SAWA UNIVERSITY

Biochemistry I

Lipids Metabolism II

Sawa University
جامعـــــــــة ســــــــاوة الاهلية

College of health and medical techniques
كليــــــة التقنيـــات الصحيـة والطبيـة

Department of Medical Laboratories
قسم تقنيات المختبرات الطبية

2^{nd} Stage
المرحلــــــــــــــــة الثانية

الجانب النظري محاضرة رقم 9

Lecture No. 9 Theoretical

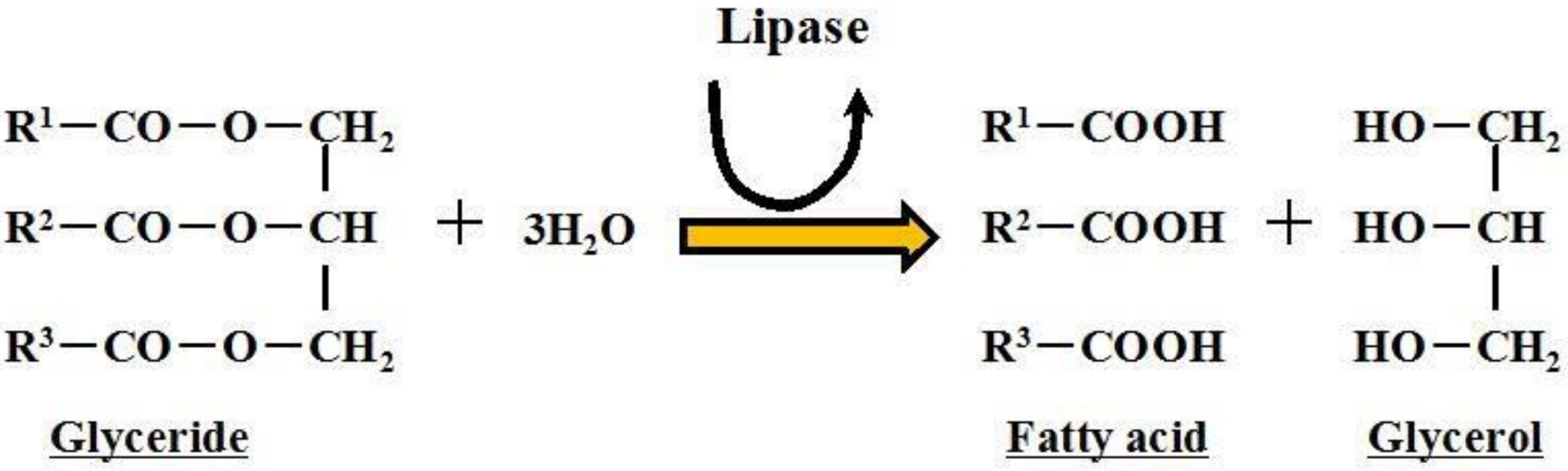
تدريسي المادة : م.د. عبدالرحمن يسر خليفة

Metabolism of Lipids

- Excess **fat**, neutralized and insoluble **triglycerides** (fat), is stored in large quantities in various parts of the body in both **animals** and **plants**.
- It decomposes and quickly destroys to provide the energy necessary for the cell.
- **Fat** is important in nutrition <u>because it has a high energy value **(9.3 kilocalories per gram)**</u>.

Triacylglycerols

- **Triacylglycerols (TAG) (triglycerides)** are the most abundant dietary lipids.
  - Each **triacylglycerol** has a **glycerol** backbone to which are esterified **3 fatty acids**
  - Most **triacylglycerols** are “**mixed**.” The **3 fatty acids** differ in chain length & number of double bonds.
  - The initial event in utilizing fat as an energy source is **the hydrolysis of triacylglycerol (Lipolysis).**
  - **Lipases** hydrolyze **triacylglycerols**, releasing **one fatty acid** at a time, yielding **diacylglycerols**, & **eventually glycerol**.

