Lecture No. 2

Lipids Metabolism

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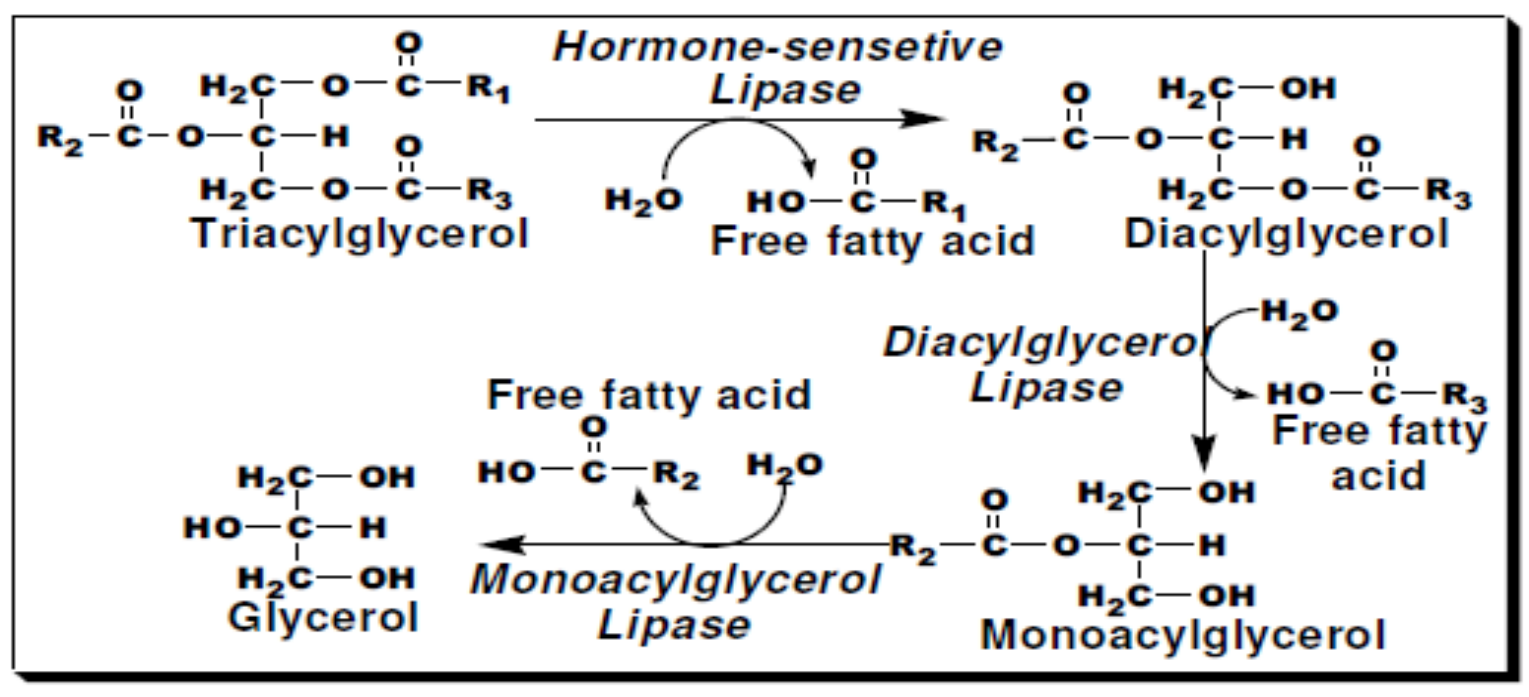
Lipolysis of TG:

- **Definition:** Lipolysis is the hydrolysis of TG to glycerol and FFA with both products leaving the adipocyte.



- The rate-limiting step is the first reaction catalyzed by the hormone-sensitive lipase.

Control of lipolysis in adipocytes:

A. Covalent modification: Hormone-sensitive lipase is activated by phosphorylation by cAMP dependent protein kinase.

B. Hormonal regulation:

1) Lipolytic Hormones:

- Epinephrine and norepinephrine activated the cell membrane-bound adenylate cyclase to convert ATP into cAMP.
- Increased cAMP activates cAMP dependent protein kinase which activates the hormone-sensitive lipase.

- **Other lipolytic factors include:**

- Glucagon, vasopressin, ACTH and TSH, all act to increase cAMP synthesis by adenylate cyclase.
- Methyl xanthine such as **caffeine** maintain cAMP level by inhibiting its phosphodiesterase.
- Thyroxine and glucocorticoids increase cAMP by increasing adenylate cyclase gene expression and inhibiting the phosphodiesterase.

2) **Antilipolytic hormones:**

- **Insulin:** It reduces cAMP level by:

a) Inducing cAMP-phosphodiesterase.

b) Induces phosphatase activity to dephosphorylate and inactivate hormone-sensitive lipase.

c) Increases glucose entry into the adipocytes, so increase glycerol-3-phosphate, so increases the rate of re-esterification of FFA to TGs.

- **Prolactin:** in large doses acts similar to insulin.
- **Prostaglandins** and **nicotinic acid** inhibit lipolysis by reducing cAMP levels.

Oxidation of fatty acids

- **FAs pool:** FAs are derived from; lipolysis, direct absorption from intestine and synthesis in the liver.
- They are taken by organs such as liver, kidney, muscles, adipose tissues and heart to be oxidized.
- **Types of oxidation:**

1) β-oxidation (the most important pathway).
2) α-oxidation (specialized pathway).
3) ω-oxidation (specialized pathway).

