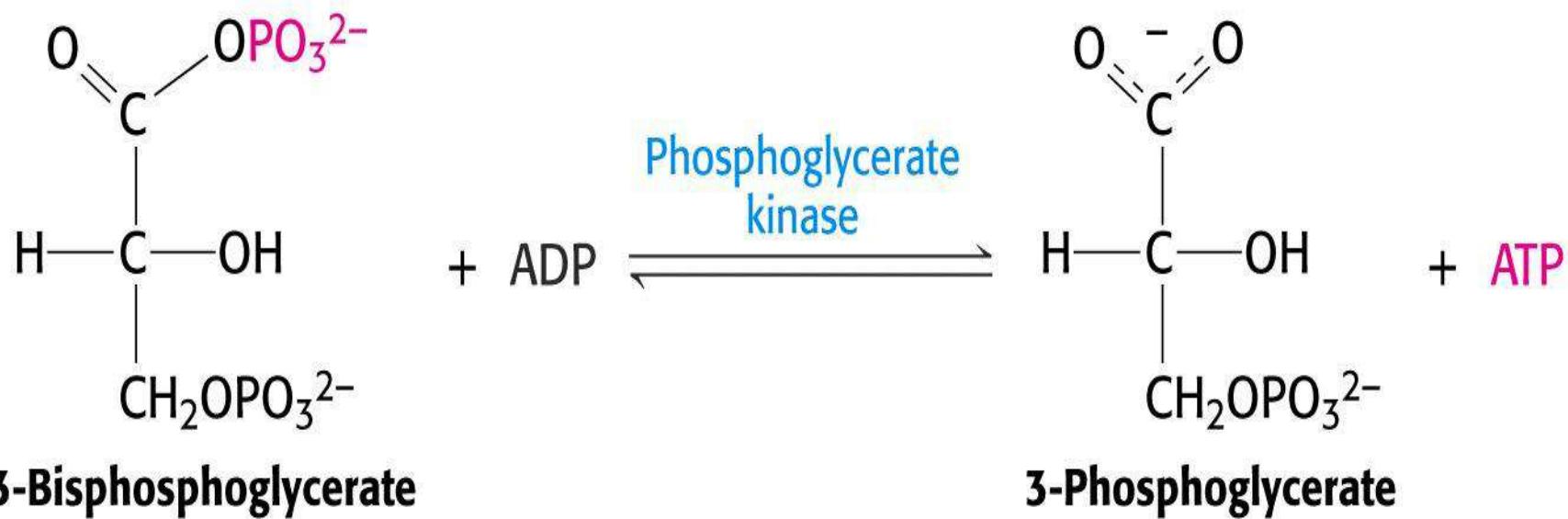
Aldehyde

Acid



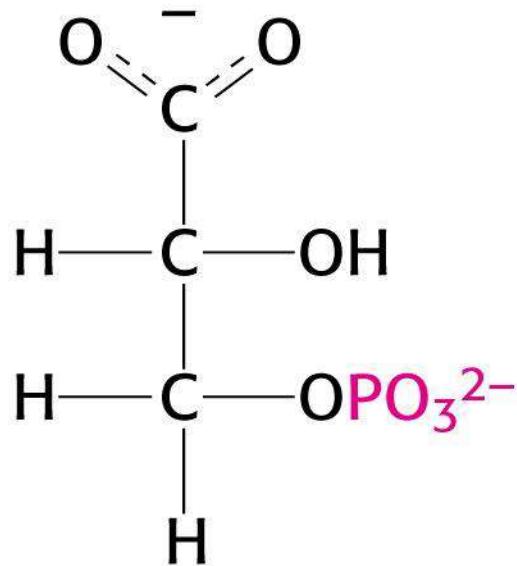
STAGE 3

Formation of ATP from ADP + 1,3-Bisphosphoglycerate

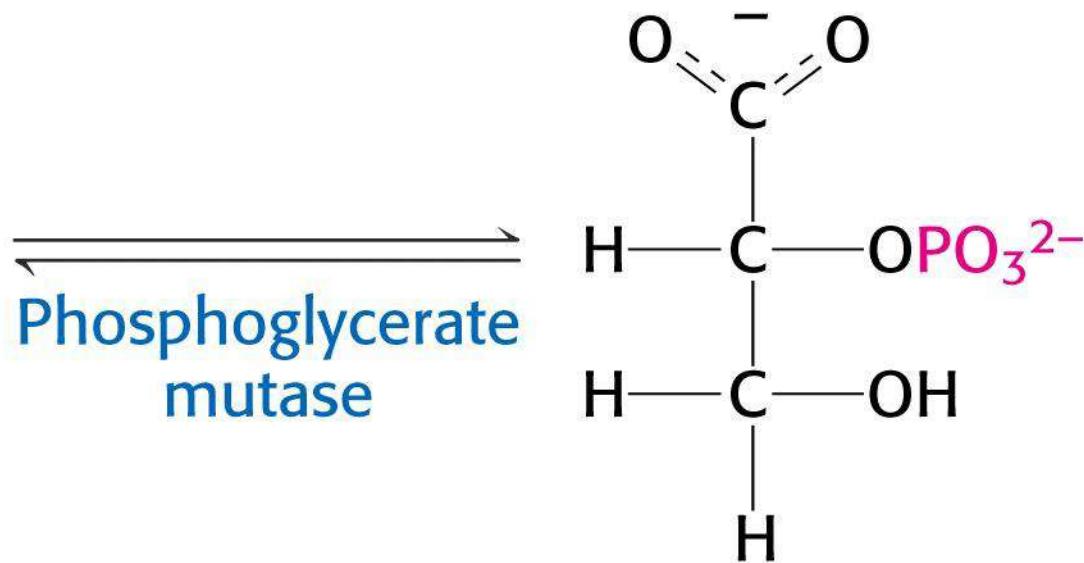


STAGE 3

Rearrangement



3-Phosphoglycerate

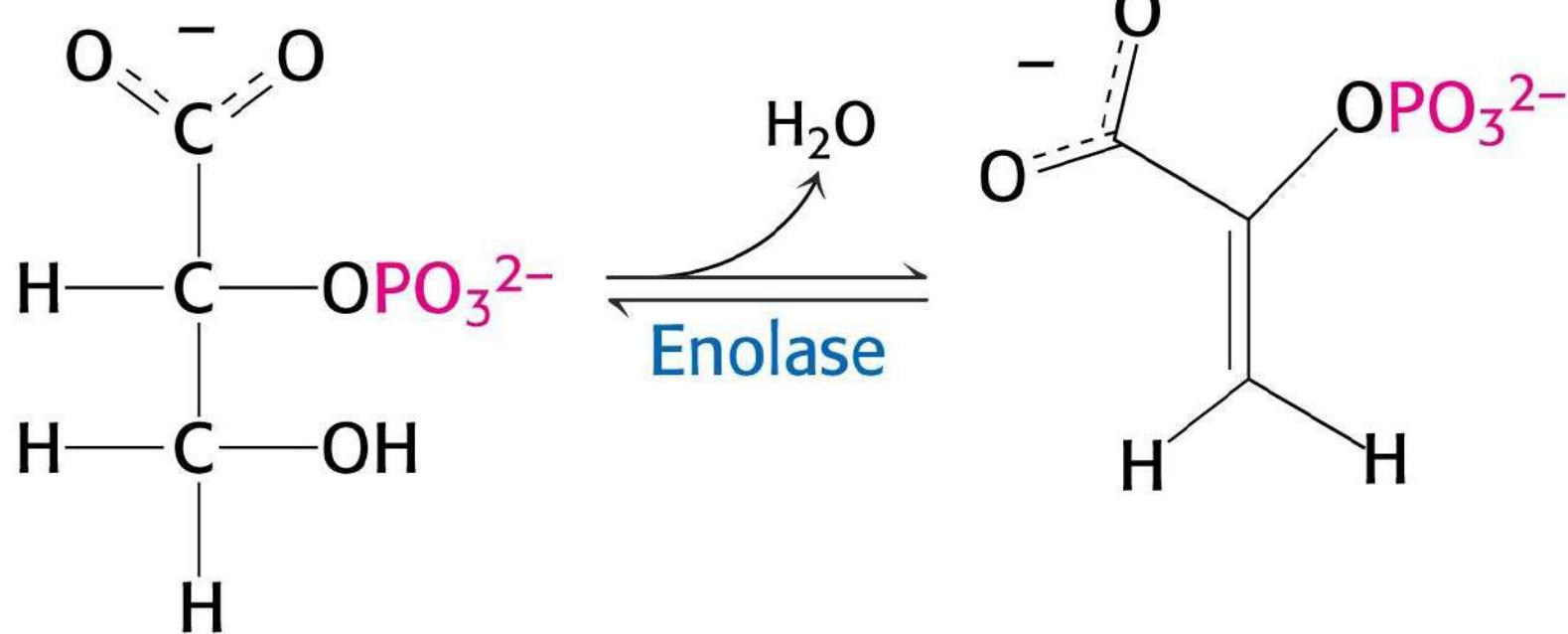


2-Phosphoglycerate

\rightleftharpoons
Phosphoglycerate
mutase

STAGE 3. An enol phosphate is formed

Dehydration elevates the transfer potential of the phosphoryl group, which traps the molecule in an unstable enol form



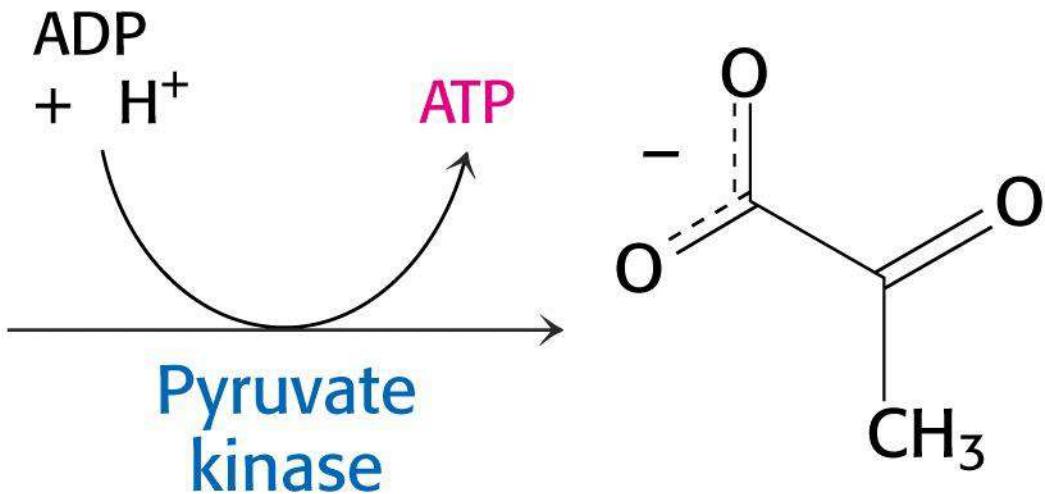
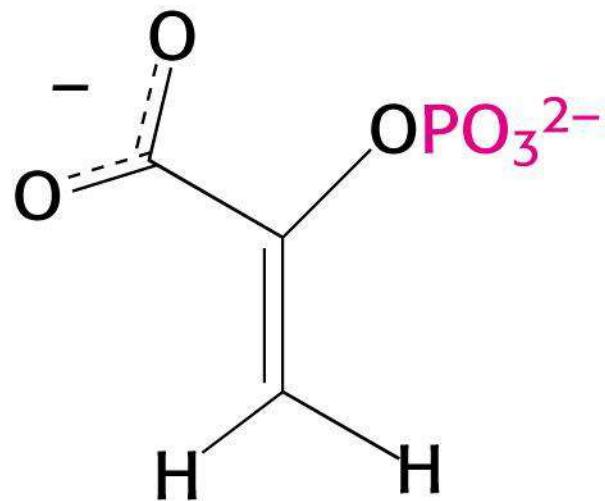
2-Phosphoglycerate

Phosphoenolpyruvate

Enol: molecule with hydroxyl group next to double bond

STAGE 3

Step 10: Formation of Pyruvate & ATP

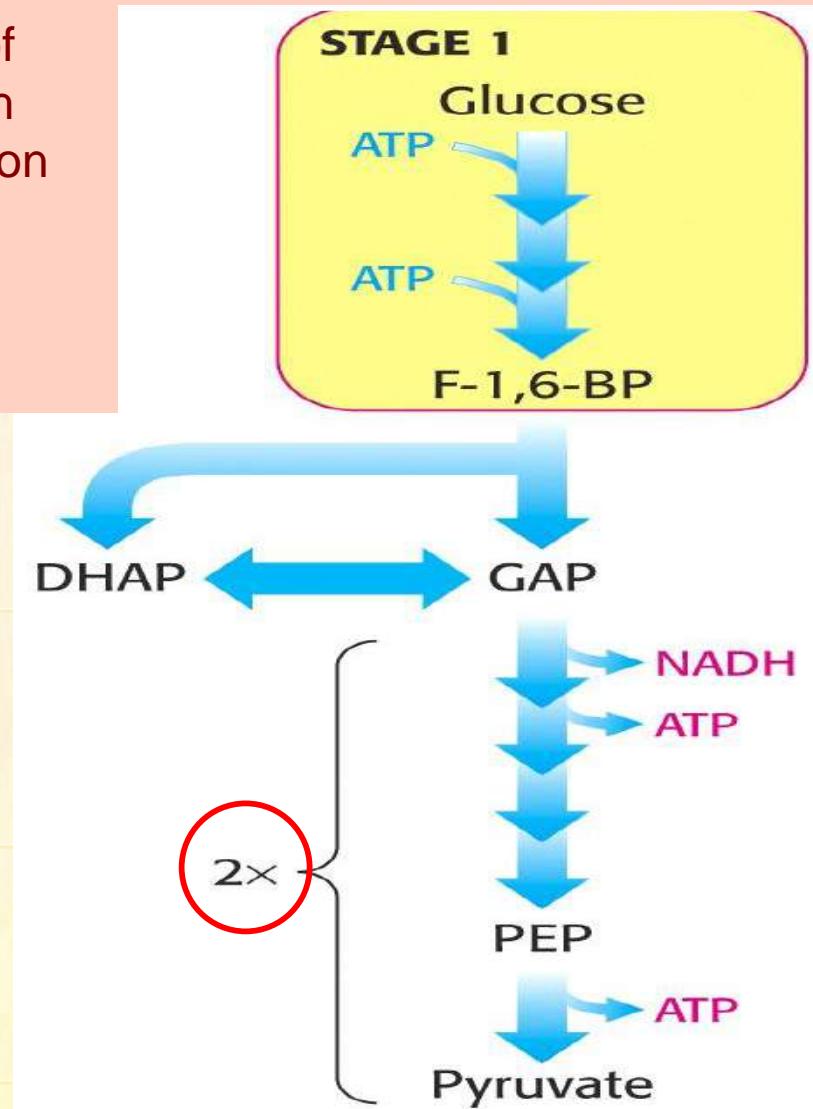


Phosphoenolpyruvate

Pyruvate

Energy utilization of Glycolysis:

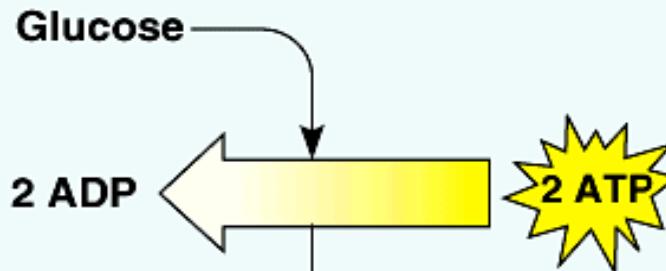
The three steps of stage 1 begin with the phosphorylation of glucose by hexokinase



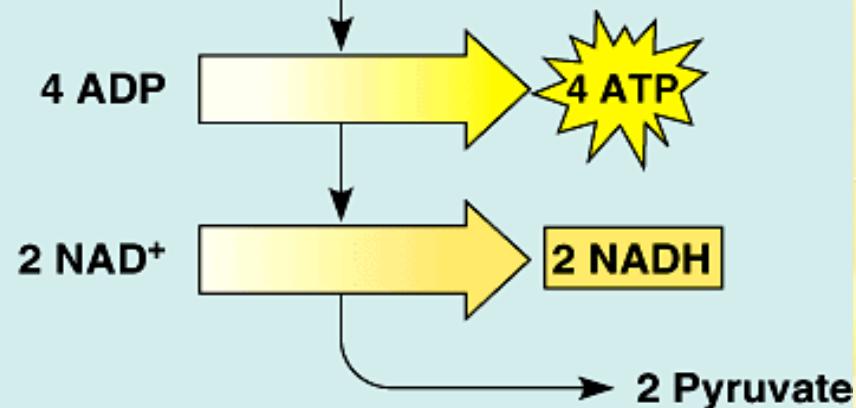
STAGE 1

Energy used,
none extracted

ENERGY INVESTMENT PHASE



ENERGY PAYOFF PHASE

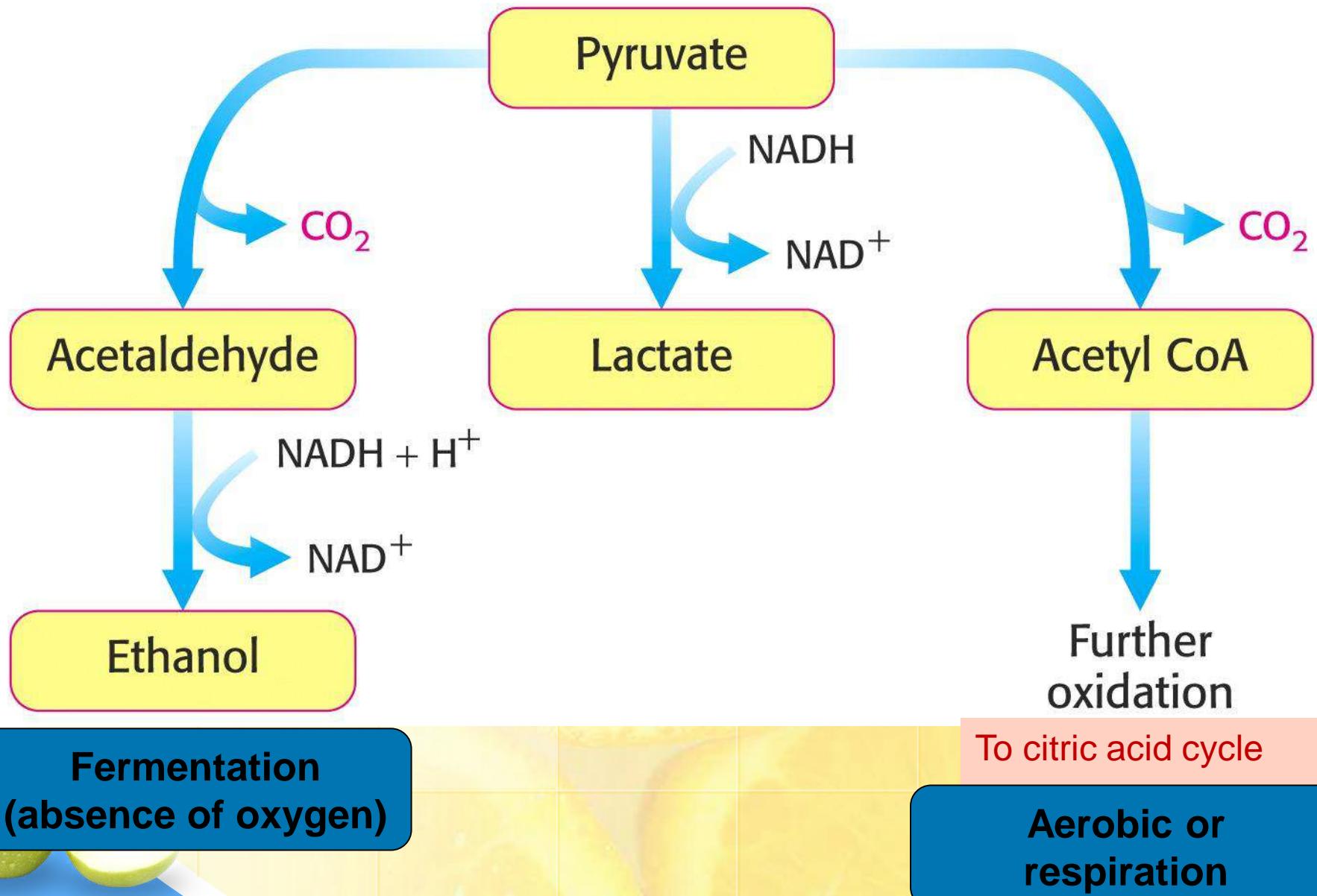


NET

3. No CO₂ is produced during glycolysis



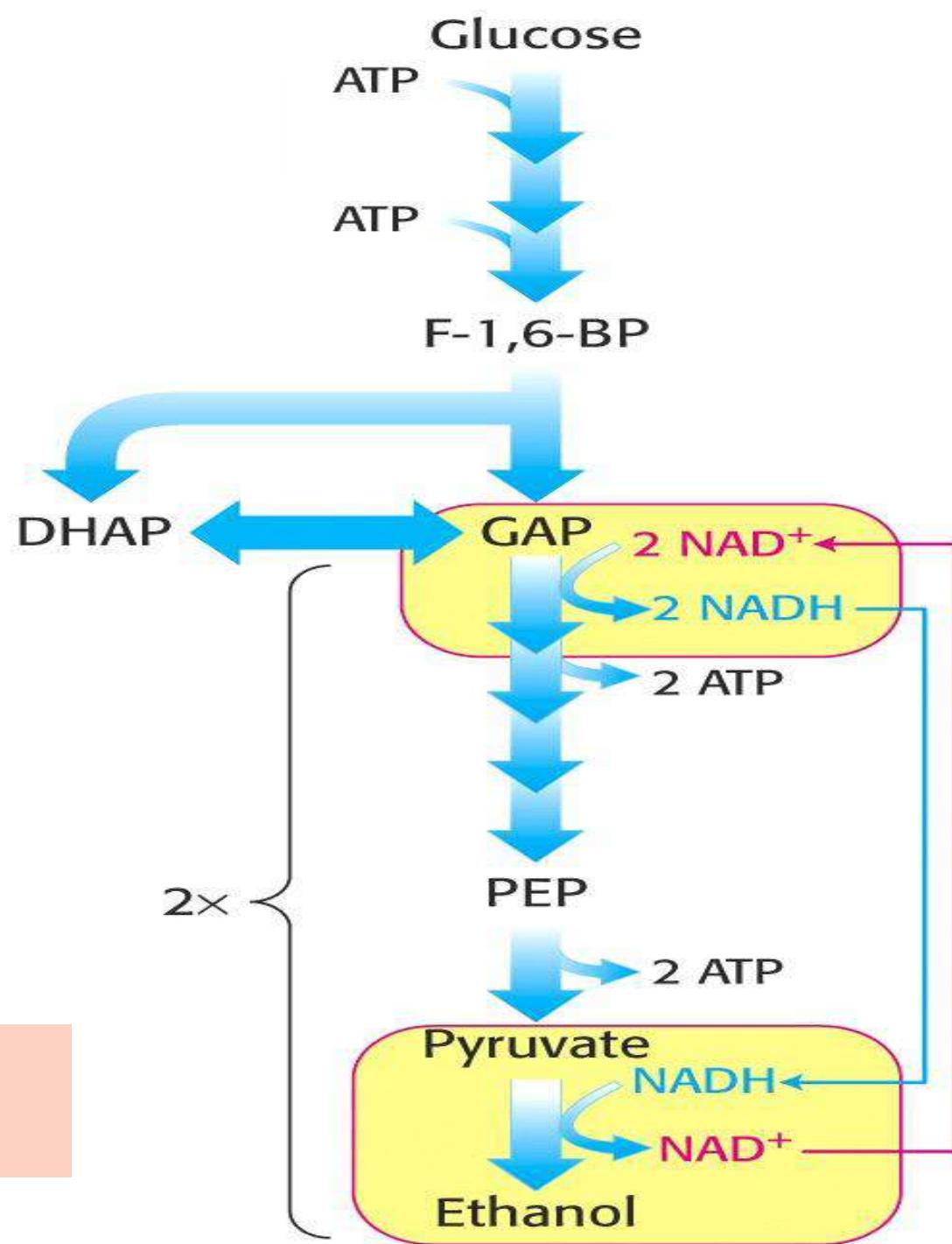
Diverse fates of pyruvate



Maintaining Redox Balance

NAD⁺ must be regenerated for glycolysis to proceed

Glycolysis is similar in all cells, the fate of pyruvate is variable



Glycolysis is tightly controlled

Pathway is regulated to meet two major needs:

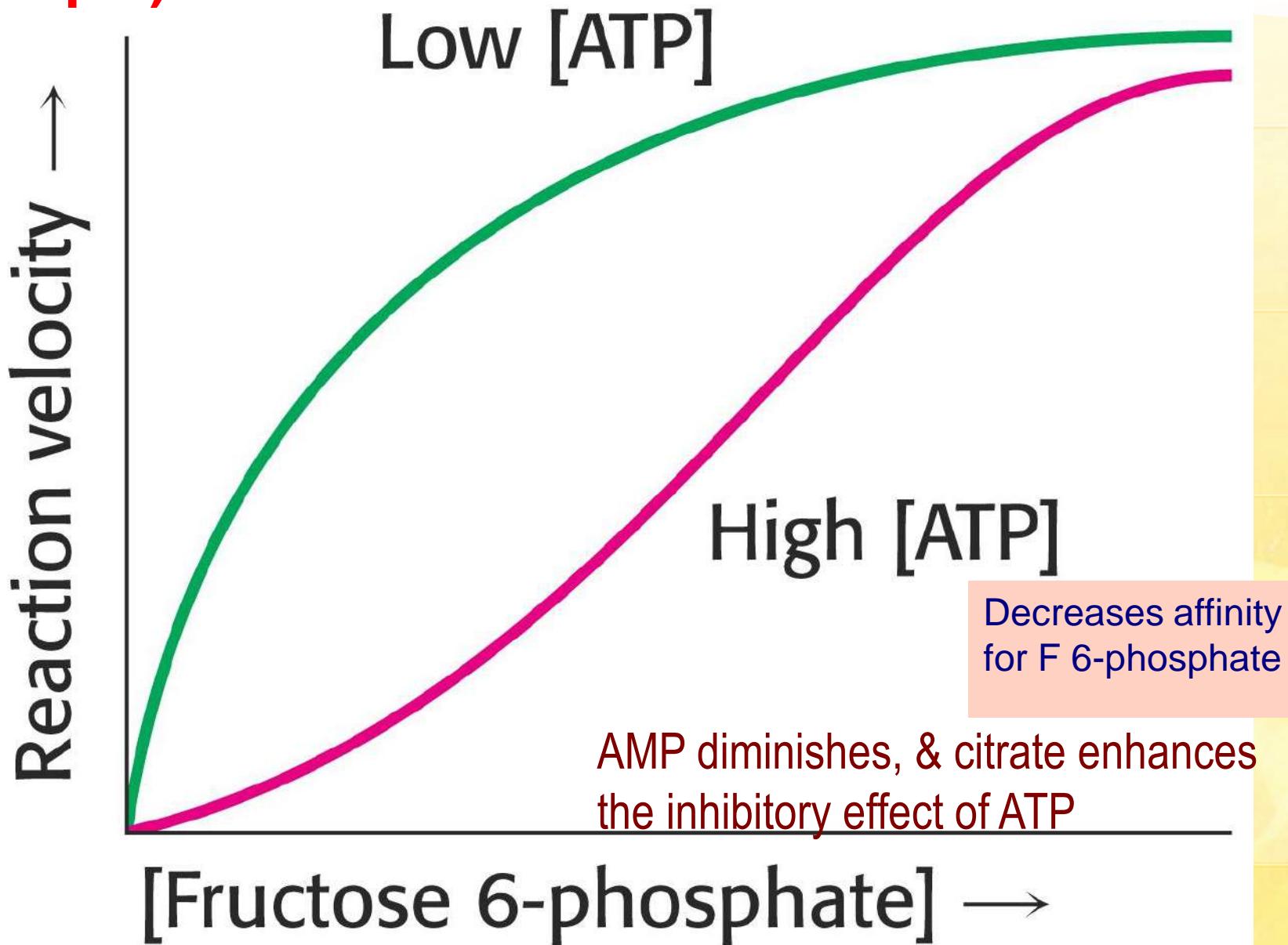
1. Production of ATP
2. Provision of building blocks for biosynthesis

Hexokinase, phosphofructokinase, & pyruvate kinase serve as control sites (their reactions are virtually irreversible)

1. Their activities are regulated by reversible binding of allosteric effectors (milliseconds), or by covalent modification (seconds)
2. The amounts of the enzymes are varied by the regulation of transcription (hours)



Allosteric regulation of phosphofructokinase (step 3)



ATP Energy from Glycolysis

- In the electron transport system

$\text{NADH} = 3 \text{ ATP}$ & $\text{FADH}_2 = 2 \text{ ATP}$

- Glycolysis

$\text{Glucose} \longrightarrow 2 \text{ pyruvate} + 2 \text{ ATP} + 2 \text{ NADH}$

$\text{NADH in cytoplasm} \longrightarrow \text{FADH}_2$ mitochondria

$\text{Glucose} \longrightarrow 2 \text{ pyruvate} + 6 \text{ ATP}$

ATP Energy from Pyruvate

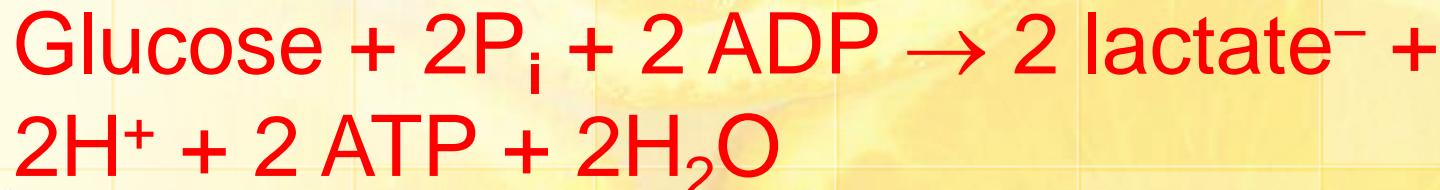
$2 \text{ pyruvate} \rightarrow 2 \text{ acetyl CoA} + 2 \text{ CO}_2 + 2 \text{ NADH}$

$2 \text{ pyruvate} \rightarrow 2 \text{ acetyl CoA} + 2 \text{ CO}_2 + 6 \text{ ATP}$

Lactic Acid Strategy

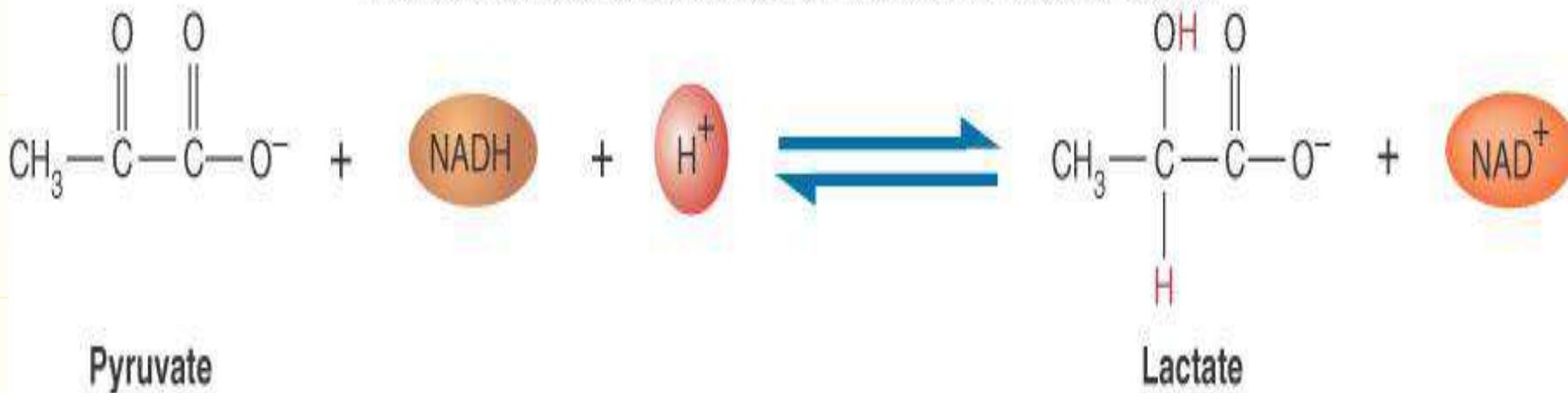
- Under anaerobic condition, in very active skeletal muscles (or in lactic acid bacteria), NADH is reoxidized to NAD⁺ by pyruvate, converting the latter into lactate
- Electron donated by glyceraldehyde 3-P
- The reduction of pyruvate is catalyzed by *lactate dehydrogenase*

- The overall balance sheet :



Lactic Acid Strategy

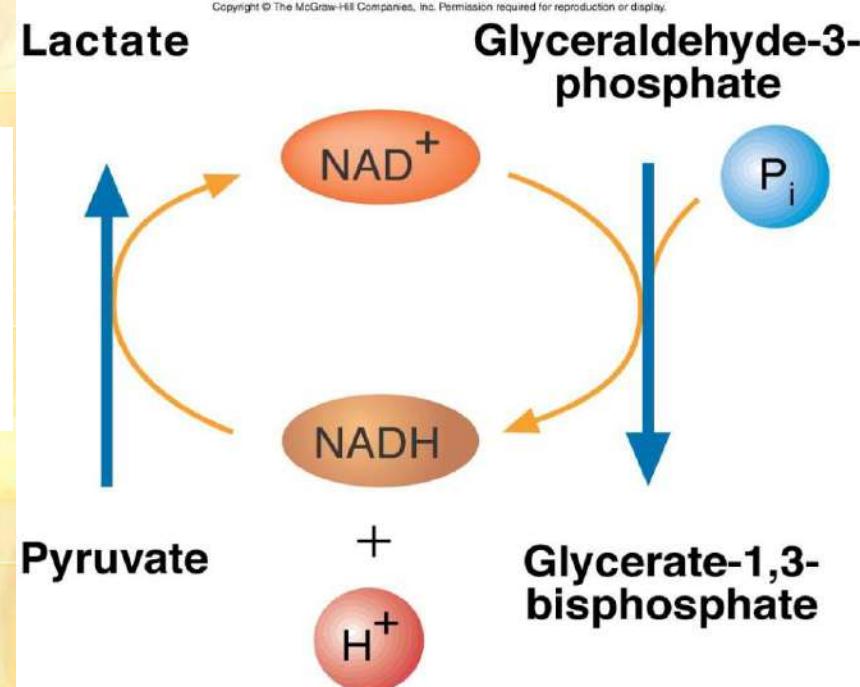
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Pyruvate

Lactate

- Occurs in muscles when exercising - unaerobic
- Accounts for the “burn”

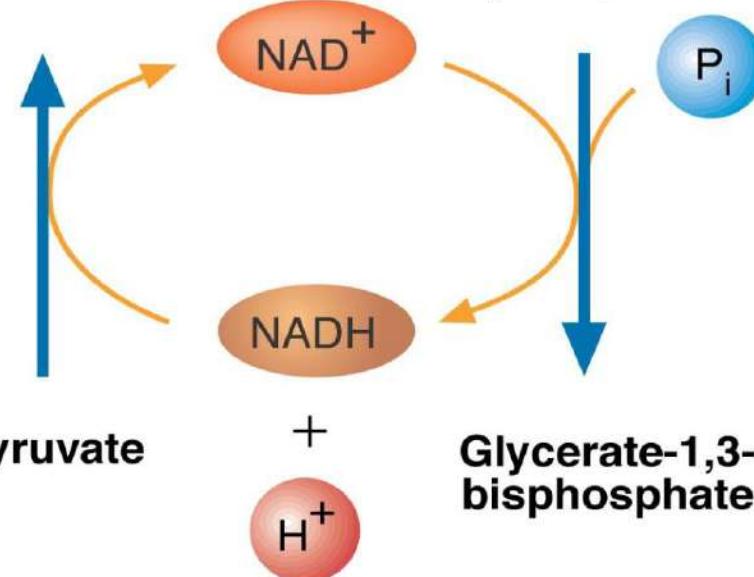


Pyruvate

Glyceraldehyde-3-phosphate

Lactate

Glyceraldehyde-3-phosphate



Feeder Pathways Lead from Glycogen & Other Carbohydrate into Central Glycolytic Pathways

- Glycogen & starch
 - Maltose, lactose, sucrose
 - Fructose, mannose, galactose
 - See the next slide : entry of glycogen & other hexoses into the first stage of glycolysis
- } have the entry point into the first stage of glycolysis

D-Glucose

Glycogen

D-Galactose

D-Fructose

Fructose 1-P

Gliseral- + Dihydroxi-
dehide

aceton P

ATP

Gliceraldehyde 3-P

ATP

3

Pi

1

Glucose 1-P

2

Glucose 6-P

6

UDP-galactose

UDP-Glucose

D-Mannosa

ATP

9

Mannosa 6-P

Fructose 6-P

10

Fructose 1,6-diP

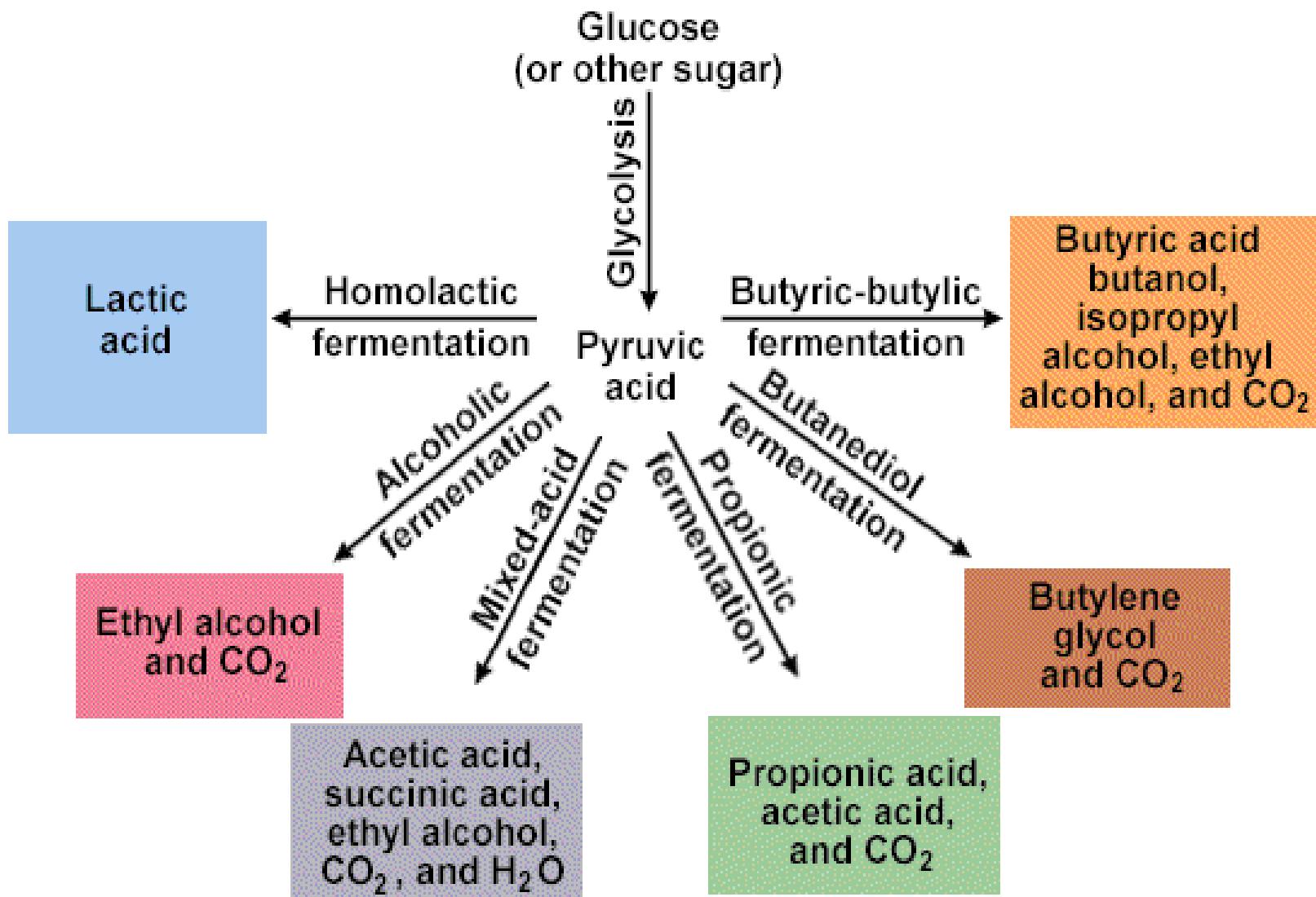
ATP

7

8



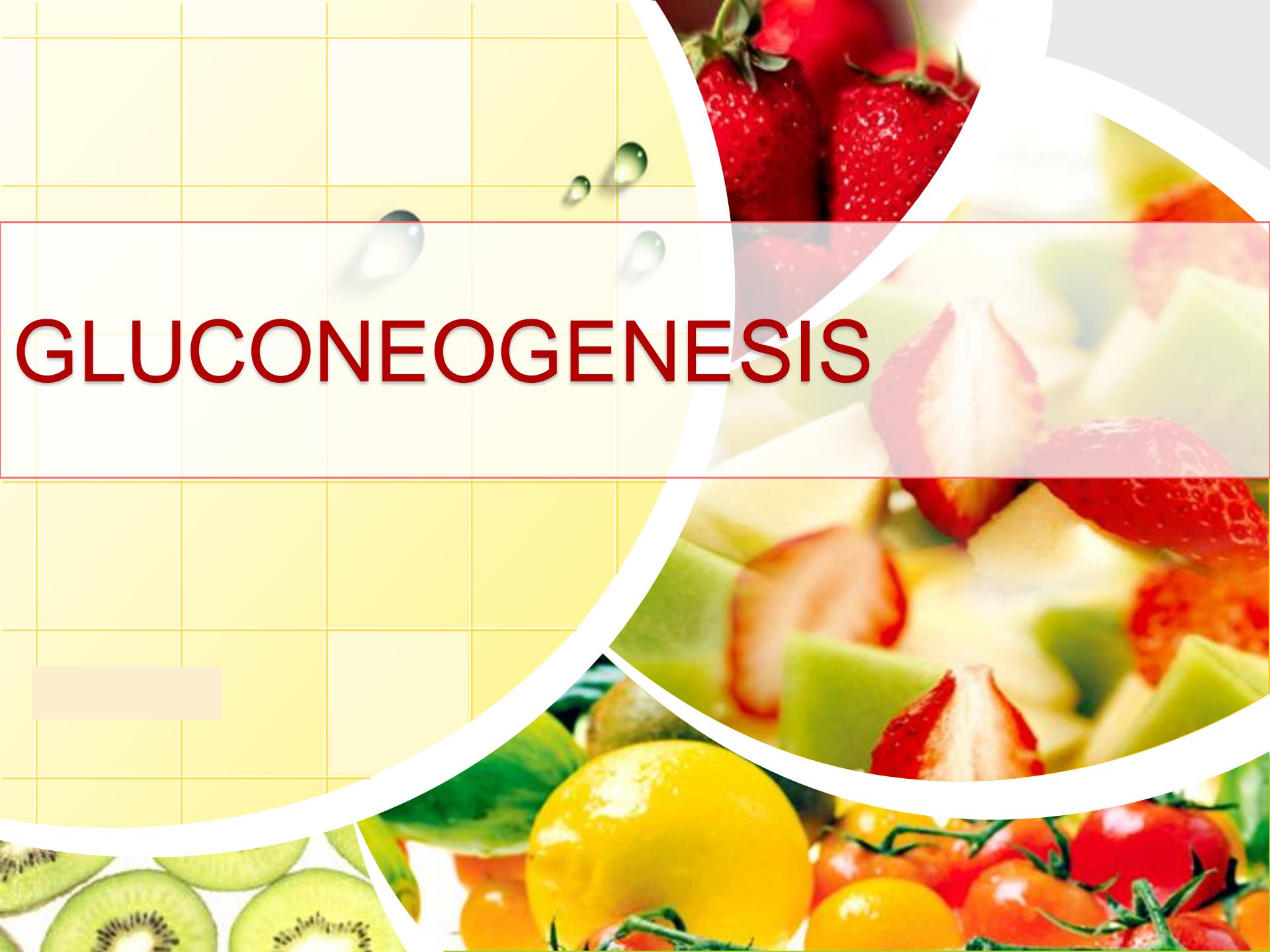
- The enzymes in the previous slide:
 1. phosphorylase
 2. phosphoglucomutase
 3. hexokinase
 4. fructokinase
 - 5 fructosephosphate aldolase
 6. hexokinase
 7. triosekinase
 8. triosephosphateisomerase
 9. hexokinase
 10. phosphomannoisomerase