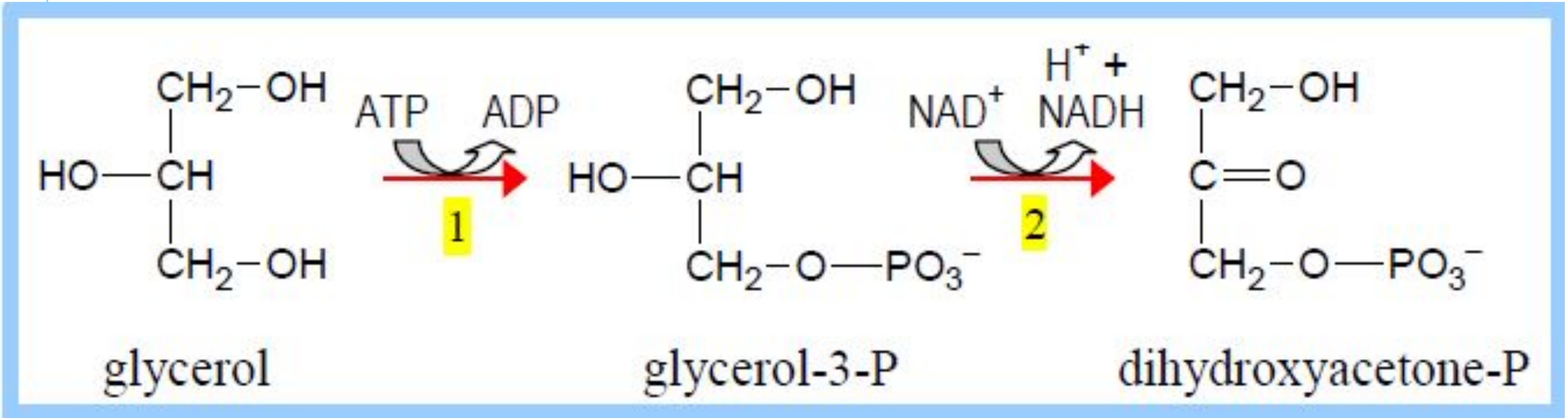


- Then **free fatty acids** move through the cell membrane of the **adipocyte** and immediately bind to **albumin** in the **plasma**. They are transported to the tissues, <u>where the **fatty acids** enter cells, get activated to **their CoA derivatives**, and **are oxidized for energy**.</u>

- **Glycerol**, arising from hydrolysis of **triacylglycerols**, is converted to the **Glycolysis** intermediate **dihydroxyacetone phosphate (DHAP)**, by reactions catalyzed by:

1- **Glycerol Kinase**

2- **Glycerol Phosphate Dehydrogenase.**



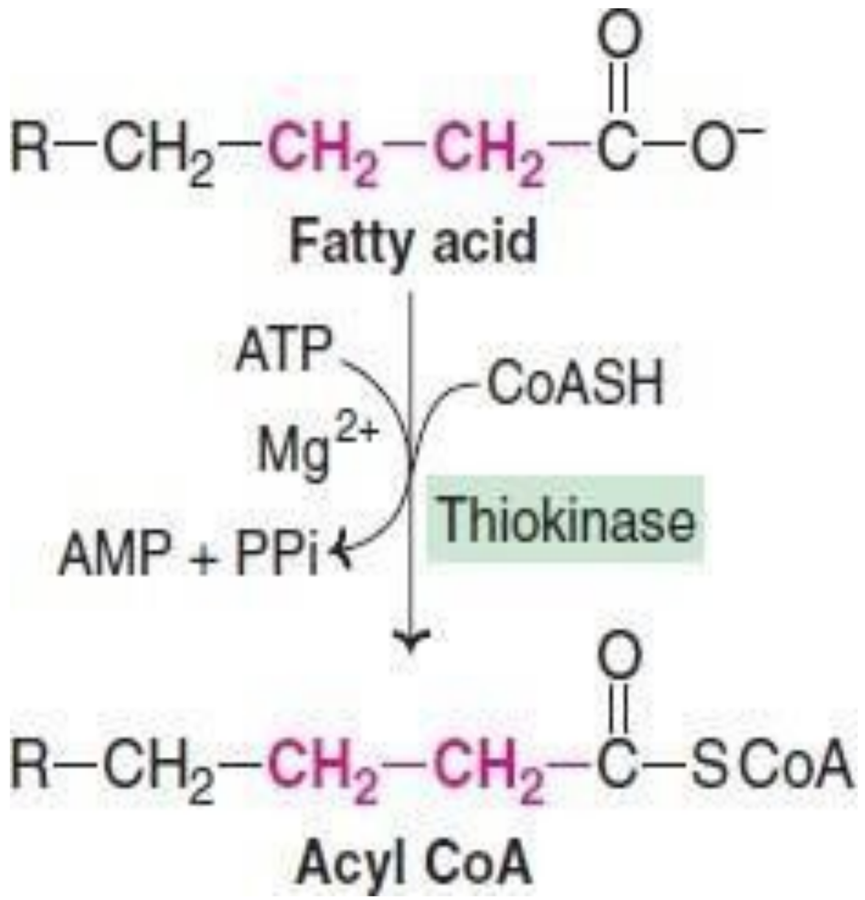
Oxidation (Catabolism) of Fatty Acid

- The main path to catabolize fatty acid is **β-oxidation**.
- **β-Oxidation** may be defined as the **oxidation of fatty acids on the β-carbon atom** (C-3).
- This results in the sequential **removal of a two carbon fragment from the carboxyl end of the fatty acyl CoA**, producing **acetyl CoA, NADH, FADH$_2$**.
- **β-oxidation of fatty acid** are performed within **mitochondrial matrix** which **contains all the enzymes and coenzymes necessary for catabolism.**

The B-oxidation of Fatty Acids Involves Three Stages

I. Activation of fatty acids occurring in the cytosol.

- **Fatty acids** exist in the **cytoplasm** in an **inactive** form and must be **activated** before entering **the mitochondria**.
- This activation is catalyzed by the enzyme **acyl-CoA synthetase (Thiokinase)** in the presence of **ATP** and **Coenzyme A** (**CoA**), converting **fatty acids** into **active** **acyl-CoA**.
- **<u>This step</u>** is the only one in **fatty acid** degradation that requires energy from **ATP**.