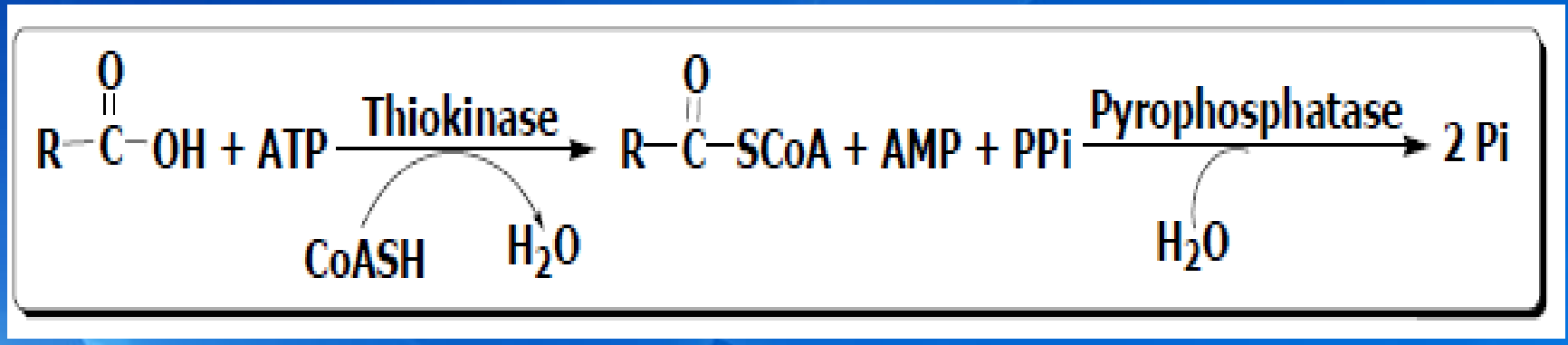
β-oxidation

- **Definition:** it is the principal pathway for FAs catabolism that involves oxidation of the β-carbon to form β-keto acid catalyzed by a number of enzymes collectively called **fatty acid oxidase**.
- **Site:** **Mitochondrial matrix** of tissues such as liver, heart (80% of its fuel is from β-oxidation), lungs, muscles, kidney, testes and adipose tissue.
- Brain cells have β-oxidation ability but BBB prevent FAs entrance.

- **Steps:**

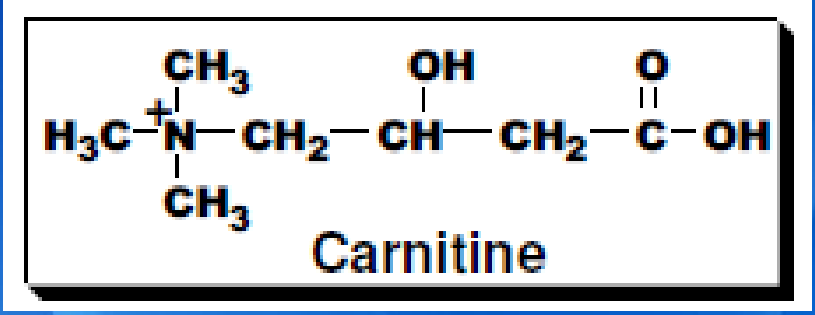
I. Activation of fatty acids:

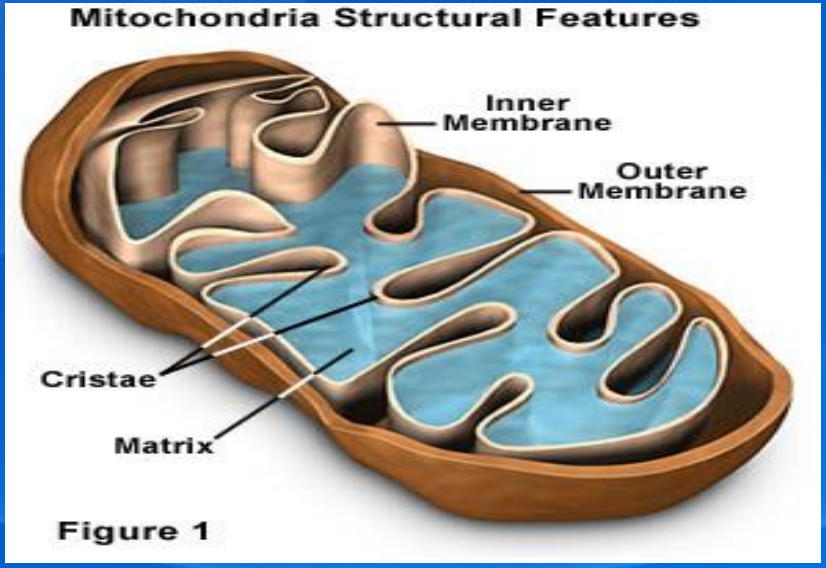
- FAs are activated by thiokinase (acyl CoA synthetase) in the presence of CoASH & ATP to acyl CoA.
- This conversion is accompanied by the consumption of (2 high-energy phosphates).



II. Transport of Acyl CoA into the mitochondrial matrix (Role of carinitine):

- Long chain fatty acyl-CoAs can not freely diffuse across the inner mitochondrial membrane.
- So, it penetrate the inner mitochondrial membrane in combination with carnitine (β-Hydroxy-γ-trimethylaminobutyric acid).