AKHIR KULIAH DENGAN
POKOK BAHASA "Glikolisis"



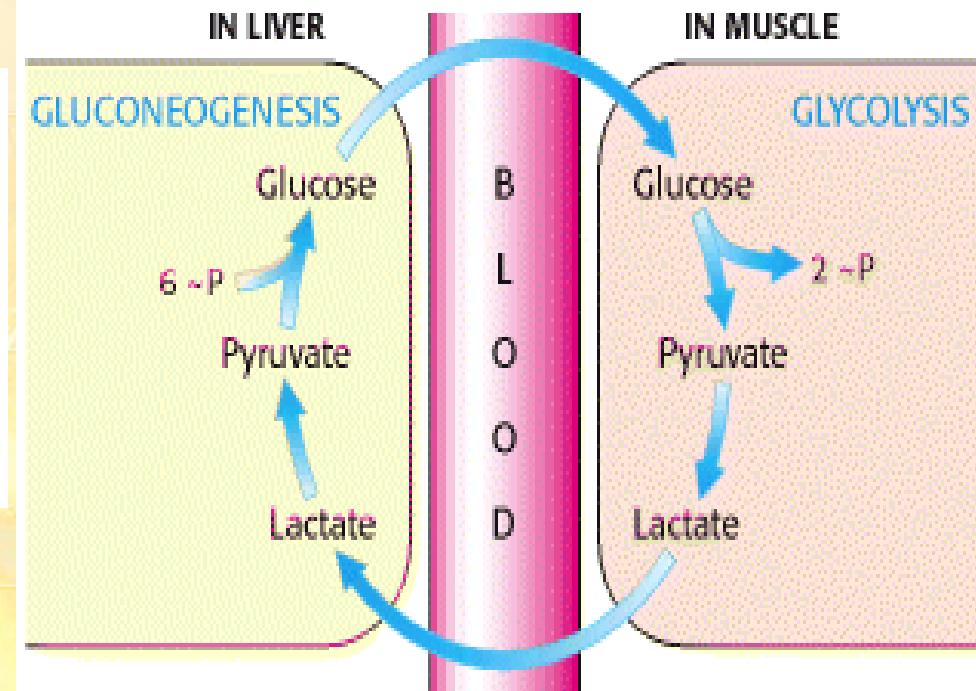
GLUCONEOGENESIS



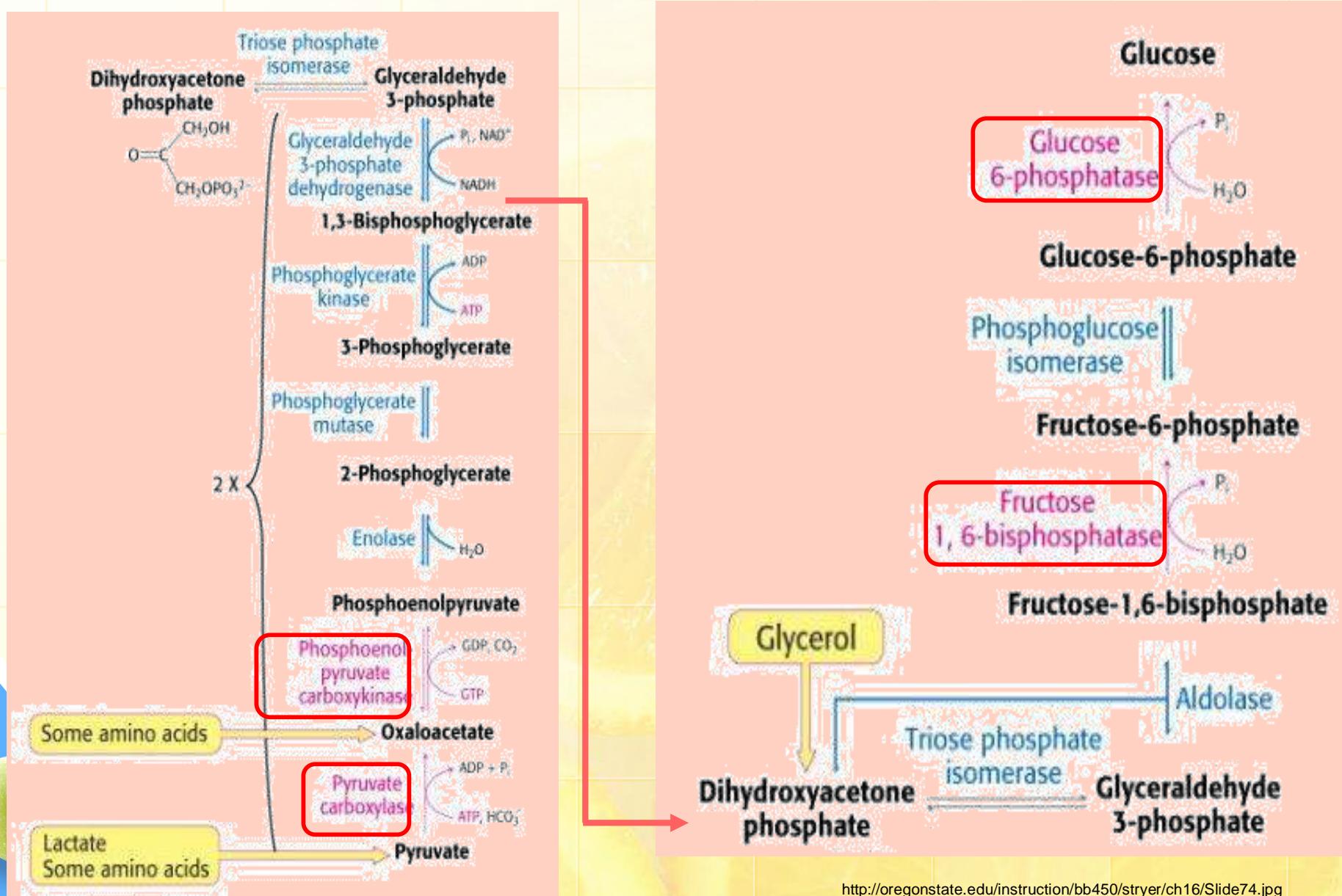
Gluconeogenesis

- Formation of new glucose molecules from noncarbohydrate precursors derived from muscle, adipose tissue: pyruvate and lactate (60%), amino acids (20%), glycerol (20%)
- Occurs primarily in the liver (90%) and sometimes in the kidney, brain, and Red Blood Cells

• Recall that steps 1, 3, and 10 of glycolysis are irreversible; therefore, these steps must be bypassed in gluconeogenesis



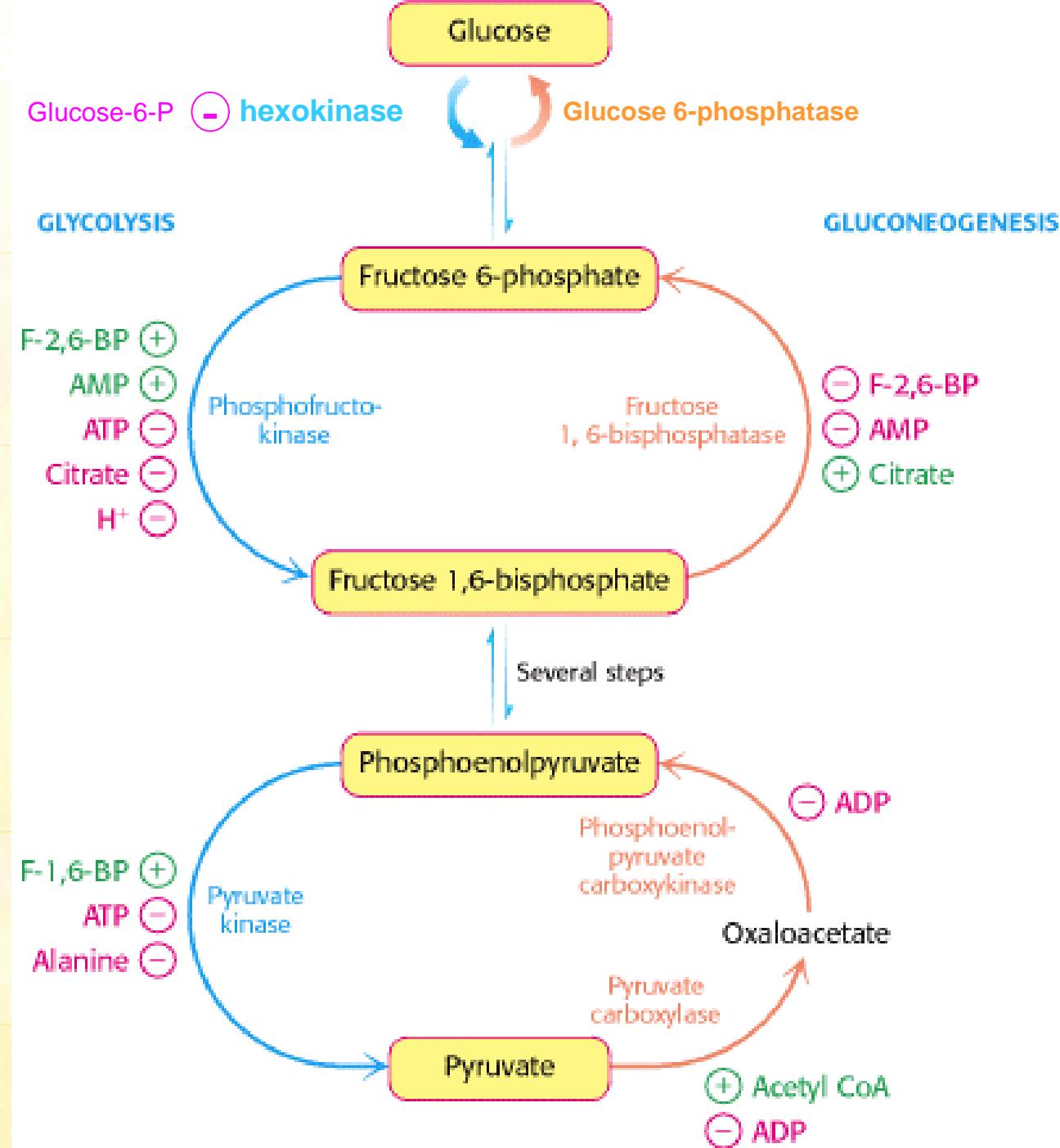
Gluconeogenesis



Converts pyruvate to glucose

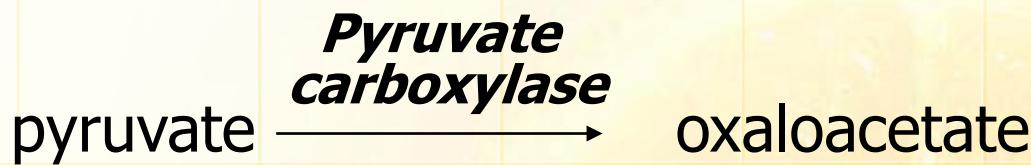
Gluconeogenesis utilizes unique enzymes (pyruvate carboxylase, PEPCK, fructose-1,6-bisphosphatase, and glucose-6-phosphatase) for irreversible reactions.

6 ATP equivalents are consumed in synthesizing 1 glucose from pyruvate in this pathway



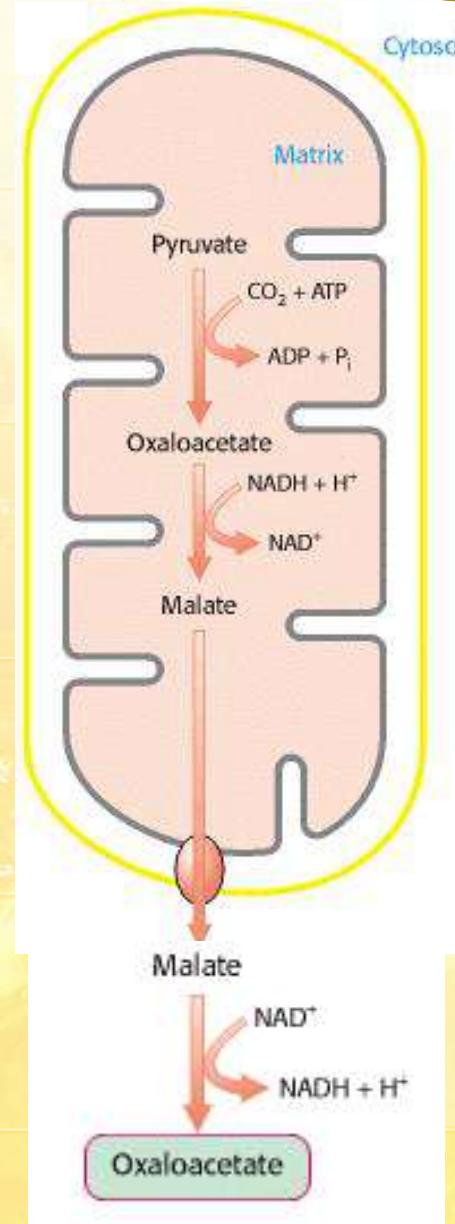
Irreversible steps in gluconeogenesis

- First step by a gluconeogenic-specific enzyme occurs in the mitochondria



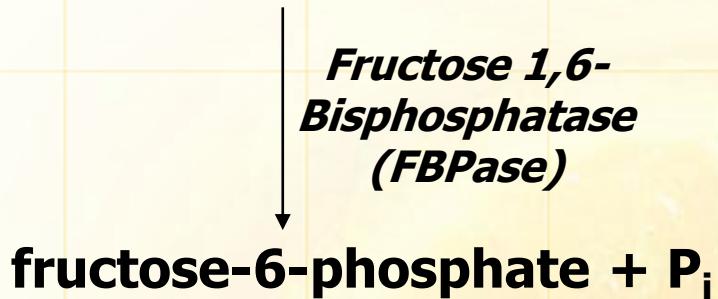
- Once oxaloacetate is produced, it is reduced to malate so that it can be transported to the cytosol. In the cytosol, oxaloacetate is subsequently decarboxylated/phosphorylated by PEPCK (phosphoenolpyruvate carboxykinase), a second enzyme unique to gluconeogenesis.

The resulting phosphoenol pyruvate is metabolized by glycolysis enzymes in reverse, until the next irreversible step



Irreversible steps in gluconeogenesis (continued)

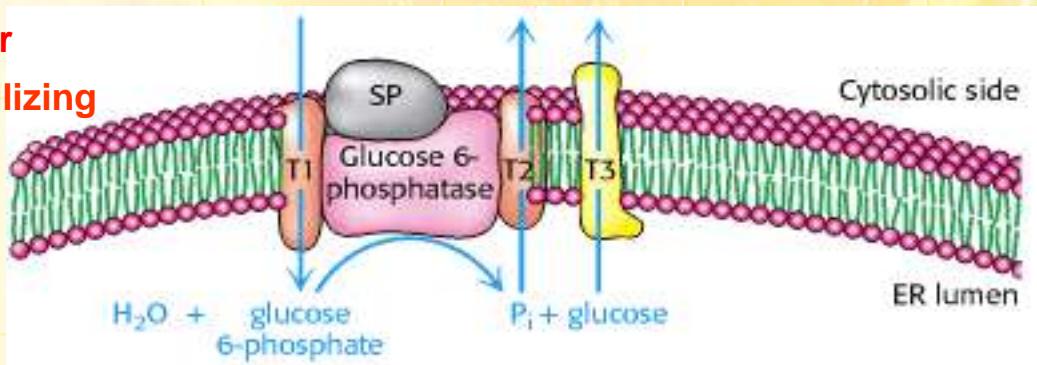
- Fructose 1,6-bisphosphate + H₂O



- In liver, glucose-6-phosphate can be dephosphorylated to glucose, which is released and transported to other tissues. This reaction occurs in the lumen of the endoplasmic reticulum.

Requires 5 proteins!

- 1) G-6-P transporter
- 2) Ca-binding stabilizing protein (SP)
- 3) G-6-Pase

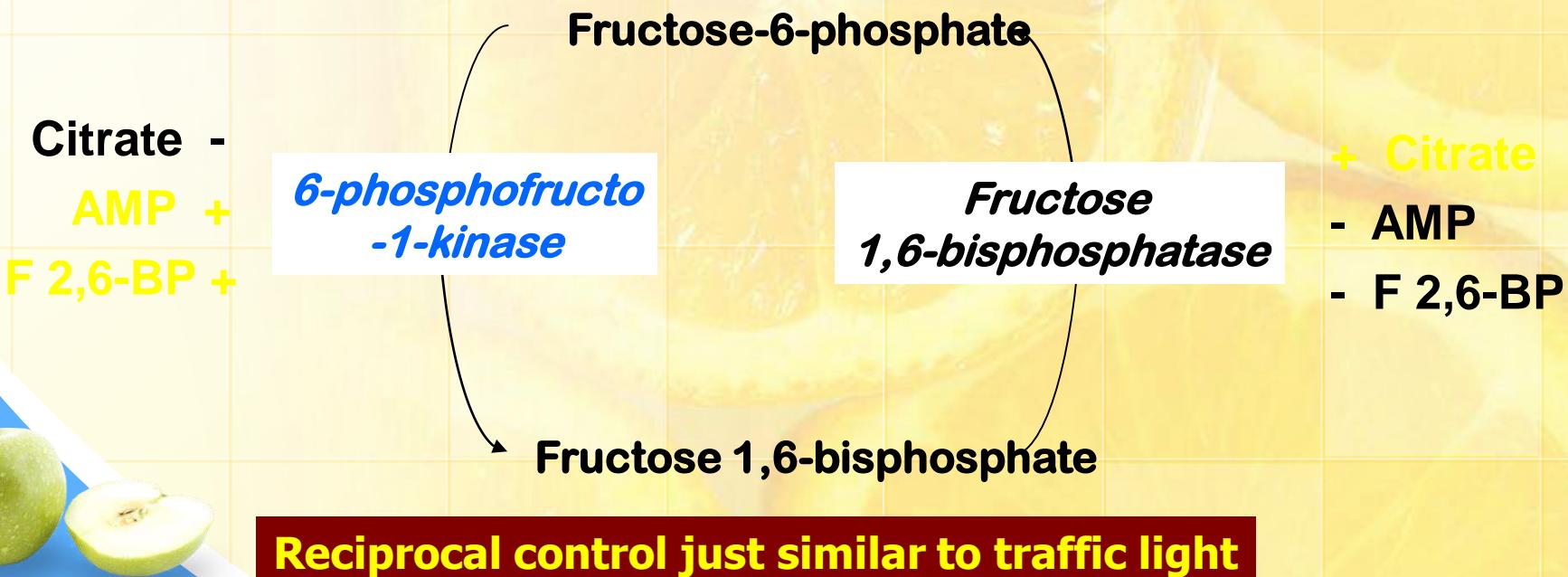


- 4) Glucose transporter
- 5) P_i transporter



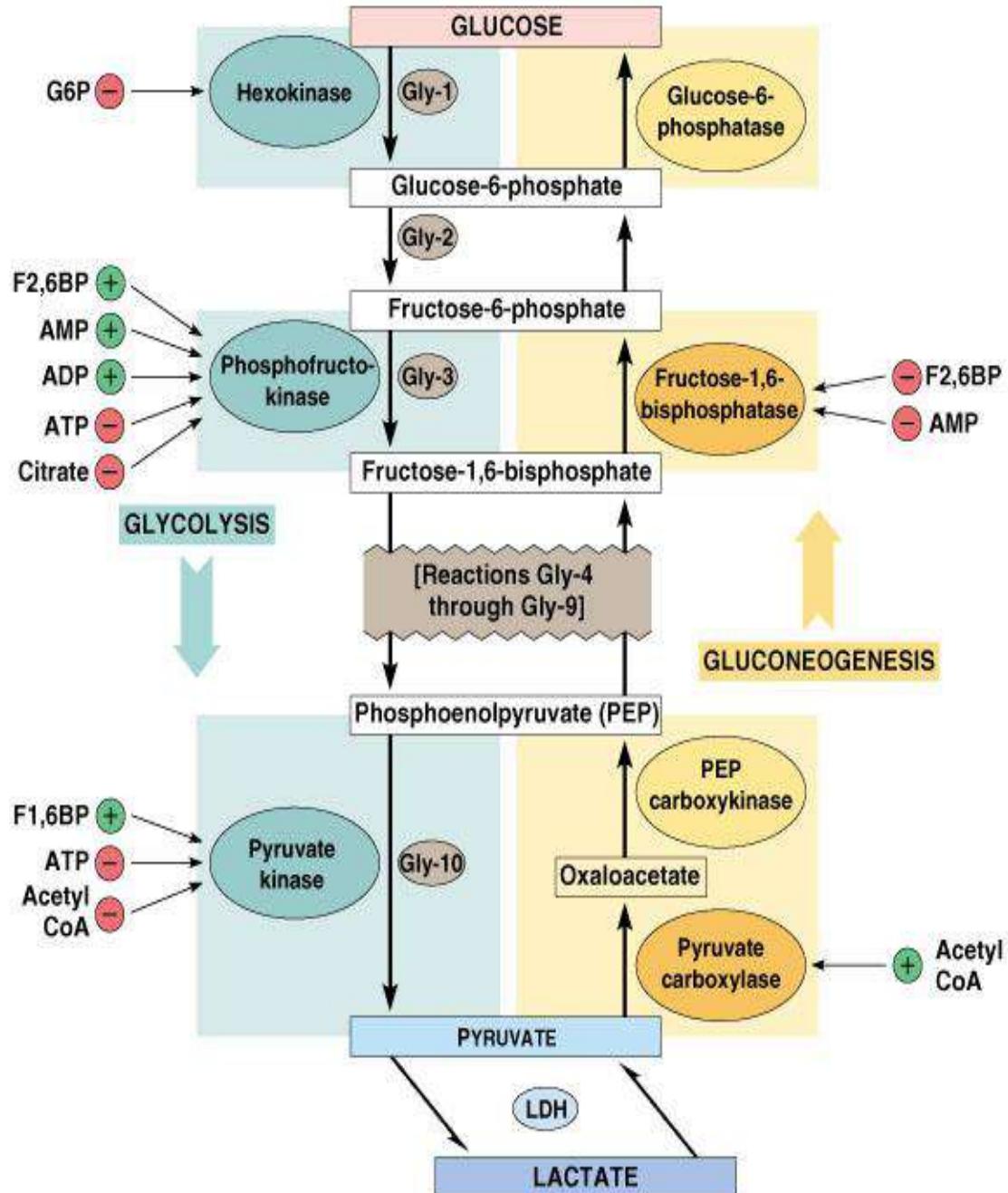
Gluconeogenesis and Glycolysis are reciprocally regulated

- Fructose 1,6-bisphosphatase is main regulatory step in gluconeogenesis.
- Corresponding step in glycolysis is 6-phosphofructo-1-kinase (PFK-1).
- These two enzymes are regulated in a reciprocal manner by several metabolites.



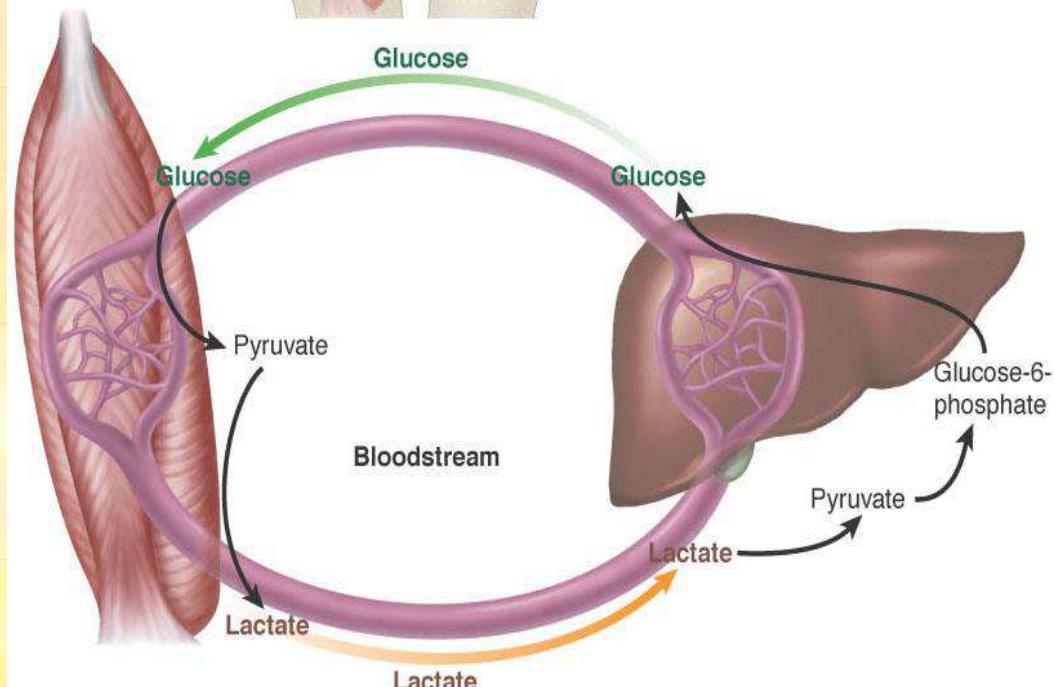
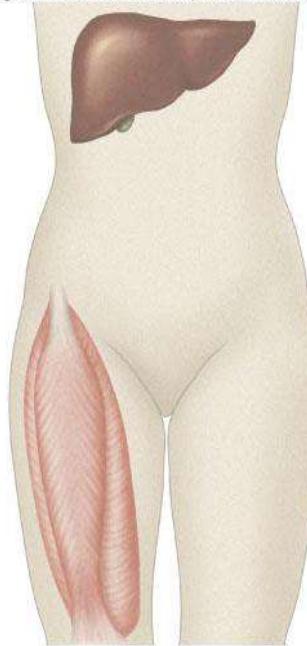
Regulation of Glycolysis/Gluconeogenesis

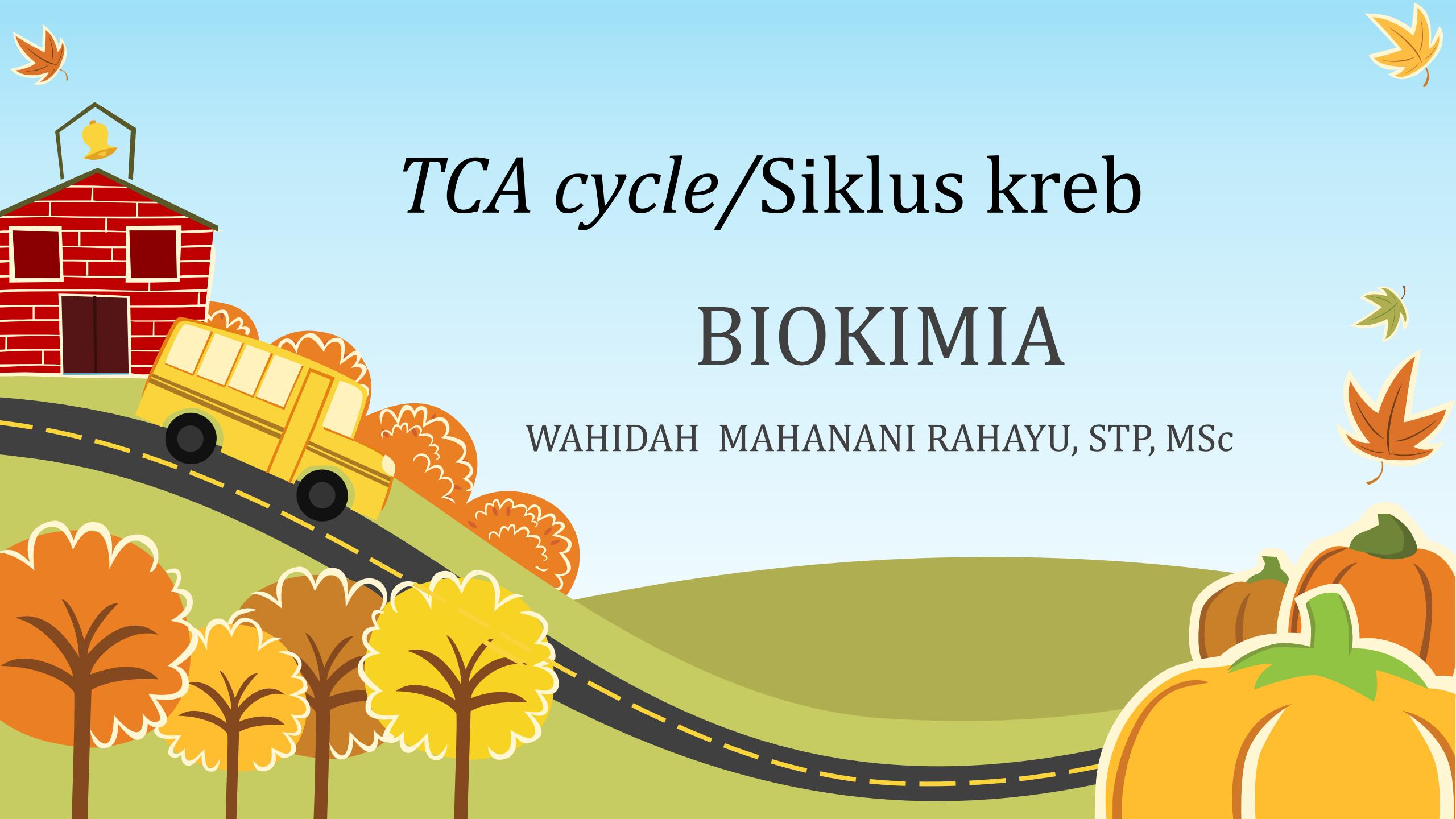
Regulated enzymes are unique to glycolysis or gluconeogenesis to allow independent regulation of each pathway



Cori Cycle

Lactate is transported from muscle to the liver where it is converted to pyruvate which then enters gluconeogenesis





TCA cycle/Siklus kreb

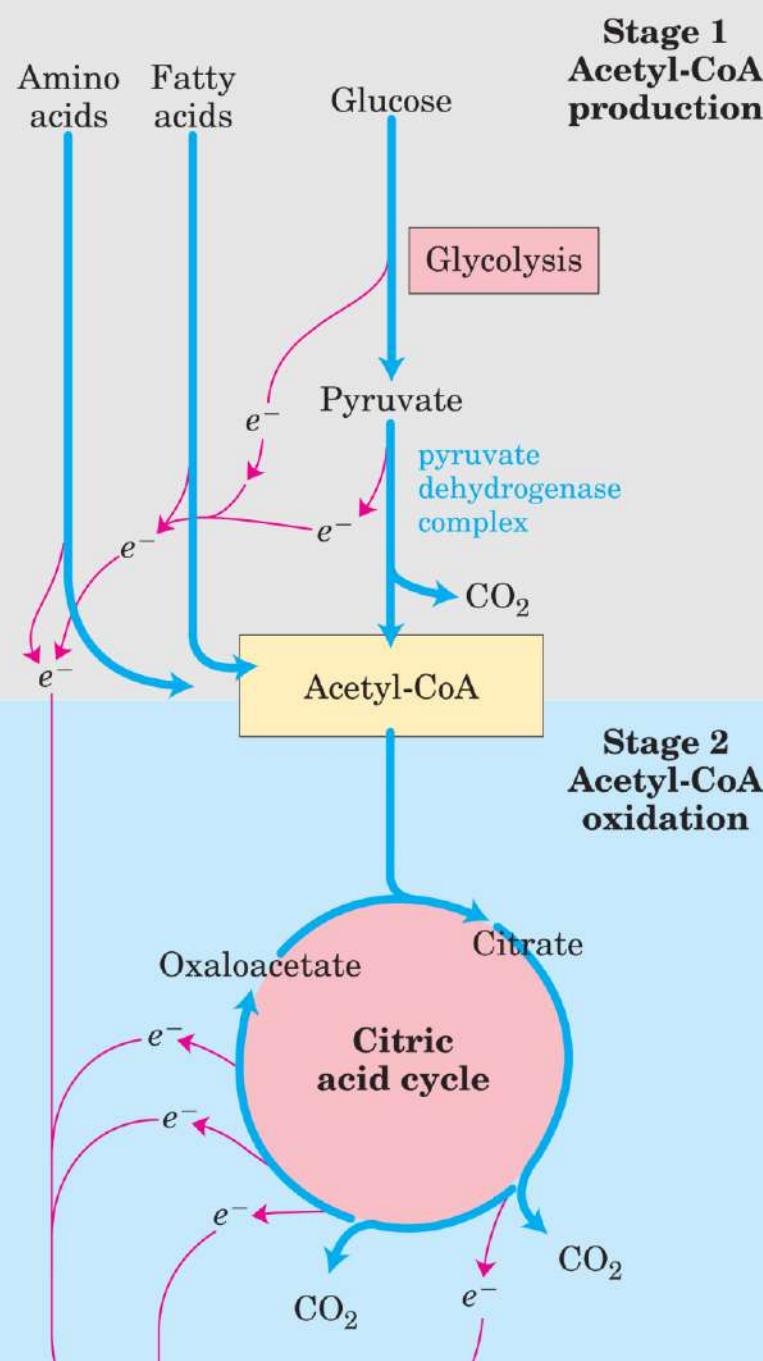
BIOKIMIA

WAHIDAH MAHANANI RAHAYU, STP, MSc



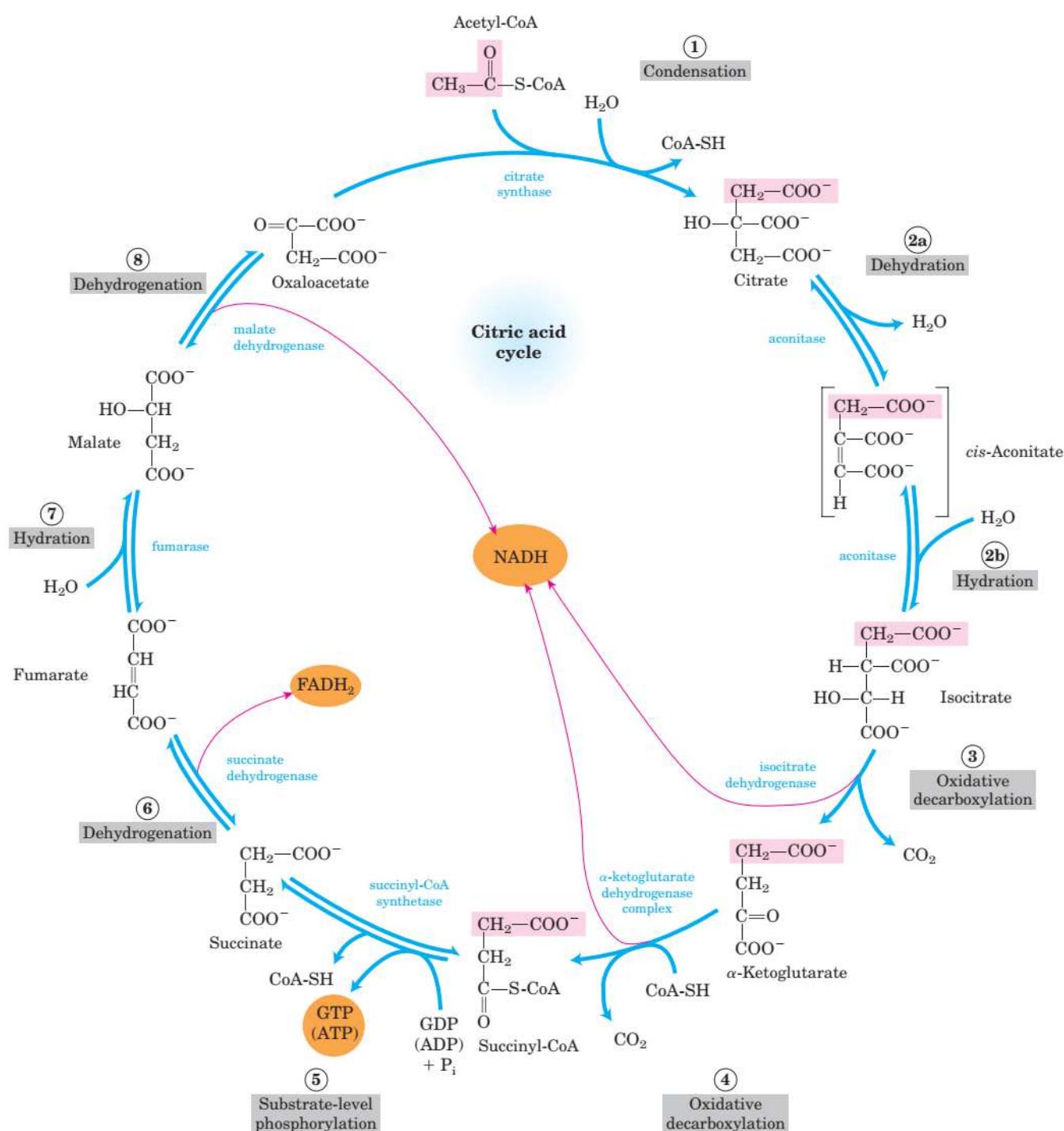
Siklus Kreb/Citric acid cycle

- **Catabolism of proteins, fats, and carbohydrates in the three stages of cellular respiration.**
- Stage 1: oxidation of fatty acids, glucose, and some amino acids yields acetyl-CoA.
- Stage 2: oxidation of acetyl groups in the citric acid cycle includes four steps in which electrons are abstracted.
- Stage 3: electrons carried by NADH and FADH₂ are funneled into a chain of mitochondrial (or, in bacteria, plasma membrane-bound) electron carriers—the respiratory chain—ultimately reducing O₂ to H₂O.
→ This electron flow drives the production of ATP.





