By :- Dr. Shubhi Avasthi (Botany Department)

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Oxidation of Fatty Acid (Unit - III)

* A fatty acid contains a long hydrocarbon chain & a terminal carboxylate group. The hydrocarbon chain may be saturated (with no double bond) or unsaturated (with double bond).

* Fatty acids can be obtained from
  - Diet
  - Adipolysis
  - and De novo synthesis

* The fatty acids of triglycerols are highly concentrated stores of energy because they are reduced and anhydrous.

* The yield from the complete oxidation of fatty acid is about 9 K cal (38 KJ g^{-1}).

*

Types of Fatty Acid oxidation

* Fatty acids can be oxidized by -

1) Beta oxidation :- Major mechanism, occur in mitochondria matrix. 2 carbon units are released as acetyl CoA per cycle.

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2. Alpha oxidation:- It takes place in brain & liver, one Carbon is lost in the form of CO_2 per cycle.

3. Omega oxidation:- Minor mechanism, but becomes important in conditions of impaired beta oxidation

4. Peroxisomal oxidation:- Mainly for the ~~trimming of~~ trimming of very long chain fatty acids.

1) β - Beta oxidation

* The beta oxidation of fatty acids involve three stages:-

1) Activation of fatty acids in cytosol
2) Transport of activated fatty acid into mitochondria (carnitine shuttle)
3) Beta oxidation proper in the ~~mitochon~~ mitochondrial matrix

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Q.1) Activation of Fatty Acids in cytosol

+ Fatty acids are activated to acyl CoA by thiokinase or acyl CoA synthetase.

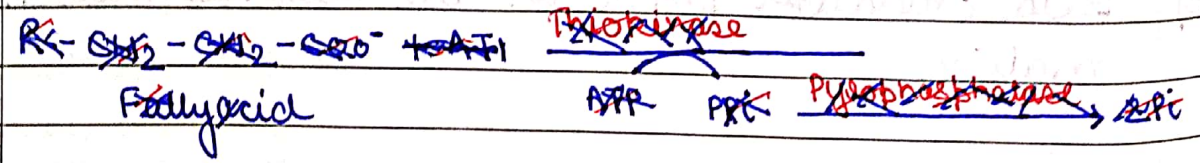
+ The reaction occur in two steps and require ATP, coenzyme A and Mg^{2+}.

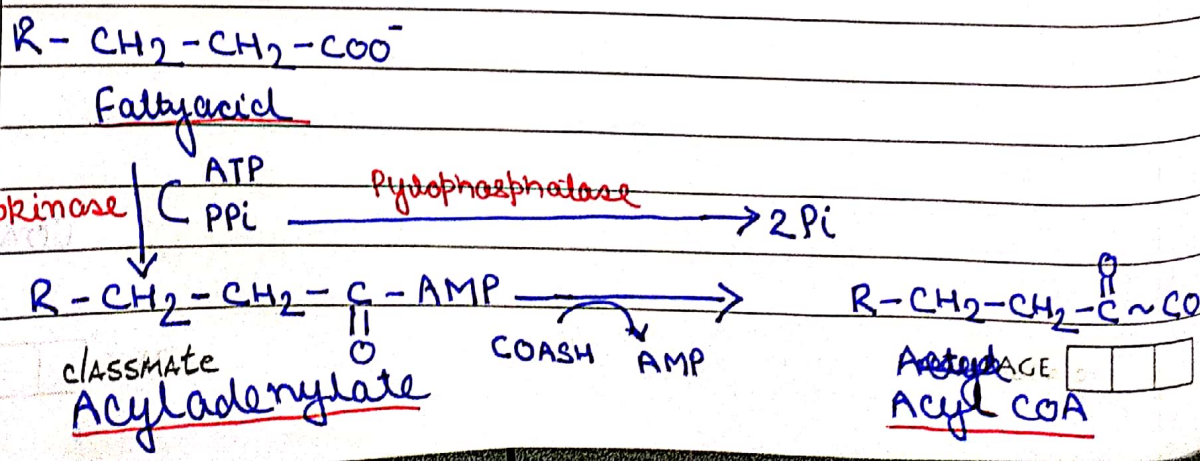
+ Fatty acid reacts with ATP to form acyladenylate which then combines with coenzyme A to produce acyl CoA.