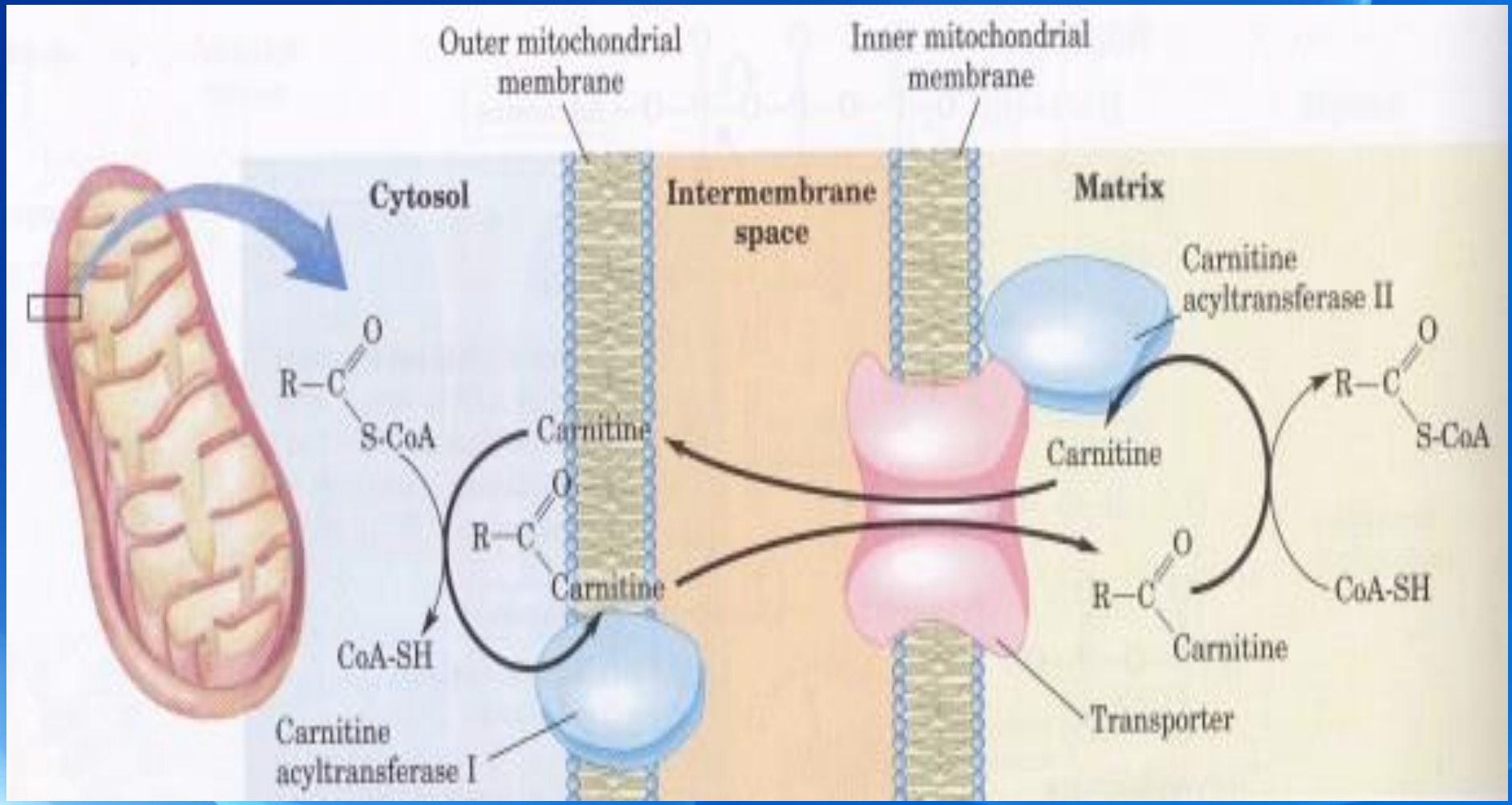


- Carnitine is synthesized from lysine and methionine in liver and kidney.
- Its blood level is 7-14 μg/ml and is excreted in urine at 50-100 μg/day.
- **Carnitine deficiency:**

- It occurs in preterm infants and in kidney disease with hemodialysis.
- Signs and symptoms of deficiency include episodic periods of hypoglycemia, high plasma FFAs and muscle weakness (impaired FAs oxidation).

Function of carnitine:

- Carnitine transports long chain FA (acyl CoA) into the mitochondria.



- **Three enzymes are essential in carnitine shuttle:**

1) **Carnitine acylcarnitine transferase I:**

- At the outer surface of the inner mitochondrial membrane.