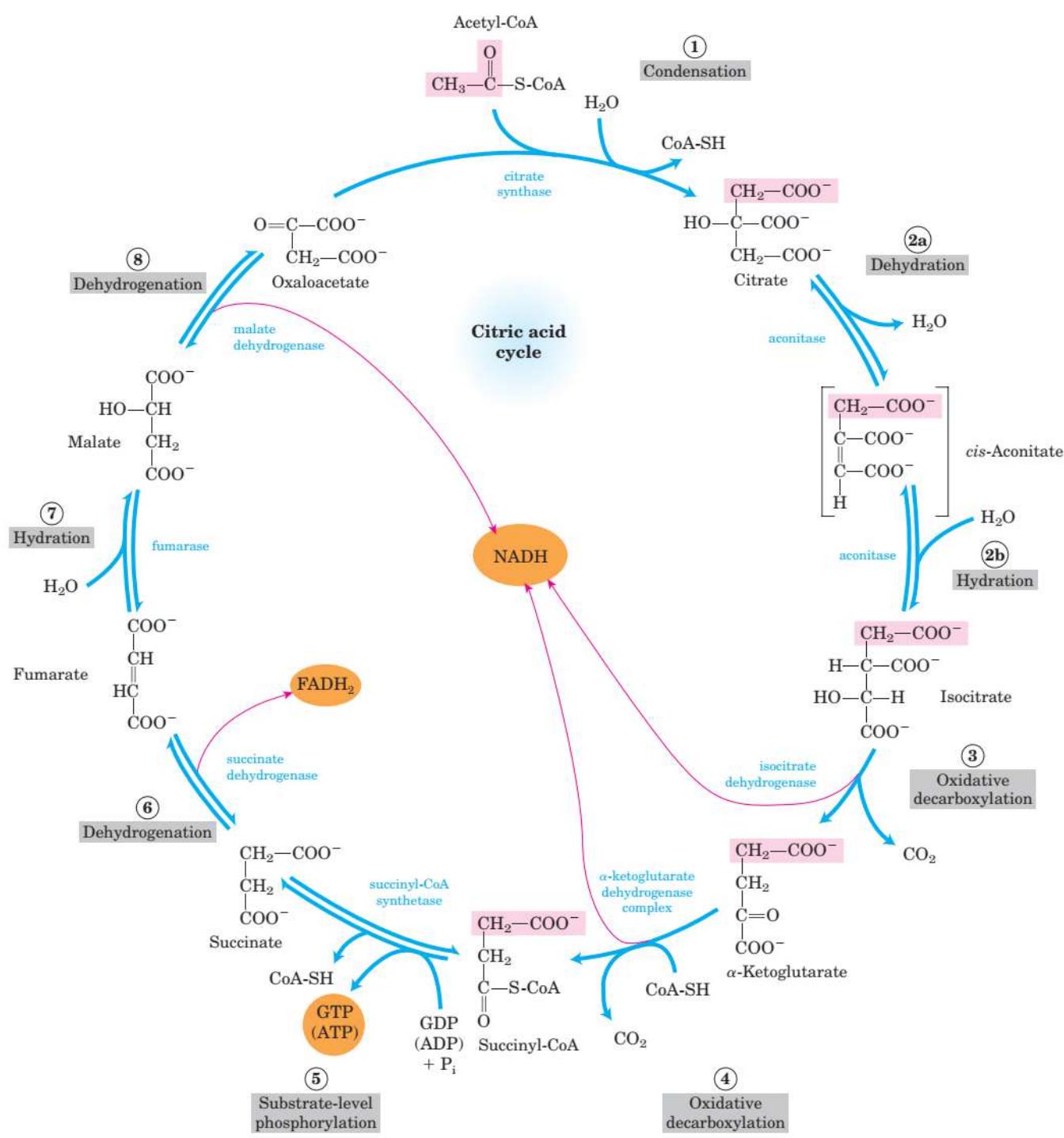
More details of the cycle



Reactions of the citric acid cycle.

- The carbon atoms **in pink** → derived from acetate of acetyl-CoA → these are *not* the carbons released as CO₂ in the first turn.
- The red arrows** show where energy is conserved by electron transfer to FAD or NAD⁺ forming FADH₂ or NADH + H⁺
- Steps 1, 3, and 4 are essentially irreversible in the cell; all other steps are reversible.
- Product of step 5 → either ATP or GTP, depending on which succinyl-CoA synthetase isozyme is the catalyst

The cycle steps



- The Citric Acid Cycle Has Eight Steps

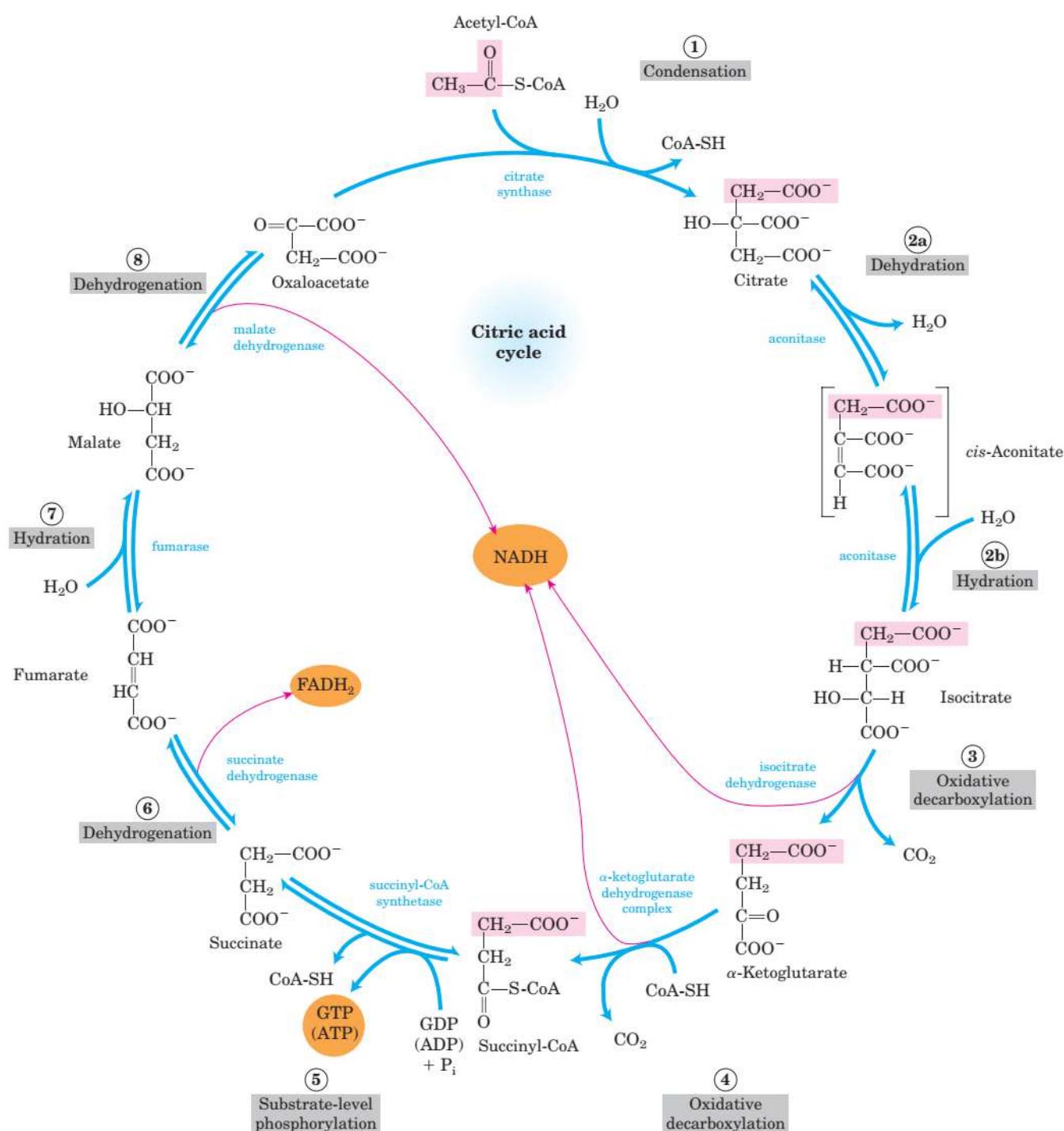
1. Formation of Citrate

The first reaction of the cycle is the **condensation of acetyl-CoA with oxaloacetate to form citrate**, catalyzed by **citrate synthase**

2. Formation of Isocitrate via cis-Aconitate

aconitase enzyme (formally: aconitate hydratase) catalyzes **the reversible transformation of citrate to isocitrate**, through the intermediary formation of the tricarboxylic acid **cis-aconitate**. Aconitase promotes the reversible addition of H₂O to the double bond of enzyme-bound *cis*-aconitate in two different ways, one leading to citrate and the other to isocitrate

The cycle steps



- The Citric Acid Cycle Has Eight Steps

3. *Oxidation of Isocitrate to α-Ketoglutarate and CO₂*

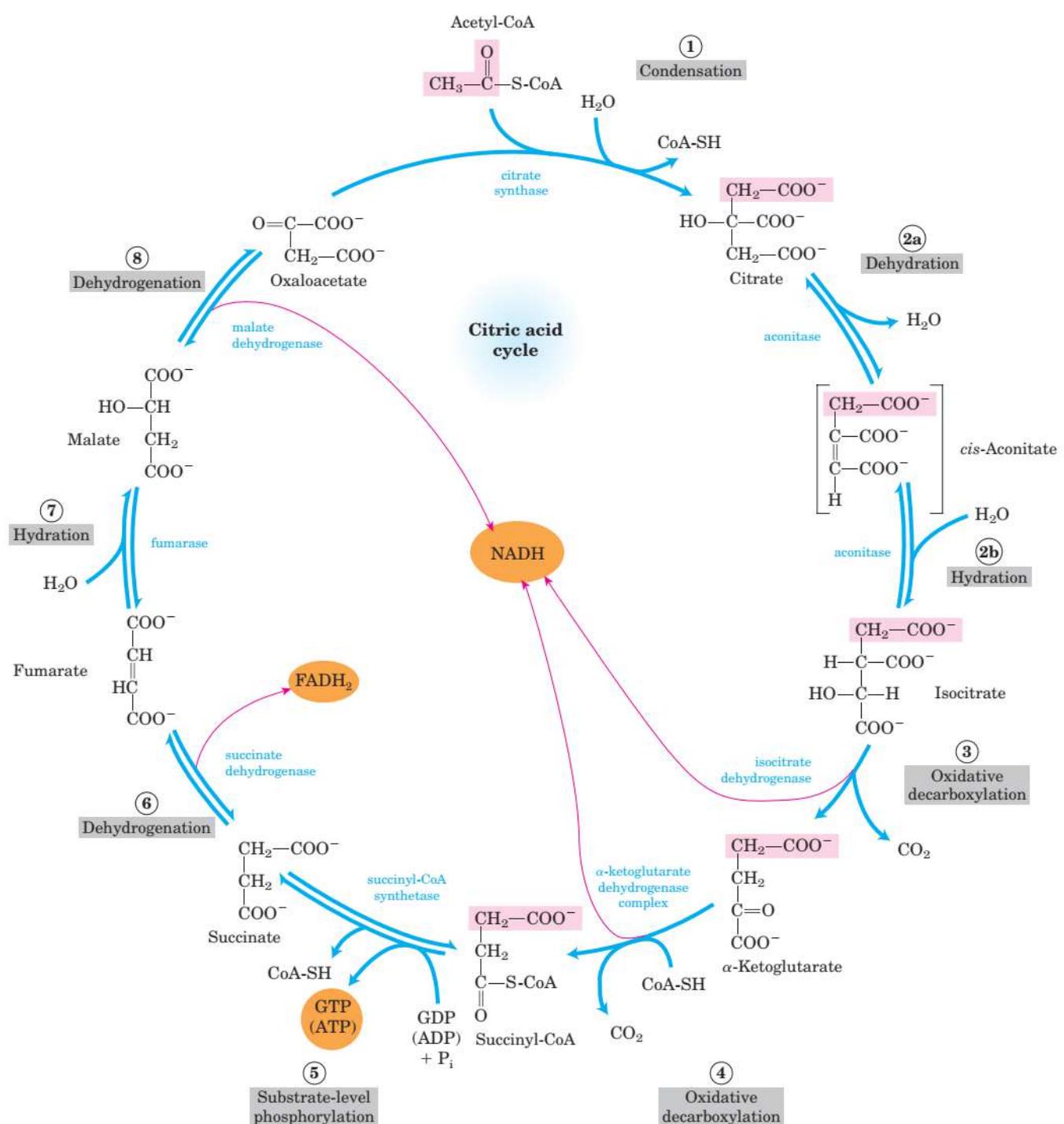
isocitrate → catalyze by **isocitrate dehydrogenase** through oxidative decarboxylation → to form **α - ketoglutarate**

Mn²⁺ in the enzyme active site interacts with the carbonyl group of oxalosuccinate → converts it to **α - ketoglutarate**.

4. *Oxidation of α - Ketoglutarate to Succinyl-CoA and CO₂*

oxidative decarboxylation → **α - ketoglutarate** is converted to **succinyl-CoA** and CO₂ by **α - ketoglutarate dehydrogenase complex**; NAD⁺ serves as electron acceptor and CoA as the carrier of the succinyl group.

The cycle steps



- The Citric Acid Cycle Has Eight Steps

5. Conversion of Succinyl-CoA to Succinate

Succinyl-CoA, like acetyl-CoA, has a thioester bond with a strongly negative standard free energy of hydrolysis (36 kJ/mol).

6. Oxidation of Succinate to Fumarate

The succinate formed from succinyl-CoA is oxidized to **fumarate** by the flavoprotein **succinate dehydrogenase**

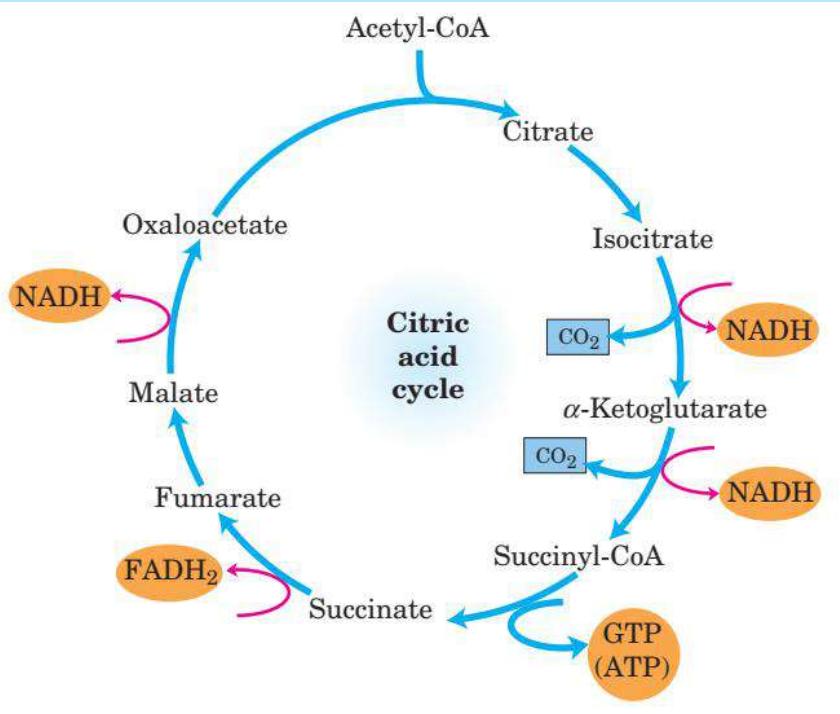
7. Hydration of Fumarate to Malate

The reversible hydration of fumarate to **L-malate** is catalyzed by **fumarase**

8. Oxidation of Malate to Oxaloacetate

In the last reaction of the citric acid cycle, NAD-linked **L-malate dehydrogenase** catalyzes the oxidation of L-malate to oxaloacetate

ENERGY PRODUCED BY THE CYCLE



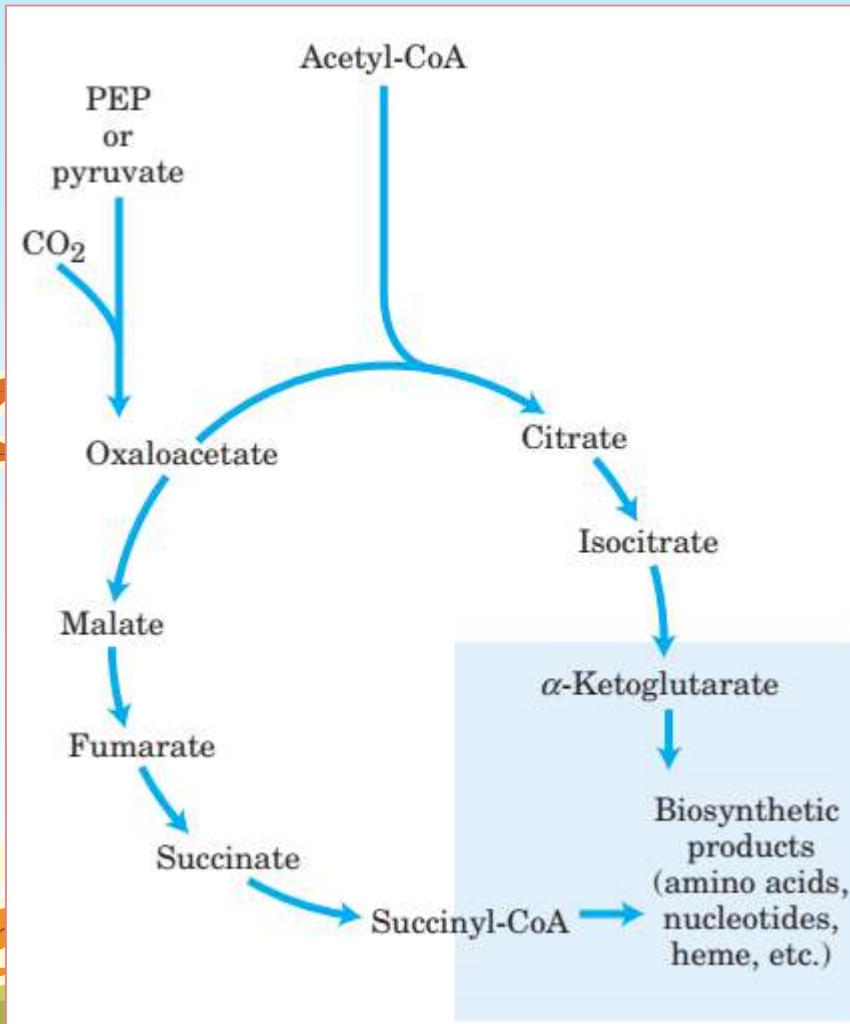
- A two-carbon acetyl group entered the cycle by combining with oxaloacetate.
- The energy released by these oxidations was conserved in the reduction of 3 NAD⁺ and 1 FAD, the production of 1 ATP or GTP. At the end of the cycle a molecule of oxaloacetate was regenerated.
- citric acid cycle directly generates only 1 ATP per turn (in the conversion of succinylCoA to succinate), 4 oxidation steps in the cycle provide large flow of electrons into the respiratory chain via NADH and FADH₂ and thus lead to formation of a large number of ATP molecules during oxidative phosphorylation
- energy yield from 1 molecule of glucose → 2 pyruvate molecules in glycolysis → 2 ATP and 2 NADH
- In oxidative phosphorylation, passage of 2 electrons from NADH to O₂ drives the formation of about 2.5 ATP, and passage of two electrons from FADH₂ to O₂ yields about 1.5 ATP.

ENERGY PRODUCED BY THE 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 |

Citric Acid Cycle components are important biosynthetic intermediates

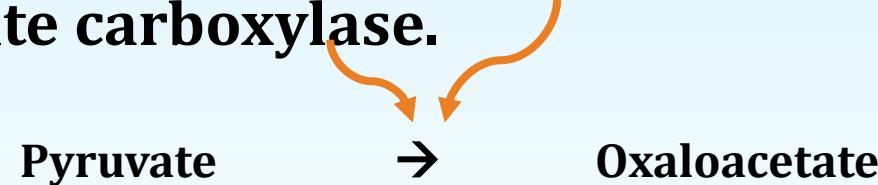


- Besides oxidative catabolism of carbohydrates, fatty acids, and amino acids, the cycle **provides precursors for many biosynthetic pathways**.
- α -Ketoglutarate and oxaloacetate → aspartate and glutamate amino acids by precursors transamination.
- aspartate and glutamate → used to build other amino acids → purine and pyrimidine nucleotides.
- Oxaloacetate is converted to glucose in gluconeogenesis
- SuccinylCoA → synthesis of the porphyrin ring of heme groups, which serve as oxygen carriers (in hemoglobin and myoglobin) and electron carriers.
- Citrate produced in some organisms is used commercially for a variety of purposes.

Anaplerotic Reactions

replenish citric acid cycle intermediates

- Intermediates of the citric acid cycle → removed to serve as biosynthetic precursors → replenished by **anaplerotic reactions**
- Conversion of either pyruvate or phosphoenolpyruvate to oxaloacetate or malate.
- Most important anaplerotic reaction in mammalian liver and kidney → reversible carboxylation of pyruvate by CO_2 to form oxaloacetate, catalyzed by **pyruvate carboxylase**.



- Citric acid cycle deficient in oxaloacetate or any other intermediates → pyruvate carboxylation to produce more oxaloacetate.

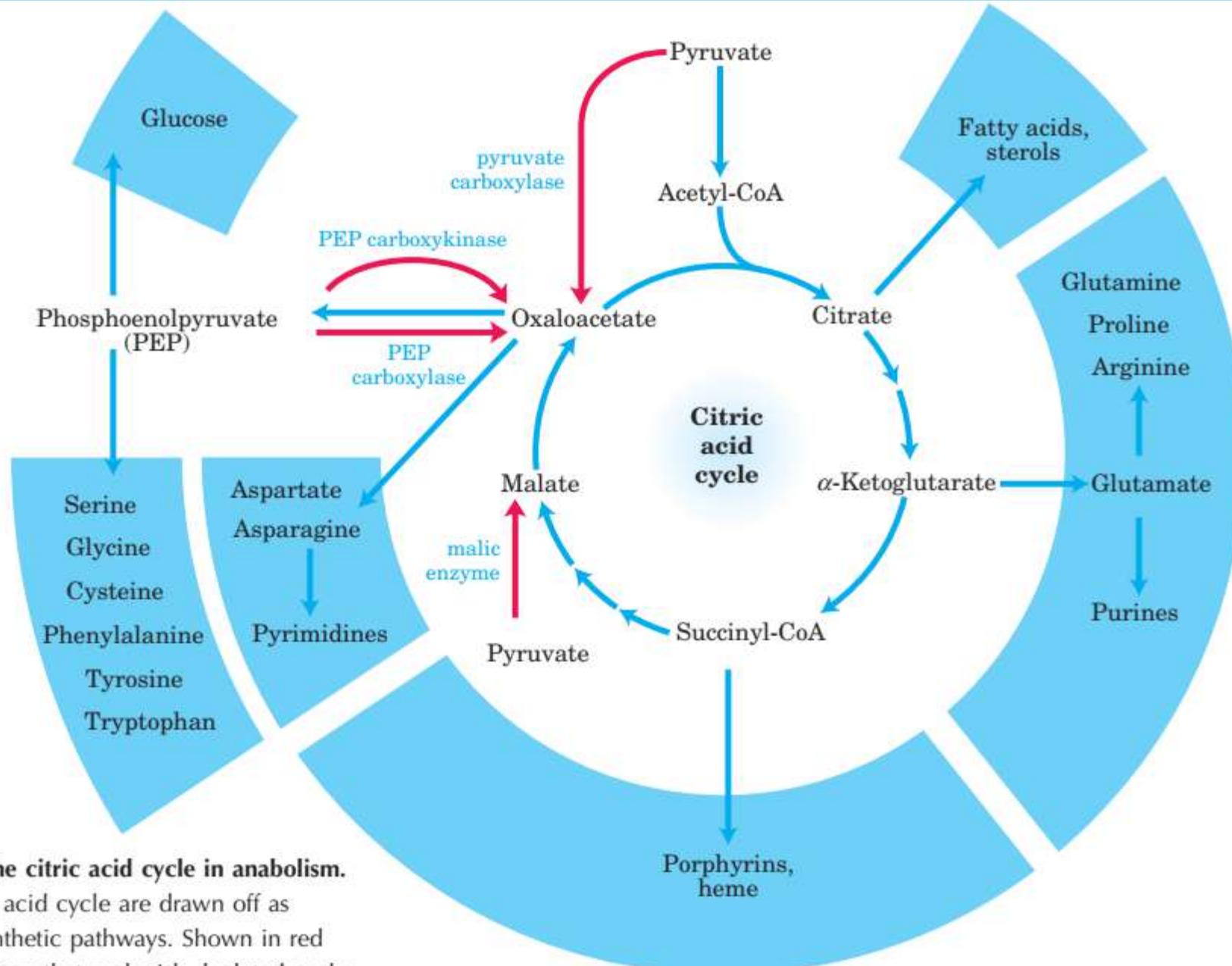


FIGURE 16-15 Role of the citric acid cycle in anabolism.

Intermediates of the citric acid cycle are drawn off as precursors in many biosynthetic pathways. Shown in red are four anaplerotic reactions that replenish depleted cycle intermediates (see Table 16-2).

Anaplerotic Reactions

replenish citric acid cycle intermediates

- Pyruvate carboxylase → regulatory enzyme → inactive in the absence of acetyl-CoA → needs biotin
- Whenever acetyl-CoA, the fuel for the citric acid cycle, is present → stimulates the pyruvate carboxylase reaction **to produce more oxaloacetate** → enabling the cycle to use more acetyl-CoA in the citrate synthase reaction.

TABLE 16-2 Anaplerotic Reactions

| Reaction | Tissue(s)/organism(s) |
|--|--|
| $\text{Pyruvate} + \text{HCO}_3^- + \text{ATP} \xrightleftharpoons{\text{pyruvate carboxylase}} \text{oxaloacetate} + \text{ADP} + \text{P}_i$ | Liver, kidney |
| $\text{Phosphoenolpyruvate} + \text{CO}_2 + \text{GDP} \xrightleftharpoons{\text{PEP carboxykinase}} \text{oxaloacetate} + \text{GTP}$ | Heart, skeletal muscle |
| $\text{Phosphoenolpyruvate} + \text{HCO}_3^- \xrightleftharpoons{\text{PEP carboxylase}} \text{oxaloacetate} + \text{P}_i$ | Higher plants, yeast, bacteria |
| $\text{Pyruvate} + \text{HCO}_3^- + \text{NAD(P)H} \xrightleftharpoons{\text{malic enzyme}} \text{malate} + \text{NAD(P)}^+$ | Widely distributed in eukaryotes and prokaryotes |

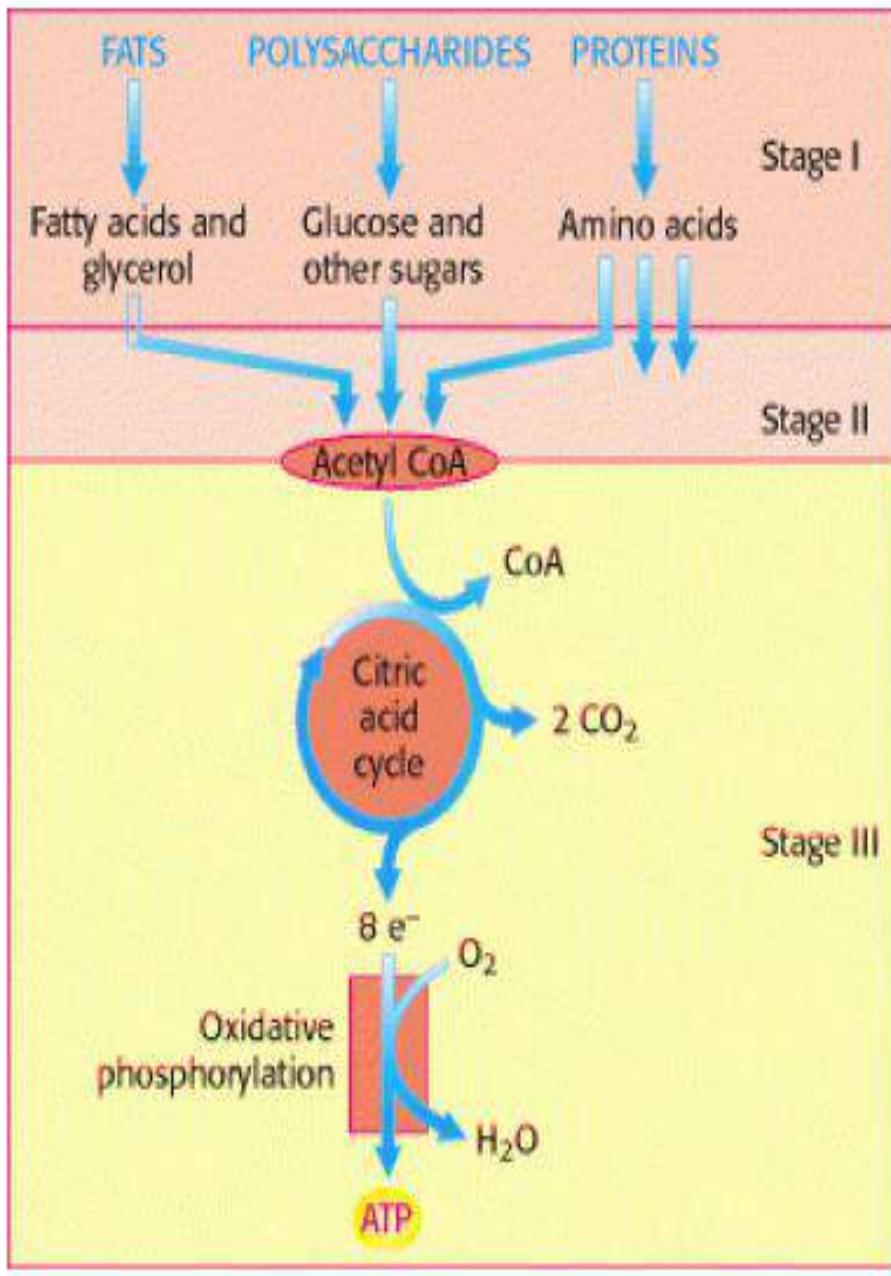
- Normal conditions, glycolysis and citric acid cycle rates are integrated so that only as much glucose is metabolized to pyruvate as is needed to supply the citric acid cycle with its fuel, the acetyl groups of acetyl-CoA.
- Pyruvate, lactate, and acetyl-CoA are normally maintained at steady-state concentrations.
- The rate of glycolysis is matched to the rate of the citric acid cycle
- Citrate, the product of the first step of the citric acid cycle, is an important allosteric inhibitor of phosphofructokinase-1 in the glycolytic pathway

Overview of Citric Acid Cycle (CAC)

1. Functions: harvesting of high-energy electrons from C2 fuels & provide precursors for synthesis
3. It removes electrons from acetyl CoA & uses them to form NADH & FADH_2 (high-energy electron carriers)
4. In oxidative phosphorylation, electrons from reoxidation of NADH & FADH_2 flow through a series of electron transport chain to generate a proton gradient
5. These protons then flow back to generate ATP
6. O_2 is the final electron acceptor at the end of the electron transport chain
7. The citric acid cycle + oxidative phosphorylation provide > 95% of energy used in human aerobic cells

Electron Transport Chain/Oxidative Phosphorilation





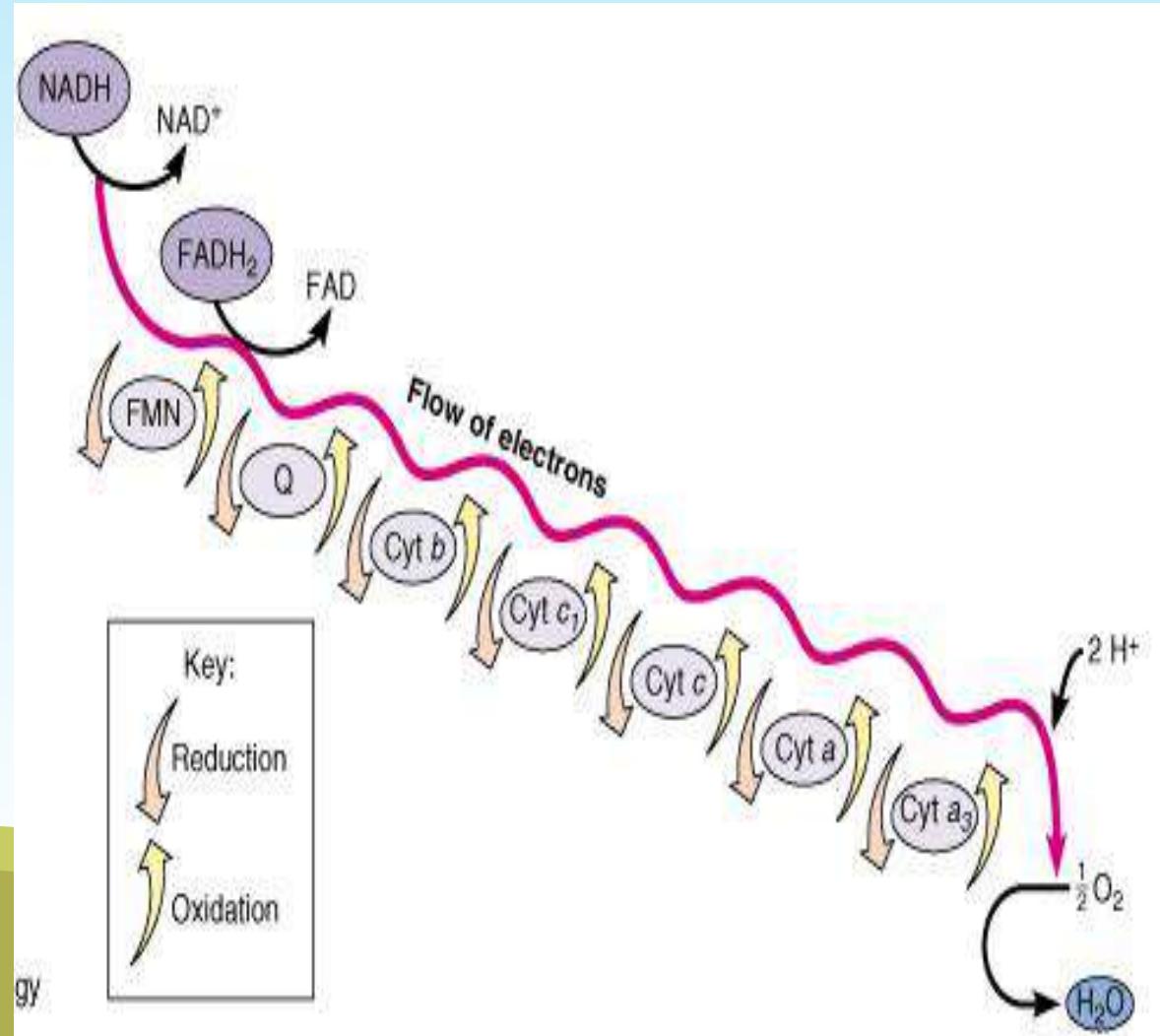
Lehninger (1982) :

- **STAGE 1** = mobilization of acetyl-CoA (from glucose, fatty acids, and some amino acids)
- **STAGE 2** = CAC cycle
- **STAGE 3** = oxidative phosphorylation

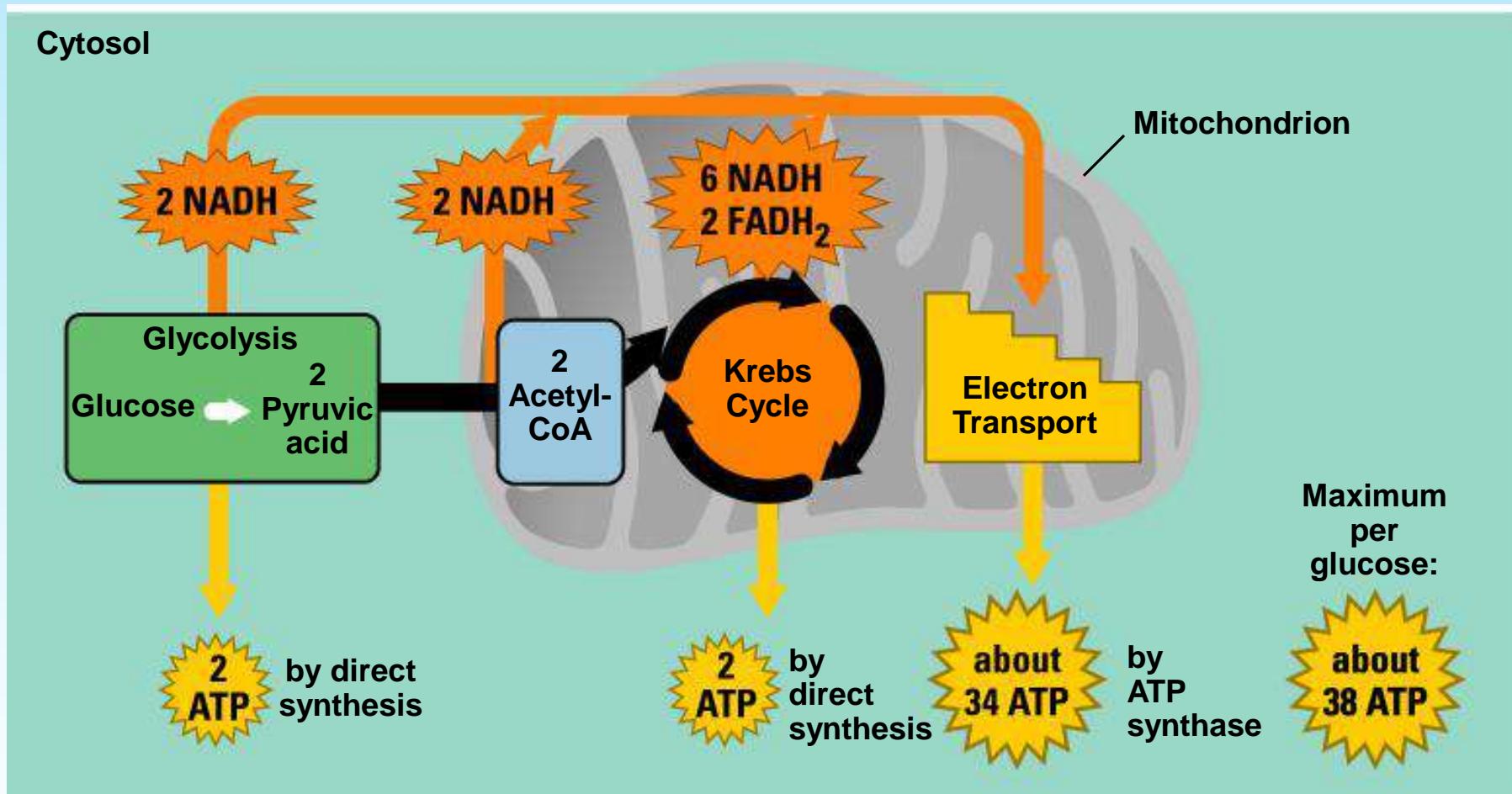
Figure 14.12. Stages of Catabolism. The extraction of energy from fuels can be divided into three stages.

Oxidative Phosphorylation

- Electrons are transferred from organic compounds through a series of electron carriers to O_2 or other oxidized inorganic or organic molecules
- The sequence of electron carriers is called the **electron transport chain**
- The transfer of electrons from one carrier to the next generates energy which is used to make ATP from ADP by **chemiosmosis**



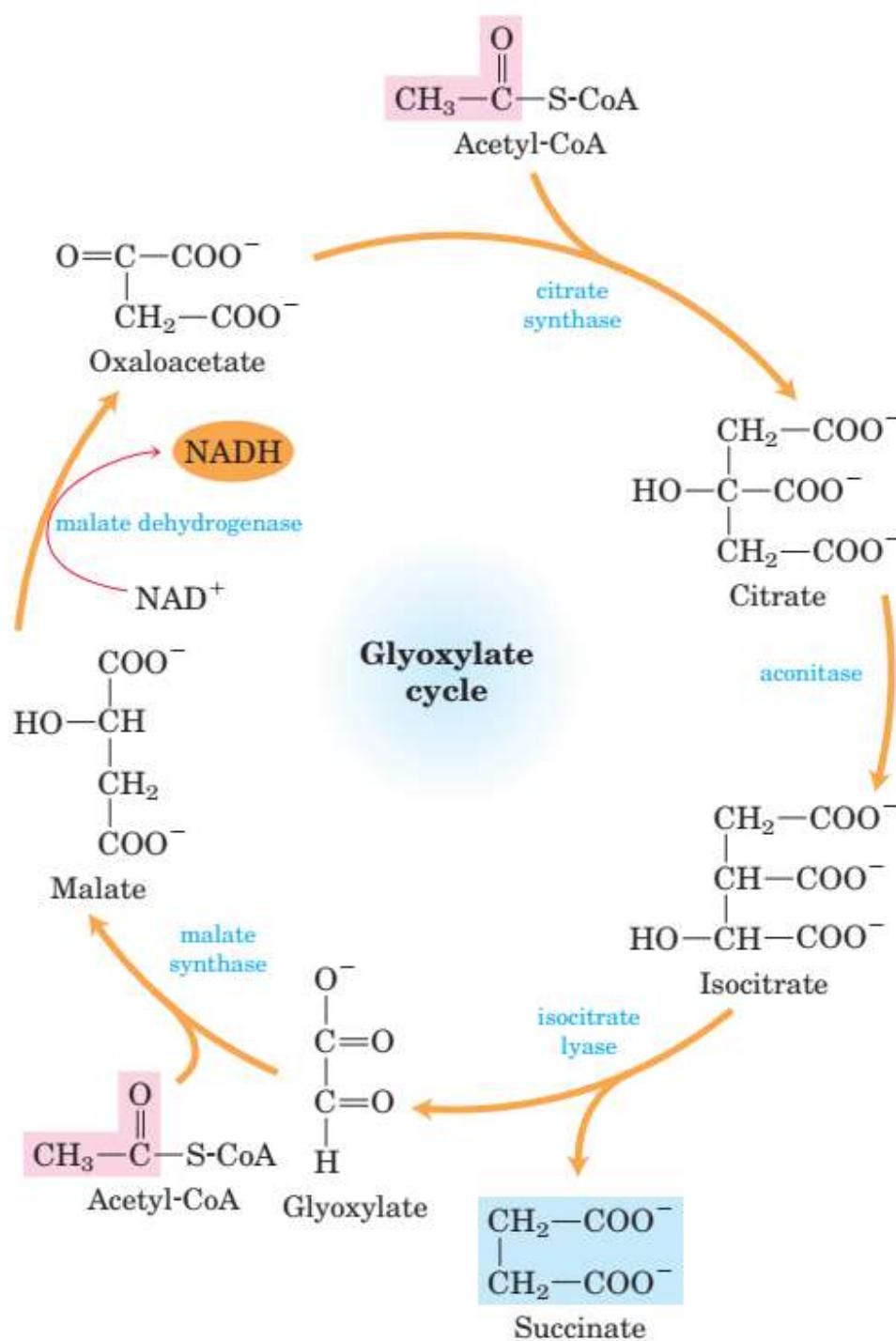
Energy Sum-Up from Cellular Respiration of 1 Glucose



The Glyoxylate Cycle

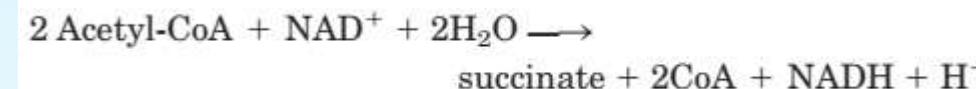


- The glyoxylate cycle is active in the germinating seeds of some plants and in certain microorganisms that can live on acetate as the sole carbon source. In plants, the pathway takes place in glyoxysomes in seedlings. It involves several citric acid cycle enzymes and two additional enzymes: isocitrate lyase and malate synthase.
- Vertebrates lack the glyoxylate cycle and cannot synthesize glucose from acetate or the fatty acids that give rise to acetyl-CoA.