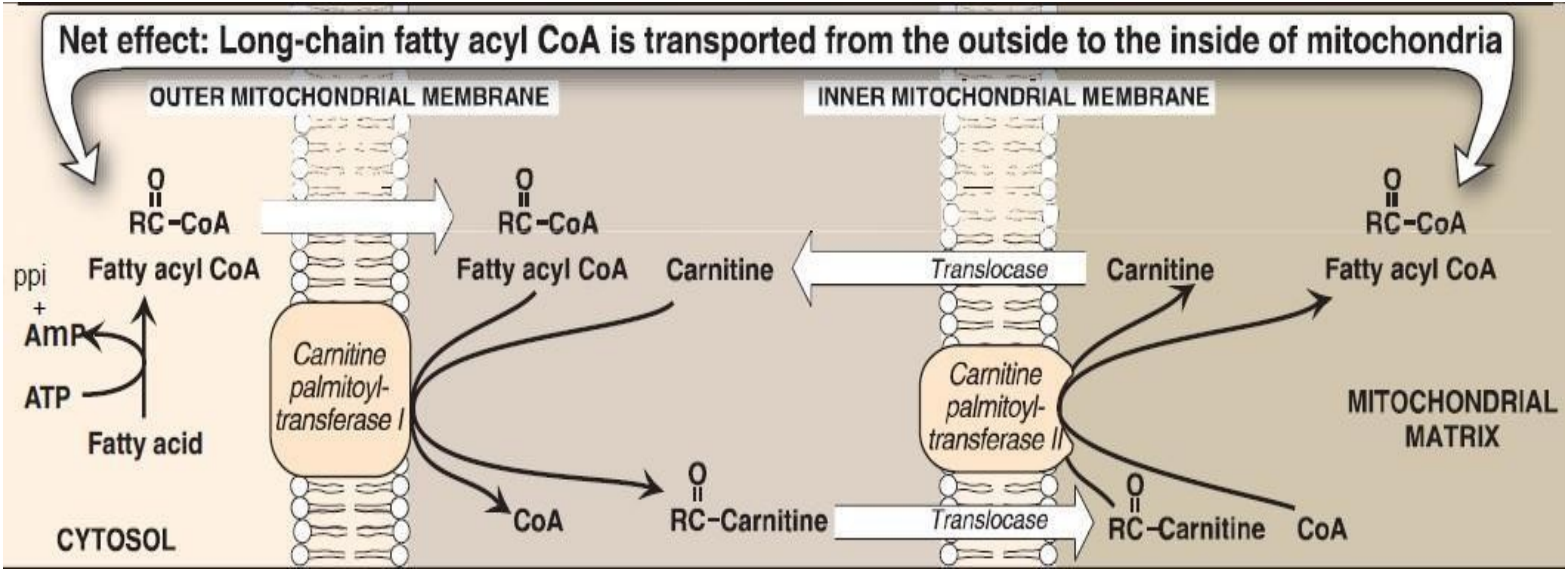


II- Transport of long-chain fatty acids into mitochondria.

- **Fatty acids** are **activated** in the **cytoplasm**; but the **β- oxidation** is in **mitochondria**. So transport of **fatty acids** through the **mitochondrial membrane** is essential. **The long-chain fatty acyl CoA** <u>cannot pass through the inner mitochondrial membrane</u>. Therefore a transporter, **carnitine** is involved in the transfer of **fatty acids**.
- **The carnitine-mediated transfer of fatty acyl moieties into the mitochondrial matrix involves three main steps:**

1) **<u>Fatty acid attachment to carnitine</u>**: **Carnitine Palmitoyl Transferase I**, located on the outer mitochondrial membrane, transfers a **fatty acid** from **CoA** to **carnitine**, forming **acyl-carnitine**.
2) **<u>Transport across membranes</u>**: An **antiporter** in the inner mitochondrial membrane exchanges **carnitine** for **acyl-carnitine**, allowing **acyl-carnitine** to enter the mitochondrial matrix.

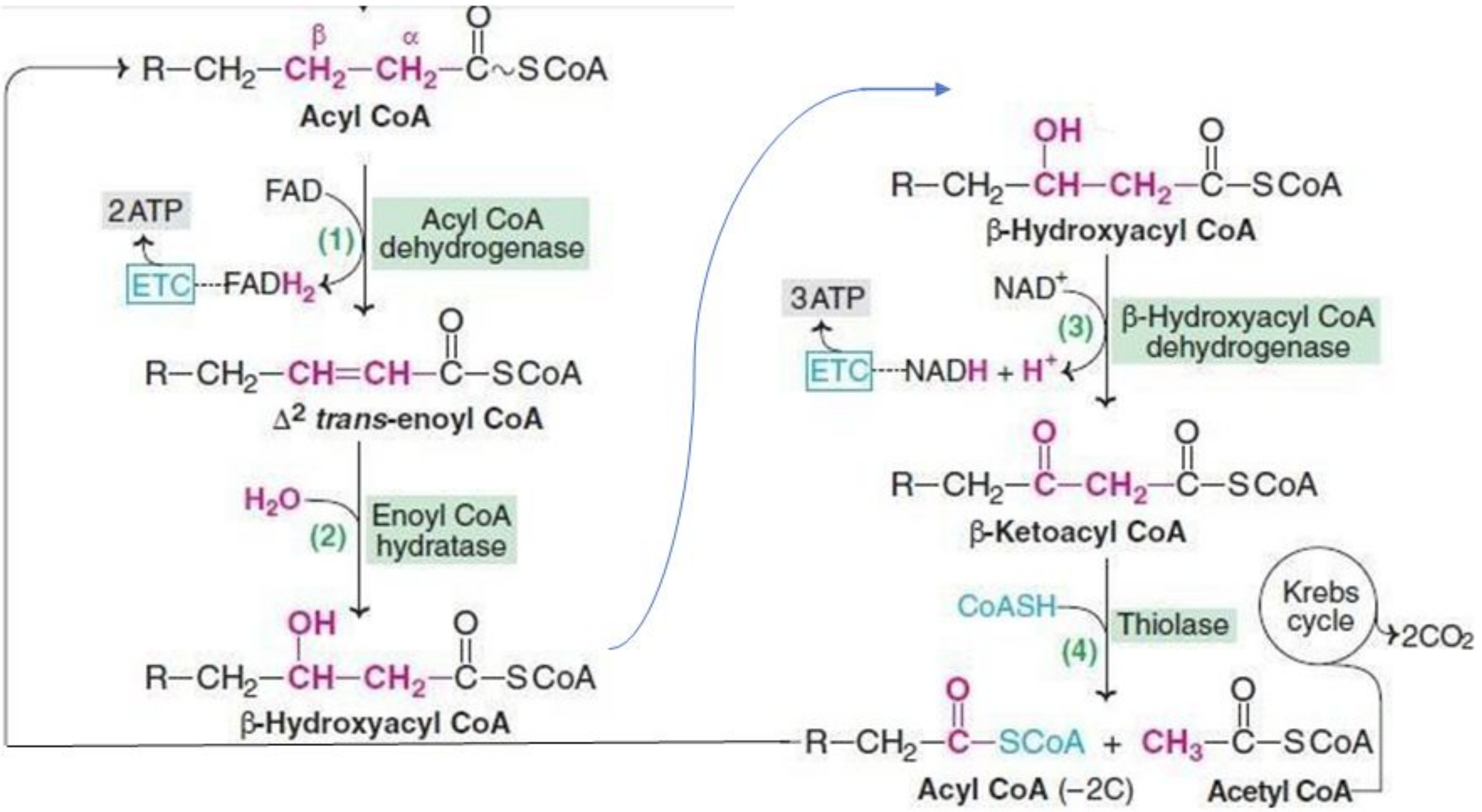
3) **<u>Fatty acid release from carnitine:</u>** Carnitine Palmitoyl Transferase II, on the inner mitochondrial membrane, transfers **the fatty acid** from a**cyl-carnitine** back to **CoA**, regenerating **acyl-CoA** for **β-oxidation** and releasing **carnitine** back to **the cytosol**.