1) **Carnitine acylcarnitine translocase:**

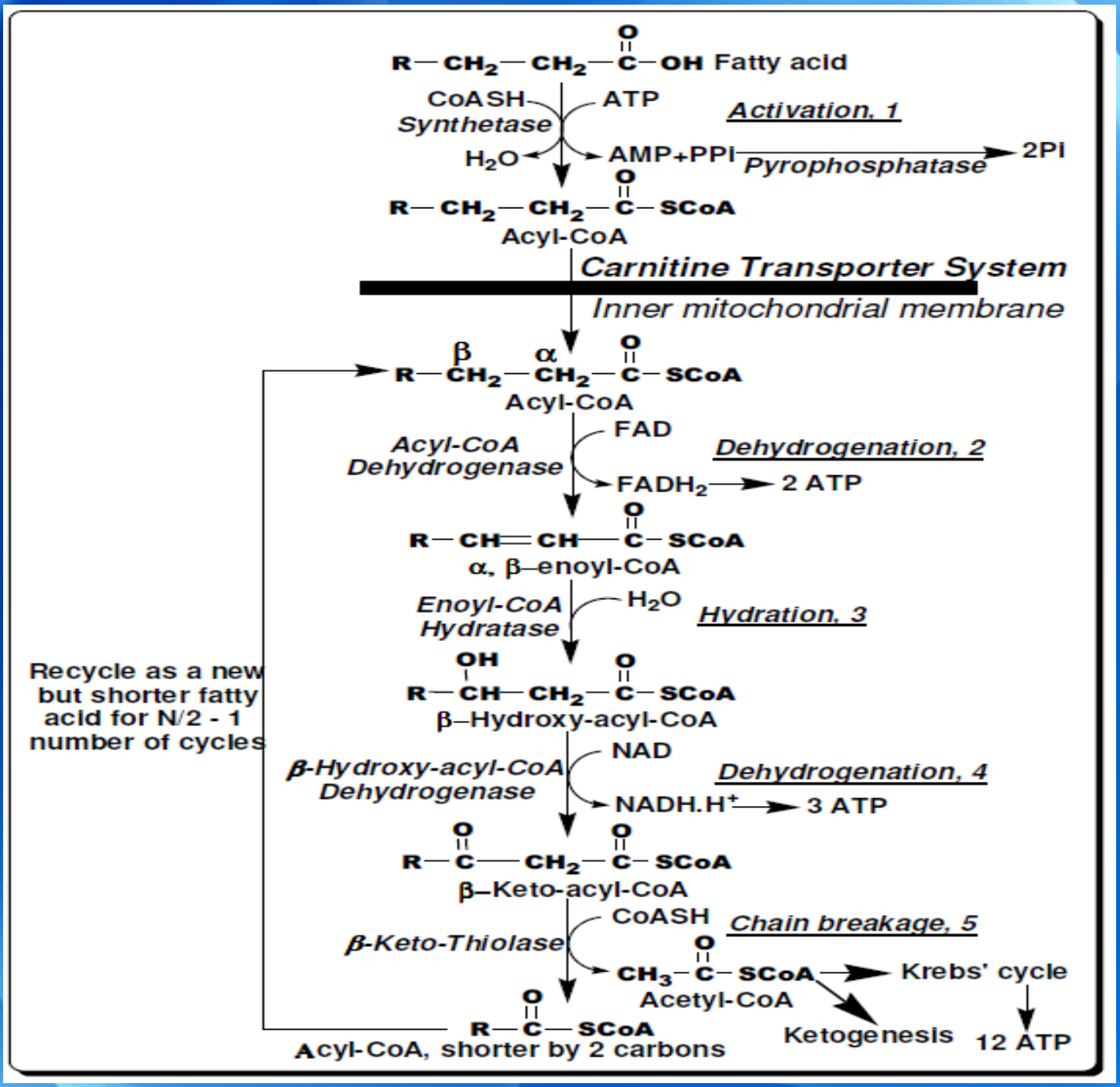
- In the inner mitochondrial membrane.

1) **Carnitine acylcarnitine transferase II:**

- At the inner surface of inner mitochondrial membrane.
- Together with fructose and lactate, acyl carnitine is an important fuel source for sperm supporting motility.

III. Steps of β-Oxidation:

- Fatty acid oxidase catalyzes the oxidation of acyl CoA to acetyl CoA with phosphorylation of ADP to ATP.
- In β-oxidation, 2 carbons (acetyl CoA) are cleaved at a time from acyl-CoA molecules, starting at the carboxyl end.
- Thus, palmitoyl-CoA (16 C) forms 8 acetyl-CoA molecules which then undergo oxidation in citric acid cycle.


R—CH2—CH2—C(=O)—OH Fatty acid
CoASH
Synthetase
ATP
Activation, 1
H2O
AMP+PPI
Pyrophosphatase
2PI
R—CH2—CH2—C(=O)—SCoA
Acyl-CoA
Carnitine Transporter System
Inner mitochondrial membrane
β α
R—CH2—CH2—C(=O)—SCoA
Acyl-CoA
Acyl-CoA Dehydrogenase
FAD
Dehydrogenation, 2
FADH2
2 ATP
R—CH=CH—C(=O)—SCoA
α, β–enoyl-CoA
Enoyl-CoA Hydratase
H2O
Hydration, 3
OH
R—CH—CH2—C(=O)—SCoA
β–Hydroxy-acyl-CoA
Recycle as a new but shorter fatty acid for N/2 - 1 number of cycles
β-Hydroxy-acyl-CoA Dehydrogenase
NAD
Dehydrogenation, 4
NADH.H+
3 ATP
R—C(=O)—CH2—C(=O)—SCoA
β–Keto-acyl-CoA
CoASH
β-Keto-Thiolase
Chain breakage, 5
CH3—C(=O)—SCoA
Acetyl-CoA
Krebs' cycle
12 ATP
Ketogenesis
R—C(=O)—SCoA
Acyl-CoA, shorter by 2 carbons

NOTES ON β-OXIDATION

Step I : Activation

- Catalyzed by fatty acid thiokinase enzyme.
- 2 high energy bonds are utilized: ATP gives AMP + PPi

Step II: Unsaturation (dehydrogenation)

- Catalyzed by acyl CoA dehydrogenase enzyme.
- The coenzyme for this reaction is flavin adenine dinucleotide (FAD) as a prosthetic group.
- $FADH_2$ is oxidized in mitochondria to give 2 ATP.