+ In the activation, two high energy phosphates are utilized, since ATP is converted to pyrophosphate (PPi).

+ The enzyme inorganic pyrophosphate hydrolyses PPi to phosphate (Pi).

+ The immediate elimination of PPi makes this reaction totally irreversible.





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2. Transport of acyl CoA into mitochondria

* The inner mitochondrial membrane is impermeable to fatty acids.

* A specialized carnitine carrier system (carnitine shuttle) operates to transport activated fatty acids from cytosol to mitochondria.

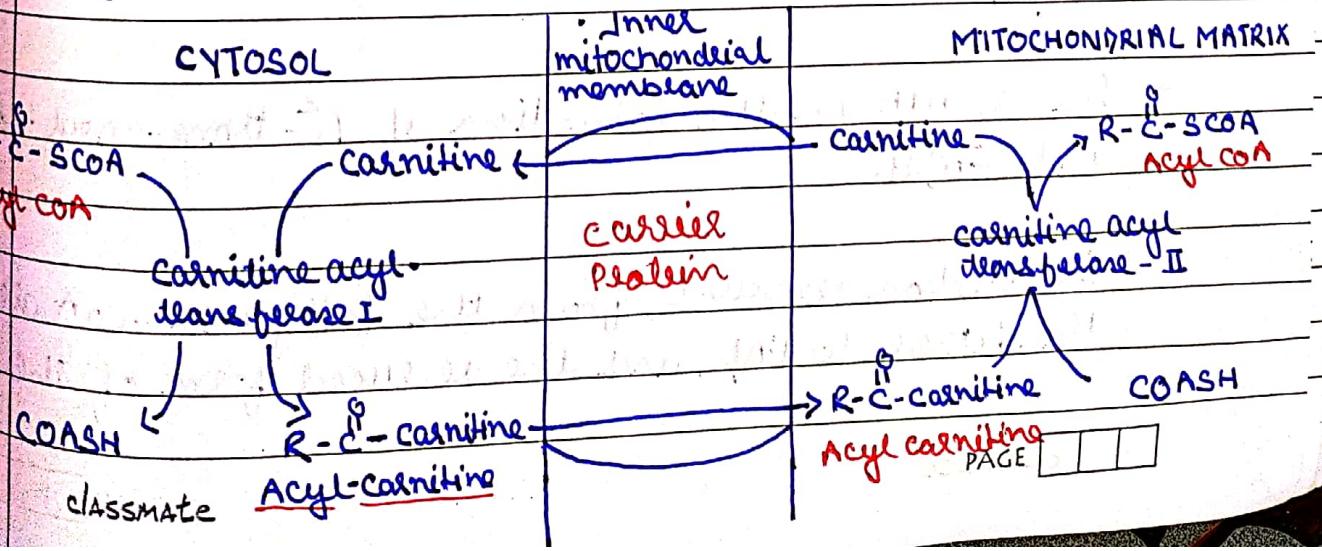
* This occur in 4 steps

1) Acyl groups from acyl CoA is transferred to carnitine to form acyl carnitine catalyzed by carnitine acyltransferase I, in the outer mitochondrial membrane

2) Acyl carnitine is then transported across the inner mitochondrial membrane by a translocase enzyme.

3) The acyl carnitine is transferred back to acyl CoA in matrix by carnitine acyl transferase II

4) Finally, carnitine is returned to the cytosolic side by translocase.



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* It should be noted that the coenzyme A used for activation is different from the one that finally combines with fatty acid in the mitochondria to form acyl CoA.

* **Inhibitor of carnitine shuttle**

* Carnitine acyl transferase I is inhibited by malonyl CoA, a key metabolite involved in fatty acid synthesis that occurs in cytosol.

3). **β-oxidation occurs in mitochondrial matrix.**

* Each cycle of β-oxidation, liberating a two carbon unit acetyl CoA, occurs in a sequence of 4 reaction

1-step **Dehydrogenation:-**

- The first step is the removal of two hydrogen atom from the 2(α) & 3(β) carbon atoms, catalyzed by acyl CoA dehydrogenase and requiring FAD.