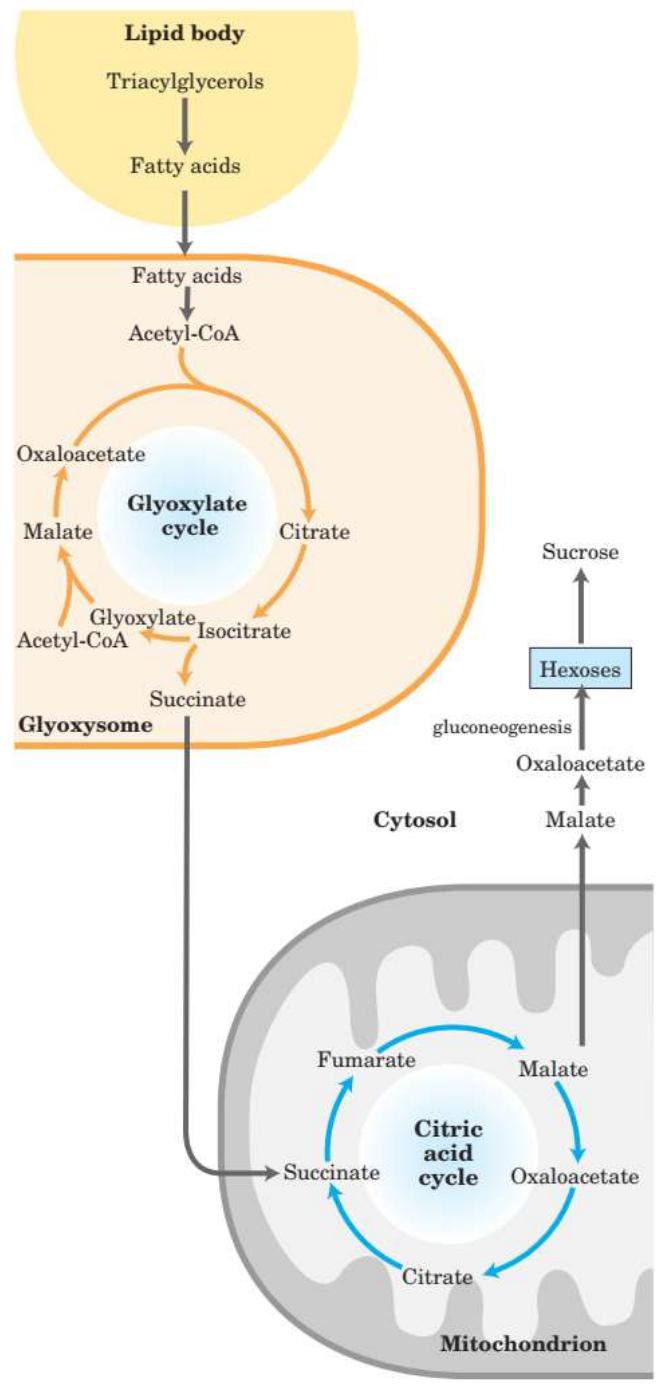


The Glyoxylate Cycle Produces Four-Carbon Compounds from Acetate

In plants, certain invertebrates, and some microorganisms (including *E. coli* and yeast) acetate can serve both as an energy-rich fuel and as a source of phosphoenolpyruvate for carbohydrate synthesis. In these organisms, enzymes of the **glyoxylate cycle** catalyze the net conversion of acetate to succinate or other four-carbon intermediates of the citric acid cycle



- In the glyoxylate cycle, acetyl-CoA condenses with oxaloacetate to form citrate, and citrate is converted to isocitrate, exactly as in the citric acid cycle.
- The next step, however, is not the breakdown of isocitrate by isocitrate dehydrogenase but the cleavage of isocitrate by **isocitrate lyase**, forming succinate and **glyoxylate**.
- glyoxylate → condenses with a second molecule of acetyl-CoA → malate, in a reaction catalyzed by **malate synthase**.
- Malate → oxidized to oxaloacetate → condense with another molecule of acetyl-CoA → start another turn of the cycle
- Each turn of the glyoxylate cycle consumes two molecules of acetyl-CoA and produces one molecule of succinate, which is then available for biosynthetic purposes.
- The succinate → converted into oxaloacetate, which can then be converted to phosphoenolpyruvate by PEP carboxykinase, and thus to glucose by gluconeogenesis.

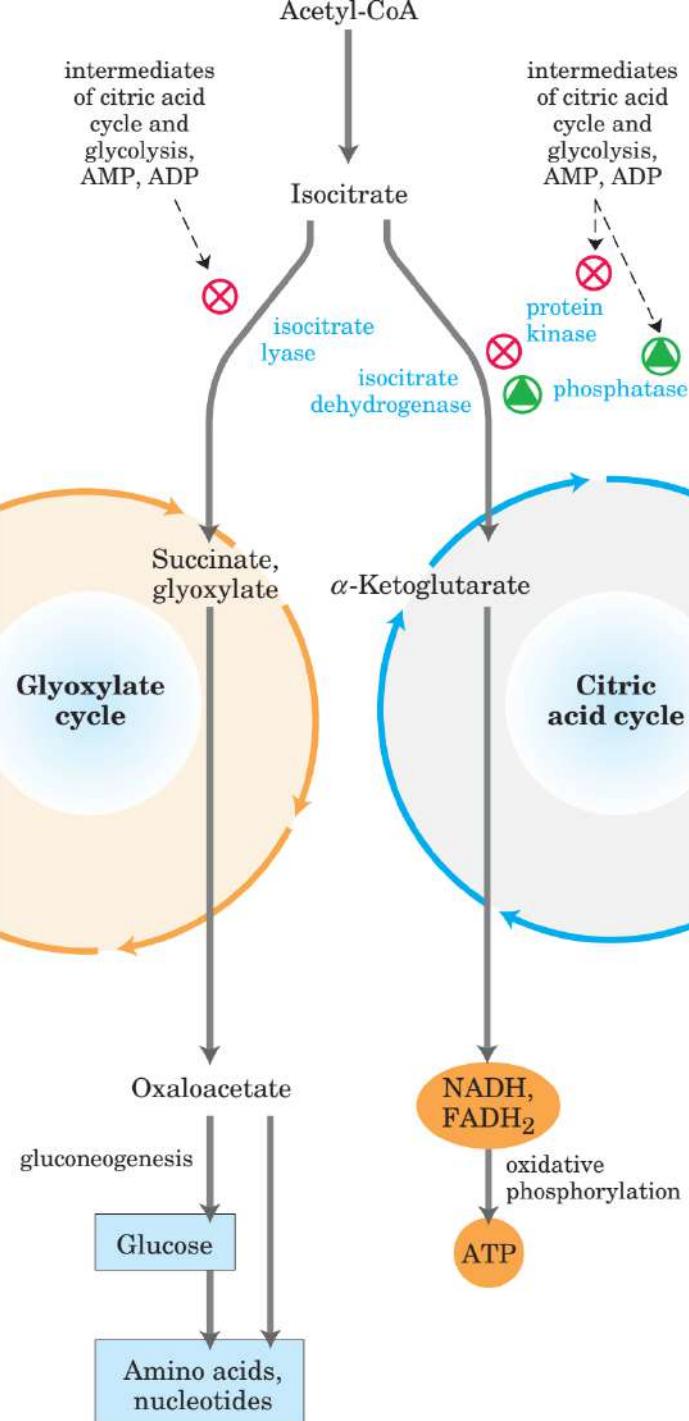


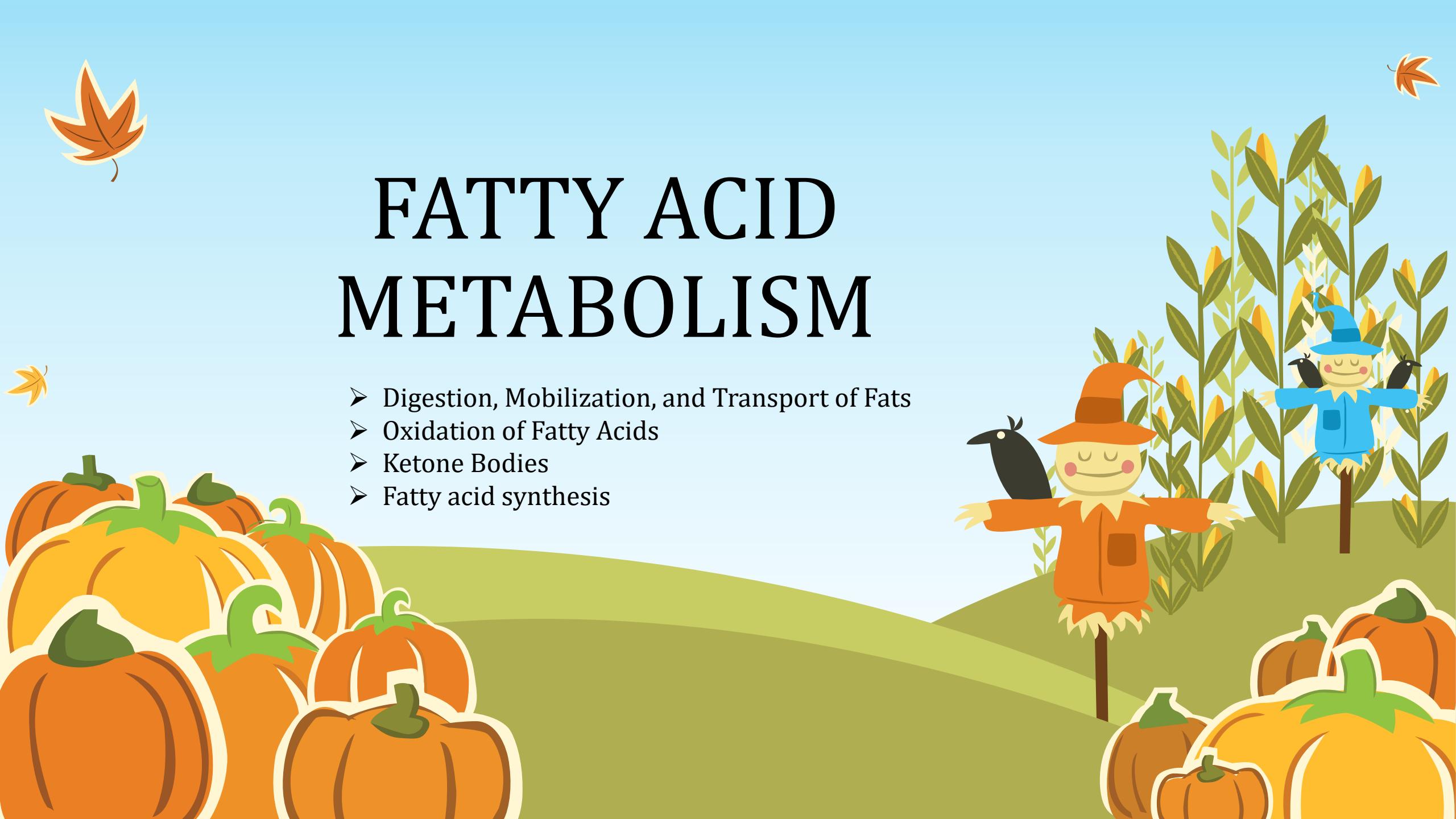
- **Relationship between the glyoxylate and citric acid cycles.**

- The reactions of the glyoxylate cycle (in glyoxysomes) proceed simultaneously with, and mesh with, those of the citric acid cycle (in mitochondria), as intermediates pass between these compartments. The conversion of succinate to oxaloacetate is catalyzed by citric acid cycle enzymes.

- **Coordinated regulation of glyoxylate and citric acid cycles.**

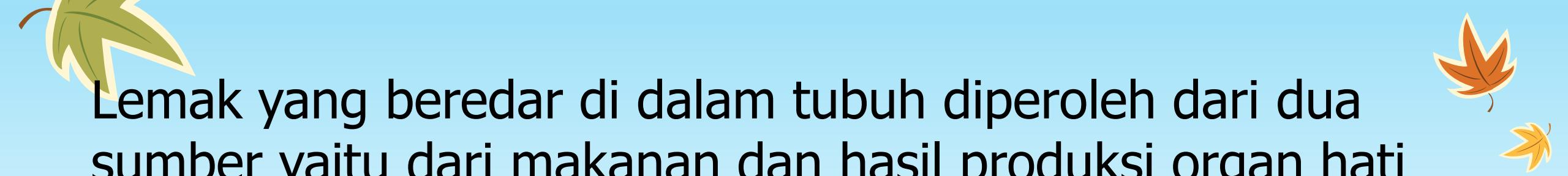
- Regulation of isocitrate dehydrogenase activity determines the partitioning of isocitrate between the glyoxylate and citric acid cycles.
- When the enzyme is inactivated by phosphorylation (by a specific protein kinase), isocitrate is directed into biosynthetic reactions via the glyoxylate cycle.
- When the enzyme is activated by dephosphorylation (by a specific phosphatase), isocitrate enters the citric acid cycle and ATP is produced.





FATTY ACID METABOLISM

- Digestion, Mobilization, and Transport of Fats
- Oxidation of Fatty Acids
- Ketone Bodies
- Fatty acid synthesis



Lemak yang beredar di dalam tubuh diperoleh dari dua sumber yaitu dari makanan dan hasil produksi organ hati (Guyton, 2007).



Lemak yang terdapat dalam makanan akan diuraikan menjadi kolesterol, trigliserida, fosfolipid dan asam lemak bebas pada saat dicerna dalam usus.

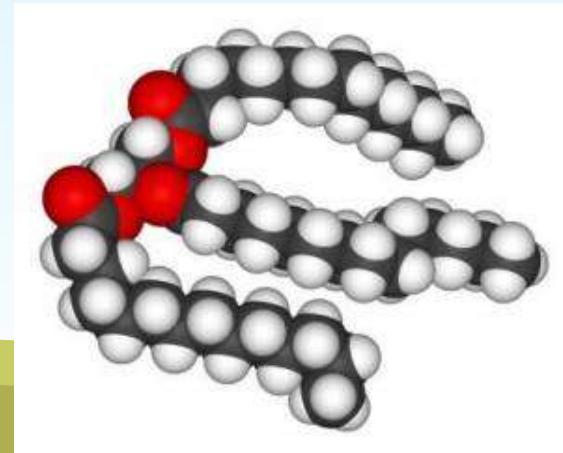
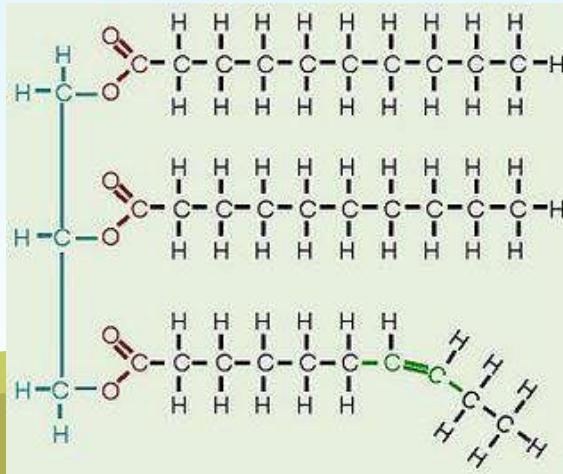


Keempat unsur lemak ini akan diserap dari usus dan masuk ke dalam darah.

1. **Trigliserida** (atau lebih tepatnya **triasilgliserol** atau triasilgliserida) adalah ester gliserol dengan tiga asam lemak.

Asam lemak yang biasanya dikenal adalah asam oleat, asam palmitat, atau stearat (ketiganya merupakan salah satu komponen asam lemak pada lemak jaringan tubuh).

- Lemak di dalam tubuh disimpan dalam kelompok jaringan ikat yaitu **jaringan adiposa (lemak)** yang menyebar di seluruh tubuh
- **Trigliserida:** penyusun utama minyak nabati dan lemak hewani.



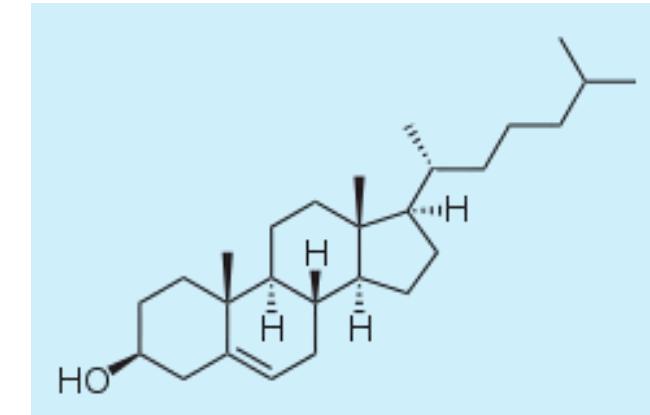
2. Kolesterol

Sterol adalah bagian dari *steroid*, dan merupakan substansi mirip lemak.

Kolesterol → bahasa yunani “kole (*chole*)” → berarti empedu.

Kolesterol merupakan sejenis sterol yang tinggi pada hewan dan merupakan prekursor asam empedu dan hormon steroid serta komponen penting dalam membran sel.

Kolesterol dihasilkan di hati dan jaringan lain, namun dapat juga berasal dari asupan makanan sehari-hari.



Kolesterol diangkut dalam plasma darah oleh lipoprotein (lipid kombinasi, gabungan lipid dan protein) tertentu. Baik tidaknya kolesterol tergantung dari lipoprotein yang membawanya (kilomikron, LDL, VLDL, dan HDL)

Kolesterol yang terakumulasi secara abnormal antara lain membentuk batu empedu dan ateroma (plak dalam pembuluh darah).

PERBEDAAN KOLESTEROL DAN TRIGLISERIDA

Trigliserida dan kolesterol merupakan jenis-jenis lemak dasar yang terdapat dalam tubuh manusia dan bersikulasi dalam aliran darah. Walaupun keduanya sama-sama jenis lemak dasar dan mirip, tetapi ada beberapa perbedaan di antara keduanya. Perbedaan tersebut dapat dilihat pada tabel berikut:

Kolesterol

- Kolesterol akan disimpan dalam jaringan hati atau dinding pembuluh darah.
- Kolesterol berfungsi membangun sel - sel dan hormon-hormon tertentu dalam tubuh.

Trigliserida

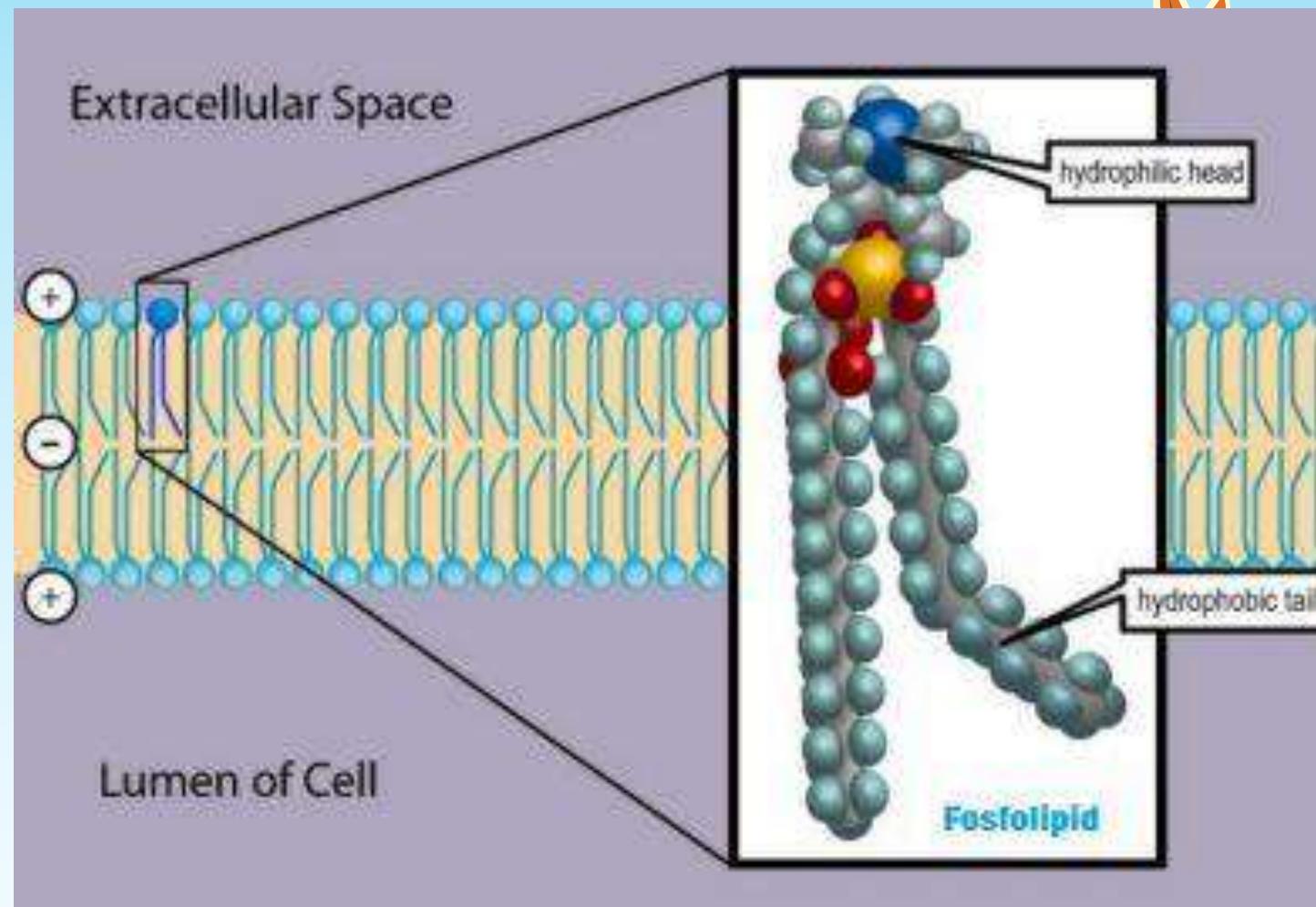
- Trigliserida akan disimpan dalam sel lemak di bawah jaringan kulit.
- Peran trigliserida adalah menghasilkan energi bagi tubuh.

3. Fosfolipid

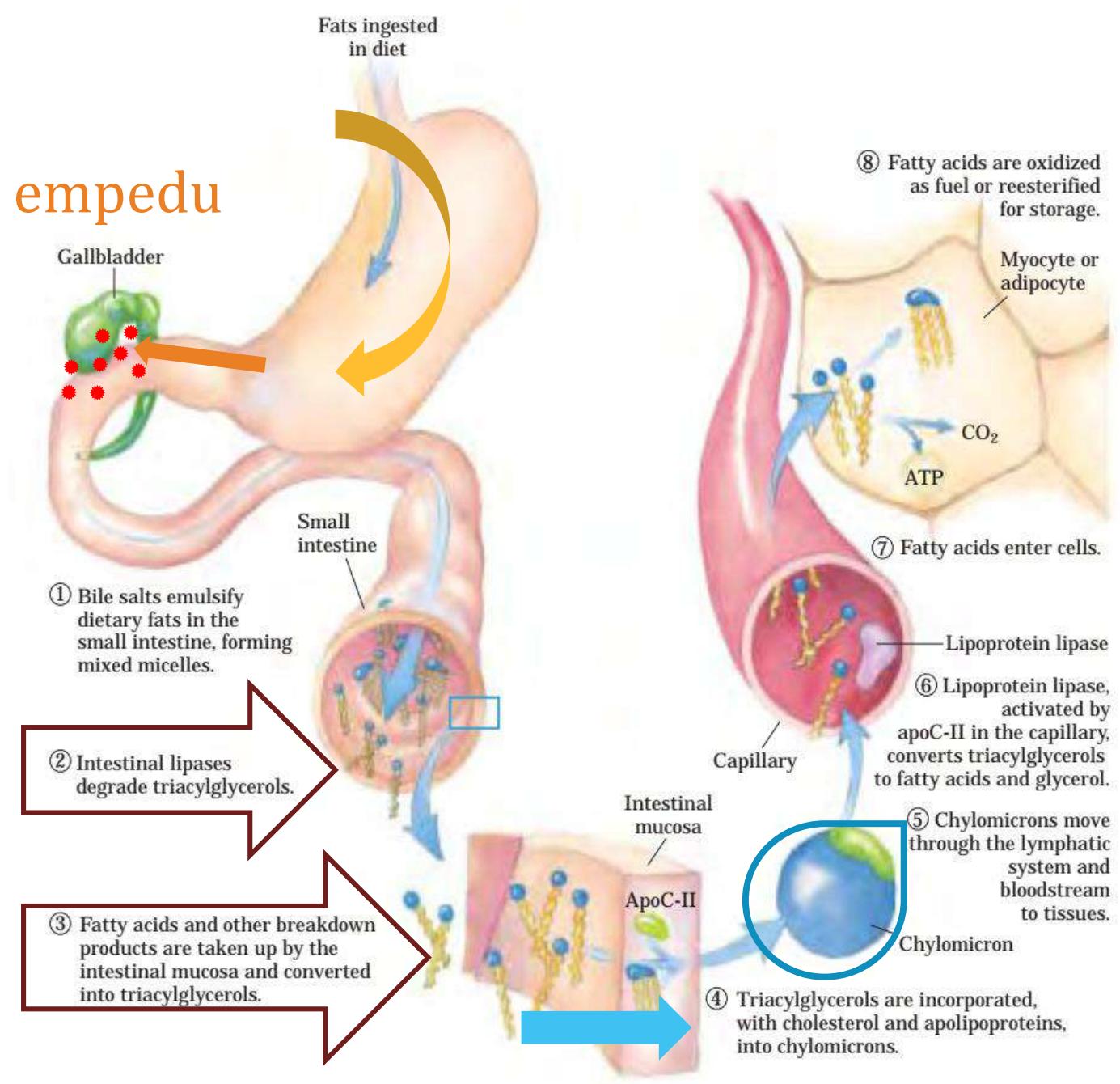
Fosfolipid → sejenis molekul lipid yang merupakan komponen utama membran sel.

Setiap fosfolipid terdiri dari **dua asam lemak, satu gugus fosfat, dan satu molekul gliserol**.

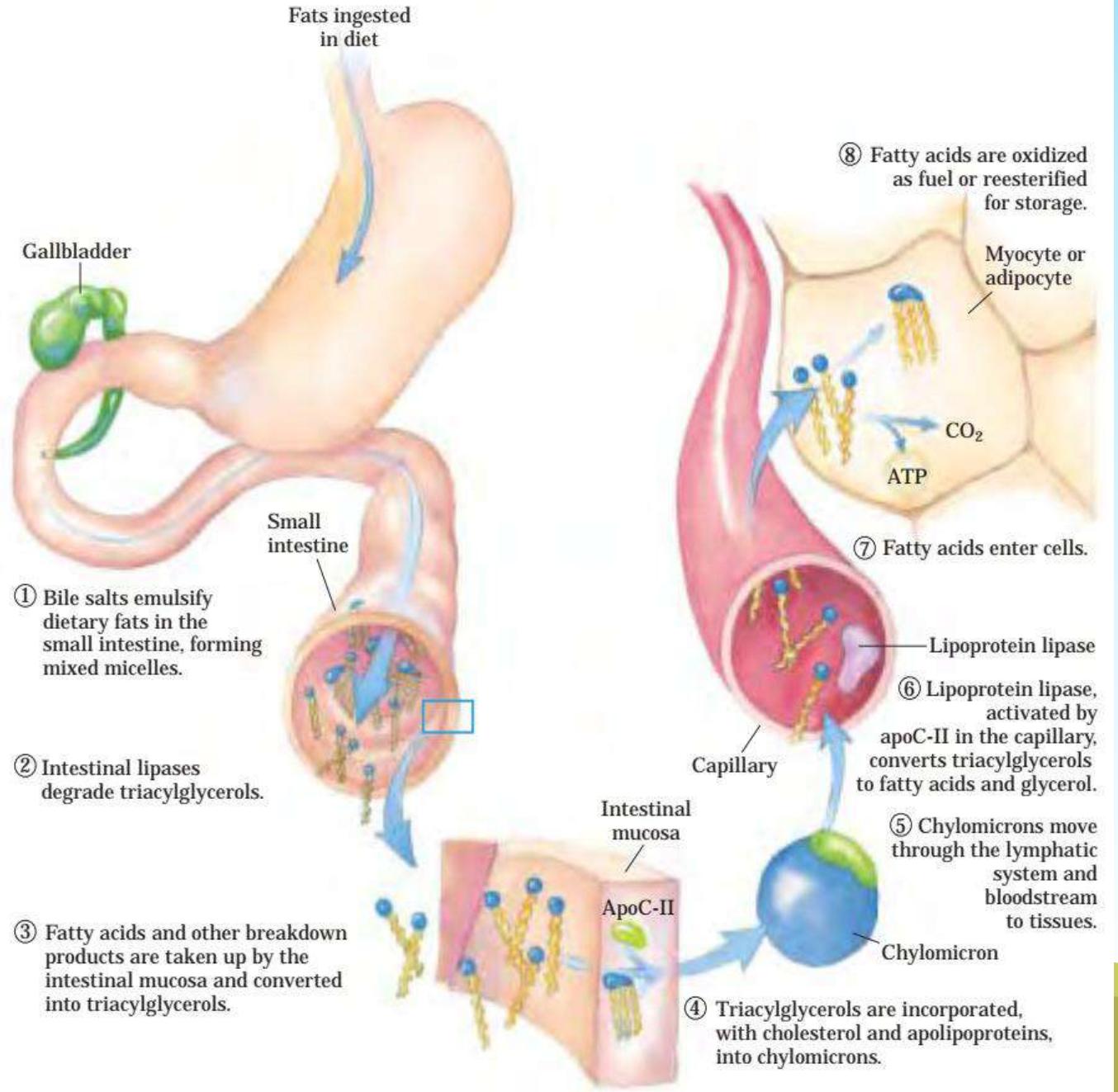
Ketika banyak fosfolipid berbaris, mereka membentuk lapisan ganda yang merupakan ciri dari semua membran sel.



PENCERNAAN LEMAK DARI MAKANAN



1. Triasilgliserol dari makanan → tidak larut dalam air.
Untuk mengangkutnya menuju usus halus dan dapat diakses oleh enzim yang larut di air seperti lipase, **triasilgliserol tersebut disolvasi oleh garam empedu seperti kolat dan glikolat** membentuk **misel**.
2. Di usus halus, **enzim lipase mendegradasi triasilgliserol menjadi asam lemak dan gliserol** → diabsorbsi ke dalam mukosa usus.
3. Asam lemak dan gliserol **diserap oleh dinding/mukosa usus** lalu **disintesis kembali menjadi triasilgliserol**
4. Triasilgliserol → digabung dengan **kolesterol** dan **lipoprotein** membentuk agregat yang disebut **kilomikron**.



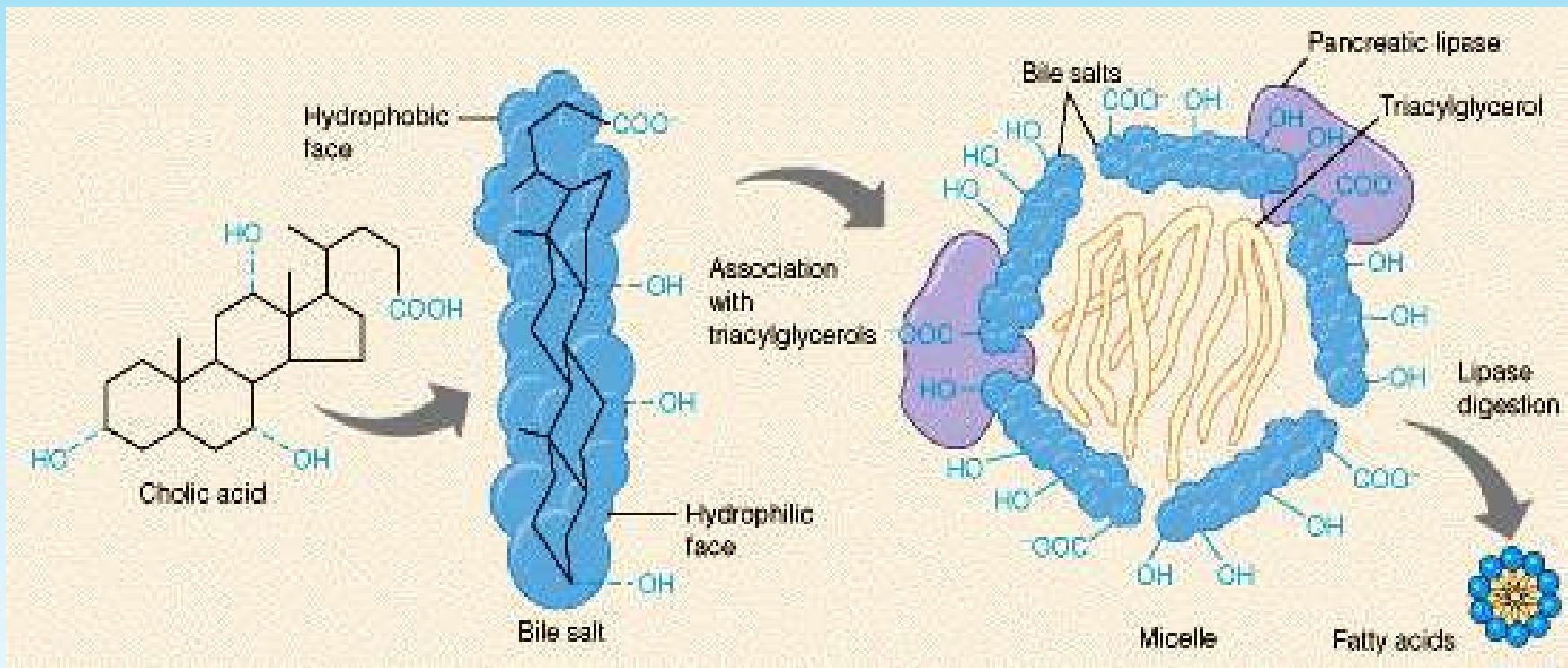
5. Kilomikron bergerak melalui sistem limfatik dan aliran darah ke jaringan-jaringan.

6. **Triasilgliserol** dipecah pada dinding kapiler oleh lipoprotein lipase menjadi asam lemak dan gliserol.

TAG → ASAM LEMAK + GLISEROL

7. Asam lemak masuk ke sel → sel otot dan sel adiposa

8. Di dalam sel otot (*myocyte*) **asam lemak dioksidasi (oksidasi-β)** menjadi **energi**, sedangkan di dalam sel adipose (*adipocyte*), **asam lemak diesterifikasi** untuk disimpan sebagai **triasilgliserol**.



Garam empedu terdiri dari asam empedu yg berasal dari kolesterol

Garam empedu → bersifat amfifatik → mengemulsi lemak → membentuk misel

Lemak → dipecah oleh lipase pankreas → hasil?

- ✓ Lemak → tidak larut dalam air → tidak bisa larut dalam plasma darah.
- ✓ Agar dapat diangkut dalam peredaran darah → di plasma darah, lemak berikatan dengan protein spesifik membentuk *kompleks makromolekul yang larut air*.
- ✓ Ikatan antara lemak (kolesterol, trigliserida, dan fosfolipid) dengan protein ini disebut lipoprotein.
- ✓ **Lipoprotein** → lipid kombinasi dari gabungan lipid dan protein sebagai alat pembawa lipid
- ✓ Berdasarkan komposisi, densitas, dan mobilitasnya, lipoprotein dibedakan menjadi:
 1. Kilomikron
 2. *Very low density lipoprotein (VLDL)*,
 3. *low density lipoprotein (LDL)*,
 4. *high density lipoprotein (HDL)*.

1. Kilomikron berfungsi mengangkut lipid, terutama trigliserida, dari saluran pencernaan ke dalam tubuh.

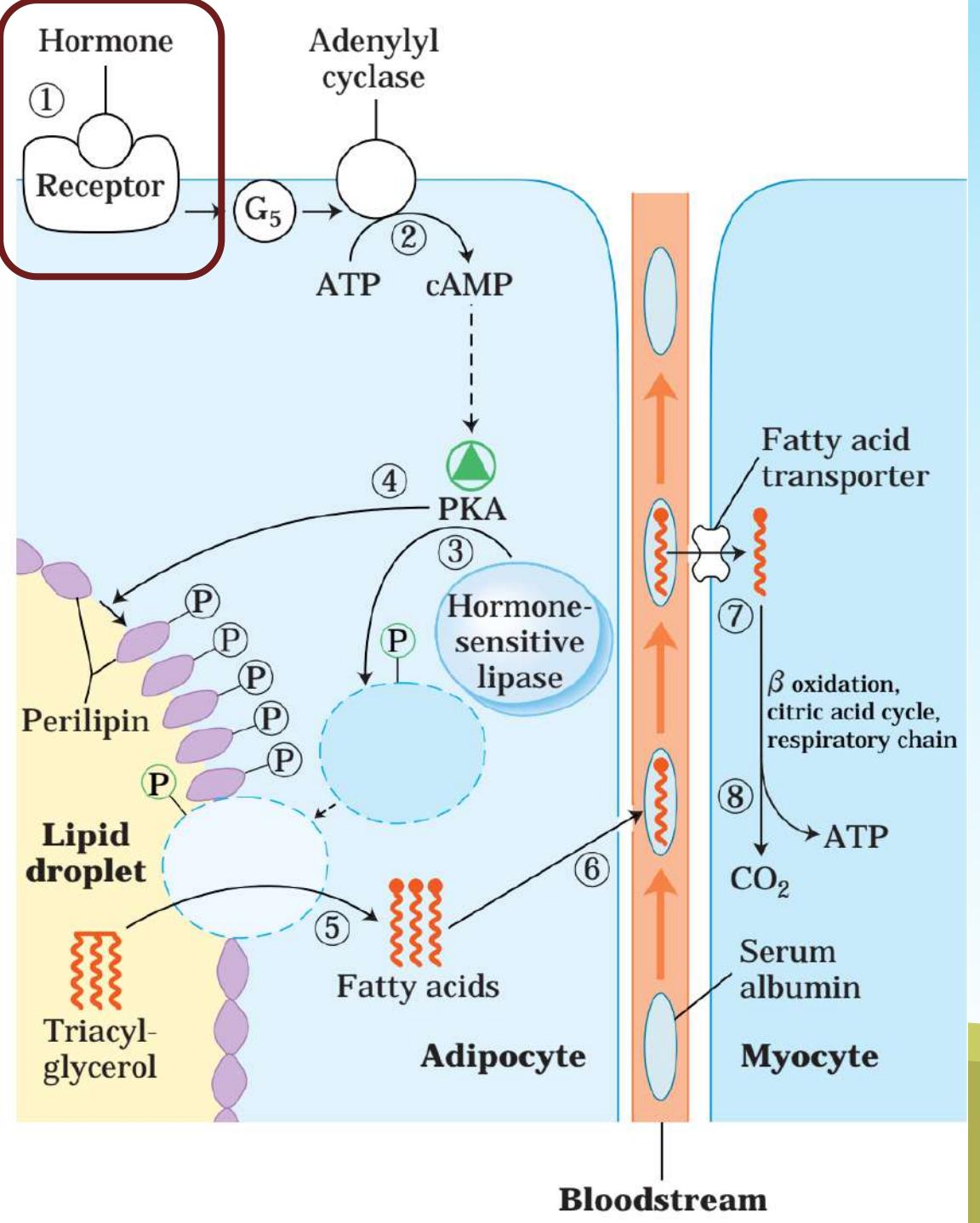
- Dalam aliran darah, trigliserida pada kilomikron dipecah menjadi gliserol dan asam lemak bebas oleh enzim lipoprotein
- Sebagian besar asam lemak → diabsorbsi oleh sel-sel otot, sel lemak, dan sel-sel tubuh lain.
- Asam lemak ini dapat langsung digunakan sebagai zat energi atau diubah menjadi trigliserida.
- Sel-sel otot cenderung menggunakannya sebagai energi,
- Sel lemak di jaringan adiposa menyimpannya sebagai trigliserida.
- Trigliserida dalam bentuk kilomikron berasal dari penyerapan usus setelah konsumsi makanan berlemak.