Step III: Hydration

- Catalyzed by enoyl CoA hydratase enzyme, which helps the addition of H_2O to saturate double bond.

- **Step IV: Oxidation (β-oxidation)**
- Catalyzed by β-hydroxyacyl CoA dehydrogenase.
- The coenzyme is Nicotinamide adenine dinucleotide NAD^+.
- Oxidation of $NADH+H^+$ gives 3 ATP.
- **Step V: Splitting of active acetate**
- It is catalyzed by thiolase which splits acyl CoA into acetyl CoA and acyl CoA (2 C shorter than the first one)
- The process is repeated until the whole FA is broken into acetyl CoA, which are then oxidized to CO_2 and H_2O in Krebs' cycle or used to form keton bodies.

Bioenergetics of fatty acid oxidation:

e.g. palmitic acid (16 C)

1) β-oxidation of palmitic acid will be repeated 7 times producing 8 molecules of acetyl CoA.
2) In each time, $FADH_2$ and $NADH + H^+$ is produced and will be transported to the respiratory chain where:

$FADH_2 \rightarrow$ 2 ATP

$NADH + H^+ \rightarrow$ 3 ATP

So 7 times = 7 x 5 ATP → 35 ATP

3) Each acetyl CoA which is oxidised in citric acid cycle gives 12 ATP.

8 x 12 ATP → 96 ATP

4) 2 high energy phosphate bonds are utilized in the activation of fatty acid (first reaction and it occurs once).

Energy gain = Energy produced – Energy utilized

= 35 ATP + 96 ATP – 2 ATP

= 131 ATP – 2 ATP

Energy gain = 129 ATP

Calculation of energetics of any fatty acid oxidation:

$= [(N/2 - 1) \times 5 \text{ ATP}] + [N/2 \times 12 \text{ ATP}] - 2 \text{ ATP}$

Where N = number of carbons of a fatty acid.

e.g.

Stearic acid: Number of carbon atoms = 18 C.

So energy produced

$= [(18/2\text{-}1) \times 5 \text{ ATP}] + [18/2 \times 12 \text{ ATP}] - 2 \text{ ATP}$

$= [(9\text{-}1) \times 5 \text{ ATP}] + [9 \times 12 \text{ ATP}] - 2\text{ATP}$

$= 40 \text{ ATP} + 108 \text{ ATP} - 2 \text{ ATP} = 146 \text{ ATP}$

➢ Importance of β-Oxidation:

1) Source of energy:

- It is a major source of energy during starvation.

2) Production of acetyl CoA:

- Acetyl CoA is converted to several useful compounds e.g. cholesterol, acetyl choline.

3) Ketone bodies formation:

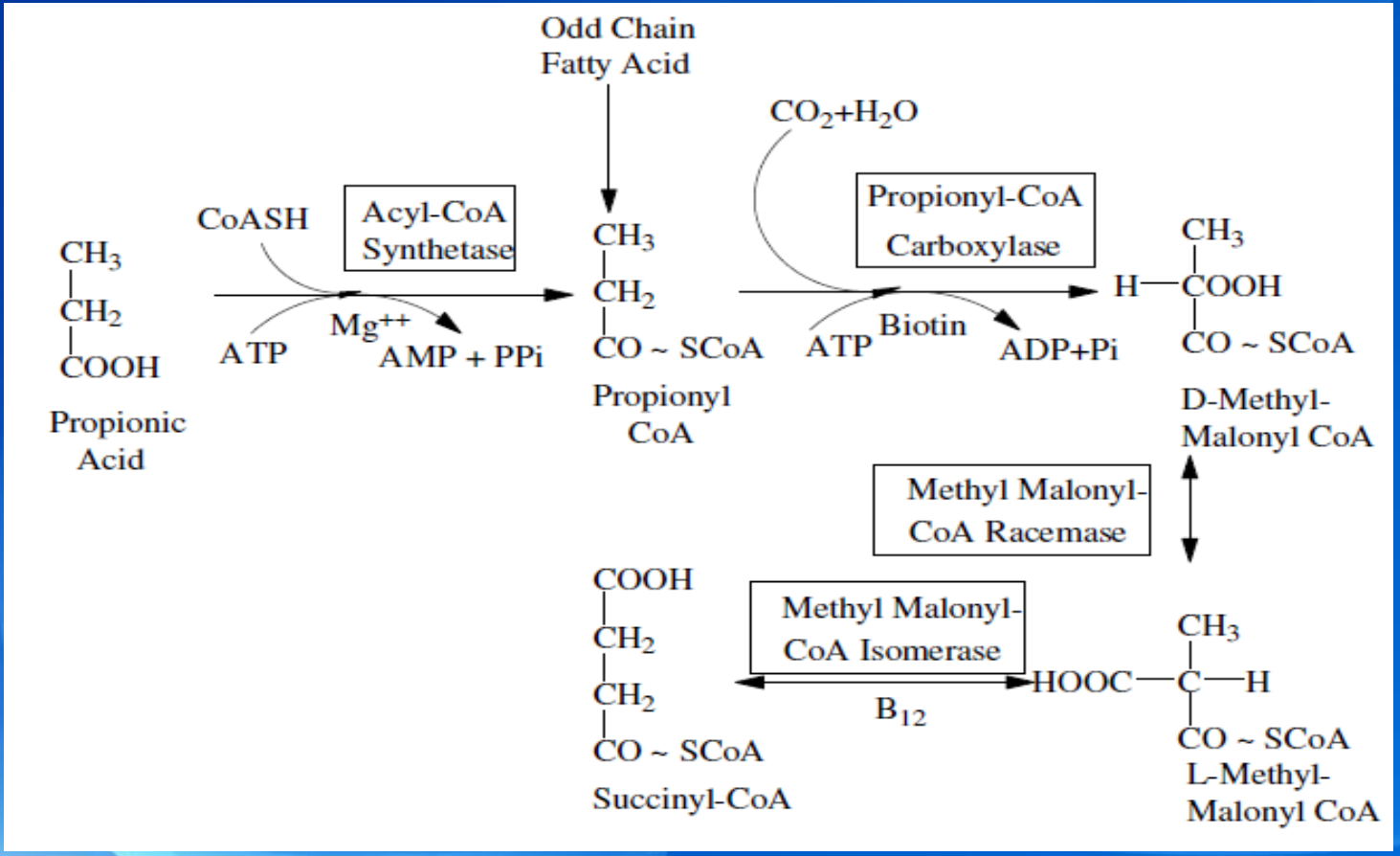
- Acetoacetyl CoA is derived from oxidation of long chain acyl CoA, i.e. last 4 carbon atoms, may be converted to acetoacetic acid (one of the ketone bodies).