- This result in the formation of Δ^2-trans-enoyl-CoA and $FADH$.

- The electron removed from the fatty acyl-CoA are transferred to FAD, and the reduced form of the

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dehydrogenase immediately donates its electrons to an electron carrier of the mitochondrial respiratory chain the electron-transferring flavoprotein (ETF).

2-Step **Hydration**

- Water is added to saturate the double bond of trans-Δ^2-enoyl-CoA to form the L-stereoisomer of 3-hydroxyacyl CoA. This reaction is catalyzed by enoyl-CoA hydratase.

3-Step **Dehydrogenation**

- 3-hydroxyacyl CoA is dehydrogenated to form β-Ketoacyl-CoA, by the action of β-hydroxyacyl-CoA dehydrogenase.

- NAD^+ is the electron acceptor. The NADH formed in the reaction donates its electron to NADH dehydrogenase

4-Step **Cleavage / Thiolysis**

- This step is catalysed by acyl-CoA acyltransferase commonly called thiolase, which promotes reaction of β-Ketoacyl CoA with a molecule of free coenzyme A to split off the carbonyl-terminal 2-carbon fragment of the original fatty acid as acetyl CoA. The other product is the coenzyme A thioester of fatty acid, now shortened by 2 carbon atoms

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- Since acetyl CoA can be oxidized to CO_2 and water via citric acid cycle the complete oxidation of fatty acid is achieved.

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$R-CH_2-CH_2-CH_2-\overset{\beta}{C}-O^-$ (Fatty acid)

ATP → AMP + PPi (Mg++) ; COASH → Thiokinase

(CYTOSOL)

$(C_N)R-CH_2-CH_2-CH_2-\overset{\beta}{C}-SCoA$ (Acyl-CoA)

II. CARNITINE TRANSPORT SYSTEM

III. → $(C_N)R-CH_2-\overset{\beta}{C}H_2-CH_2-\overset{O}{\overset{\|}{C}}-SCoA$ (Acyl CoA)

FAD → 2ATP (ETC ... FADH) ; Acyl CoA dehydrogenase

$R-CH_2-\overset{OH}{C}H=CH-\overset{\beta}{C}-SCoA$ (Δ^2 trans-enoyl CoA)

H_2O → Enoyl CoA hydratase

$R-CH_2-\overset{OH}{C}H-CH_2-\overset{O}{\overset{\|}{C}}-SCoA$ (β-hydroxyacyl CoA)

NAD+ → 3ATP (ETC ... NADH + H+) ; β-hydroxyacyl CoA dehydrogenase

$R-CH_2-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-SCoA$ (β-ketoacyl CoA)

COASH → Thiolase

$R-CH_2-\overset{O}{\overset{\|}{C}}-SCoA$ + $CH_3-\overset{O}{\overset{\|}{C}}-SCoA$

Acyl CoA (-2C) ; Acetyl CoA

Krebs cycle → $2CO_2$

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The over all reaction can be represented as follows -

$$Cn\text{-acyl CoA} + FAD + NAD^+ + H_2O + CoA \longrightarrow Cn\text{-}2 \text{ acyl CoA} + FADH_2 + NADH + \text{acelyl CoA} + H_2O$$

Beta oxidation - yield Energy.

* Energy yield by the complete oxidation of one molecule of Palmitic acid

+ The degradation of palmitoyl CoA (C_{16} acyl CoA) requires 7 reaction cycles.

* In the 7th cycle, the C_4-Ketoacyl CoA is thiolyzed to 2 molecule of acelyl CoA.

$$\text{Palmitoyl CoA} + 7FAD + 7NAD^+ + 7CoA + 7H_2O \longrightarrow 8\text{Acelyl CoA} + 7FADH_2 + 7NADH + 7H^+$$

* 129 ATP are produced by the complete oxidation of one molecule of Palmitic acid

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Energetics of β-oxidation

→ The ultimate aim of fatty acid oxidation is to generate energy.