2. LDL → lipoprotein dengan densitas sangat rendah, terutama terdiri atas trigliserida.

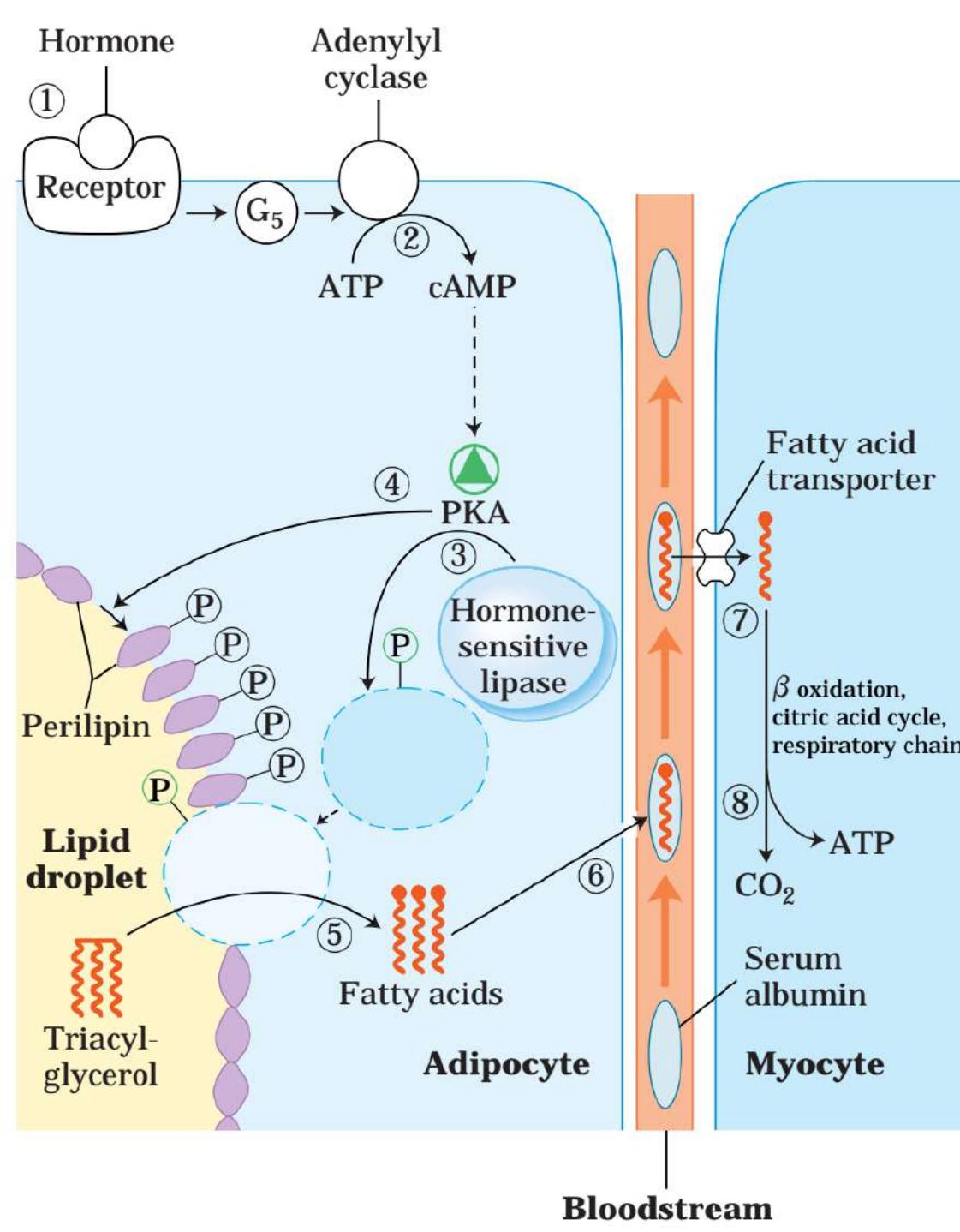
Trigliserida yang diserap usus dan masuk ke dalam plasma darah yang kemudian akan disalurkan ke seluruh jaringan tubuh dalam bentuk kilomikron dan VLDL. Sebagai LDL, trigliserida dibentuk oleh hati dengan bantuan insulin.

- Trigliserida di luar liver, berada dalam jaringan misalnya pembuluh darah, otot, jaringan lemak akan dihidrolisis oleh enzim lipoprotein lipase.
- Sisa hidrolisis kemudian akan dimetabolisme oleh hati menjadi kolesterol LDL.

LIPOLISIS



1. Jika **glukosa dalam darah rendah** → memicu pelepasan **epinefrin** atau **glukagon**. Kedua hormon meninggalkan aliran darah dan mengikat molekul reseptor yang ditemui di dalam membran *adipocyte* atau sel lemak.
2. Hal ini menyebabkan adenilat siklase melalui protein G mengubah ATP menjadi cAMP.
3. cAMP kemudian mengaktifkan protein kinase. Protein kinase aktif mengaktifkan triasilgliserol lipase (*Hormone-sensitive lipase*) melalui forforilasi.
4. Protein kinase aktif juga mengkatalisis fosforilasi molekul perlipin pada permukaan butiran lemak (*lipid droplet*) sehingga triasilgliserol lipase dapat mengakses permukaan butiran lemak.



5. Triasilgliserol diuraikan menjadi asam lemak bebas dan gliserol oleh triasilgliserol lipase.

6. Molekul asam lemak yang dihasilkan dilepaskan dari *adipocyte* dan diikat oleh protein serum albumin dalam darah untuk diangkut melalui pembuluh darah menuju *myocyte* (sel otot) jika dibutuhkan.

Jumlah asam lemak yang dilepaskan oleh jaringan adiposa ini tergantung pada aktivitas triasilgliserol lipase. **Hanya asam lemak rantai pendek yang dapat larut dalam air, sedangkan asam lemak rantai panjang tidak** → untuk pengangkutannya, asam lemak rantai panjang diikatkan pada serum albumin.

7. Asam lemak tersebut dilepaskan dari albumin dan masuk ke *myocyte* melalui transport khusus

8. Di *myocyte* asam lemak mengalami β -oksidasi yang menghasilkan CO₂ dan energi ATP.

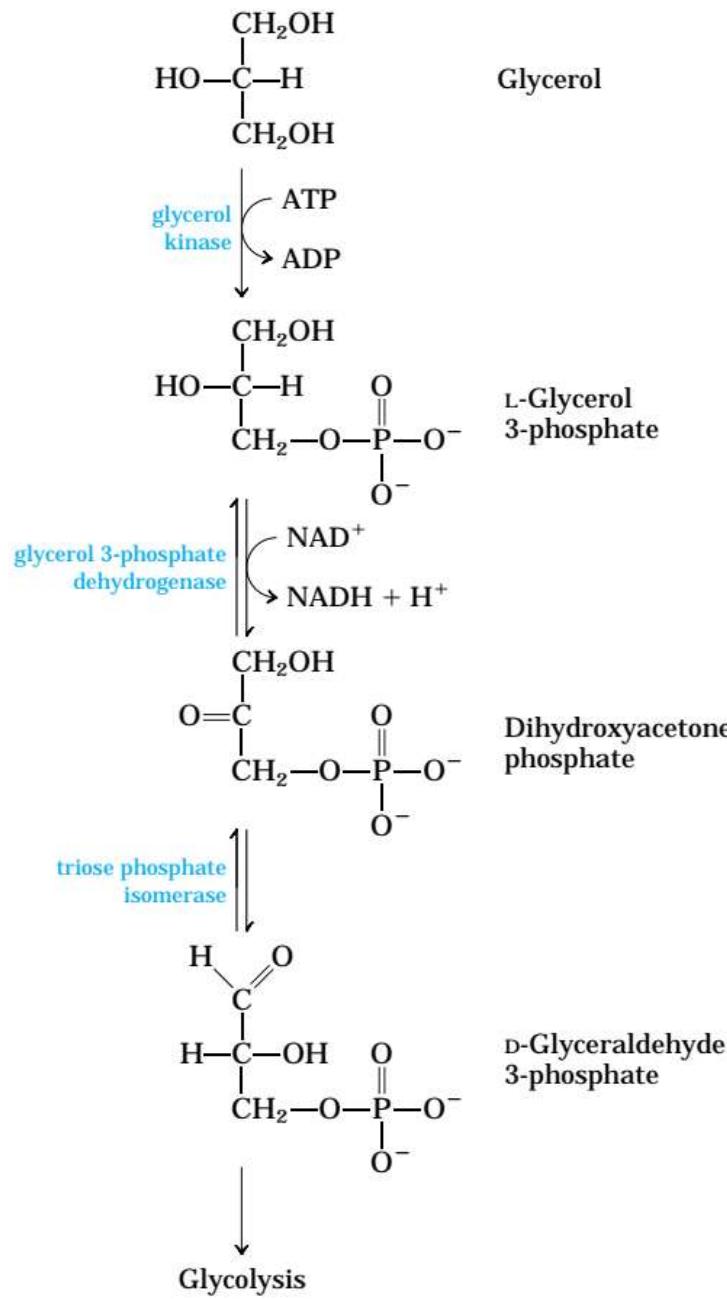


note

Lipolisis → LISIS LEMAK di jaringan adipose →
distimulasi oleh adrenalin pada saat
olahraga/aktivitas tinggi dan noradrenalin pada
kondisi non-adrenergic



Lipolisis dihambat oleh insulin

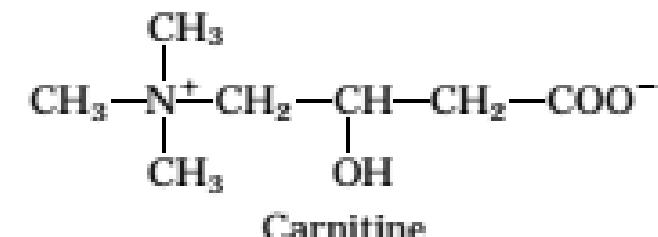


Gliserol masuk ke jalur glikolisis

FIGURE 17-4 Entry of glycerol into the glycolytic pathway.

Oksidasi β

- Proses terpenting dari degradasi asam lemak \rightarrow oksidasi β dalam mitokondria.
- Asam lemak di sitoplasma diaktivasi dengan pengikatan pada coenzyme A \rightarrow sistem masuk ke mitokondria dengan transport karnitin \rightarrow melalui proses β -oksidasi didegradasi menjadi acetyl-CoA.
- Acetyl-CoA dioksidasi lanjut menghasilkan CO_2 melalui siklus kreb dan rantai respirasi \rightarrow menghasilkan ATP.
- Enzim-enzim oksidasi asam lemak terletak di dinding mitokondria
- Asam-asam lemak dengan panjang 12 karbon atau kurang masuk mitokondria tanpa bantuan transporter membran.
- Asam lemak dengan panjang rantai karbon 14 atau lebih, tidak bisa secara langsung melewati directly membrane mitochondria \rightarrow harus melalui 3 tahap reaksi enzimatis yang disebut **carnitine shuttle**.

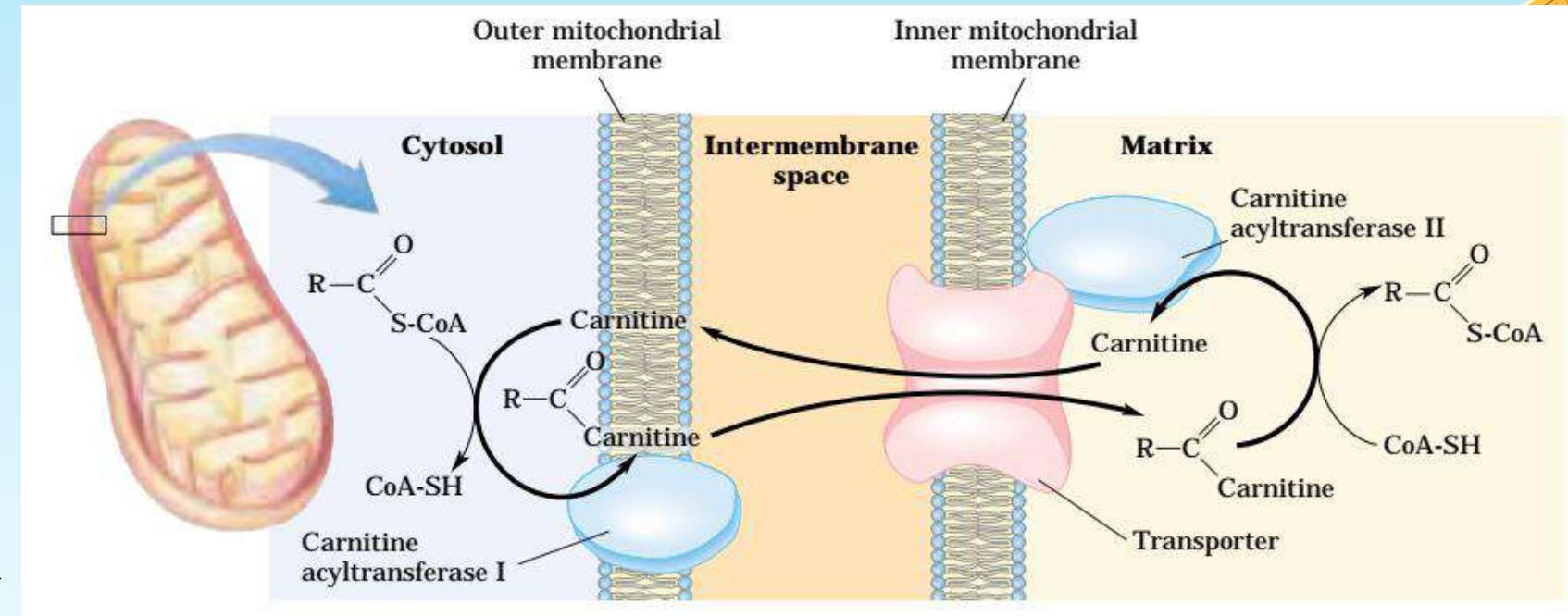


β -oxidation

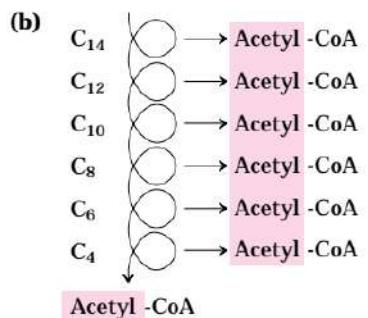
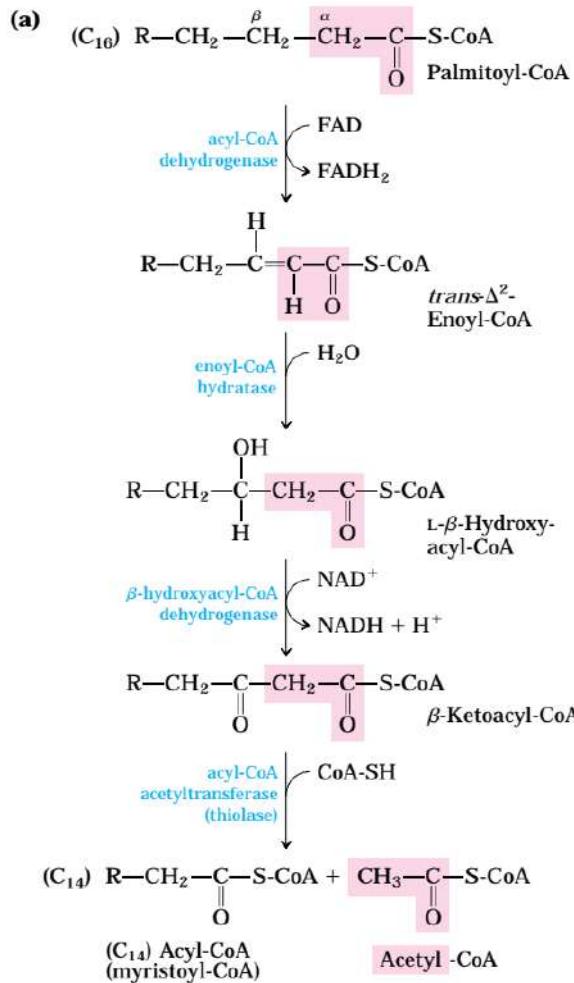
Degradasi asam lemak terjadi di mitokondria dalam beberapa tahap:

Tahap 1: aktivasi asam lemak di sitoplasma.

Asam lemak difosforilasi dengan satu molekul ATP → diaktifkan dengan asetil Co-A menghasilkan asam lemak-CoA, AMP, dan pirofosfat inorganic.



Tahap 2: Pengangkutan asam lemak-CoA dari sitoplasma ke mitokondria dengan bantuan *carnitine* sebagai molekul pembawa dalam membran mitokondria



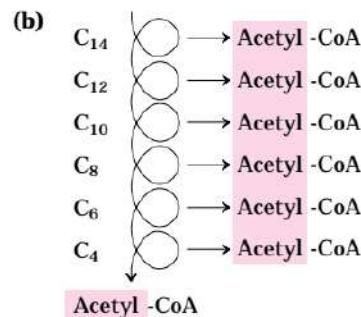
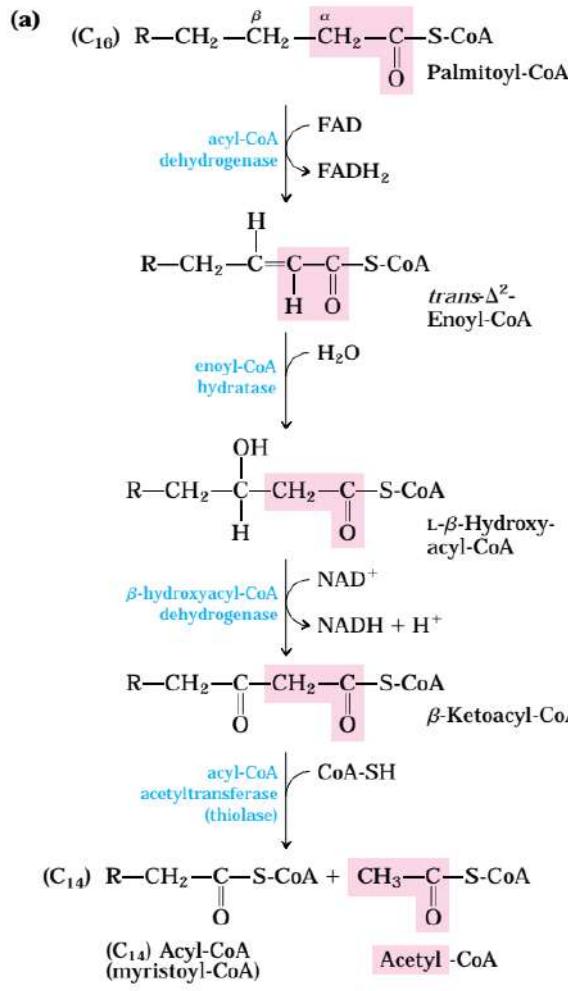
β -oxidation

The β -Oxidation of Saturated Fatty Acids Has Four Basic Steps

Tahap 3: Reaksi β -oksidasi, berlangsung dalam 4 tahap, yaitu (1) dehidrogenasi I, (2) hidratisasi, (3) dehidrogenasi II, dan (4) tiolasi (tahap pemotongan)

1. Dehidrogenasi I, yaitu dehidrogenasi Asam lemak-CoA yang sudah berada di dalam mitokondrion oleh enzim *acyl-CoA dehydrogenase*, menghasilkan senyawa enoyl-CoA. Pada reaksi ini, FAD (flavin adenin dinukleotida) yang bertindak sebagai koenzim direduksi menjadi FADH₂. Dengan mekanisme fosforilasi bersifat oksidasi melalui rantai pernafasan, suatu molekul FADH₂ dapat menghasilkan dua molekul ATP.

2. Hidratisasi, yaitu ikatan rangkap pada enoylCoA dihidratisasi menjadi 3-hidroxyacylCoA oleh enzim *enoyl-CoA hidratase*.



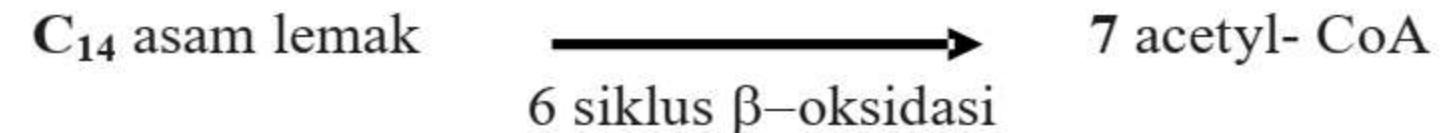
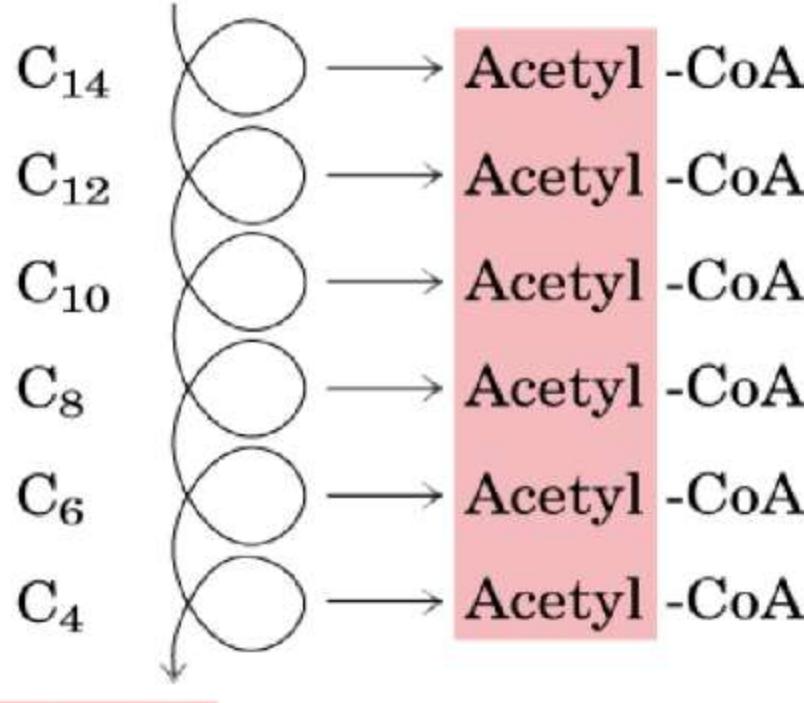
β-oxidation

The β -Oxidation of Saturated Fatty Acids Has Four Basic Steps

3. Dehidrogenase II, yaitu dehidrogenasi 3-hidroxyacyl-CoA oleh enzim β -hidroxyacyl-CoA dehidrogenase dengan NAD^+ sebagai koenzimnya menjadi β -ketoacylCoA. NADH yang terbentuk dari NAD^+ dapat dioksidasi kembali melalui mekanisme fosforilasi oksidatif yang dirangkaikan dengan rantai pernafasan menghasilkan tiga molekul ATP

4. Pemecahan molekul dengan enzim β -ketoacyl-CoA thiolase. Pada reaksi ini satu molekul ketoacyl-CoA menghasilkan satu molekul asetyl-CoA dan sisa rantai asam lemak dalam bentuk CoA-nya, yang mempunyai rantai dua atom karbon lebih pendek dari semula.

Proses degradasi asam lemak selanjutnya adalah pengulangan mekanisme β -oksidasi secara berurutan sampai panjang rantai asam lemak tersebut habis dipecah menjadi molekul acetylCoA. Dengan demikian satu molekul asam miristat (C14) menghasilkan 7 molekul acetylCoA (C2) dengan melalui 6 kali β -oksidasi.



Tiap satu siklus β -oksidasi dihasilkan energi sebesar:

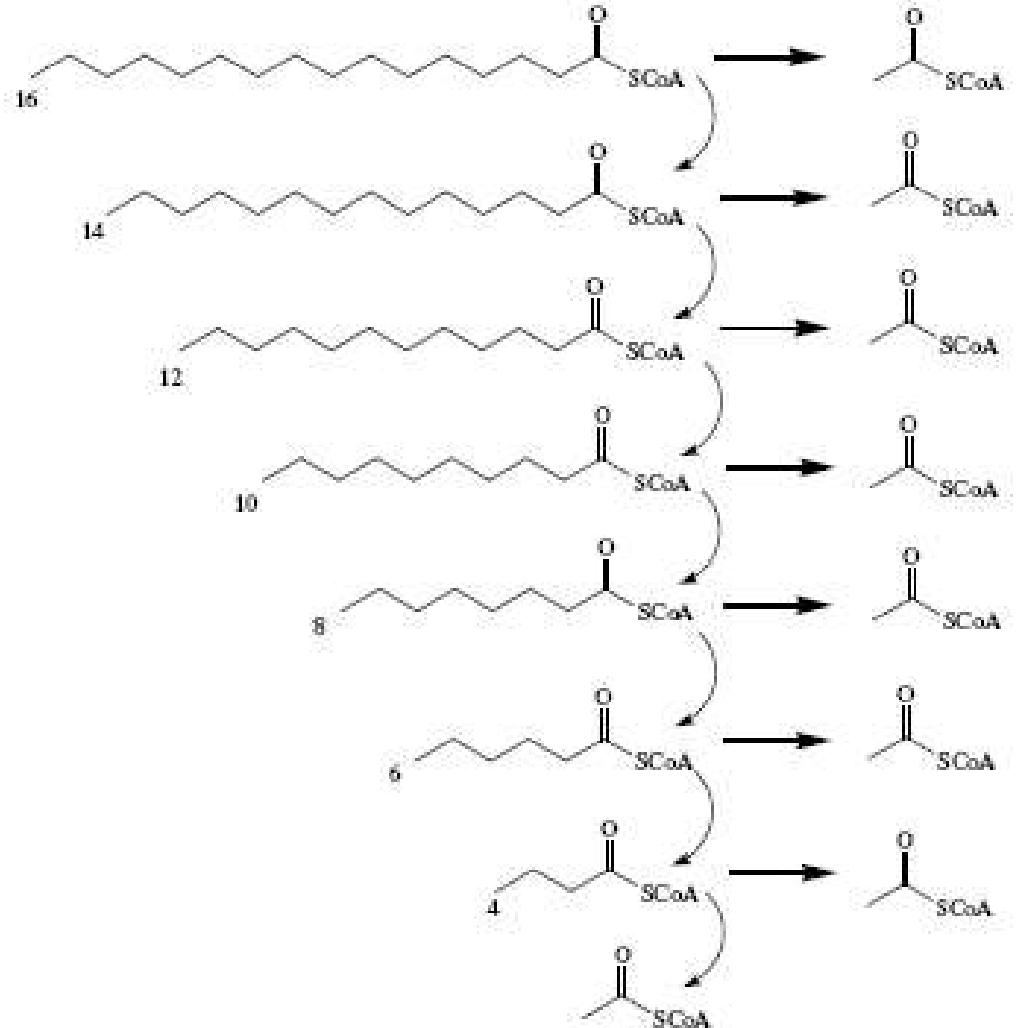
$$1 \text{ FADH}_2 = 2 \text{ ATP} \quad (\text{pada dehidrogenasi 1})$$

$$1 \text{ NADH} = 3 \text{ ATP} \quad (\text{pada dehidrogenasi 2})$$

dan 1 Acetyl-CoA. Satu Acetyl-CoA dioksidasi melalui siklus TCA menghasilkan energi = 12 ATP

Jadi jumlah ATP yang dihasilkan dalam satu siklus β oksidasi = $(3 + 3 + 12)$ ATP = 17 ATP

β oxidation degrades an acyl-CoA to produce acetyl-CoA molecules for TCA cycle



Each progressive step releases acetyl-CoA and reduces carbon chain length by 2 carbons

Oksidasi Asam Lemak Rantai Ganjil

- Oksidasi berlangsung dengan cara yg sama sampai terbentuk penggal tiga karbon, propionil KoA.
- Karboksilasi propionil KoA menghasilkan metilmalonil KoA, selanjutnya menjadi suksinil KoA (zat antara pada siklus asam sitrat).
- Suksinil KoA dioksidasi lebih lanjut dalam siklus asam sitrat.

Oksidasi Asam Lemak Tidak Jenuh

- Oksidasi berlangsung dengan cara yg sama dgn oksidasi- β , sampai bertemu dengan atom C yg mengandung ikatan tak jenuh.
- Proses ini memerlukan suatu enzim reduktase & isomerase .
- Reduktase bekerja pada ikatan rangkap lebih dari satu, sampai tinggal hanya satu ikatan rangkap.
- Isomerase merubah konfigurasi *sis* ke *trans*.
- Kemudian oksidasi- β berlangsung kembali.

Oksidasi- α

- Oksidasi ini berlangsung pada asam lemak dengan rantai cabang (asam fitanat)
- Proses oksidasi berlangsung pada C- α , dengan satu karbon dikeluarkan dari ujung karboksil rantai asam lemak dan dibebaskan sebagai CO₂.
- Karbon asam lemak sisanya dapat meneruskan oksidasi- β .

Oksidasi- ω

- Oksidasi ini berlangsung pada asam lemak rantai cabang yang mengandung banyak atom C.
- Gugus metil di ujung- ω diubah menjadi gugus karboksil, sehingga terbentuk suatu asam dikarboksilat.
- Sesudah terikat dengan KoA, oksidasi- β dapat berlangsung dari kedua ujung karboksil.

Oksidasi- β pada Asam Stearat (18:0)

- Aktivasi = (-) 2
 - Oksidasi asam stearat → asetil-KoA
 - 8 FADH₂ (8 x 2) = 16
 - 8 NADH (8 x 3) = 24
 - Oksidasi 9 asetil-KoA
 - 1 FADH₂ (9 x 1 x 2) = 18
 - 3 NADH (9 x 3 x 3) = 81
 - 1 GTP (9 x 1) = 9
-
- Menghasilkan ATP sebanyak = 146

Oksidasi- β pada Asam Oleat (18:1;9)

- Aktivasi = (-) 2
 - Oksidasi asam stearat → asetil-KoA
 - 7 FADH₂ (7 x 2) = 14
 - 8 NADH (8 x 3) = 24
 - Oksidasi 9 asetil-KoA
 - 1 FADH₂ (9 x 1 x 2) = 18
 - 3 NADH (9 x 3 x 3) = 81
 - 1 GTP (9 x 1) = 9
- Menghasilkan ATP sebanyak = 144

Contoh soal

Jelaskan tahap oksidasi asam palmitat ($C_{15}H_{33}COOH$) dan berapa energi yang dihasilkan?

Jawab:

Tahap 1: Asam palmitat (mengandung 16 atom C) β -oksidasi dalam 7 siklus menjadi 8 residu acetyl dalam bentuk acetyl-CoA

C16 asam lemak \rightarrow 8 Acetyl- CoA

7 siklus β -oksidasi

Tahap 2: tiap acetyl-CoA dioksidasi menghasilkan 2 CO_2 dan 8 elektron dalam siklus TCA.

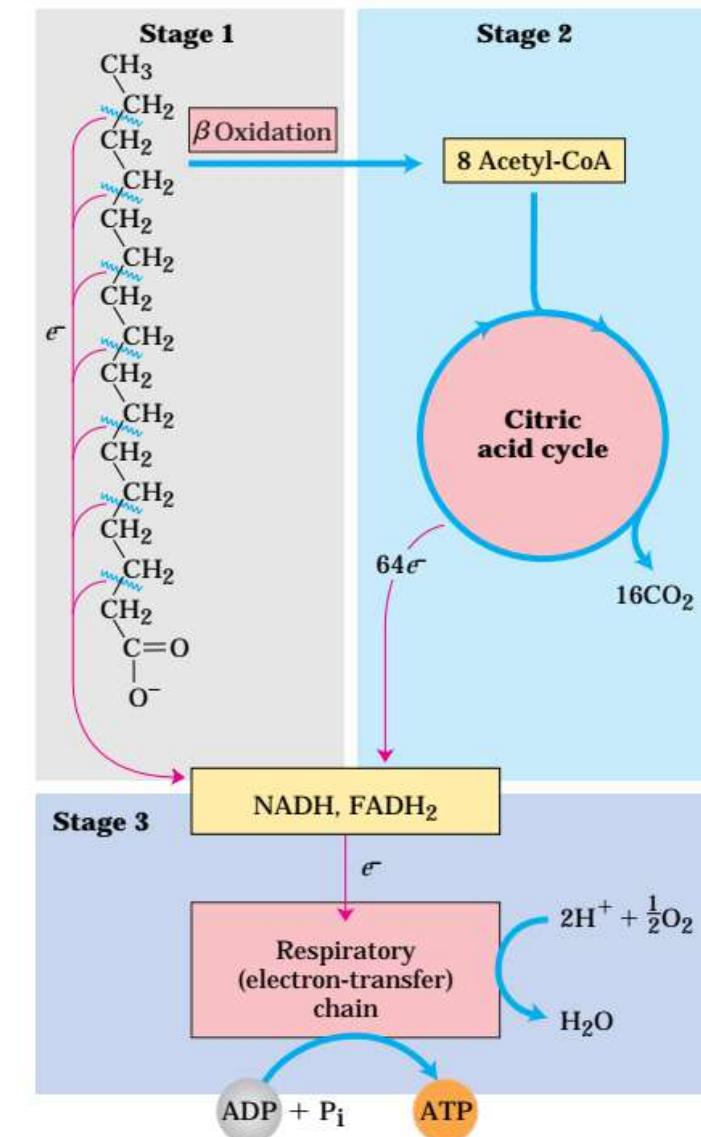


FIGURE 17-7 Stages of fatty acid oxidation. Stage 1: A long-chain fatty acid is oxidized to yield acetyl residues in the form of acetyl-CoA. This process is called β oxidation. Stage 2: The acetyl groups are oxidized to CO_2 via the citric acid cycle. Stage 3: Electrons derived from the oxidations of stages 1 and 2 pass to O_2 via the mitochondrial respiratory chain, providing the energy for ATP synthesis by oxidative phosphorylation.

Contoh soal

Tahap 3: Elektron yang dihasilkan dari tahap 1 & 2 masuk ke rantai respirasi mitokondria dengan menghasilkan energi untuk sintesis ATP dengan forforilasi oksidatif. Jadi dengan 7 siklus β -oksidasi dihasilkan energi sebesar:

$$7 \text{ FADH}_2 = 7 \times 2 \text{ ATP} = 14 \text{ ATP}$$

$$7 \text{ NADH} = 7 \times 3 \text{ ATP} = 21 \text{ ATP}$$

$$\underline{8 \text{ Acetyl-CoA}} = 8 \times 12 \text{ ATP} = 96 \text{ ATP}$$

$$\text{Jumlah ATP} = 131 \text{ ATP}$$

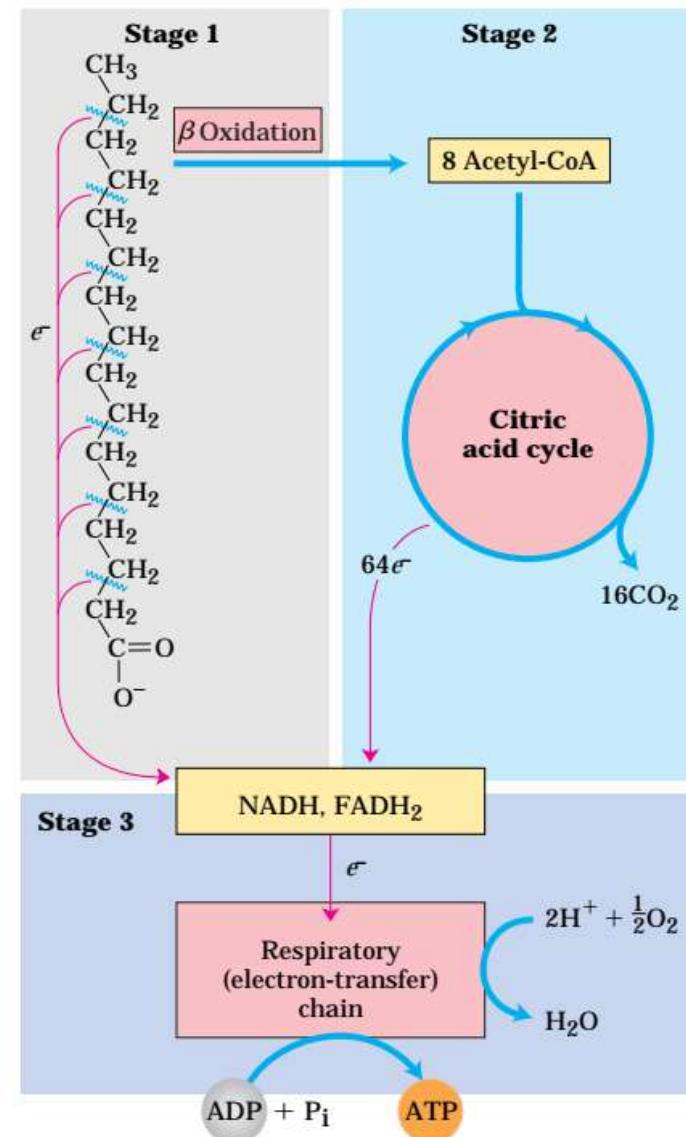


FIGURE 17-7 Stages of fatty acid oxidation. Stage 1: A long-chain fatty acid is oxidized to yield acetyl residues in the form of acetyl-CoA. This process is called β oxidation. Stage 2: The acetyl groups are oxidized to CO_2 via the citric acid cycle. Stage 3: Electrons derived from the oxidations of stages 1 and 2 pass to O_2 via the mitochondrial respiratory chain, providing the energy for ATP synthesis by oxidative phosphorylation.

Reaksi katabolismenya:

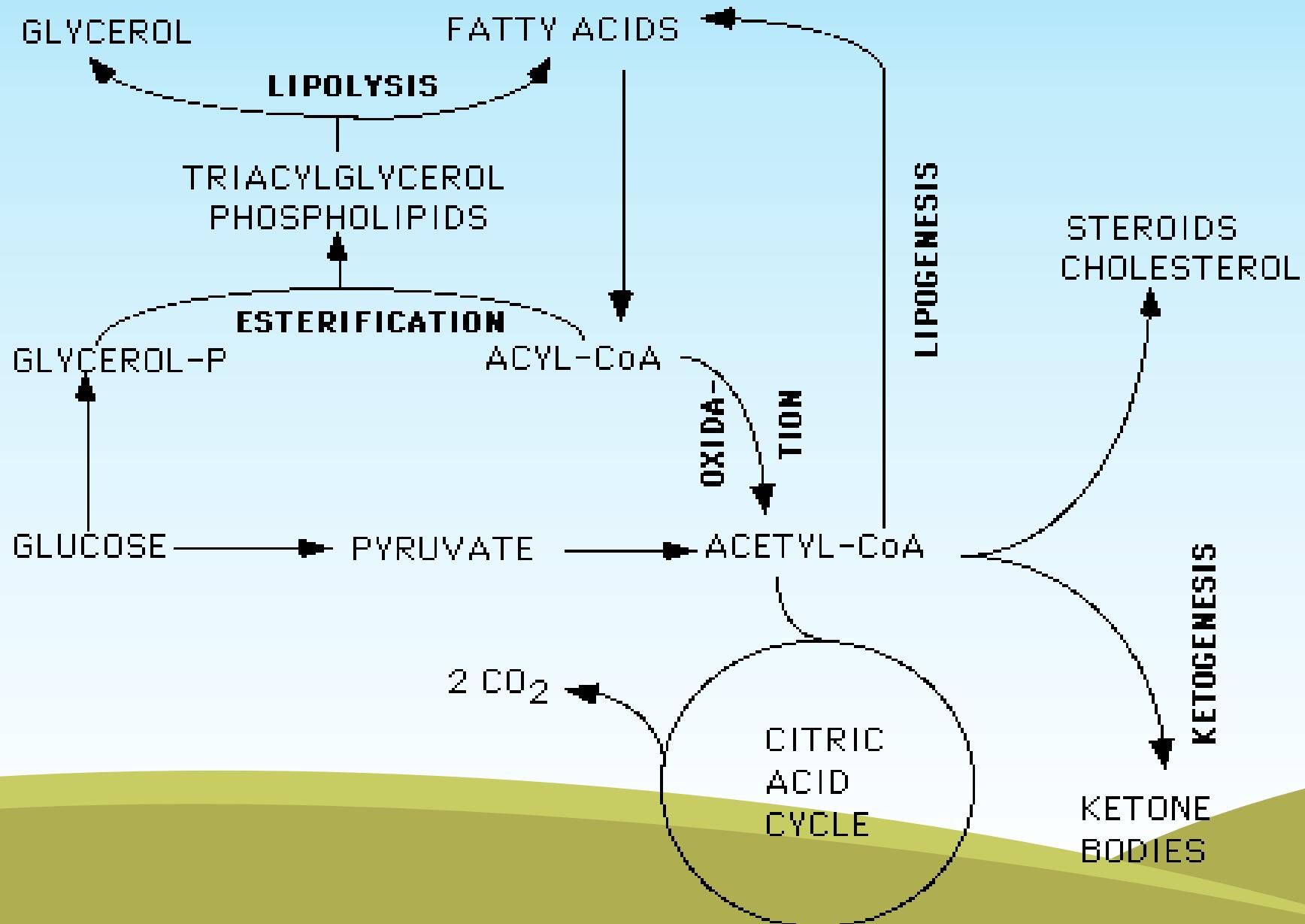


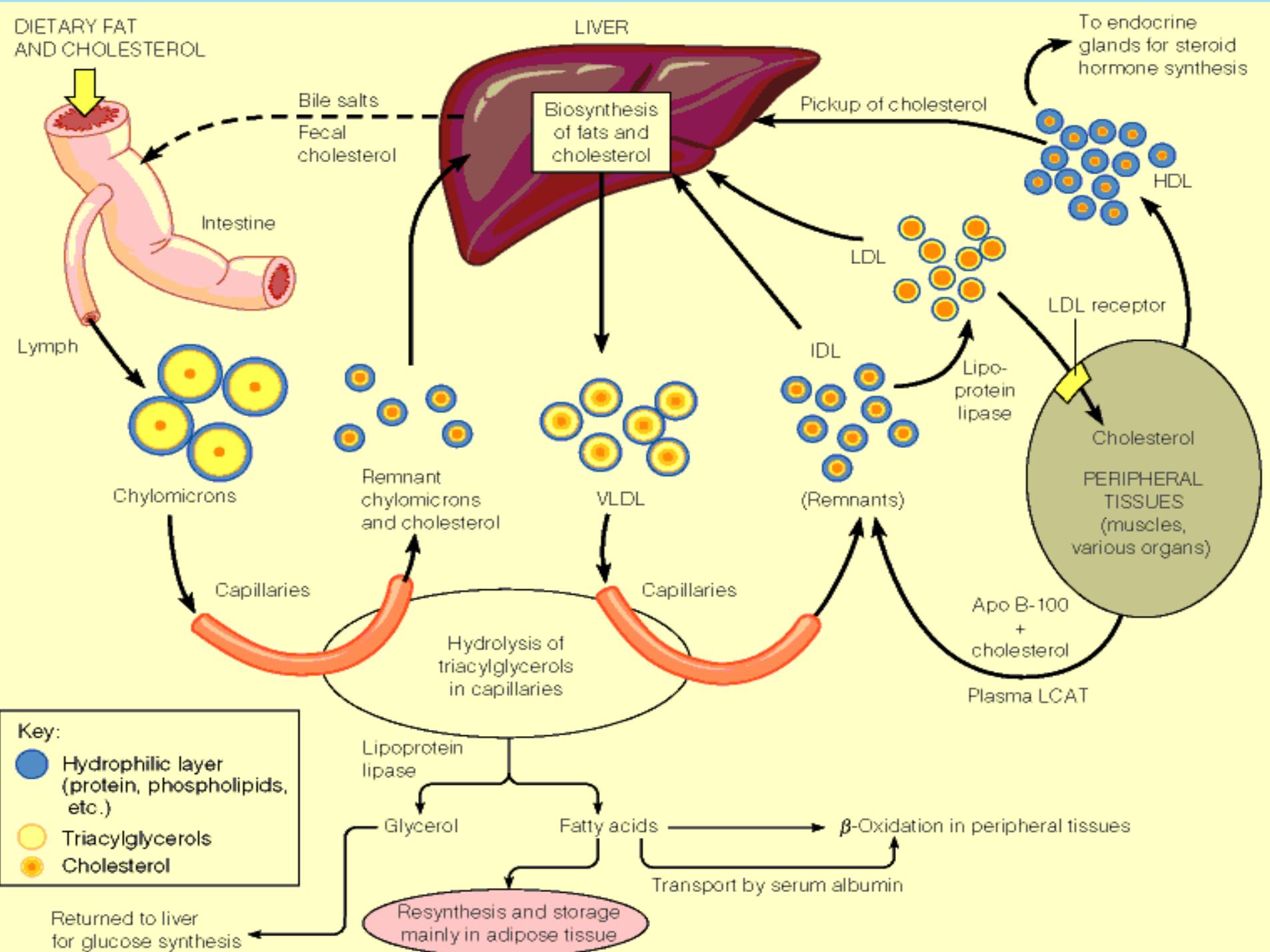
Karena pada proses aktivasi dibutuhkan 1 ATP dengan reaksi:

$\text{ATP} + 2 \text{ H}_2\text{O} \rightarrow \text{AMP} + 2 \text{ Pi}$, maka reaksi katabolismenya menjadi:



Integrasi Metabolisme Lipid







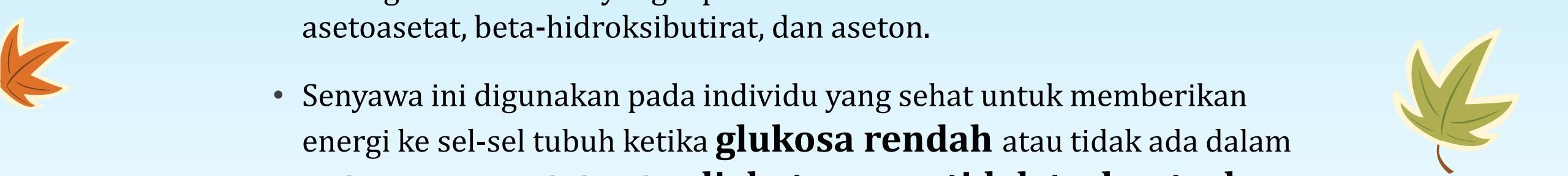
KETONE BODIES – Badan keton

- Tempat pembentukan asetoasetat dan D-3-hidroksibutirat : liver
- Senyawa ini berdifusi dari mitokondria liver menuju darah kemudian ditransport ke jaringan-jaringan perifer.
 - Otot jantung dan korteks ginjal menggunakan asetoasetat sebagai pengganti glukosa
 - Otak juga dapat beradaptasi ketika dalam kondisi berpuasa atau diabetes sehingga dapat menggunakan asetoasetat
 - Selama puasa jangka lama, 75 % bahan bakar yang diperlukan otak dipenuhi oleh badan-badan keton.