Regulation of β-Oxidation:

- It is regulated by energy which is needed by the cells:
  - When energy increases (Excess ATP), β-oxidation is inhibited and vice versa.
  - Excess ATP moles in the cells inhibit respiratory chain.
  - Thus the reduced $FADH_2$ and $NADH + H^+$ can not undergo oxidation in respiratory chain, and remain as such.

➢ Oxidation of FAs with odd number of carbon atoms:

- The same β-oxidation pathway until a 3-carbon (propionyl-CoA) residue remains which is then converted to succinyl-CoA.



- **Fate of succinyl CoA:**

1) Enters krebs cycle to be oxidized.
2) Enters in the formation of haem.
3) May be converted to glucose (gluconeogenesis).
4) Used in activation of ketone bodies.
5) Used in detoxication reactions.

α-oxidation

- It occurs in α-position and is characterized by:

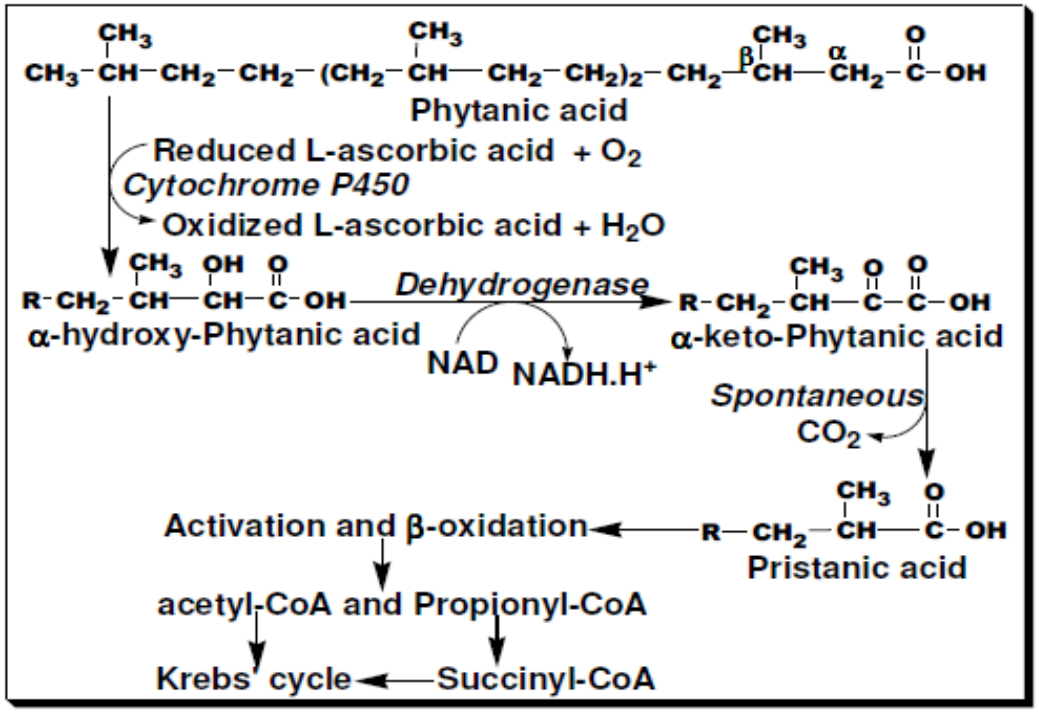
1) It occurs in microsome of brain tissue.
2) It is a minor pathway for fatty acid oxidation.
3) One carbon atom is removed at a time from α-position.
4) It does not require CoASH and does not generate high energy phosphate.

Biological importance of α-oxidation:

- Production of α-hydroxy FA (hydroxy lignoceric and hydroxy nervonic acid), required for brain lipids.
- Oxidation of phytanic acid.