The standard free energy of palmitate = 2,340 cal

The energy yield by its oxidation = 129 ATP
(129 × 7.3 cal) = 940 cal

The efficiency of energy conservation by fatty acid oxidation

$$= \frac{940}{2,340} \times 100 = 40\%$$

Energenetics of Palmitic Acid oxidation

	Mechanism	ATP Yield
1.	β oxidation Cycle	14
2.	From β Acetyl CoA	96
	Total energy from 1 molecule of Palmitoyl CoA	131
	Energy utilized for activation	- 2
	Net yield of oxidation of 1 molecule of Palmitate	= 129

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Disorder associated with β-oxidation

1. SIDS (Sudden infant death syndrome)

- The real cause of SIDS is not known.
- It is now estimated that at least 10% of SIDS is due to deficiency of medium chain acyl CoA dehydrogenase.
- The enzyme defect has a frequency of 1 in 10,000 birth.
- The occurrence of SIDS is as follows –

Glucose is the principal source of energy, soon after eating or feeding ~~bobi~~ babies. After few hours, the glucose level & its utilization decrease & the rate of fatty acid oxidation must increase to meet the energy.

- The sudden death of infants is due to a blockade in β-oxidation caused by deficiency in medium chain acyl CoA dehydrogenase.

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2. Jamaican vomiting sickness

- It is characterized by severe hypoglycemia, vomiting, convulsion, coma & death.
- It is caused by eating unripe ackee fruit which contain an unusual toxic amino acid, hypoglycin A. This inhibits the enzyme acyl CoA dehydrogenase and thus β-oxidation of fatty acid is blocked, leading to various complications.

Oxidation of odd carbon chain fatty acid

- The β-oxidation of saturated fatty acids containing odd number of carbon atoms proceeds in same manner as described previous.
- The only difference is that in last & final β-oxidation cycle, a 3 carbon fragment is left behind (in place of 2 carbon unit for saturated fatty acid).
- This compound is propionyl CoA which is converted to succinyl CoA as follows.

1) Propionyl CoA is carboxylated in the presence of ATP, CO_2 & vitamin biotin to D-methylmalonyl CoA.

2) Methylmalonyl CoA racemase converts the methylmalonyl CoA to L-form. This reaction is essential for the entry of this compound into metabolic reaction of body.