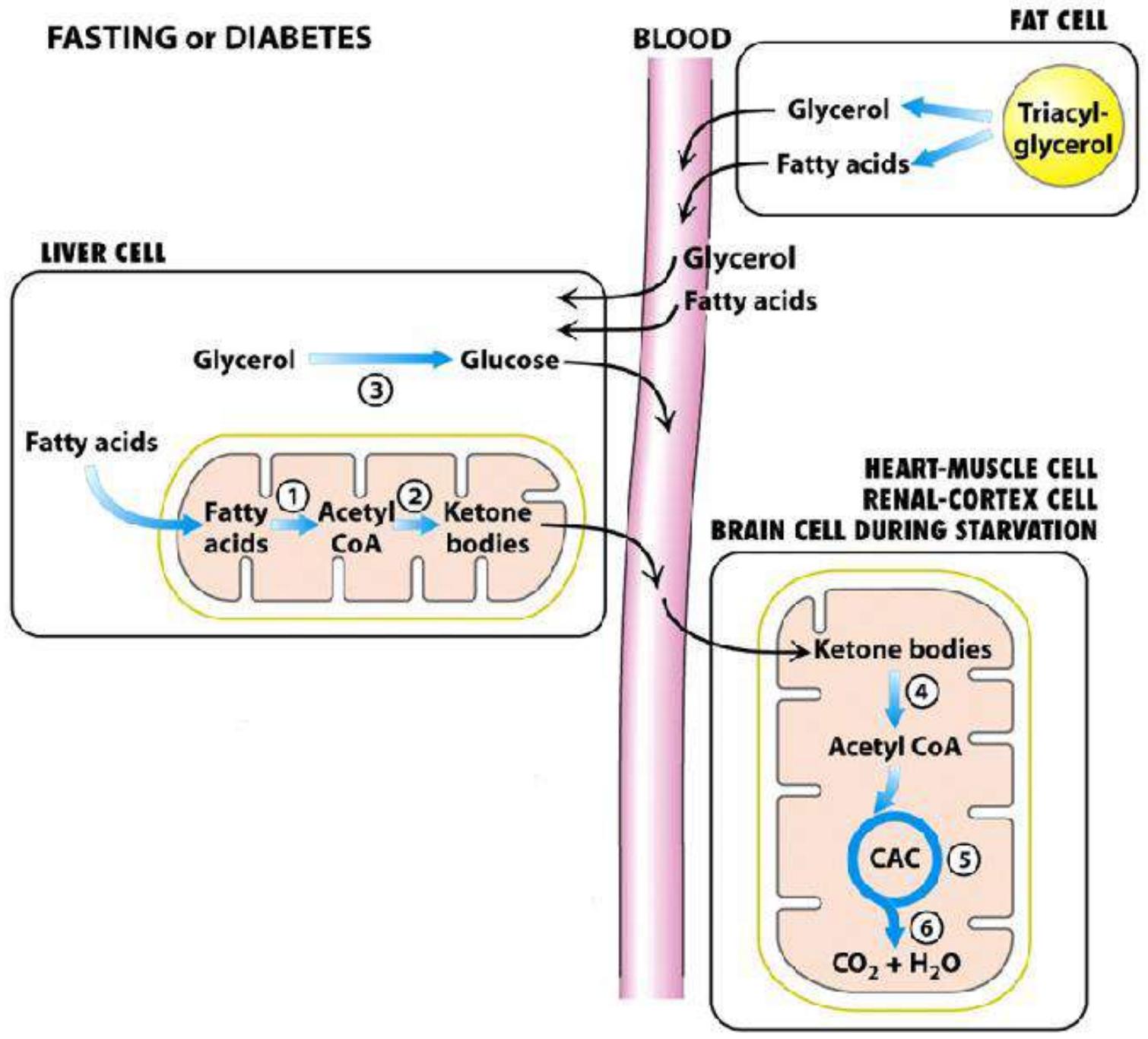




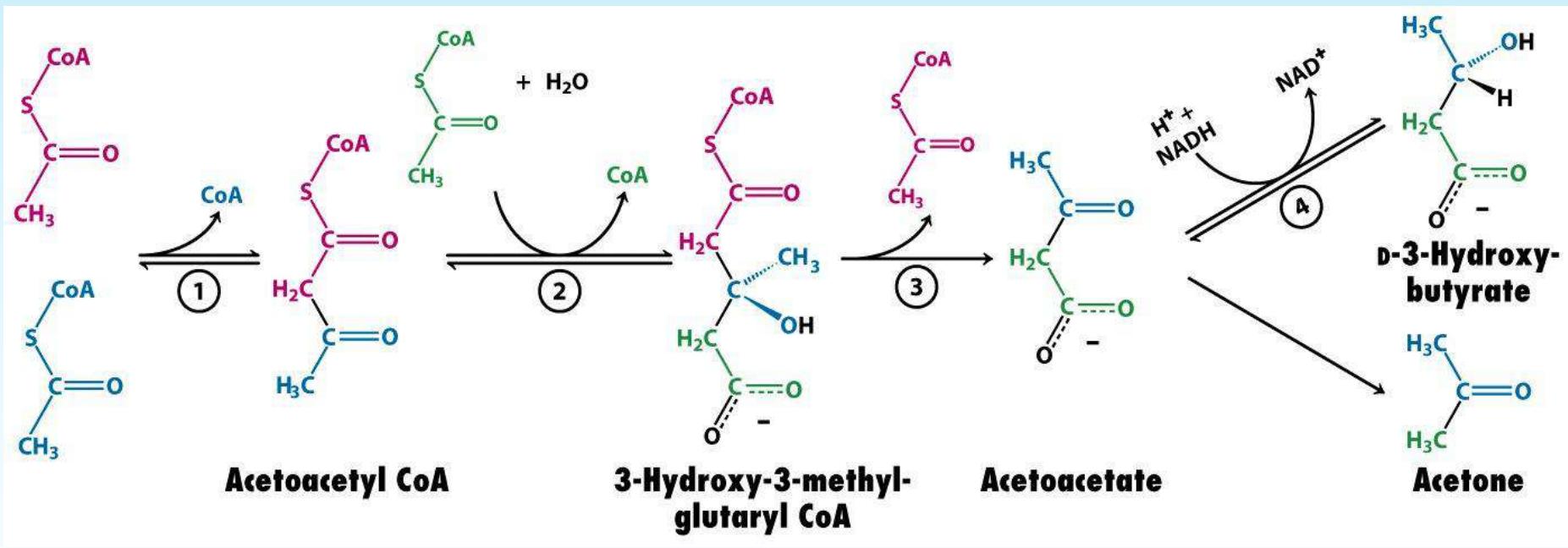
KETONE BODIES – Badan keton

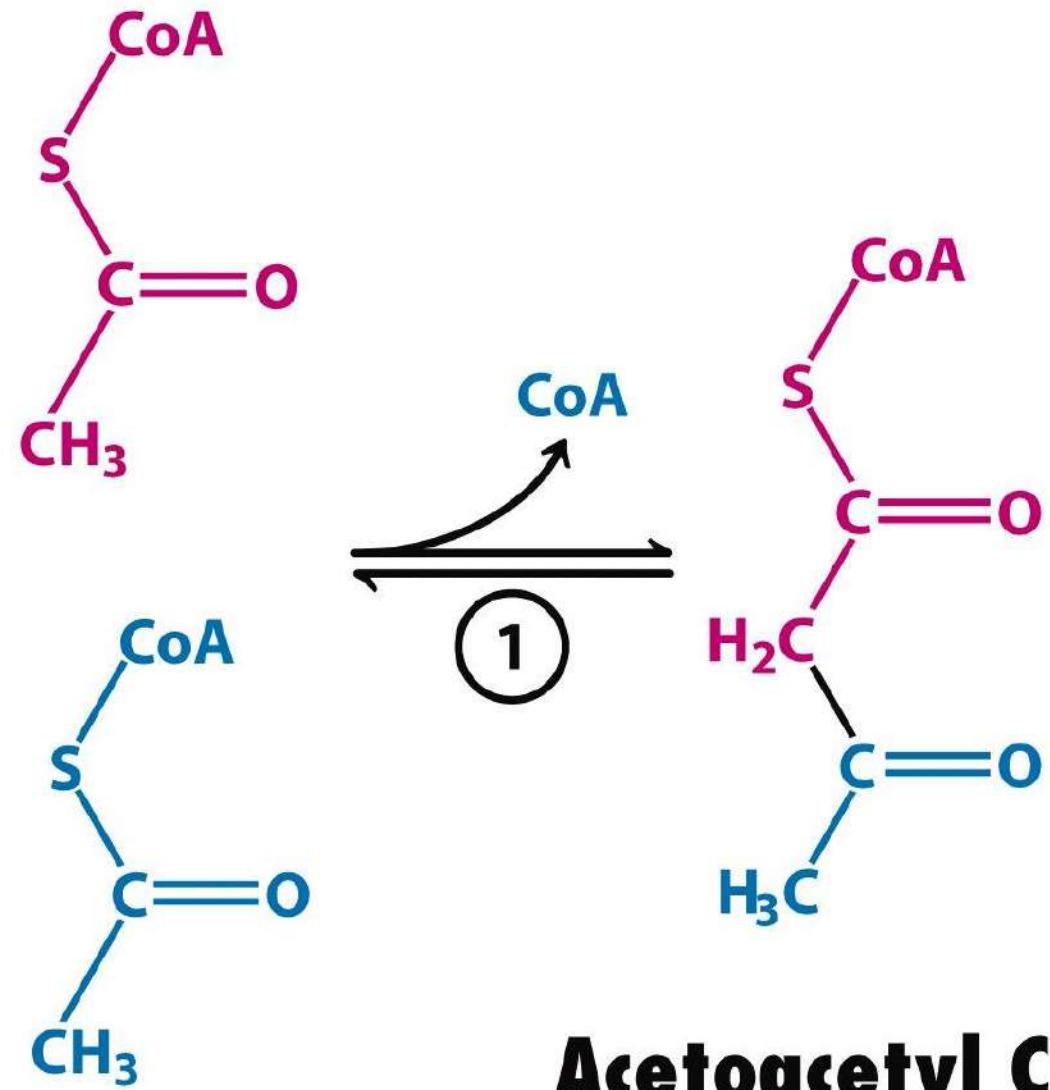
- Badan keton, atau hanya keton adalah zat yang diproduksi oleh hati selama glukoneogenesis, sebuah proses yang menciptakan glukosa pada saat berpuasa dan kelaparan.
 - Ada tiga badan keton yang diproduksi oleh hati. Mereka adalah asetoasetat, beta-hidroksibutirat, dan aseton.
 - Senyawa ini digunakan pada individu yang sehat untuk memberikan energi ke sel-sel tubuh ketika **glukosa rendah** atau tidak ada dalam makanan atau pada kondisi **diabetes yang tidak terkontrol**.
- 

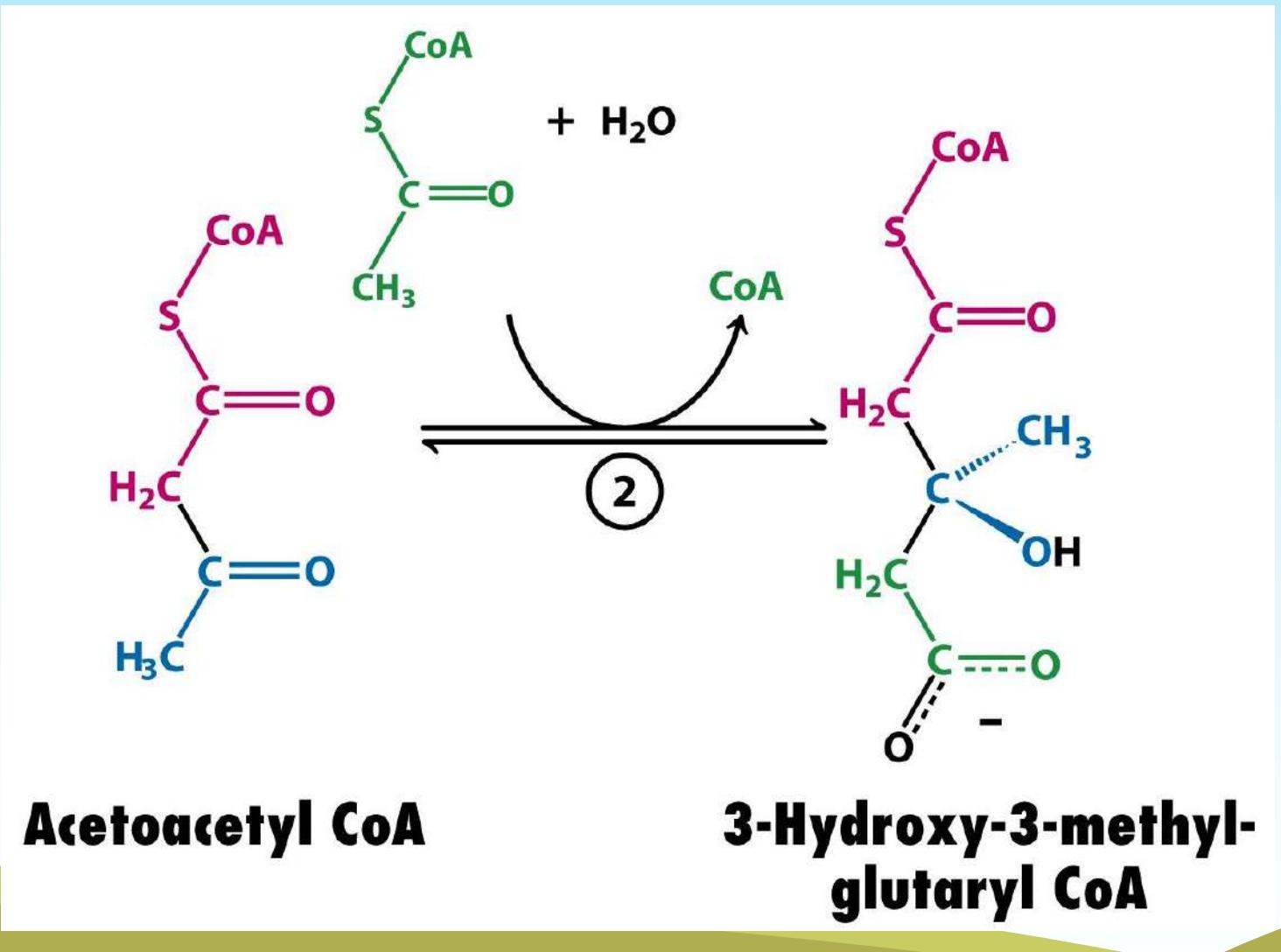
FASTING or DIABETES

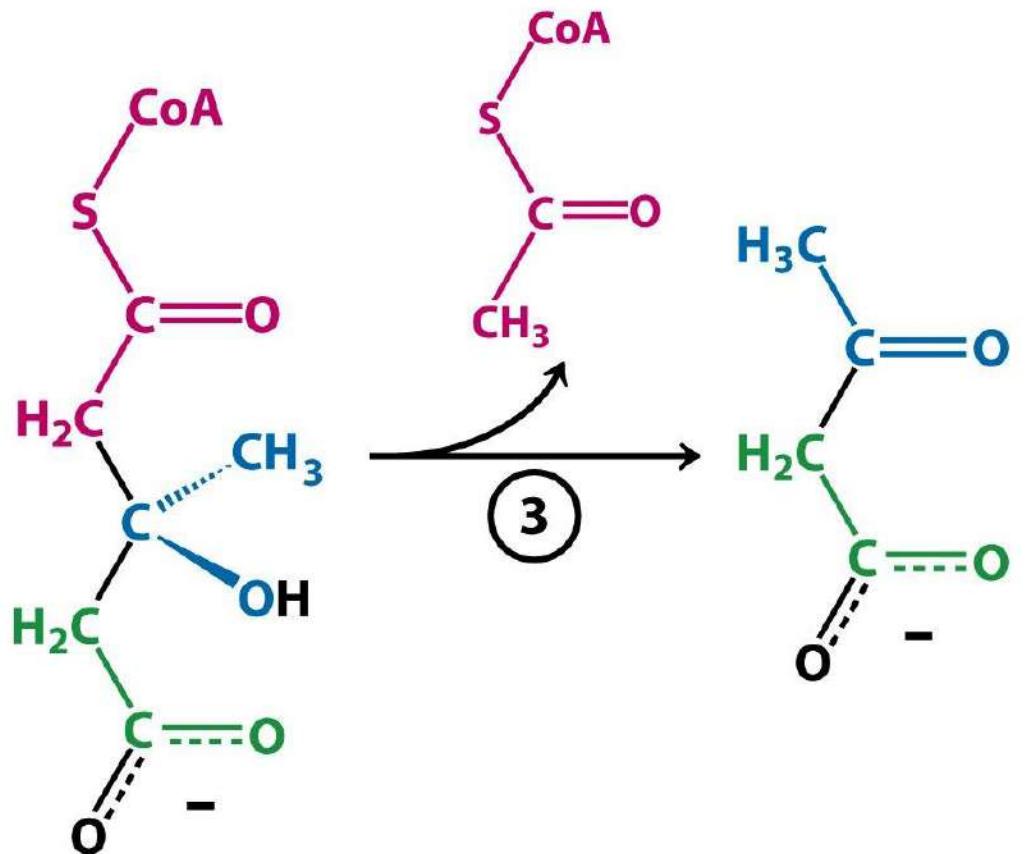


Reaksi pembentukan badan keton





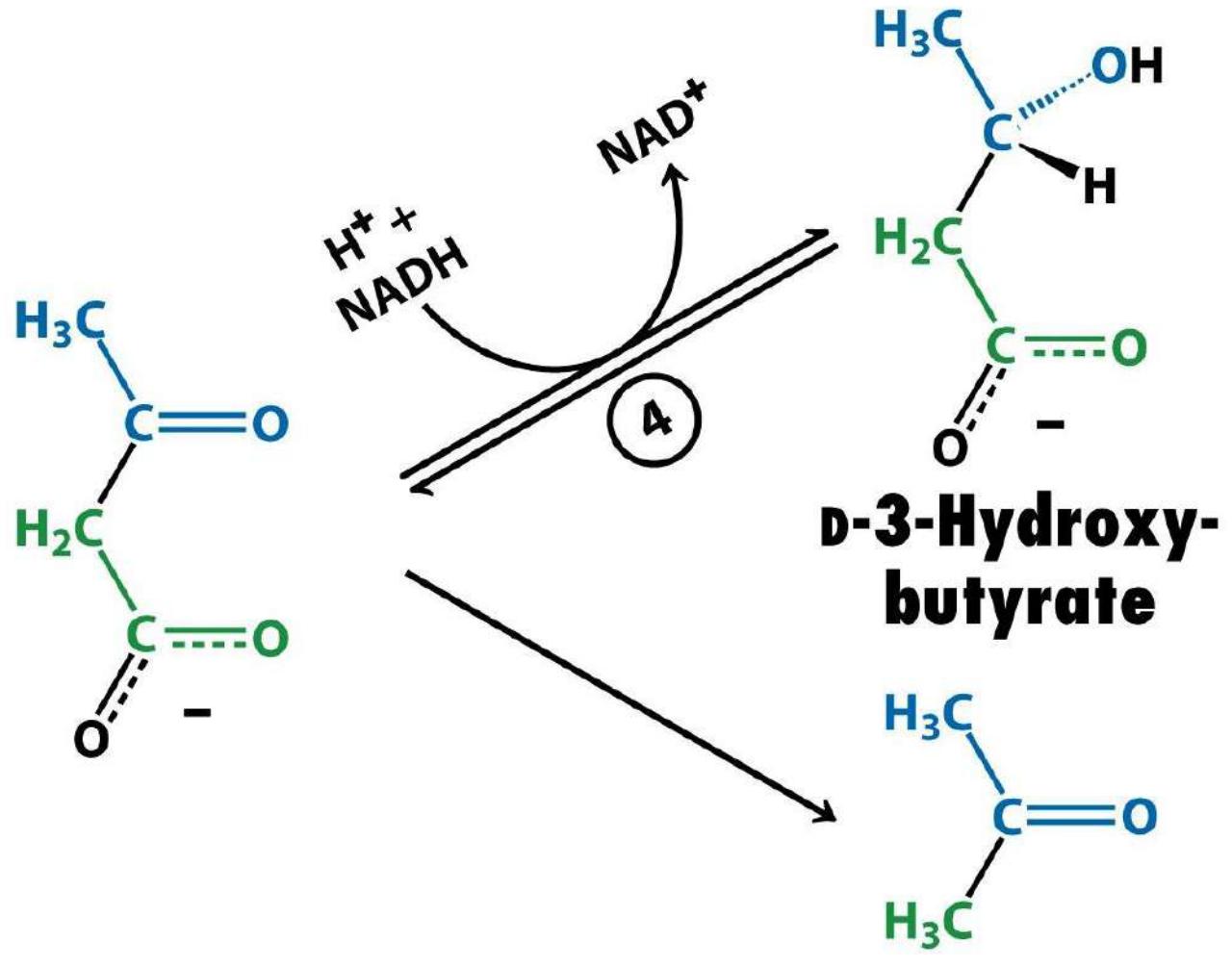




3-Hydroxy-3-methyl-glutaryl CoA

Acetoacetate

Acetoacetate

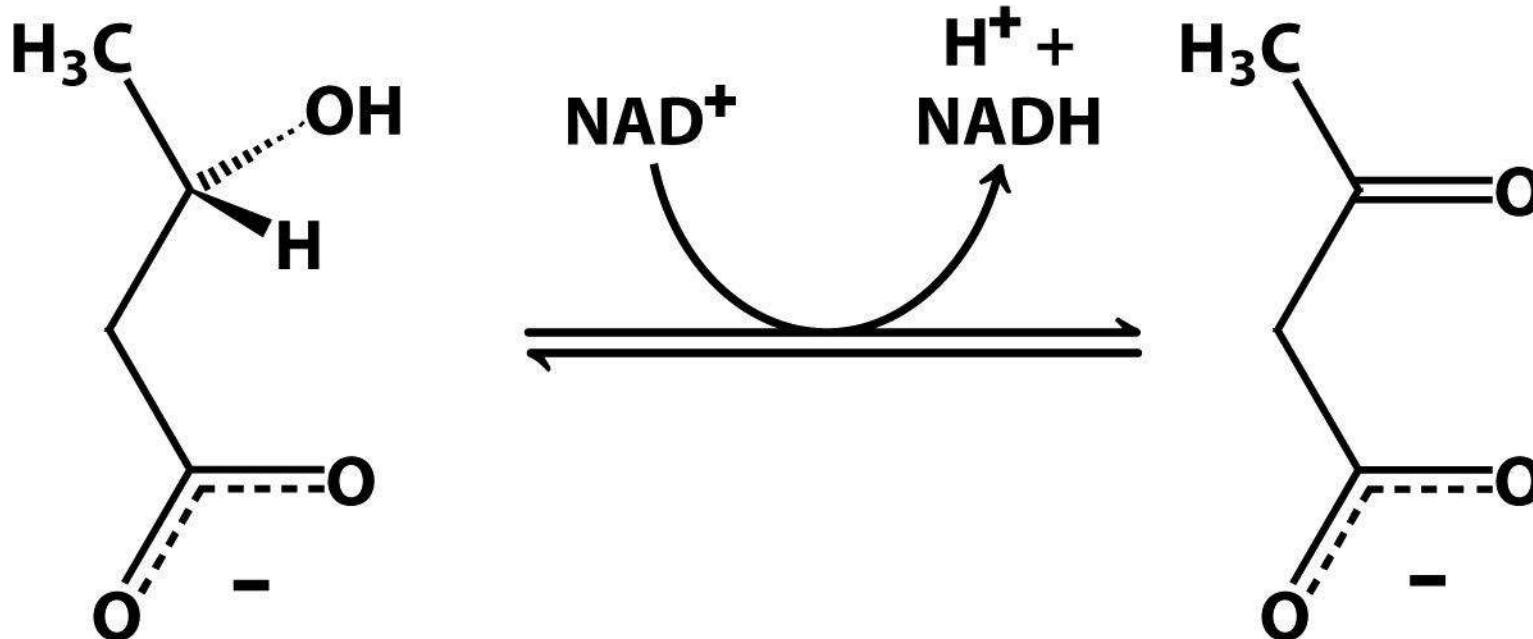


Acetone

D-3-Hydroxybutyrate

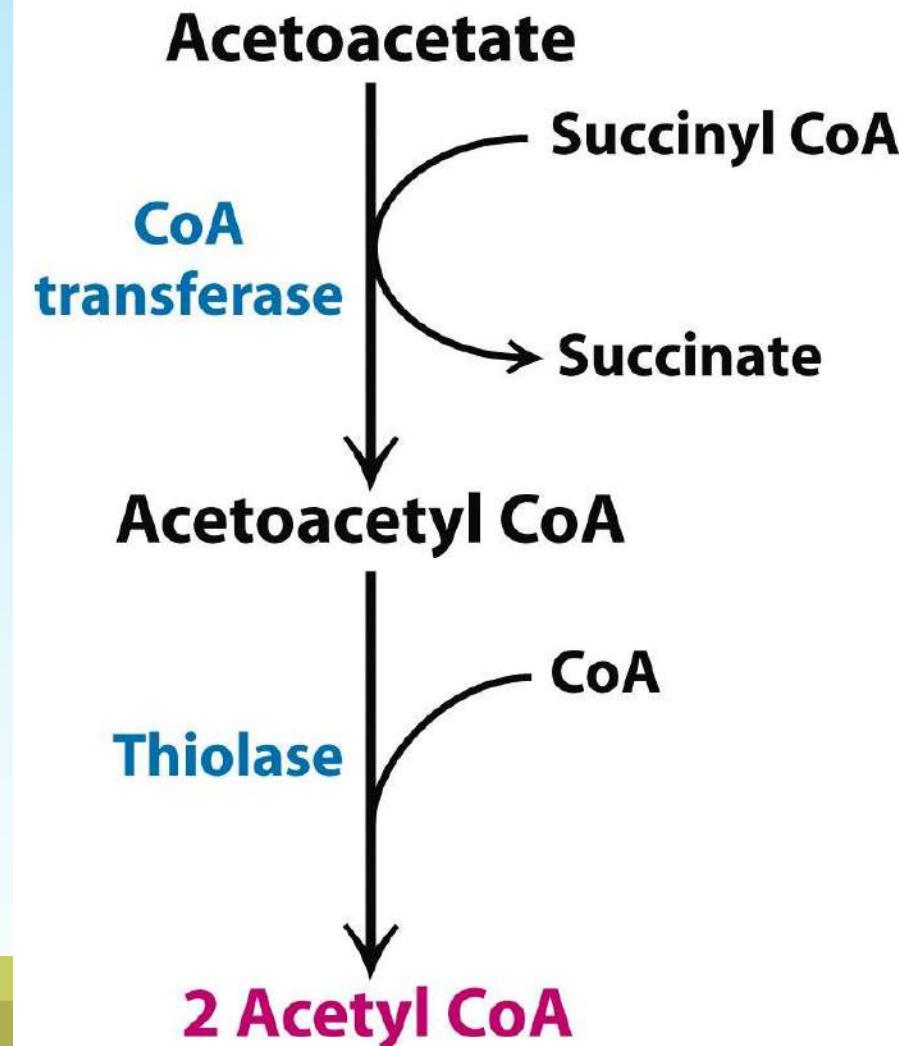
Reaksi degradasi badan keton

- 3-hidroksibutirat dioksidasi menghasilkan asetoasetat dan NADH (selanjutnya diproses di rantai fosforilasi oksidatif menghasilkan energi)
- Asetoasetat diaktivasi melalui transfer KoA dari suksinil KoA membentuk asetoasetil KoA oleh enzim KoA transferase. Kemudian asetoasetil KoA didegradasi oleh tiolase menghasilkan asetil KoA (siap diproses di siklus asam sitrat untuk menghasilkan energi)



D-3-Hydroxybutyrate

Acetoacetate



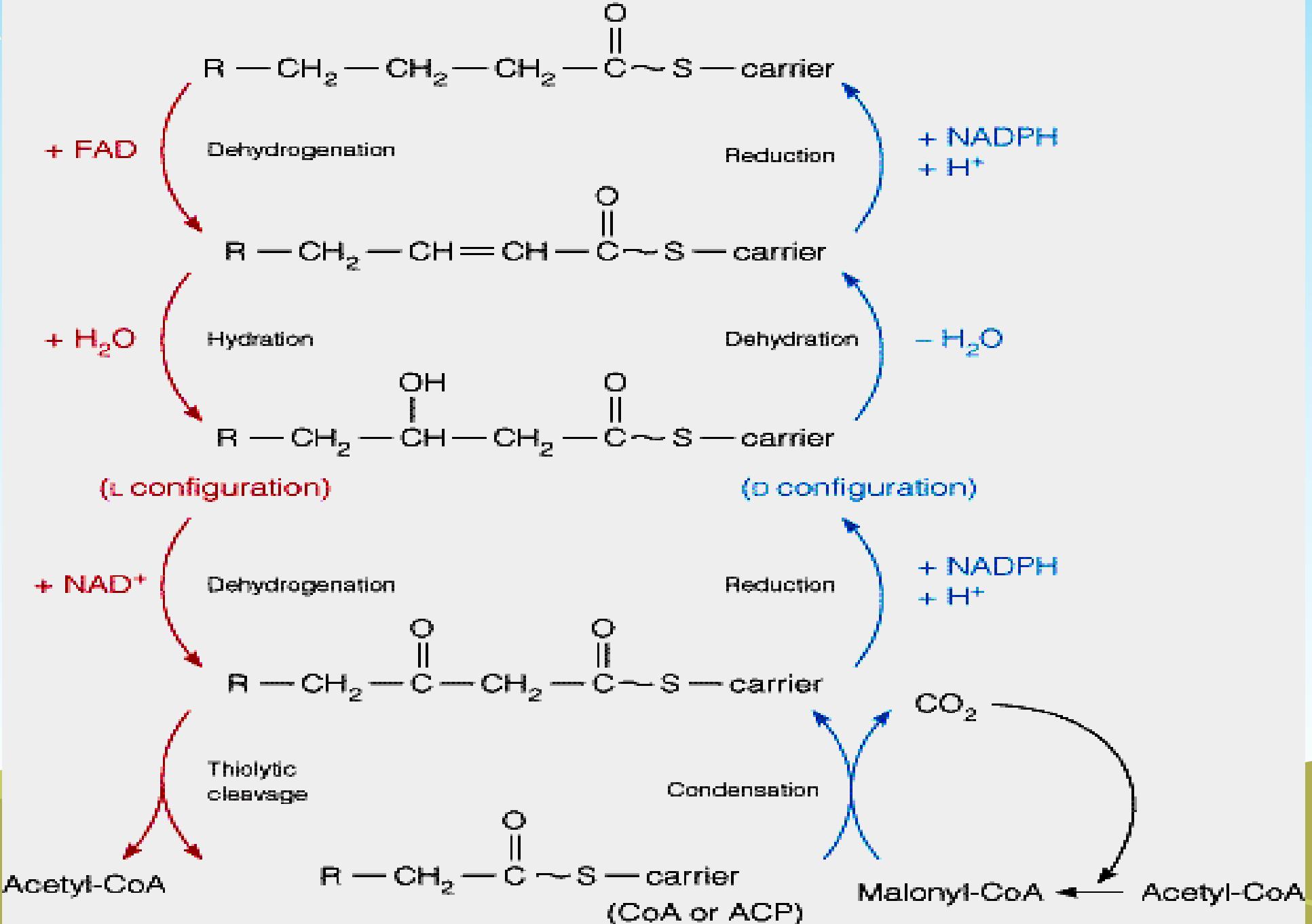
Sintesis Asam Lemak

- Tidak sepenuhnya merupakan kebalikan dari degradasi asam lemak
- Enzim yang berbeda bekerja dalam reaksi yang berlawanan : degradasi vs biosintesis

Perbedaan jalur sintesis dan degradasi asam lemak

| Perbedaan | Sintesis asam lemak | Degradasi asam lemak |
|--------------------------------|--|---|
| Lokasi | Terjadi di sitosol | Terjadi di matriks mitokondria |
| Bentuk senyawa antara | Terikat secara kovalen pada karier gugus asil yang dinamakan ACP (<i>acyl carrier protein</i>) | Terikat secara kovalen pada Koenzim A (KoA) |
| Enzim-enzim yang terlibat | Berasosiasi dalam sebuah rantai polipeptida yang dinamakan <i>fatty acid synthase</i> | Tidak berasosiasi |
| Kebutuhan oksidator / reduktor | Memerlukan senyawa reduktor NADPH | Memerlukan senyawa oksidator NAD ⁺ dan FAD |

Oxidative degradation



Sintesis Asam Lemak

- Sintesis Asam lemak →
 - pada eukariotik dan prokariotik : sama
- Biosintesis terdiri dari 3 langkah :
 - Biosintesis asam lemak dari asetil CoA (di sitosol)
 - Pemanjangan rantai asam lemak (di mitokondria & ER)
 - Desaturasi (di ER)
- Biosintesis as lemak →
 - membutuhkan malonil Co A sebagai substrat
 - Diperlukan ATP
- Reaksi biosintesis asam palmitat:

Dari 8 acetyl-CoA diperlukan → 7 ATP +14 NADPH
- Enzim untuk sintesis asam lemak : kompleks **fatty acid synthase**

Tahapan Sintesis Asam Lemak

1. Reaksi awal

- Karboksilasi gugus asetil menjadi malonil-KoA
- Reaksi dikatalis oleh asetil KoA karboksilase
- $\text{Biotin-enzim} + \text{ATP} + \text{HCO}_3^- \rightarrow \text{CO}_2\text{-biotin-enzim} + \text{ADP} + \text{P}_i$
- $\text{CO}_2\text{-biotin-enzim} + \text{asetil KoA} \rightarrow \text{malonil KoA} + \text{biotin-enzim}$

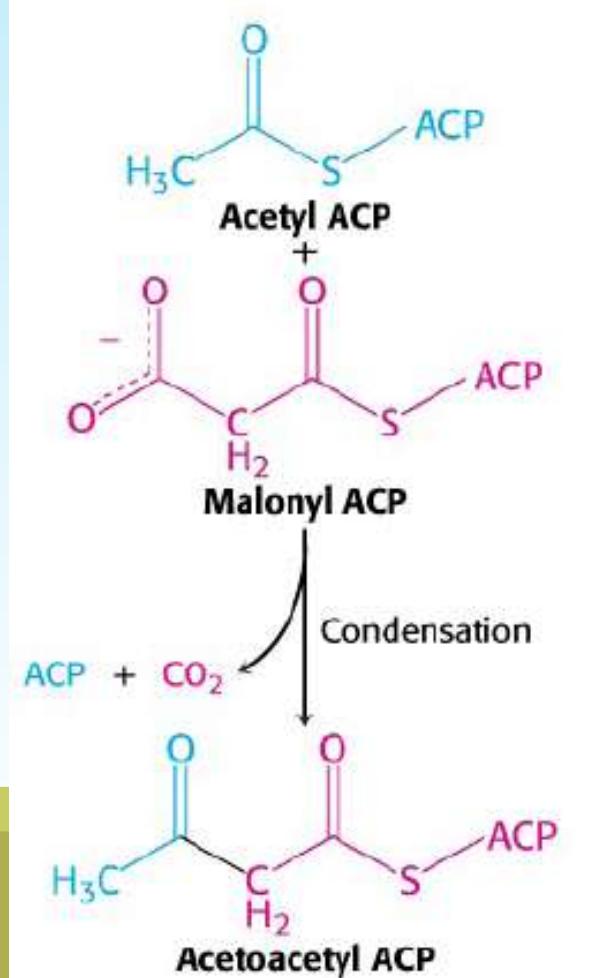
2. Pemanjangan rantai putaran 1:

- pembentukan asetil ACP dan malonil ACP
- reaksi dikatalis oleh asetil transasilase dan malonil transasilase



- Reaksi kondensasi
 - $\text{Asetil ACP} + \text{malonil ACP} \rightarrow \text{asetoasetil ACP} + \text{ACP} + \text{CO}_2$

- Reaksi Kondensasi

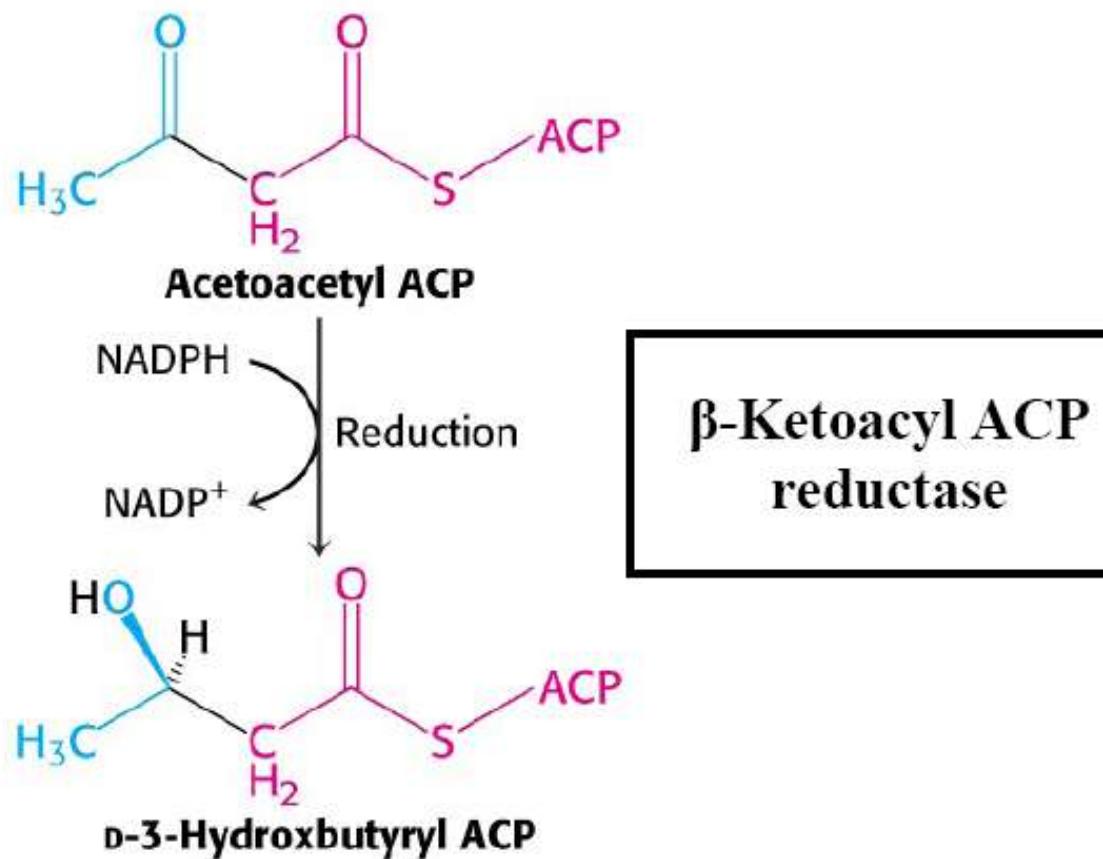


**Acyl-malonyl ACP
condensing enzyme**

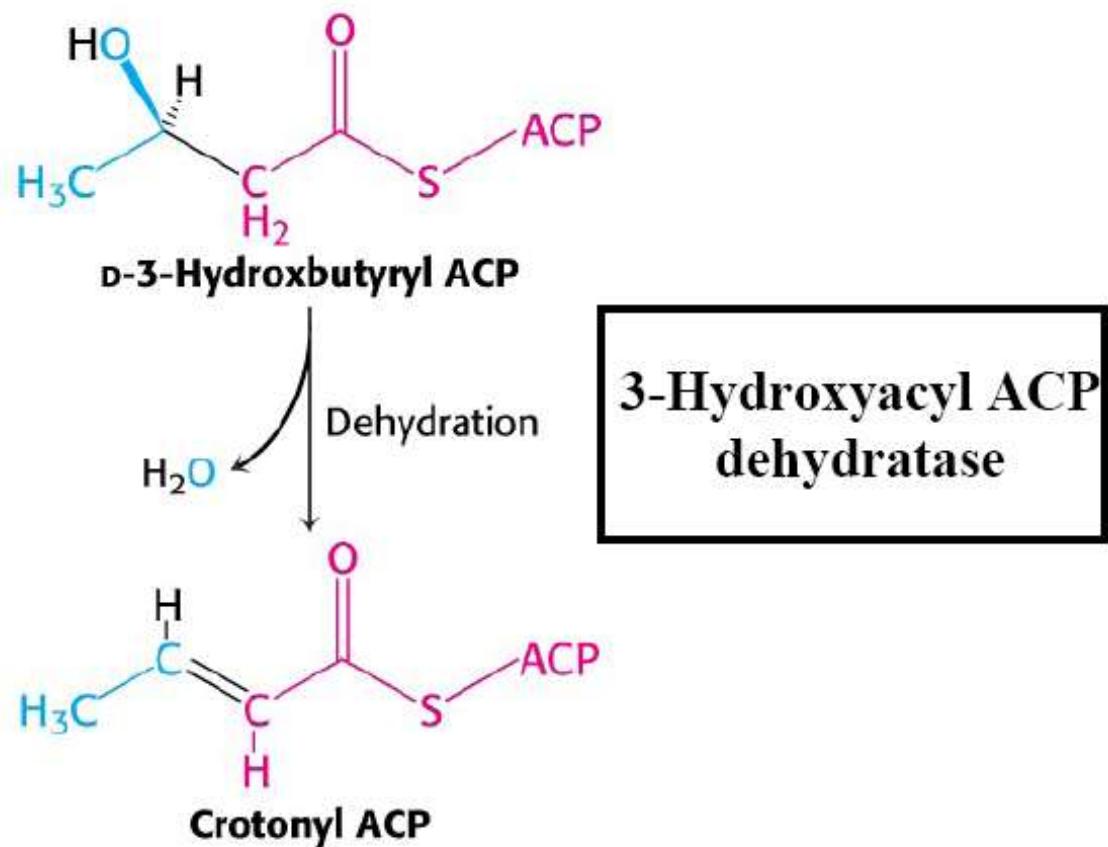
Reduksi gugus keto pada C-3 menjadi gugus metilen

- (1) asetoasetil ACP direduksi menjadi 3-hidroksi butiril ACP. Reaksi ini memerlukan NADPH sebagai pereduksi.
- (2) Dehidrasi 3-hidroksi butiril ACP menjadi krotonil ACP (merupakan trans- Δ^2 enoyl ACP).
- (3) Reduksi krotonil ACP menjadi butiril ACP dengan menggunakan senyawa peredusi NADPH, yang dikatalis oleh enzim enoyl ACP reduktase.