Steps:

The following figure illustrates the steps of α-oxidation,

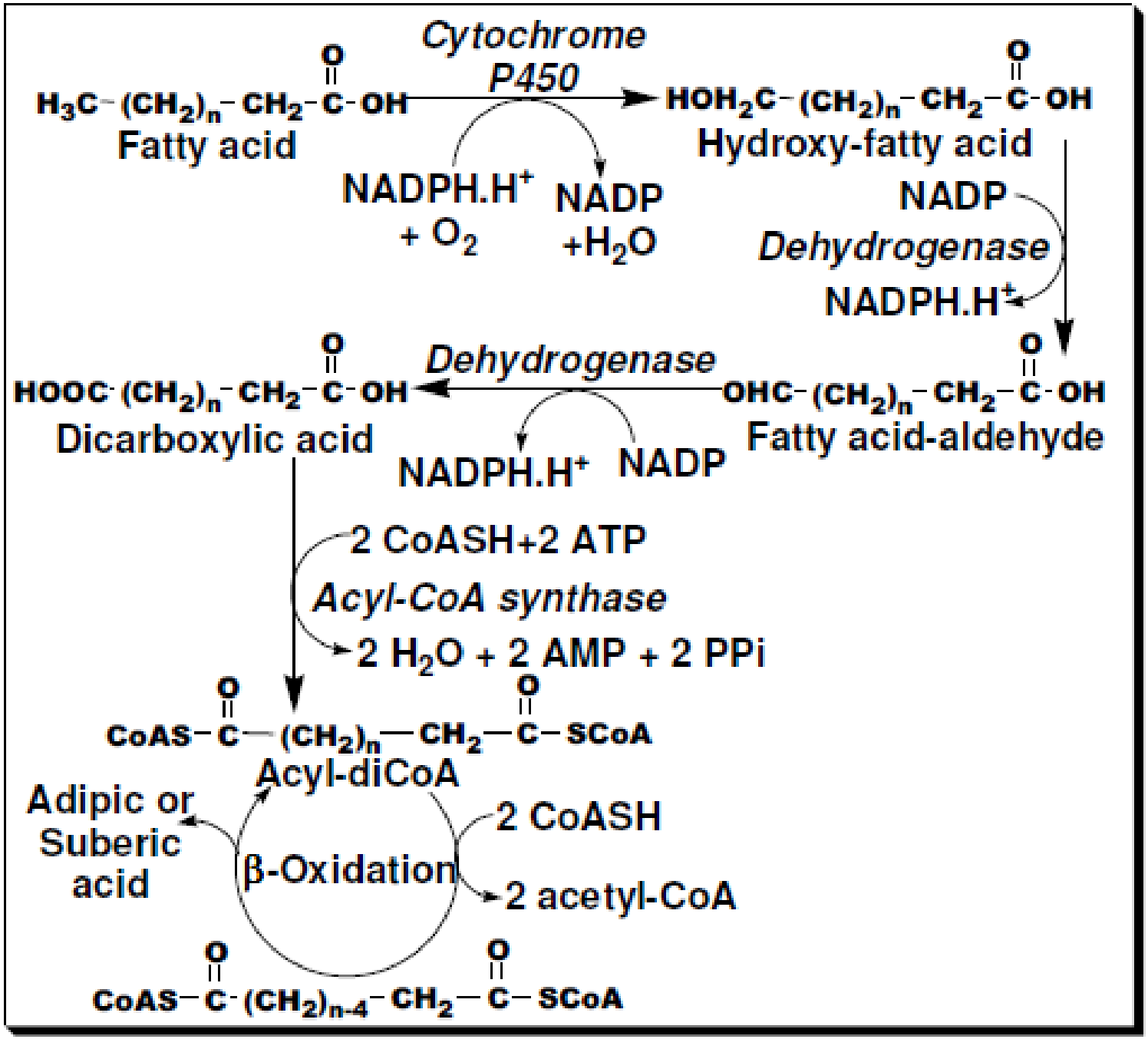


Refsum's disease

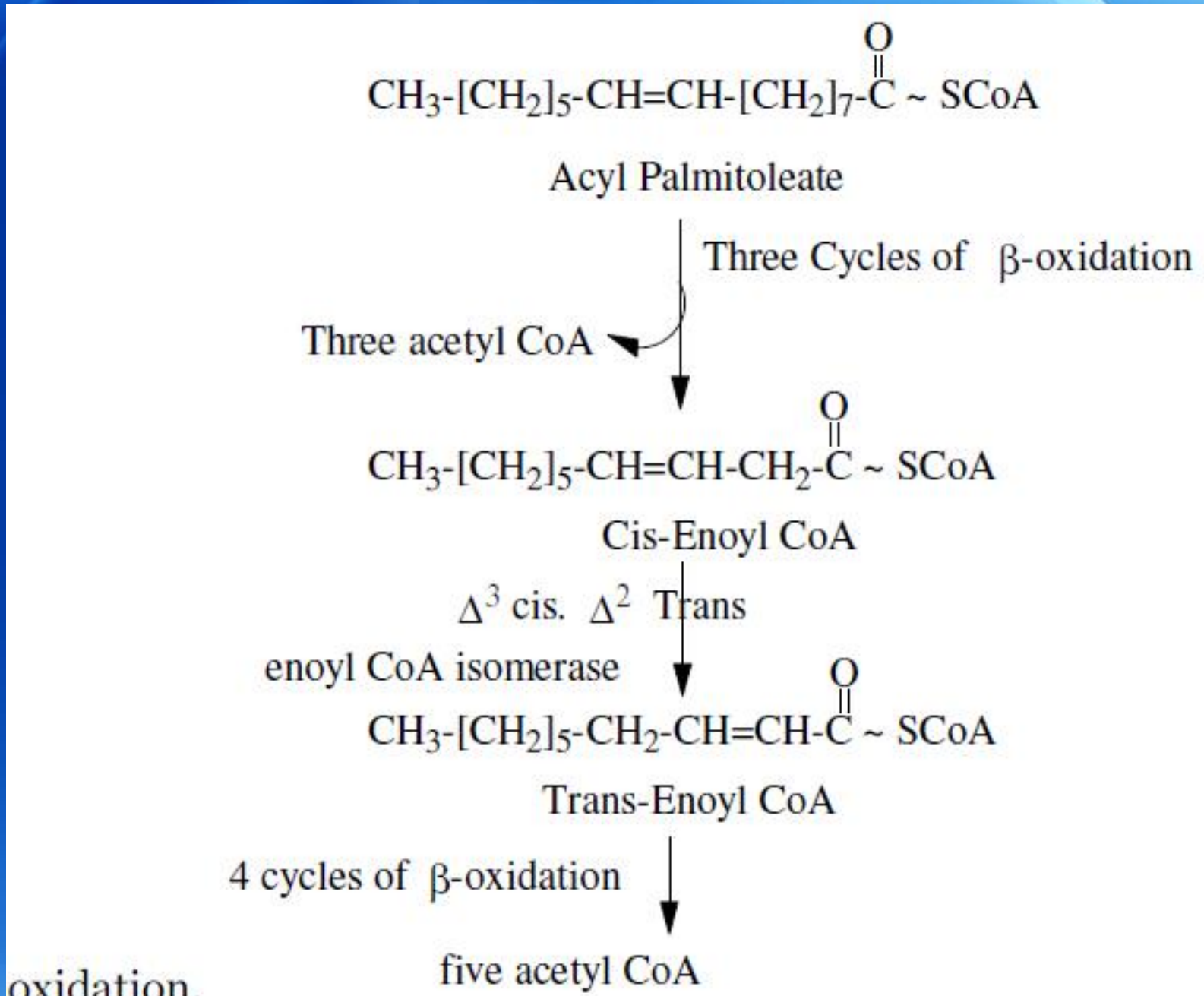
- This is an inherited defect in α-oxidation that prevents oxidation of phytanic acid (in plant foodstuffs) due to deficiency of phytanate α-oxidase.
- Accumulation of phytanic acid may cause damage to cell membrane.
- **Toxicity symptoms include:** Retinitis pigmentosa, night blindness, cataract, peripheral neuropathy, distal muscular atrophy, cerebellar ataxia, scaly skin (ichthyosis) and difficulty hearing.

ω-oxidation

- It is a very minor pathway.
- It is achieved by hydroxylase enzymes involving cytochrome P_{450} in the endoplasmic reticulum.
- In ω-oxidation the omega carbon is oxidized at first to CH_2-OH and subsequently to COOH.
- This gives rise to a dicarboxylic acid that can be oxidized at both its free ends by β-oxidation to give adipic (C6) and suberic (C8) acids which are excreted in urine.


Cytochrome
P450
Fatty acid
Hydroxy-fatty acid
NADPH.H+
+ O2
NADP
+H2O
NADP
Dehydrogenase
NADPH.H+
Dehydrogenase
Dicarboxylic acid
Fatty acid-aldehyde
NADPH.H+
NADP
2 CoASH+2 ATP
Acyl-CoA synthase
2 H2O + 2 AMP + 2 PPi
Acyl-diCoA
Adipic or
Suberic
acid
β-Oxidation
2 CoASH
2 acetyl-CoA

- **Oxidation of unsaturated fatty acids:**
- In the human body, 50% of the FAs are unsaturated.
- A wide range of USFAs can be degraded by β-oxidation with the assistance of some other enzymes.