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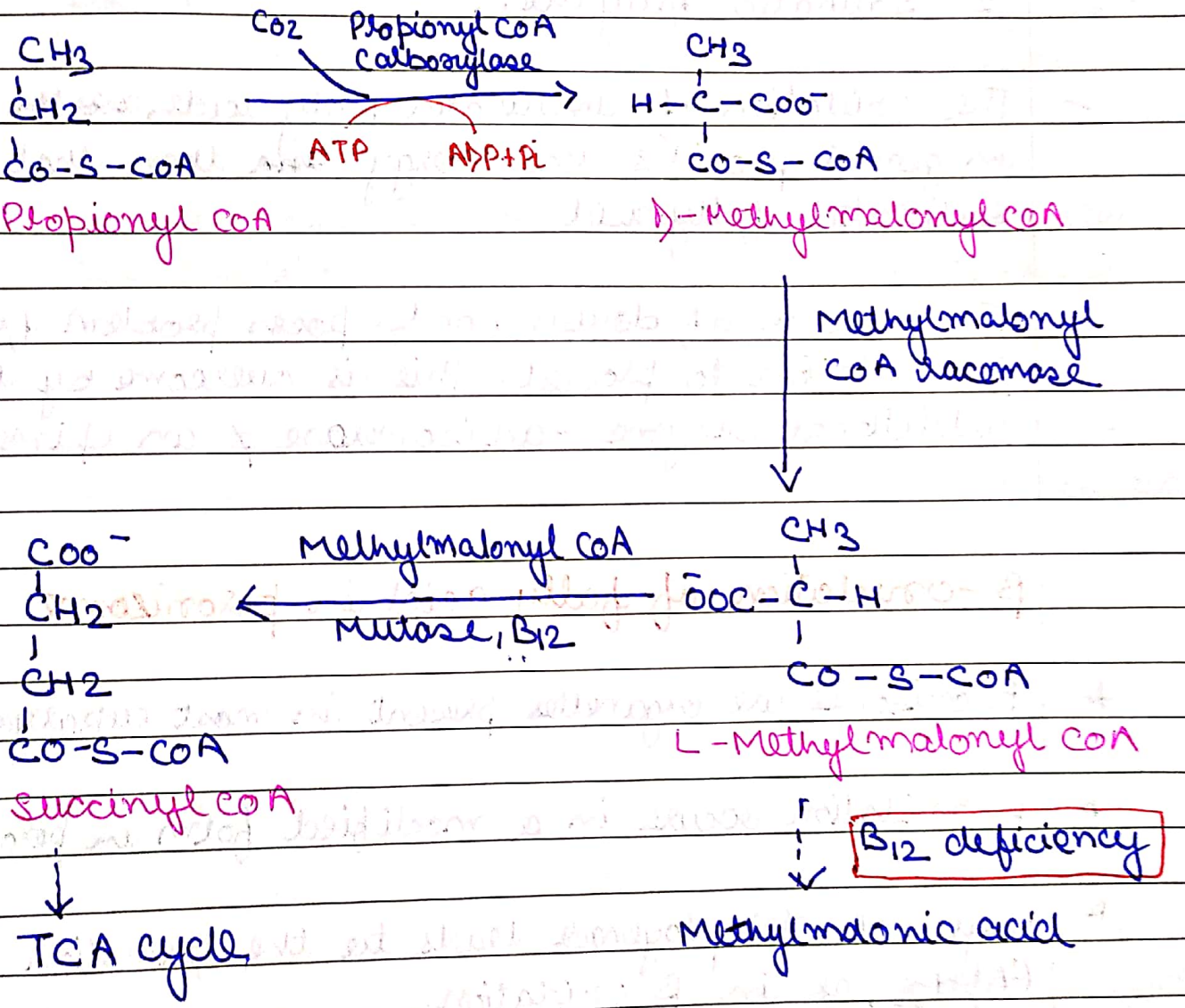
3. The next enzyme, methylmalonyl CoA mutase, is dependent on vitamin B_{12}. It catalyse the conversion of methylmalonyl CoA to succinyl CoA, which can enter citric acid cycle.



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Oxidation of unsaturated fatty acids

- Due to the presence of double bonds, the unsaturated fatty acids are not reduced to the same extent as Saturated fatty acid.

- The oxidation of unsaturated fatty acids, ~~also the same~~ in general provides less energy ~~than~~ than that of saturated fatty acid

- The presence of double bonds poses problem for β-oxidation to proceed. This is overcome by two additional enzyme – an isomerase & an epimerase.

β-oxidation of fatty acid in peroxisomes

- Peroxisomes are organelles present in most eukaryotic ~~cells~~ cells.
- β-oxidation occurs in a modified form in peroxisomes
- Acyl CoA dehydrogenase leads to the formation of $FADH_2$, as in β-oxidation.
- The reducing equivalents from $FADH_2$ are not transferred to the ETC chain, but handed over directly to O_2.
- This results in the formation of H_2O, which is cleared by Catalase

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$E\text{-}FAD H_2 + O_2 \longrightarrow E\text{-}FAD + H_2O$

$H_2O_2 \xrightarrow{\text{Catalase}} H_2O + \frac{1}{2} O_2$

+ There is no ATP synthesized in peroxisomal β-oxidation of fatty acids, since the reducing equivalent do not pass through ETC.

+ It is ~~beliv~~ believed that peroxisomes carry out the initial oxidation of long chain fatty acids which is followed by mitochondrial oxidation.

Peroxisomal oxidation is induced by high fat diet & administration of hypolipidemic drug (eg clofibrate)

Disorders

1). Zellweger Syndrome

+ This is a rare syndrome, characterized by the absence of peroxisomes in almost all the tissues. As a result the long chain fatty acids (C_{26} - C_{38}) are not oxidized.

+ They accumulate in tissue, particularly in brain, liver and kidney.

+ Hence, the disorder is also known as Cerebrohepatorenal syndrome