III- β-Oxidation proper in the mitochondrial matrix.

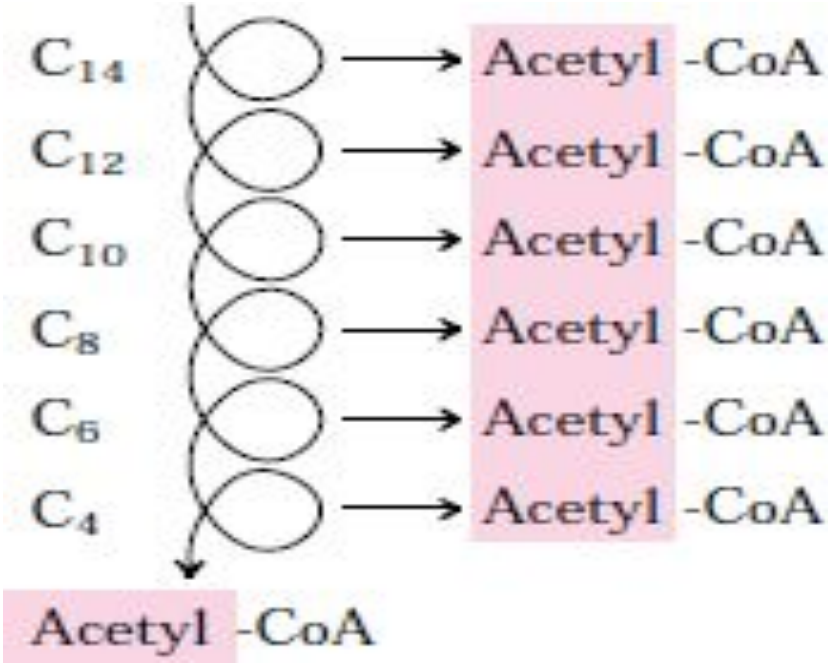
Each cycle of **β-oxidation**, liberating a **two-carbon unit-acetyl CoA**, occurs in a sequence of four reactions.