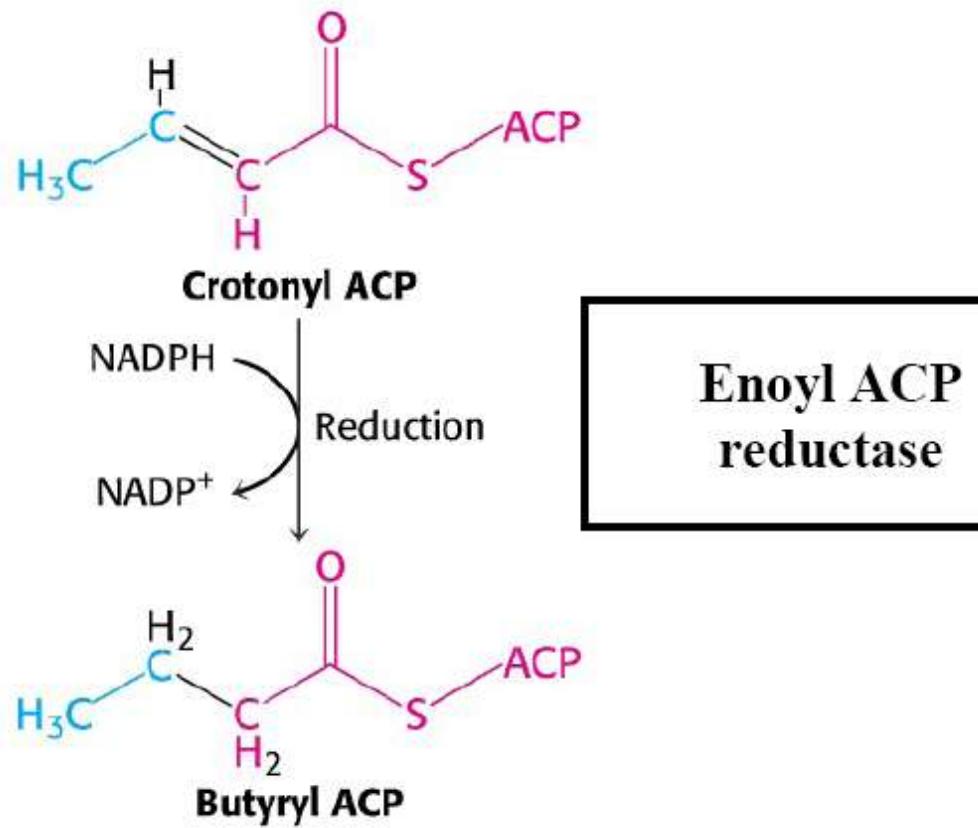
Reaksi reduksi I



Reaksi dehidrasi



Reaksi reduksi II



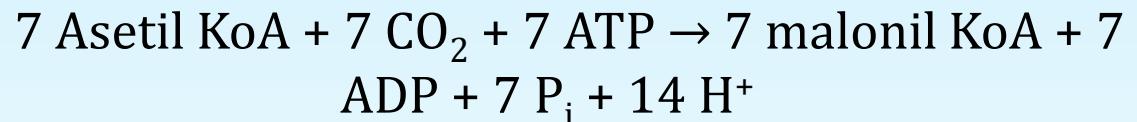
3. Pemanjangan rantai 2

Reaksi pemanjangan rantai putaran 2 : kondensasi burutil ACP dengan malonil ACP membentuk C_6 - β -ketoasil ACP

Reaksi ini sama dengan reaksi pemanjangan rantai putaran 1. Selanjutnya pemanjangan rantai diteruskan sampai terbentuk C_{16} asil ACP

Stoikiometri Sintesis Asam palmitat

- Asetil KoA + 7 Malonil KoA + 14 NADPH + 20 H⁺
→ palmitat + 7 CO₂ + 14 NADP⁺ + 8 KoA + 6 H₂O
- Reaksi tersebut memerlukan malonil KoA yang disintesis dari :



- Jadi stoikhiometri keseluruhan sintesis palmitat adalah:



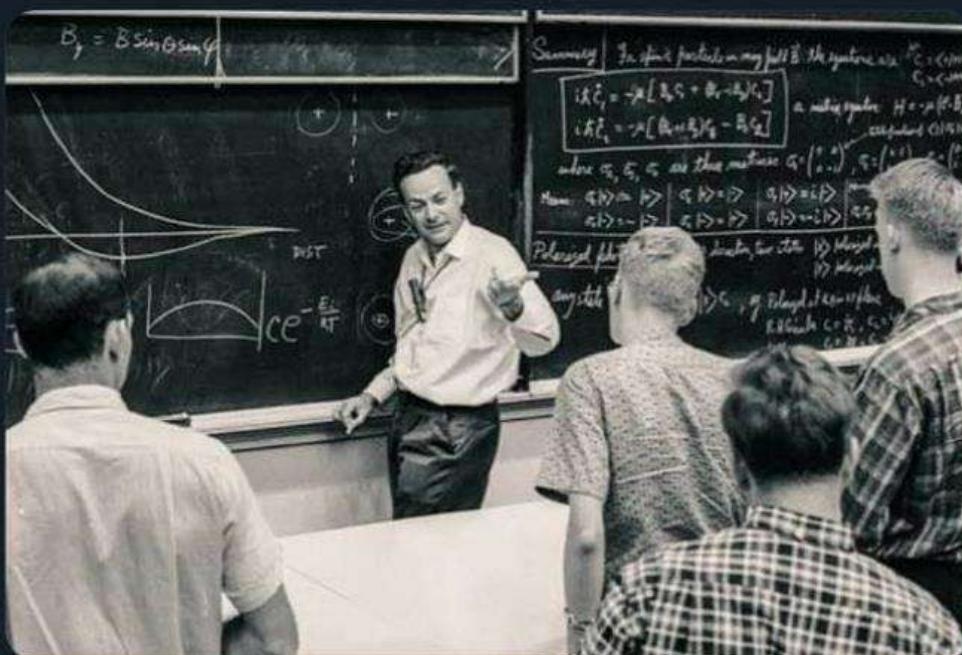
METABOLISME PROTEIN DAN ASAM AMINO

**WAHIDAH MAHANANI RAHAYU, S.T.P., M.Sc.,
TEKNOLOGI PANGAN
UNIVERSITAS AHMAD DAHLAN**



Richard Feynman
@ProfFeynman

If you want to master something, teach it. The more you teach, the better you learn. Teaching is a powerful tool to learning.



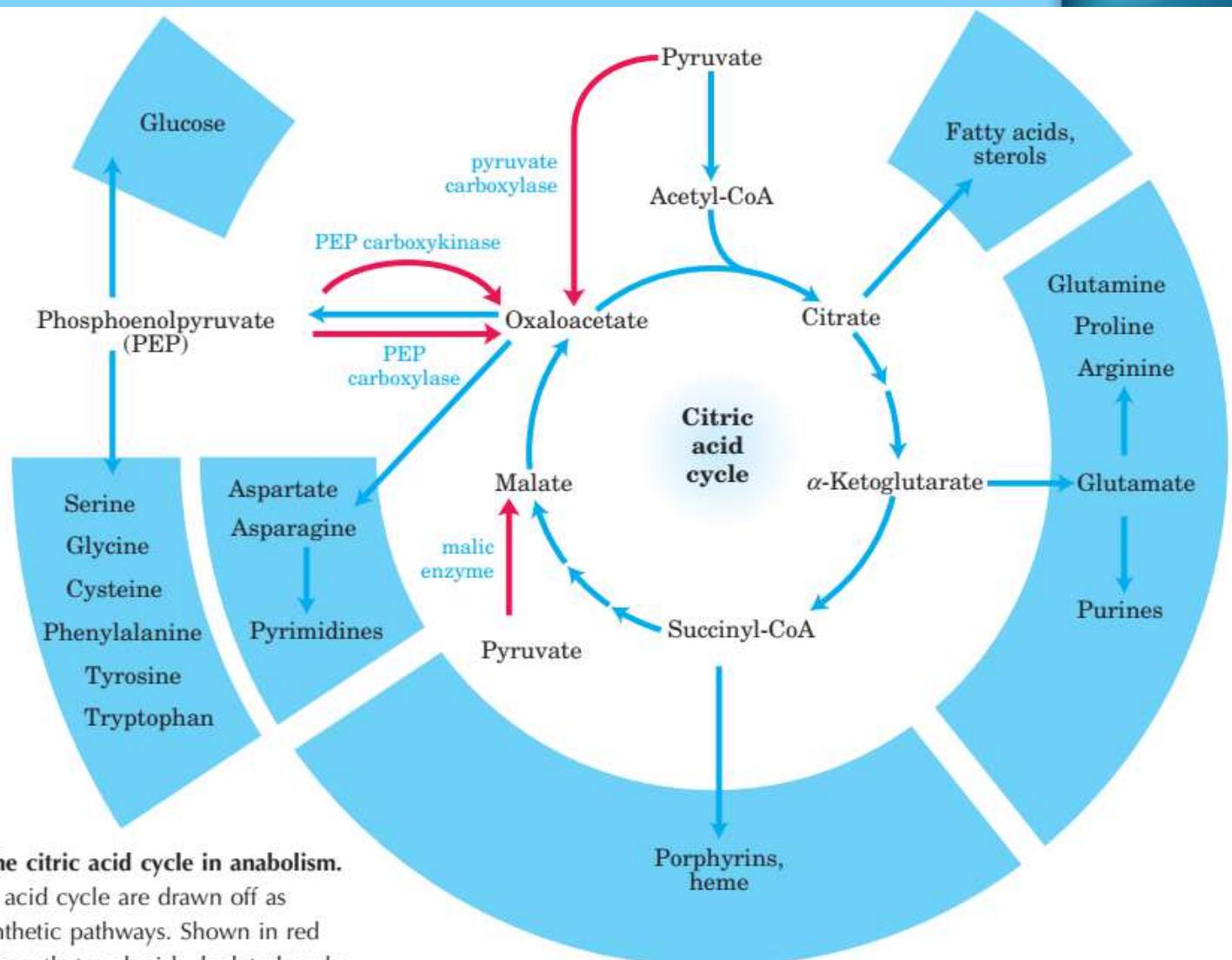


FIGURE 16-15 Role of the citric acid cycle in anabolism.

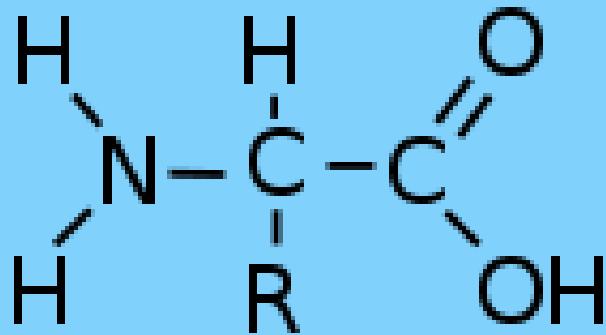
Intermediates of the citric acid cycle are drawn off as precursors in many biosynthetic pathways. Shown in red are four anaplerotic reactions that replenish depleted cycle intermediates (see Table 16-2).

PENGERTIAN

ASAM AMINO

Senyawa organik yang memiliki gugus fungsi karboksilat (-COOH) dan amina (-NH₂).

**STRUKTUR
ASAM AMINO**



**SIFAT- SIFAT
ASAM AMINO**

❖ Bersifat amfoter
dapat membentuk ion zwitter
bersifat optis- aktif kecuali glisin
dapat berpolimerisasi membentuk protein

PROTEIN

SEDERHANA

KOMPLEK

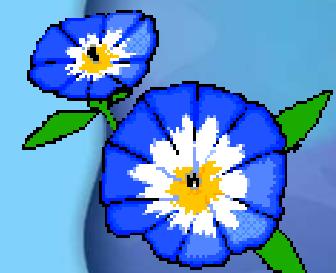
Sec. Nutrisi

ASAM AMINO
ESENSIAL

ASAM AMINO
NON ESENSIAL

Asam amino & bhn lain

- Heme
- Lipid
- KH



MACAM-MACAM ASAM AMINO MENURUT SIFAT ATAU STRUKTUR KIMIAWINYA

Asam amino alifatik sederhana



Asam amino hidroksi-alifatik

Gly, Ala, Val, Leu, Ile

Ser, Thr

As. Asp, As. Glu

Asn, Gln.

Arg, His

Cys, Met.

Pro

Phe, Tyr, Trp.

Asam amino dikarboksilat (asam)

Amida

Asam amino basa

Asam amino dengan sulfur

Prolin

Asam amino aromatik

ASAM AMINO

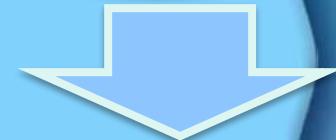
Esensial



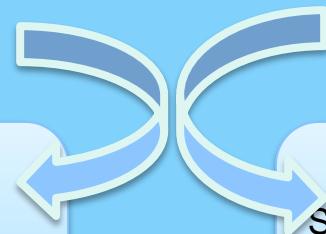
Asam amino yang tidak dapat dibuat/diproduksi oleh tubuh

Arginine, Leusin, Isoleusin, Methionine, Lisin, Treonin, Valin, Fenilalanin, Triptofan.

Non- Esensial



Asam amino yang dapat dibuat/diproduksi oleh tubuh



Serine, Asparagin, Prolin & Hidroksiprolin, Aspartat, Glutamin & glutamat, Hidroksilisin, Alanin, Triosin, Sistein

KEBUTUHAN ASAM AMINO PADA MANUSIA

» Secara gizi

ESENSIAL

1. Arginin * (Arg) R
2. Histidin * (His) H
3. Isoleusin (Ile) I
4. Leusin (leu) L
5. Lisin (Lys) K
6. Metionin (Met) M
7. Fenilalanin (Phe) F
8. Treonin (Thr) T
9. Triptofan (Trp) W
10. Valin (Val) V

NON ESENSIAL

- | | | |
|------------------------------|-------|---|
| Alanin | (Ala) | A |
| Asparagin | (Asn) | N |
| Aspartat | (Asp) | D |
| Sistein | (Cys) | C |
| Glutamat | (Glu) | E |
| Glutamin | (Gln) | Q |
| Glisin | (Gly) | G |
| Prolin | (Pro) | P |
| Serin | (Ser) | S |
| Tirosin | (Tyr) | Y |
| Hidroksi prolin (Hyp) | | |
| Hidroksi lisin (Hyl) | | |

KATABOLISME



Menguraikan molekul kompleks menjadi senyawa sederhana.

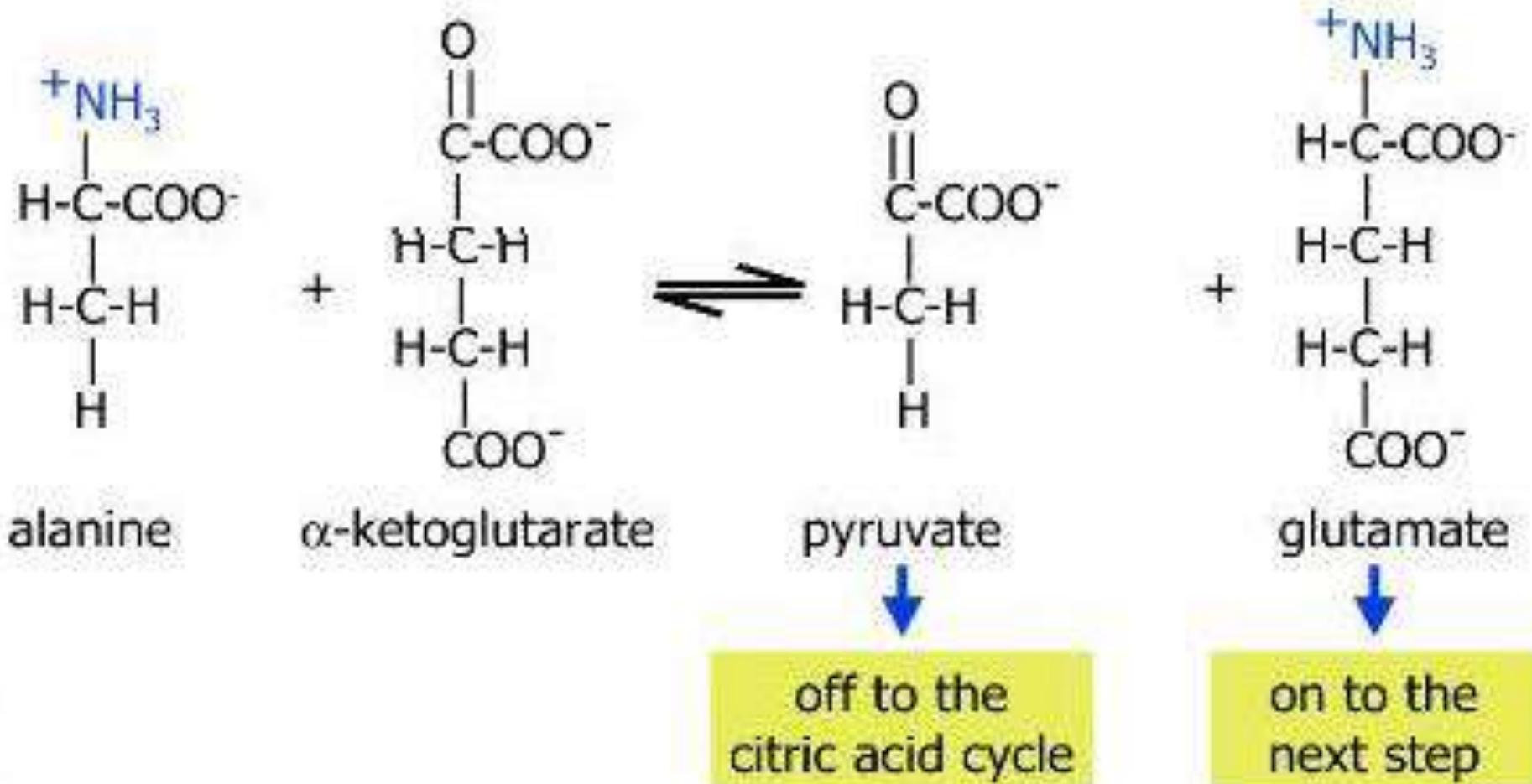
PELEPASAN GUGUS AMIN DALAM ASAM AMINO

Transminasi

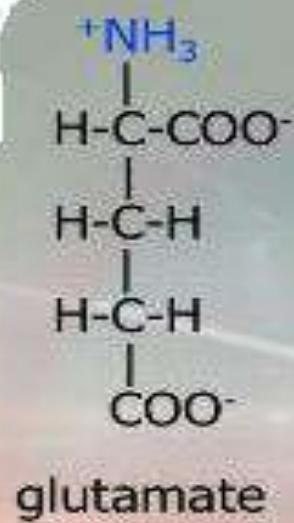
Deaminasi oksidatif

Enzim aminotransferase memindahkan amin kepada α -ketoglutarat menghasilkan glutamat atau oksaloasetat menghasilkan aspartat

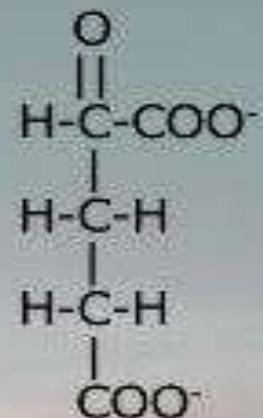
Pelepasan amin dari glutamat menghasilkan ion amonium



Contoh reaksi transminasi



+ NAD⁺ + H₂O



Energy

NADH

+

H⁺

+

NH₄⁺

off to the
urea cycle

Contoh reaksi deaminasi oksidatif

Arginin & Histidin

- * **Secara nutrisi semiesensial**

- Disintesis dgn kecepatan yang kurang memadai untuk mendukung pertumbuhan pada anak.

Hidroksi prolin & Hidroksi lisin

- Tidak diperlukan untuk sintesis protein
 - tetapi terbentuk selama pemrosesan pasca translasi kolagen (protein yang paling berlimpah jumlahnya pd jar. tubuh mamalia)

Dari 12 asam amino esensial

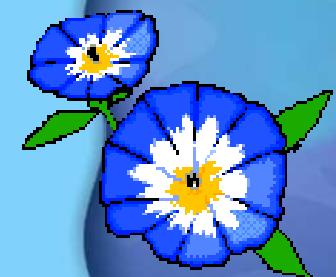
- 9 dibentuk dr senyawa amfibolik
- Cys, Tyr, Hyl dibentuk dr asam esensial
- **3 mekanisme pembentukan asam amino nonesensial (a.amino yang dpt disintesis oleh manusia) yaitu**
 - **asimilasi dari amonia bebas**
 - **transaminasi: reaksi yang menyangkut pemindahan gugus α -amino dr asam amino ke α - karbon asam keto, mmbtk a. amino dan a.keto baru mis:alanin, glutamat, aspartat.**
 - **modifikasi rangka karbon dari asam amino yang ada misal sistein, glisin, tirosin, prolin**

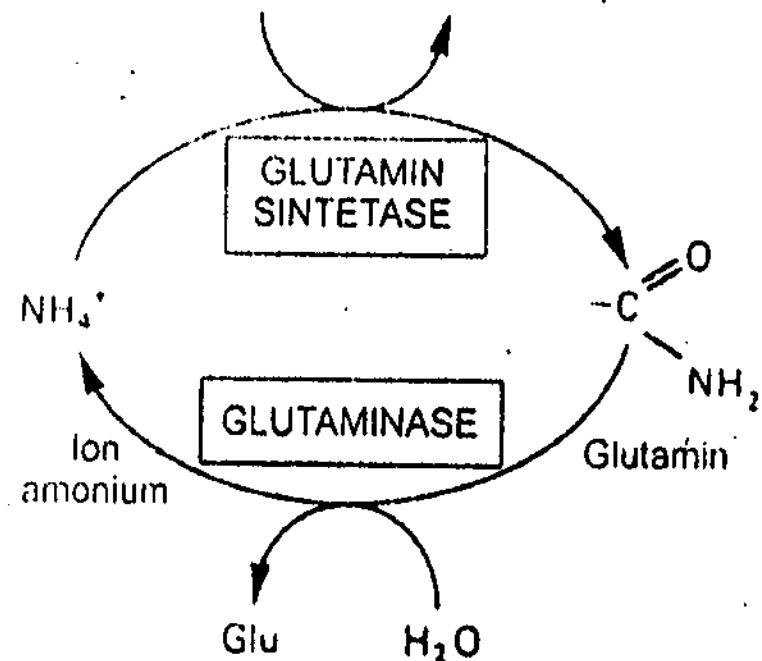
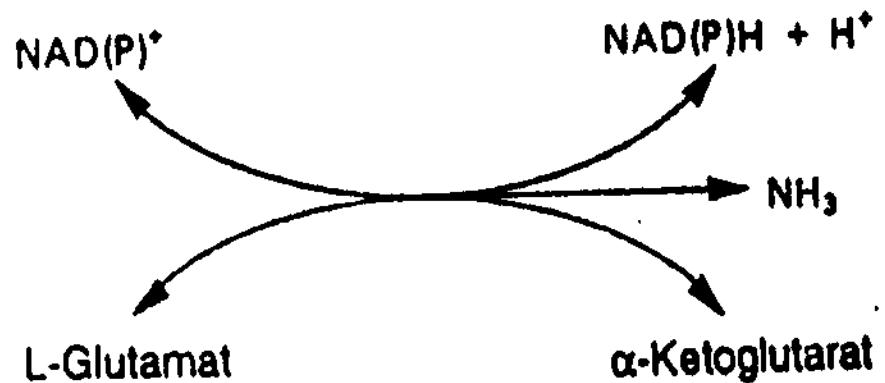
Glutamat

- Reaksi aminasi reduktif α ketoglutarat dikatalisis oleh glutamate dehidrogenase

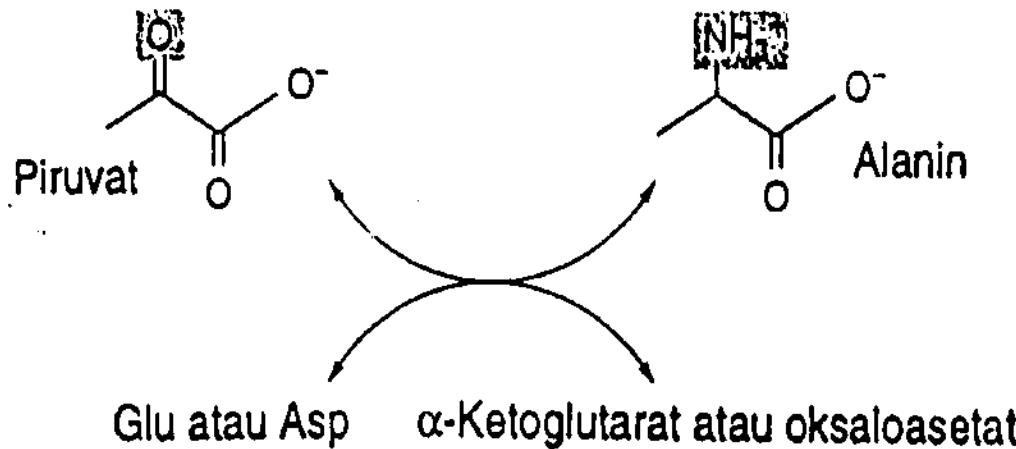
Glutamin

- Biosintesis glutamin dari glutamat dikatalisis oleh glutamin sintetase



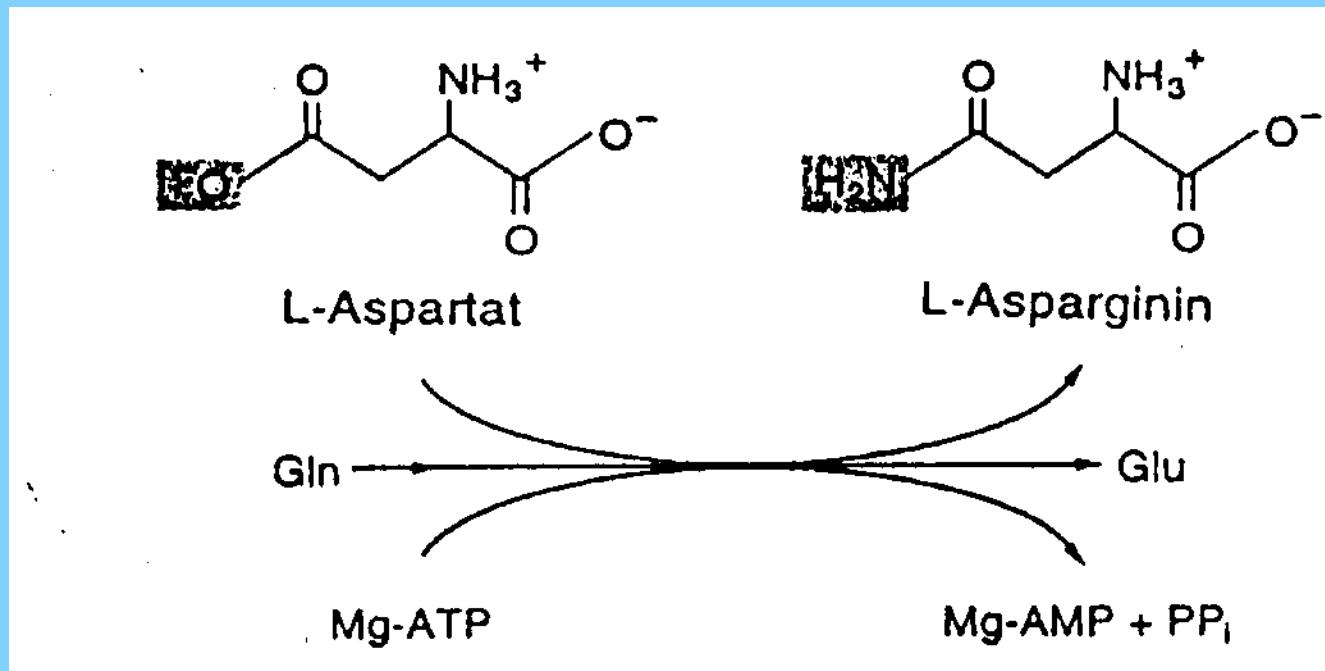


- 3. Alanin dan Aspartat
- Transaminasi piruvat menjadi L alanin. Pada alanin ini donor amino dapat dari glutamat maupun aspartat. Aspartat berasal dari Transaminasi Oksalo asetat.



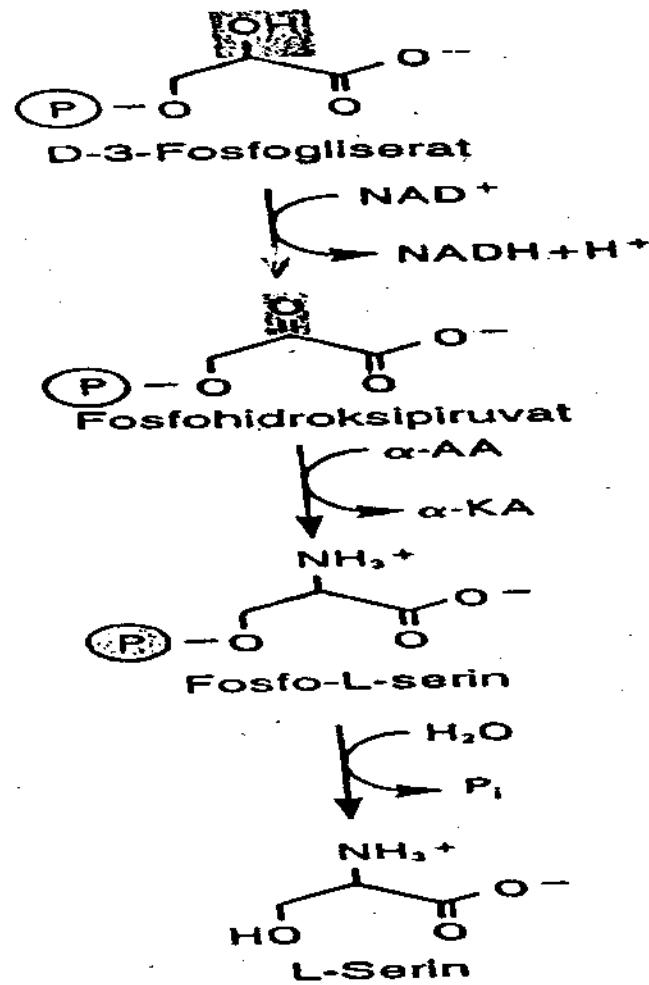
ASPARTAT

Aspartat menerima gugus amida dr glutamin untuk membentuk asparagin



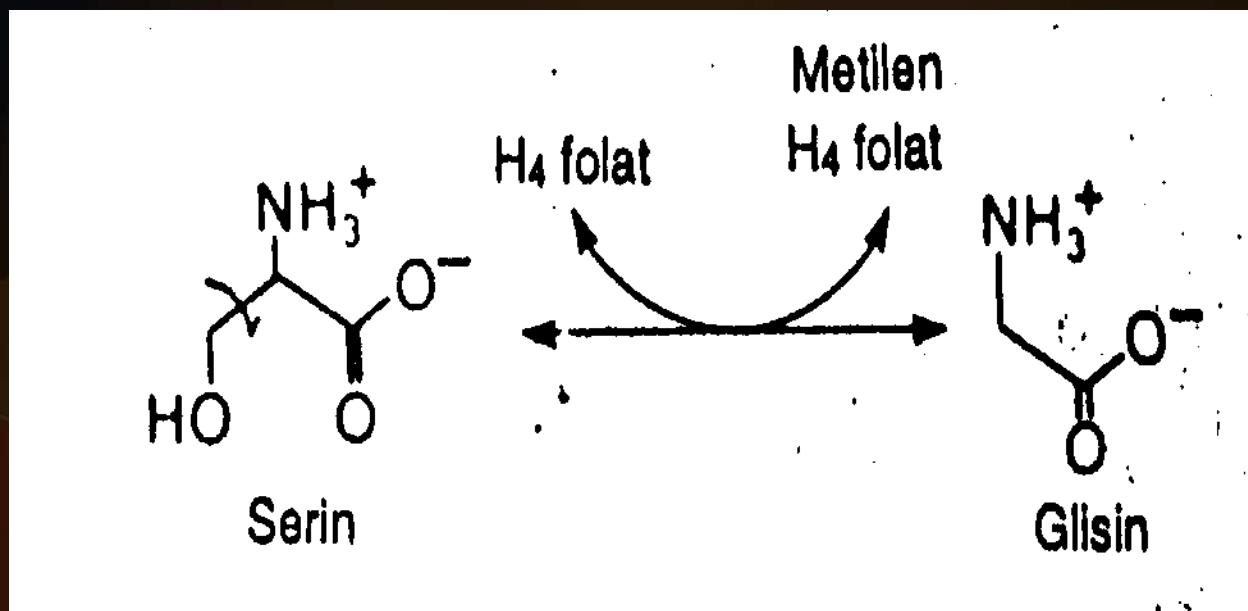
SERIN

Serin dibentuk dari senyawa *glikotik D-3-fosfogliserasat*. Gugus α -hidroksi direduksi menjadi gugus okso oleh NAD $+$, kemudian mengalami transaminasi membentuk fosfo serin selanjutnya mengalami defosfo membentuk serin.

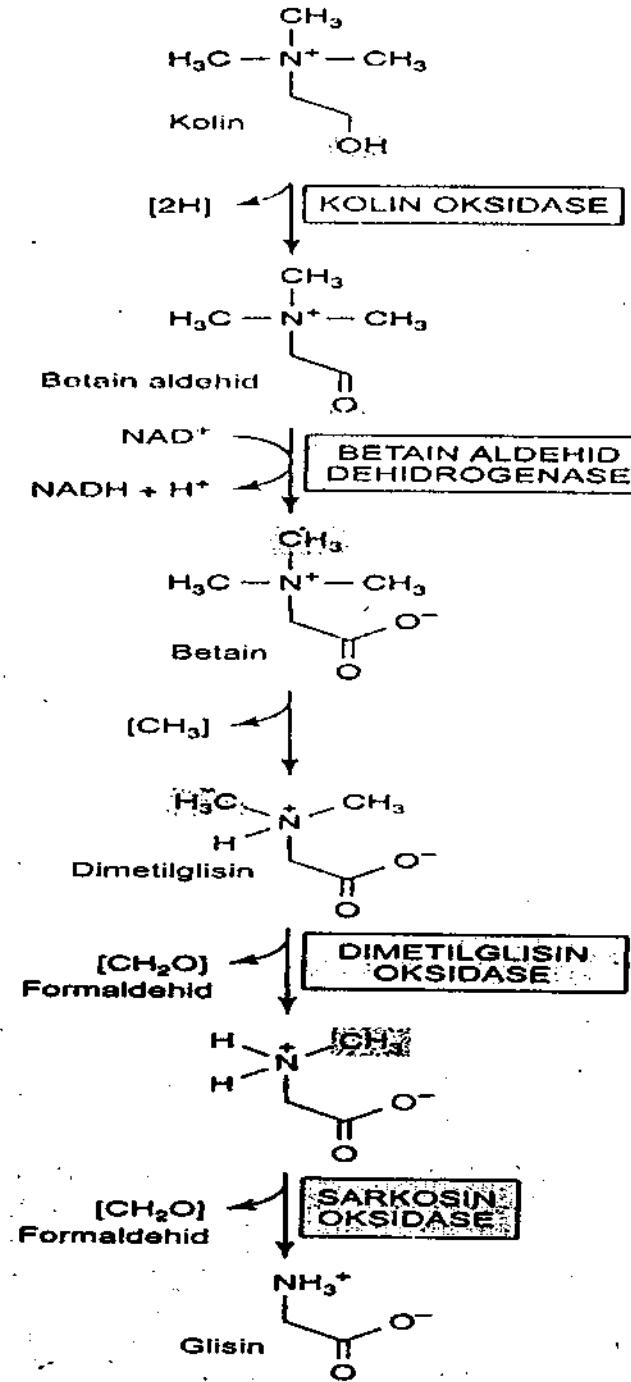


GLISIN

- Glisin disintesis dari
 - a. Glioksilat, glutamat atau alanin yang dikatalisis oleh glisin transaminase yang terdapat pada sitosol hati.
 - b. Serin lewat reaksi serin hidroksi metil transferase, reaksi nya bersifat reversibel
 - c. kolin

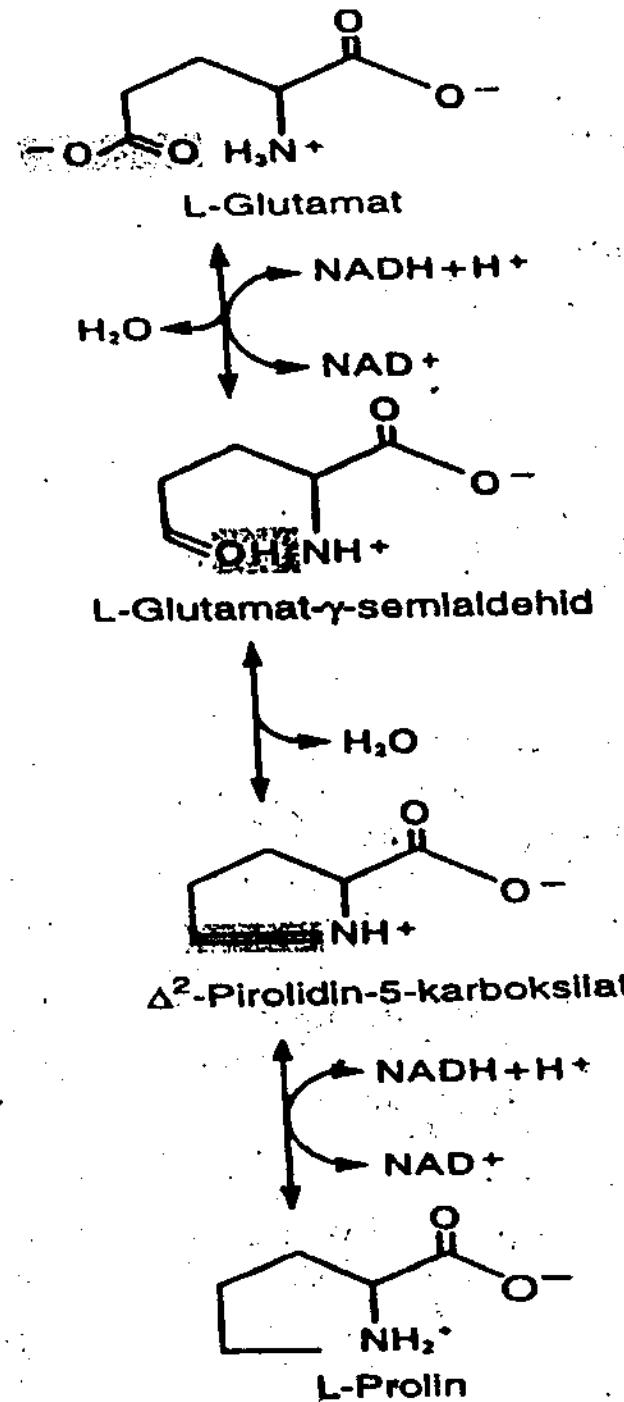


Kolin lewat reaksi oleh kolin oksidase menjadi betain aldehid, kemudian oleh betain aldehyde dehidrogenase menjadi betain kemudian menjadi dimetil glisin, dimetil glisin oleh dimetil oksidase dan sarkosin oksidase menjadi glisin.