- For example: the double bonds in the naturally occurring FAs are *cis*, and the β-oxidation pathway can only deal with *trans* double bonds.


CH3-[CH2]5-CH=CH-[CH2]7-C ~ SCoA
Acyl Palmitoleate
Three Cycles of β-oxidation
Three acetyl CoA
CH3-[CH2]5-CH=CH-CH2-C ~ SCoA
Cis-Enoyl CoA
Δ3 cis. Δ2 Trans
enoyl CoA isomerase
CH3-[CH2]5-CH2-CH=CH-C ~ SCoA
Trans-Enoyl CoA
4 cycles of β-oxidation
five acetyl CoA

oxidation.

- **Sources of active acetate (acetyl CoA):**

1) **Fat:** The richest source is the FAs e.g. plamitic acid (give 8 molecules) whereas glucose (gives only 2 molecules).
2) **Carbohdydrate:** Glucose oxidation gives pyruvic acid which undergo oxidative decarboxylation in mitochondria to give active acetate.
3) **Proteins:** Ketogenic amino acids are converted to active acetate or acetoacetic acid which gives active acetate.

- Glucogenic amino acids: can be converted to pyruvate which then gives active acetate

4) **Ethanol oxidation**

- **Fate of active acetate:**

1) **Oxidation:** through tricarboxylic acid cycle.
2) **Lipogenesis:** formation of FAs and its elongation.
3) **Ketogenesis:** formation of ketone bodies.
4) **Steroids formation:** Cholesterol, bile acids, Vit D3 and steroid hormones.
5) **Acetylation reactions** e.g., formation of acetylcholine, detoxcation reactions, covalent modification and histone acetylation.


Acylglycerols
Next lecture??


Thank You