1) **Oxidation**: **Acyl CoA** undergoes **dehydrogenation** by a **FAD-dependent flavoenzyme**, **acyl CoA dehydrogenase**. A double bond is formed between **β and α carbons** (i.e., **2** and **3 carbons**).
2) **Hydration: Enoyl CoA hydratase** brings about the hydration of the double bond to form **β-hydroxyacyl CoA**.
3) **Oxidation**: **β-Hydroxyacyl CoA dehydrogenase** catalyzes the second oxidation and generates **NADH**. The product formed is **β-ketoacyl CoA**.
4) **Cleavage**: The final reaction in **β-oxidation** is the liberation of a **2-carbon fragment**, **acetyl CoA** from **acyl CoA**. This occurs by a **thiolytic cleavage** catalyzed by **β-ketoacyl CoA thiolase** (or simply **thiolase**).



Acyl CoA
FAD
2 ATP
(1)
Acyl CoA dehydrogenase
ETC
FADH2
Δ2 trans-enoyl CoA
H2O
(2)
Enoyl CoA hydratase
β-Hydroxyacyl CoA
β-Hydroxyacyl CoA
NAD+
3 ATP
(3)
β-Hydroxyacyl CoA dehydrogenase
ETC
NADH + H+
β-Ketoacyl CoA
CoASH
Thiolase
(4)
Krebs cycle
2CO2
Acyl CoA (−2C)
+
Acetyl CoA

- The new **acyl CoA**, containing <u>two carbons less than the original, reenters the **β- oxidation cycle**</u>. The process continues till the **fatty acid** is completely oxidized.



<u>**Summary**</u> of one round of the **β-oxidation** pathway:

Fatty acyl-CoA + FAD + NAD$^+$ + HS-CoA $\longrightarrow$ Fatty acyl-CoA (2 C less) + FADH$_2$ + NADH + H$^+$ + acetyl-CoA

Exp. Complete Beta Oxidation of Palmitoyl CoA (16 C)

$$CH_3CH_2\vdots{-}CH_2CH_2\vdots{-}CH_2CH_2\vdots{-}CH_2CH_2\vdots{-}CH_2CH_2\vdots{-}CH_2CH_2\vdots{-}CH_2CH_2\vdots{-}CH_2COSCoA$$

$$\Big\downarrow \textbf{ 7 Cycles}$$

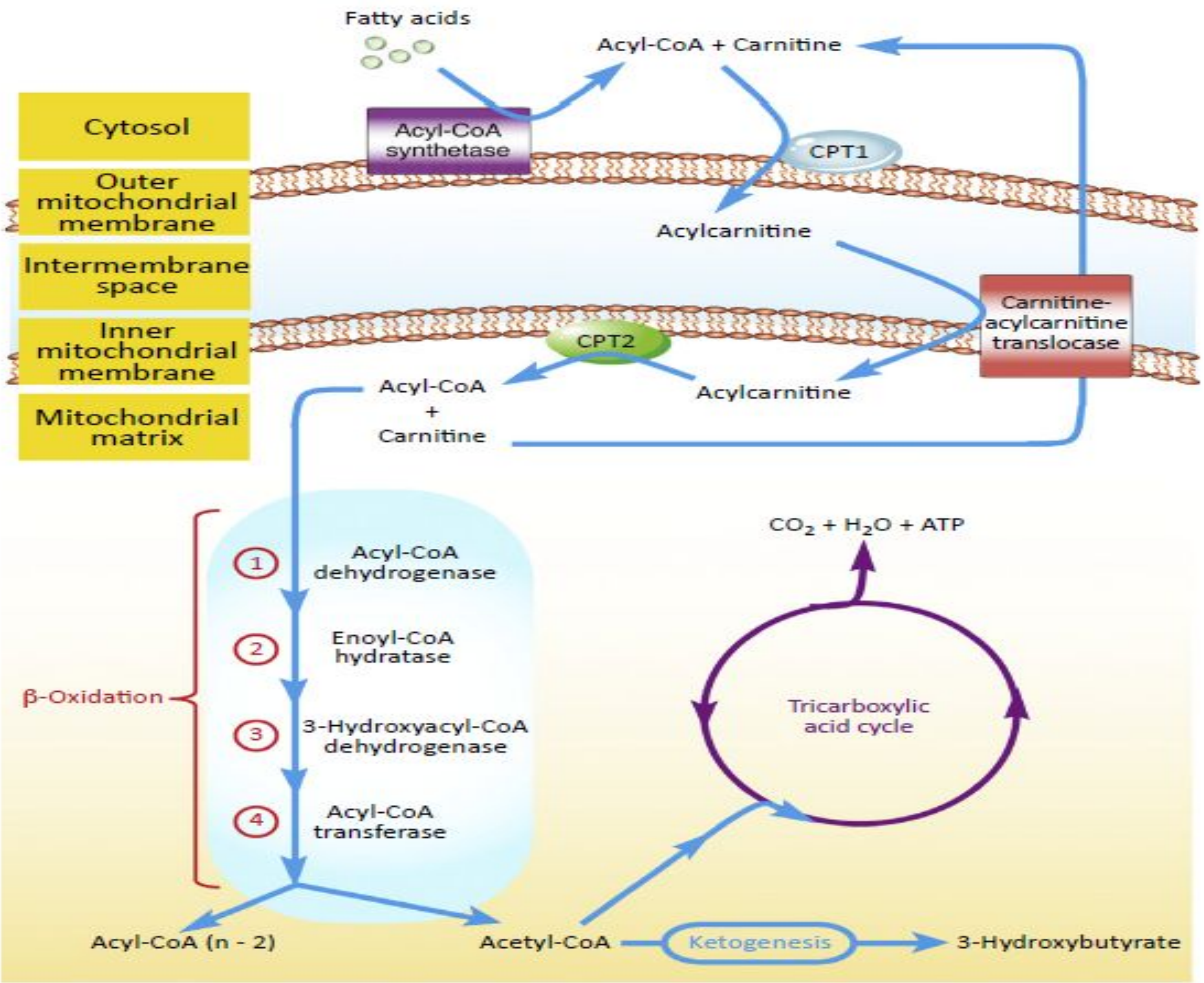
$$\mathbf{8\ CH_3COSCoA + 7\ FADH_2 + 7\ NADH + 7\ H^+}$$