PROLIN

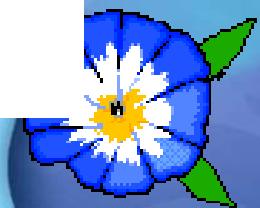
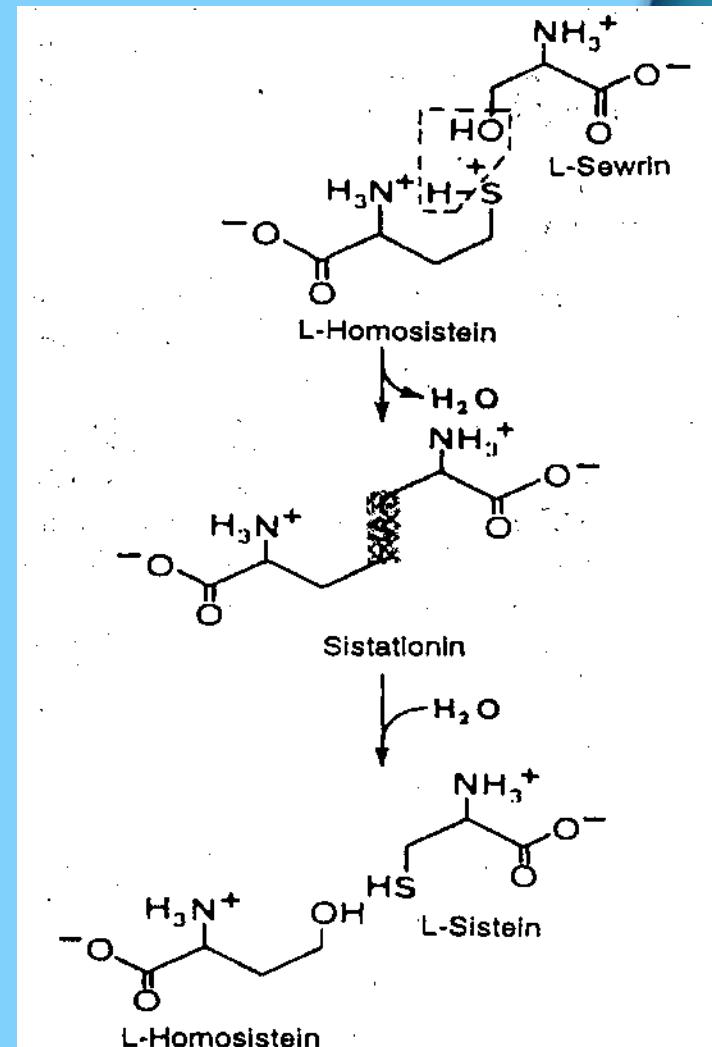
Biosintesis prolin dari glutamat
Mell pembalikan reaksi
katabolisme prolin



SISTEIN (non esensial)

metionin (esensial)

serin (non esensial)



TIROSIN

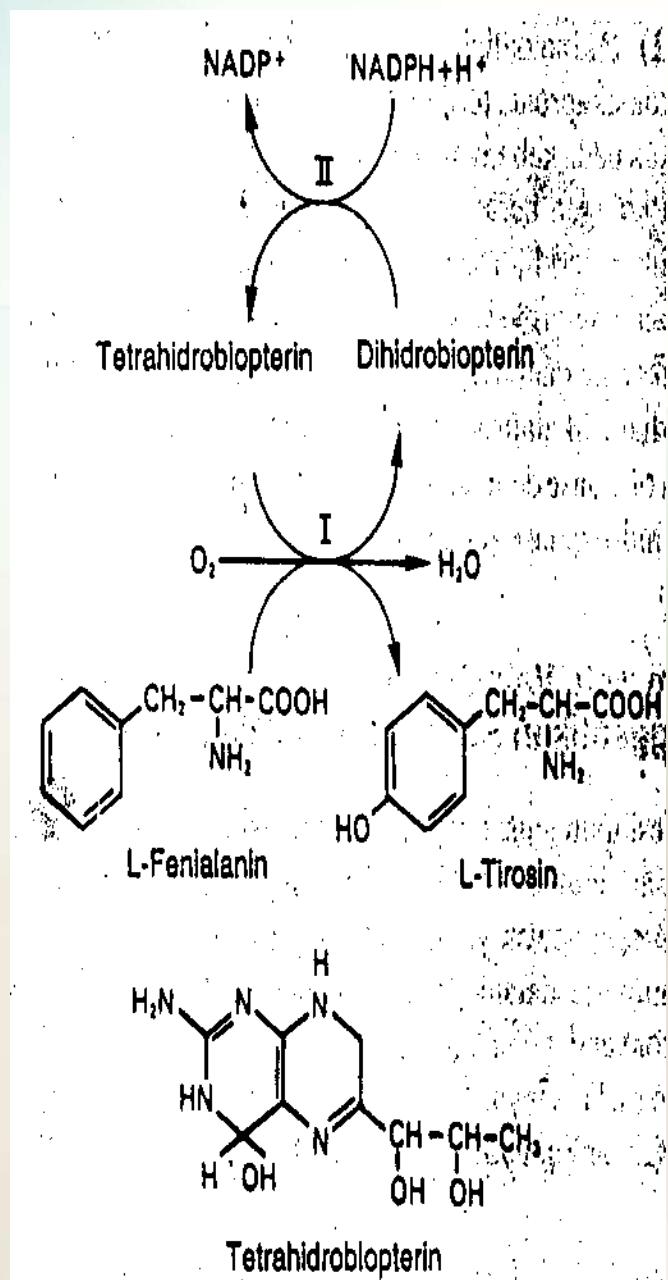
Tirosin dibentuk oleh fenilalanin (a.a. esensial)

Reaksi: Fenilalanin hidroksilasi

I. Mengkatalisis reduksi dihidrobiopterin oleh NADPH

II. Mengkatalisis reduksi $O_2 \rightarrow H_2O$

Mengkatalisis reduksi
Fenilalanin → tirosin



BIOSINTESIS ASAM AMINO NON ESENSIAL DARI SENYAWA AMFIBOLIK

- LIHAT SKEMA

- DARI SEYAWA AMFIBOLIK

1. ALFAKETOGLUTARAT → GLU → GLN

2. PYR → ALA

3. OKSALOASETAT → ASP → ASN

4. D-3 FOSFOGLISERAT → SER

5. KHOLIN/ GLIOKSILAT → GLY

- DARI ASAM AMINO NON ESENSIAL LAIN

- GLU → PRO → HIDROKSIPROLIN

- SER → GLY

- DARI ASAM AMINO ESENSIAL

- MET + SER (A.A. NON ESS) → CYS

- PHE → TYR

- LYS → HIDROKSILISIN

RINGKASAN BIOSintesis ASAM AMINO

| A. AMINO | PREKURSOR | CIRI yang MENONJOL |
|-----------|--|--|
| Alanin | Piruvat | Dgn transaminasi |
| Glutamat | α ketoglutarat | Dgn aminasi reduktif Dgn transaminasi |
| Glutamin | Glutamat | ADP + Pi adalah produk |
| Aspartat | Oksaloasetat | Dgn transaminasi |
| Serin | 3-fosfo-D-gliserat 3- fosfogliserat glisin | Seny. Antara fosfoserin Seny. Antara hidroksi piruvat Metil THF (tetra hidrofolat) |
| Glisin | Serin serin | Membutuhkan THF Seny. Antara glioksilat |
| Sistein | Serin & metionin | SEny. Antara sistationin |
| Tirosin | Fenilalanin | Ko-enzim biopterin (fenilketonuria) |
| Prolin | Glutamat&arginin | Glutamat semialdehid |
| Asparagin | aspartat | AMP+PPi adalah produk |



BIOSINTESIS ASAM AMINO NON ESENSIAL DARI SENYAWA AMFIBOLIK

- LIHAT SKEMA

- DARI SEYAWA AMFIBOLIK

1. ALFAKETOGLUTARAT → GLU → GLN

2. PYR → ALA

3. OKSALOASETAT → ASP → ASN

4. D-3 FOSFOGLISERAT → SER

5. KHOLIN/ GLIOKSILAT → GLY

- DARI ASAM AMINO NON ESENSIAL LAIN

- GLU → PRO → HIDROKSIPROLIN

- SER → GLY

- DARI ASAM AMINO ESENSIAL

- MET + SER (A.A. NON ESS) → CYS

- PHE → TYR

- LYS → HIDROKSILISIN



SENYAWA AMFIBOLIK

- SENYAWA AMFIBOLIK:
 - DAPAT DISINTESIS MENJADI SENYAWA LAIN (ANABOLISME)
 - DAPAT DIKATABOLISME / DIOKSIDASI
- CONTOH : ANGGOTA SIKLUS ASAM SITRAT
- BIOSINTESIS, MISALNYA DARI α -KETOGLUTARAT DAPAT DISINTESIS MENJADI GLUTAMAT
- ASAM KETO + GUGUS AMINO → ASAM AMINO

KATABOLISME PROTEIN DAN NITROGEN ASAM AMINO

Cara nitrogen dikeluarkan dari asam amino serta diubah menjadi *urea*, dan permasalahan medis yang terjadi bila terdapat gangguan pd reaksi ini.

Makna biomedis yang penting

Amonia adalah senyawa yang toksik bg manusia → mekanisme belum diketahui.

Tubuh membuang amonia dgn mengubahnya menjadi senyawa non toksik → urea → melalui siklus urea.

Gangguan

1. gangguan faal hati → Amonia tertumpuk di darah → gejala klinik
 - Sirosis hepatis yang masif
 - hepatitis berat
2. Bayi yang lahir dgn defisiensi aktivitas salah satu enzim pd siklus urea.

Keseimbangan Nitrogen

Perbedaan antara total masukan nitrogen dan total kehilangan nitrogen

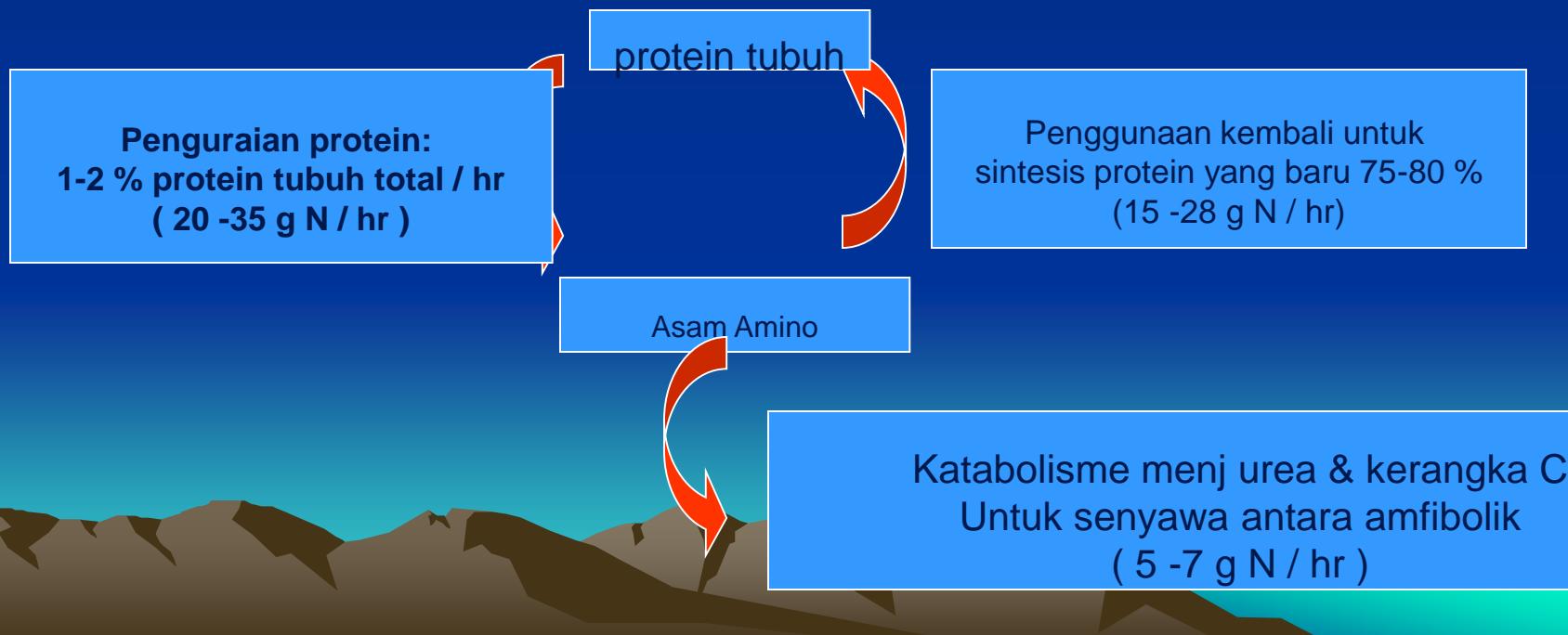
1. Keseimbangan nitrogen +
 - ▣ Konsumsi N > diekskresikan
 - ▣ Misal: Anak yang sedang tumbuh
Bumil
2. Keseimbangan nitrogen
 - ▣ Manusia dewasa, masukan N mengimbangi pengeluaran melalui feces dan urin.
3. Keseimbangan nitrogen negatif
 - ▣ - Pasien pasca bedah
 - Penyakit kanker stadium lanjut.
 - Konsumsi nitrogen dlm jumlah tidak memadai (kwashiorkor)
 - Konsumsi makanan dgn protein bermutu rendah.

Proses pertukaran protein terjadi pada segala bentuk kehidupan

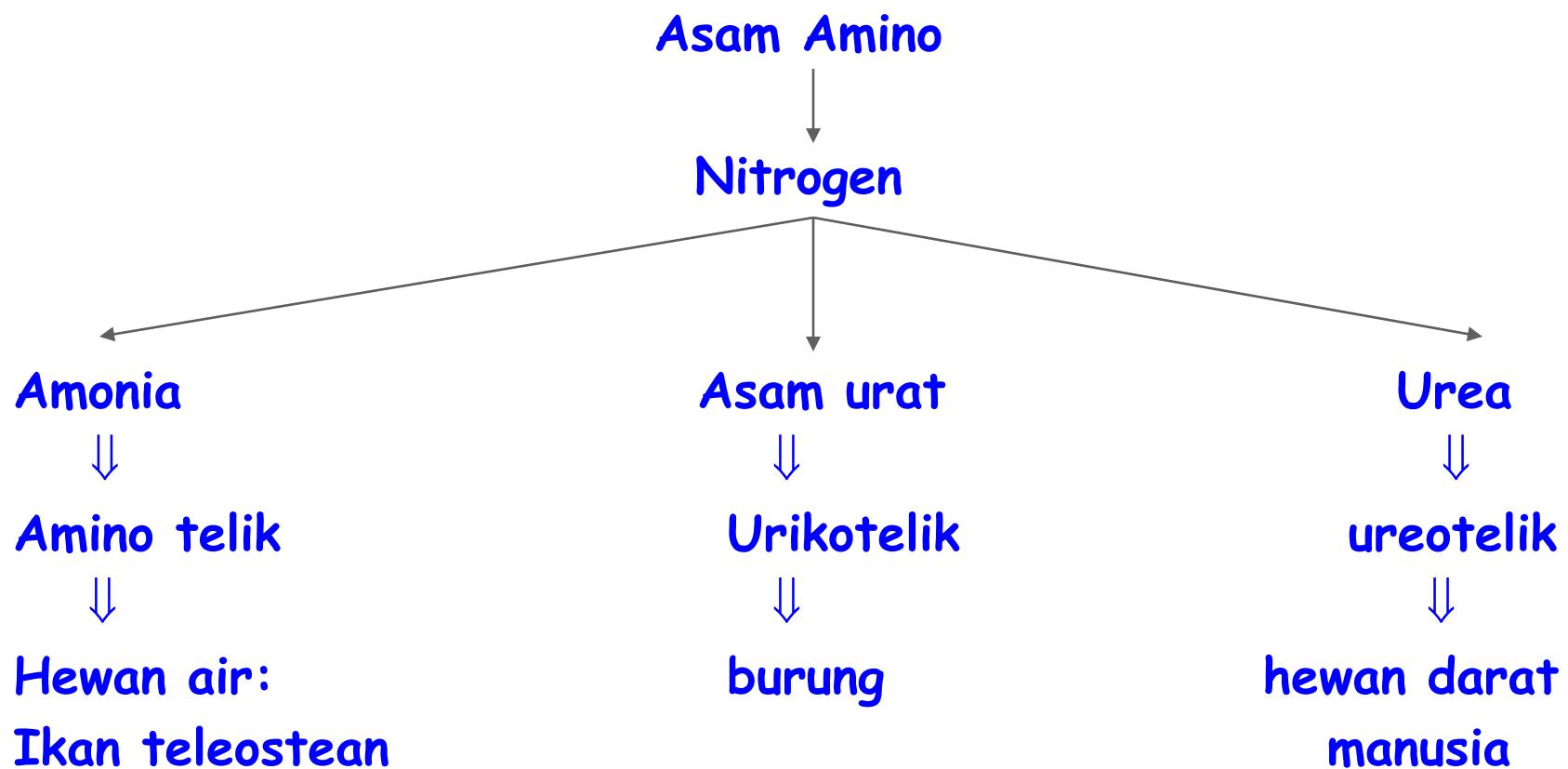
Proses pd sel hidup terus menerus akan diperbarui melalui proses pertukaran protein:

- sintesis
- penguraian protein dan asam amino

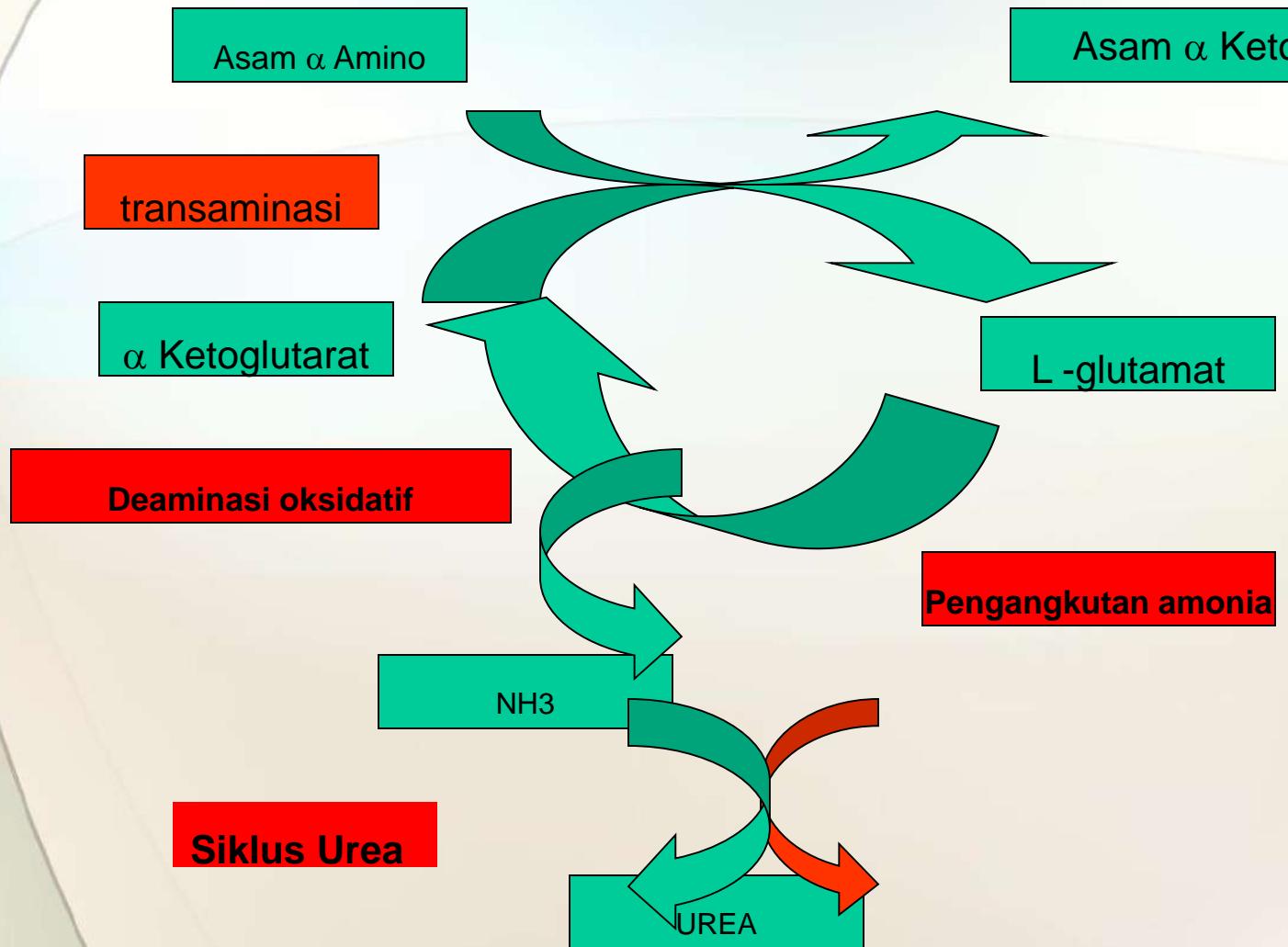
Hubungan kualitatif untuk proses pertukaran protein & a. amino



Nitrogen asam amino menjadi berbagai hasil akhir

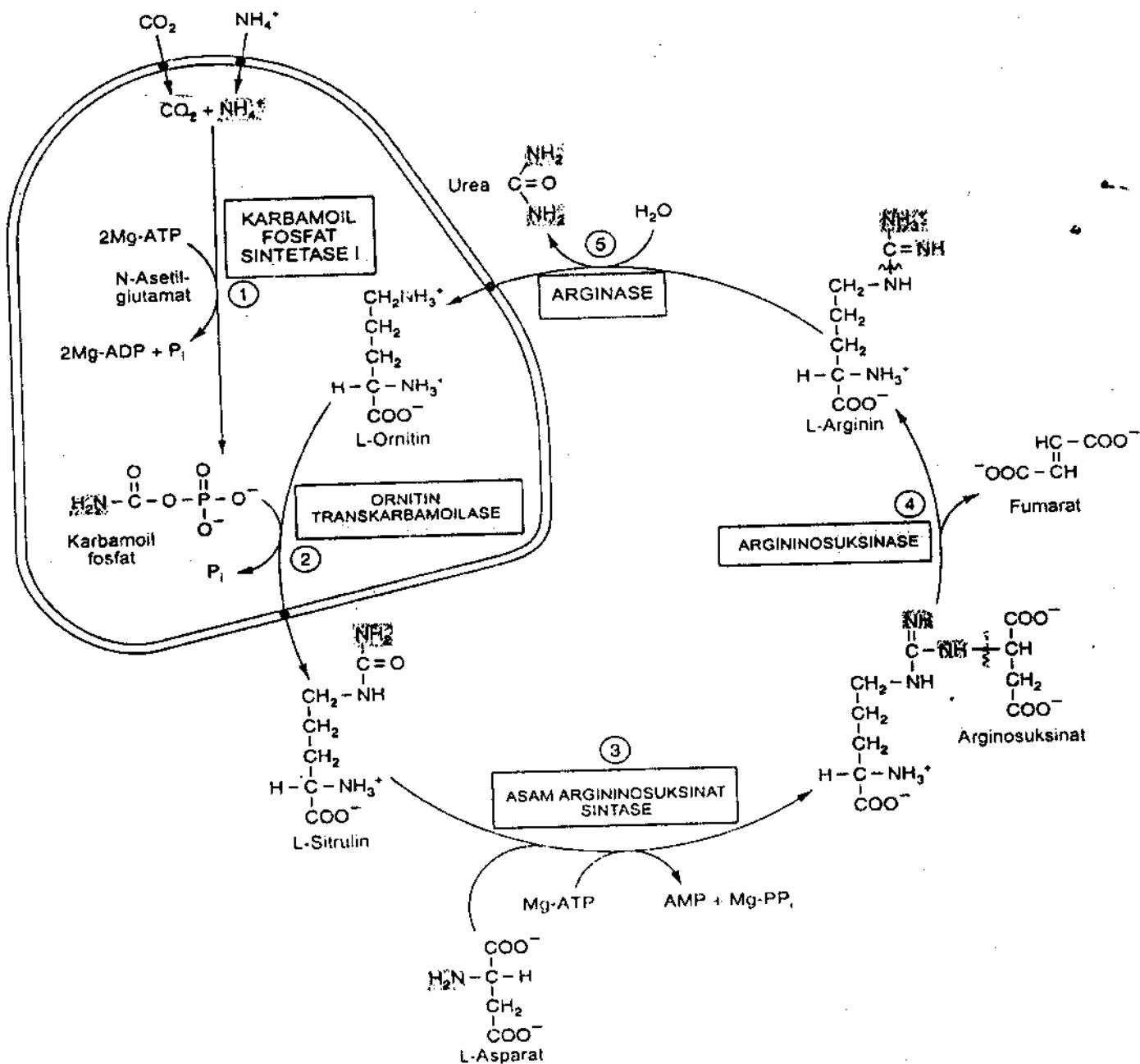


BIOsintesis UREA DIBAGI 4 TAHAP

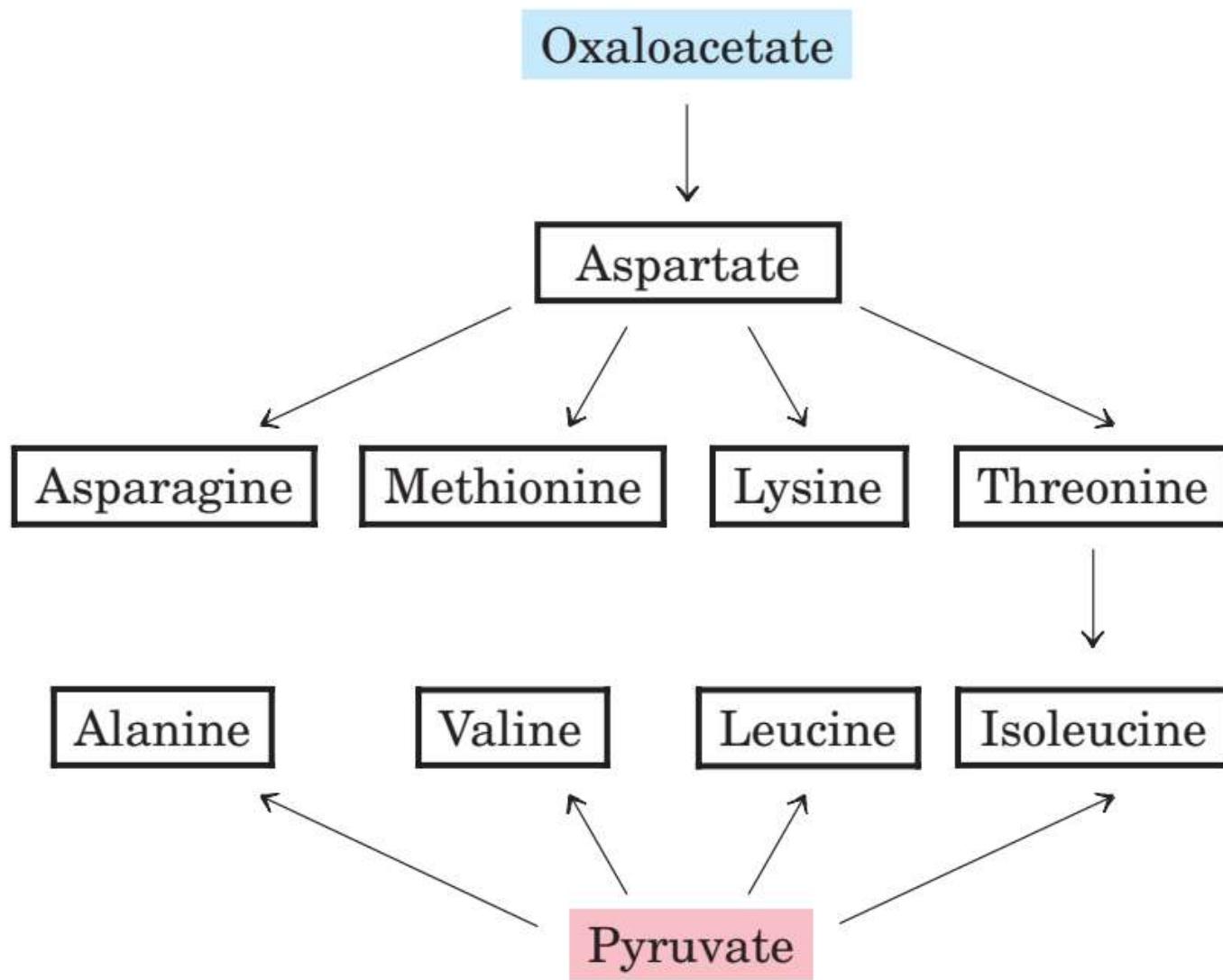


- α Pemindahan ggs α amino dari A. Amino ke α karbon asam keto.
- Ada 12 dr 20 AA yang m' alami transaminasi
- Dikatalisis oleh E. Transaminasi / Amino transferase
Ko Enzim: Vit B6 (piridoksal fosfat)
- Transaminase adalah enzim spesifik
Hanya bagi satu pasang A α amino & α keto
- 3 Enzim transaminase
 - Alanin piruvat transaminase (Alanin Trans)
 - Glutamat α ketoglutarat transaminase
(Glutamat transaminase)
 - Aspartat transaminase

SIKLUS UREA



Three Nonessential and Six Essential Amino Acids Are Synthesized from Oxaloacetate and Pyruvate



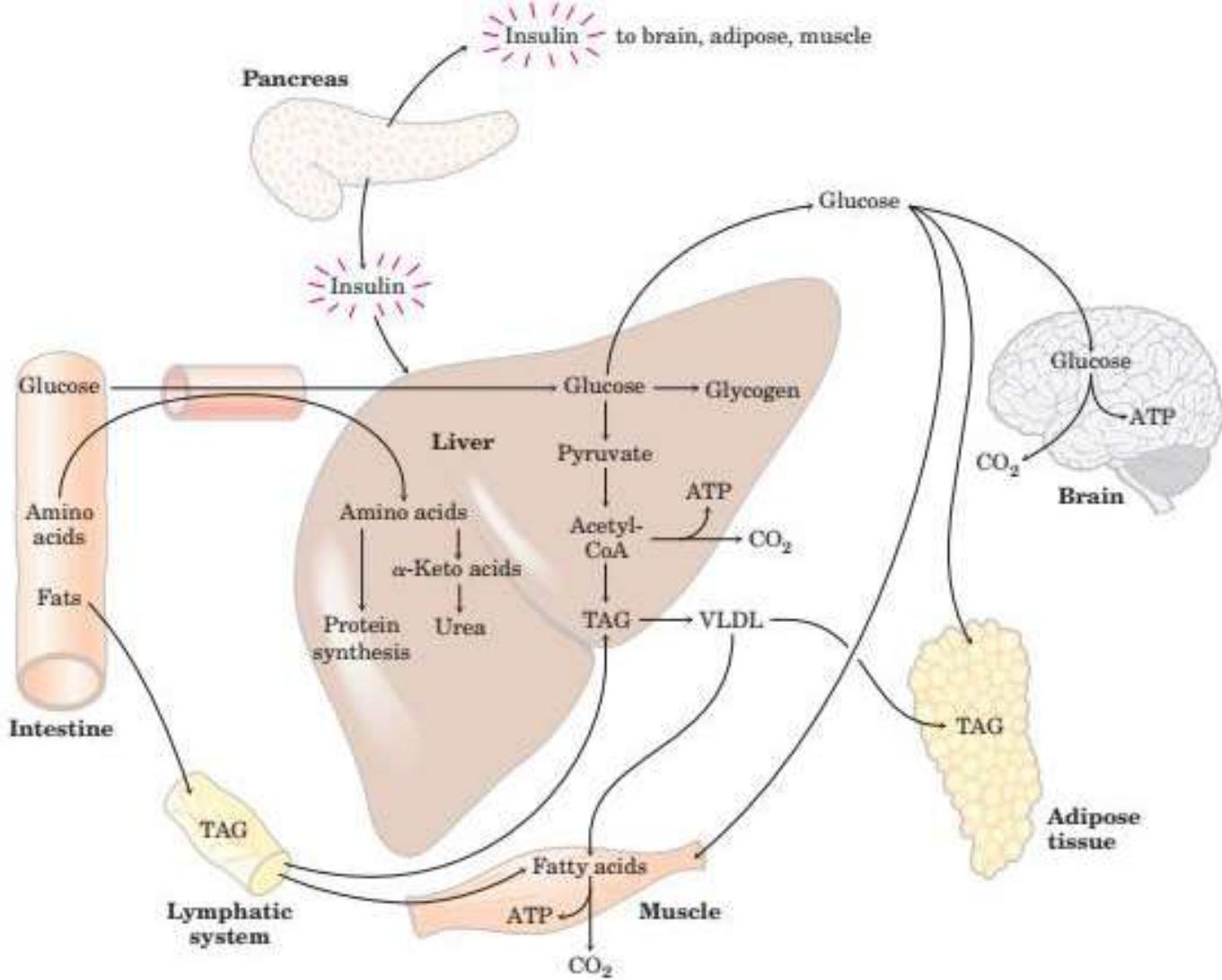
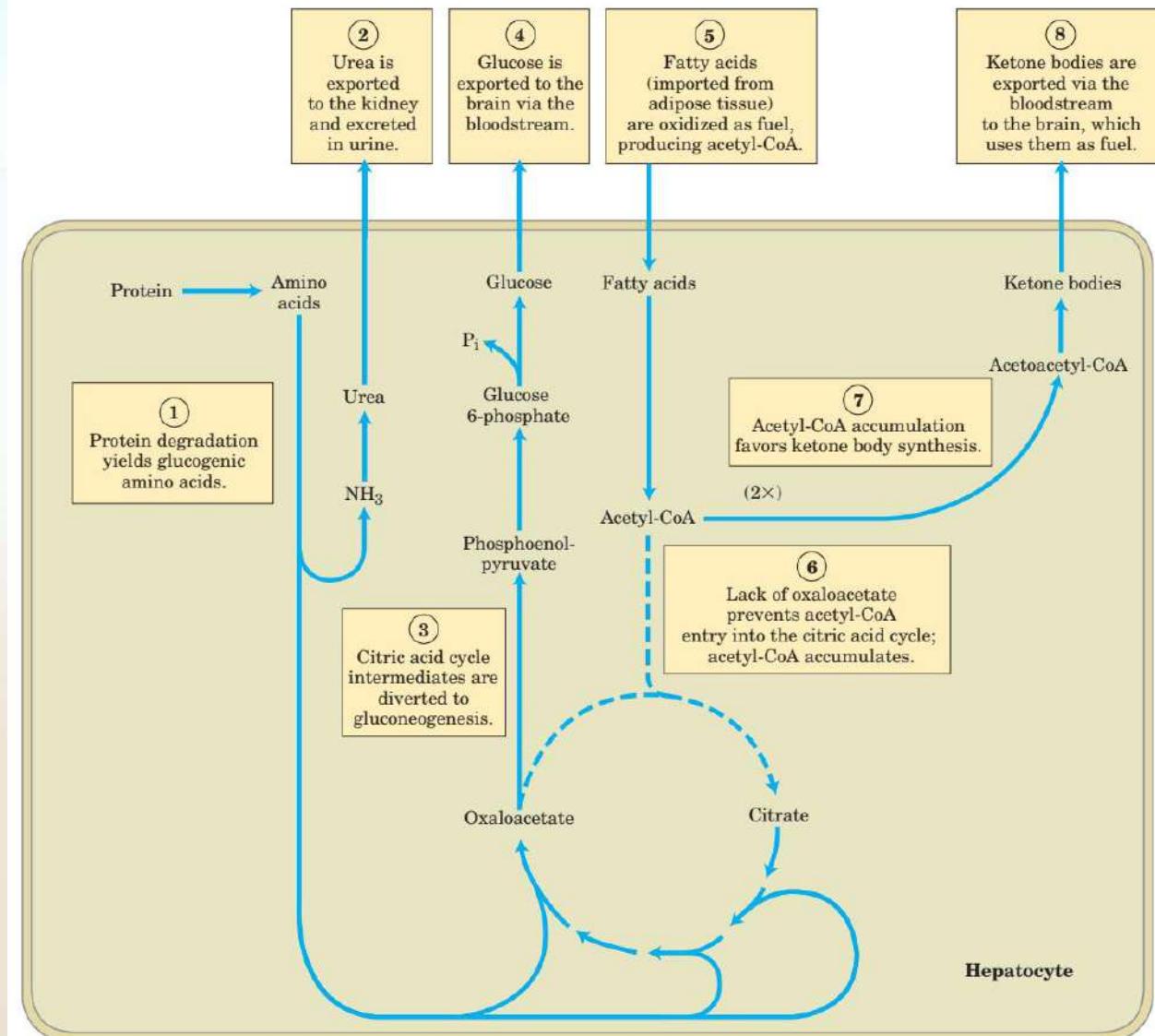


FIGURE 23-26 The well-fed state: the lipogenic liver. Immediately after a calorie-rich meal, glucose, fatty acids, and amino acids enter the liver. Insulin released in response to the high blood glucose concentration stimulates glucose uptake by the tissues. Some glucose is exported to the brain for its energetic needs, and some to fat and muscle tissue. In the liver, excess glucose is oxidized to acetyl-CoA, which is used to synthesize fatty acids for export as triacylglycerols in

VLDLs to fat and muscle tissue. The NADPH necessary for lipid synthesis is obtained by oxidation of glucose in the pentose phosphate pathway. Excess amino acids are converted to pyruvate and acetyl-CoA, which are also used for lipid synthesis. Dietary fats move via the lymphatic system, as chylomicrons, from the intestine to muscle and fat tissues.

During Fasting and Starvation, Metabolism Shifts to Provide Fuel for the Brain

Fuel metabolism in the liver during prolonged fasting or in uncontrolled diabetes mellitus. After depletion of stored carbohydrates,¹ proteins become an important source of glucose, produced from glucogenic amino acids by gluconeogenesis.⁵ Fatty acids imported from adipose tissue are converted to ketone bodies for export to the brain. Broken arrows represent reactions with reduced flux under these conditions. The steps are further described in the text.



- Hub. Siklus krebs dgn siklus urea

Arginosuksinat → arginin + fumarat

Fumarat → Malat ← oksaloasetat

Fumarase *malat DH ase*

Oksaloasetat → Aspartat

transaminasi

Satu mol urea membutuhkan

- Ⓐ 1 mol amonium
- Ⓐ 1 mol CO_2 .
- Ⓐ α amino nitrogen pada aspartat
- Ⓐ 3 mol ATP
- Ⓐ 5 enzim
- Ⓐ Asam amino
 - N Asetil Glutamat → pengaktif enzim
 - Sitrulin
 - Aspartat
 - Argino suksinat
 - Arginin
 - Ornitin

② KELN METABOLISME PD SIKLUS UREA

- ③ GK: Muntah 2 pd bayi.
 - Mual thd mkn berprotein tinggi
 - Ataksia intermiten
 - Iritabilitas
 - Letargia
 - Retardasi mental

④ Penata Laksanaan

- Diet rendah protein.
- Makanan sedikit2 tp sering

KELN. SIKLUS UREA BERUPA

➤ 1. Hiperamonia Tipe I.

- Def. Karbamoil Fosfat Sintetase
- Keln. Familial

➤ 2. Hiperamonemia tipe II

- Def. Ornitin transkarbomoilase
- Kenaikan kadar glutamin dlm darah, LCS,
urin krn glutamin sintetase meningkat

➤ 3. Sitrulinemia

- Sitrulinemia banyak diekskresi ke urin
(1-2 gram /hr) → >> Plasma, LCS
- Def. Arginosuksinat sintetase

KELN. SIKLUS UREA BERUPA

➤ 4. Asiduria Arginosuksinat

- GK : Arginosuksinat tinggi di drh, LCS, urin.

Rambut rapuh & beruntai (trikoreksis nodusa)

- Def: Arginosuksinase
- Enzim ini trdpt di sel2 fibroblas kulit, otak, hati, ginjal & eritrosit

➤ 5. Hiper argininemia

- Arginin meningkat di darah, LCS
- Enzim arginase eritrosit yang rendah