- **Each round (4 enzyme steps) generates one molecule of:**

1) **$FADH_2$**
2) **NADH**
3) **Acetyl CoA**
4) **Fatty acyl CoA (2 carbons shorter each round)**

- **Fates of the products of β-oxidation**

1) **NADH** and **$FADH_2$** - are used in electron respiratory chain.
2) **acetyl CoA** - enters the **citric acid cycle.**
3) **acyl CoA-undergoes** the next cycle of oxidation.


Fatty acids
Acyl-CoA + Carnitine
Cytosol
Acyl-CoA synthetase
CPT1
Outer mitochondrial membrane
Acylcarnitine
Intermembrane space
Carnitine-acylcarnitine translocase
Inner mitochondrial membrane
CPT2
Acyl-CoA
+
Carnitine
Acylcarnitine
Mitochondrial matrix
CO_2 + H_2O + ATP
1 Acyl-CoA dehydrogenase
2 Enoyl-CoA hydratase
β-Oxidation
3 3-Hydroxyacyl-CoA dehydrogenase
4 Acyl-CoA transferase
Tricarboxylic acid cycle
Acyl-CoA (n - 2)
Acetyl-CoA
Ketogenesis
3-Hydroxybutyrate

❑ Energy yield from fatty acid oxidation

✔ The energy yield from the **β-oxidation** pathway is high.

✔ **For example**, the oxidation of a molecule of **palmitoyl-CoA (16 carbon)** yields **129 ATPs**

$$CH_3CH_2 - CH_2CH_2 - CH_2CH_2 - CH_2CH_2 - CH_2CH_2 - CH_2CH_2 - CH_2CH_2 - CH_2COSCoA$$

$$\Big\downarrow \text{ 7 Cycles}$$

$$8\ CH_3COSCoA + 7\ FADH_2 + 7\ NADH + 7\ H^+$$

8 acetyl-CoA	**8 x 12 = 96 ATP**
7 FADH2	**7 x 2 = 14 ATP**
7 NADH	**7 x 3 = 21 ATP**
	131 ATP
ATP expended to activate palmitate	**-2 ATP**
	Net yield: 129 ATP

Any questions?

Thank You