Lipid Metabolism

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- Definition: lipids are hetrogenous group of compound related by their physical rather than chemical , they are relatively insoluble in water and soluble in organic solvents such as ether, benzene and chloroform .

Biomedical importance

1- Surve as efficient source of energy.

2- As thermal insulator in the subcutaneous tissue and around organs.

3- As electrical insulator as myelin.

- 4-They are structural components of the cell membrane.
- 5-. Serve as precursors for hormones (steroid hormones).

6- Lipoproteins are important in cell membrane , in transport of lipid in the blood.

, atherosclerosis .

7-In nutrition and health as polyunsaturated fatty acids

.

Classes of lipid

I. **Simple lipids:- esters of fatty acids with different alcohols.**

Fats and oils:- These are esters of fatty acids with glycerol.

Waxes:- Esters of fatty acids with high molecular weight monohydric alcohols

2. **Complex lipids:- Esters of fatty acids and alcohols together with some other head**
groups.

A. **Phospholipids:- Esters of the above type containing phosphoric acid residue.**

a) Glycerophospholipids:- The alcohol is glycerol

b) Sphingophospholipids:- The alcohol is shingosine.

B. **Glycolipids:- Lipids containing fatty acid, sphingosine and carbohydrate residues.**

C. **Others:- Include sulfolipids, amino lipids and lipoproteins, which are modified forms of**
lipids.

FATTY ACIDS

Fatty acids are building block of most lipids, made of long chain organic acids having one polar carboxyl group (head) and a non-polar hydrocarbon chain (tail). The latter makes them water insoluble.
They are not found free in nature but found as esterified forms. Most naturally occurring fatty acids have got even number of carbons. They may be saturated or unsaturated, with one or more double bonds. Mostly the double bond occurs at the 9th carbon as we count from the carboxyl group end.

There are two systems of numbering the carbon atoms in a fatty acid

n 3 2 1

CH3 (CH 2)n CH = CH CH2 CH2 CH2 COOH

ω β α

1. Numbering starts from carboxyl carbon. The last carbon is the "n" carbon
2. The second carbon is the "α"and the third the "β" Carbon. The last carbon atom is omega.

Eg:- CH3 (CH2)7 CH2CH2 (CH2)7 COOH stearic acid (saturated fatty acid)

Eg:- CH3 (CH2)7 CH=CH (CH2)7 COOH oleic acid (Unsaturated fatty acid)

Fatty acids can be represented as shown below where the delta indicates the position of the
double bond and the next number shows the number of carbon atoms and the last number
indicates the number of double bonds. In a different way the position of the double bond(s) can
be indicated as shown in the second expression without the delta.

C18:1, Δ9 or 18:1(9)

C18:1, Δ9 or 18:1(9)

C18 indicates 18 carbons, **1** indicates the number of double bonds, delta **9(Δ9)** indicates the position of double bond between 9th and 10th carbon atoms.

- Double bonds in naturally occuring fatty acids are in the cis- configuration and saturated fatty acids of C12 to C24 are solids at body temperature but the unsaturated once are liquids.

PUFA (Polyunsaturated fatty acids): They have two or more double bonds .they are called as
essential fatty acids because they are required in the body and cannot be synthesized. So they
need to be include in the diet.

18 Linoleic acid 18: 2; (9 ,12)

18 Linolenic acid 18: 3; (9 ,12, 15)

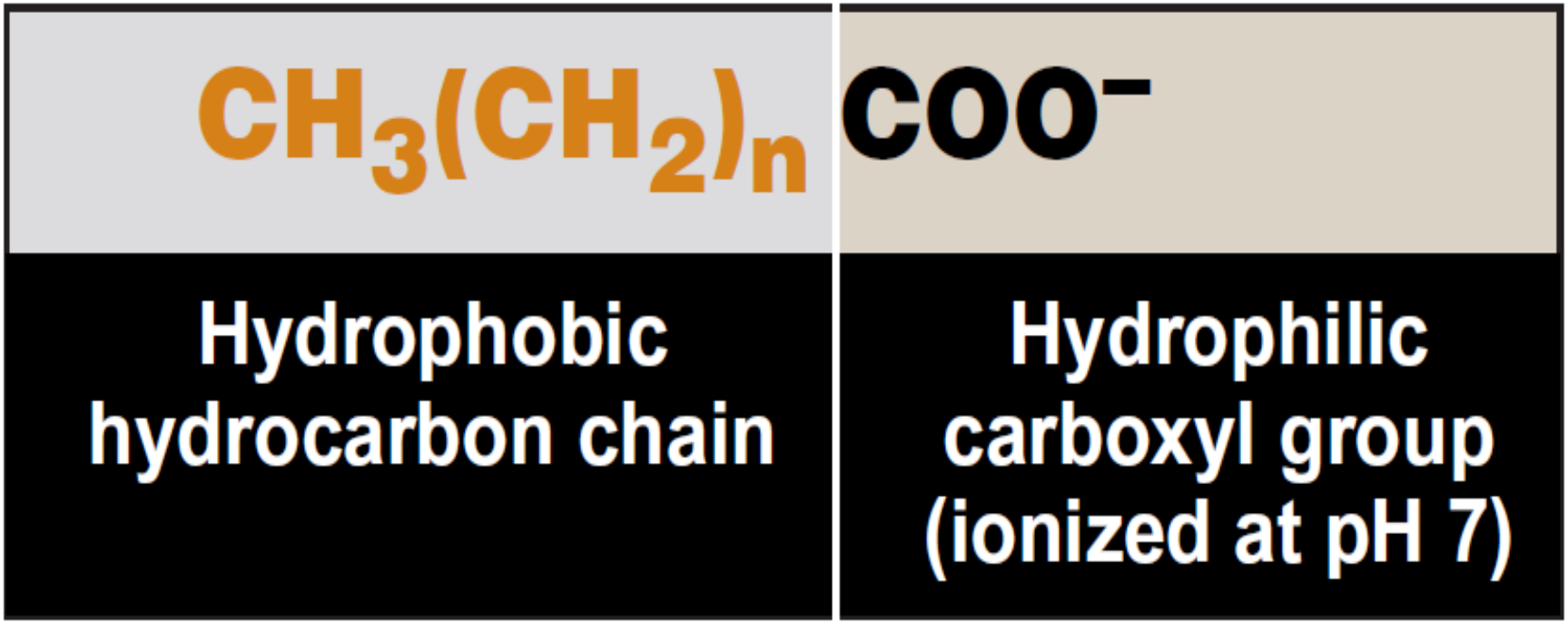
These two are called essential fatty acids.

20 Arachidonic acid 20: 4; (5, 8, 11, 14)

Arachidonic acid is semi essential fatty acid because it can be synthesized from the above two
essential fatty acids.

II. Structure of Fatty Acids

- A fatty acid consists of a hydrophobic hydrocarbon chain with a terminal carboxyl group that has a pKa of about 4.8.
- At physiologic pH, the terminal carboxyl group (–COOH) ionizes, becoming –COO-. This anionic group has an affinity for water, giving the fatty acid its amphipathic nature.
- However, for long-chain fatty acids (LCFAs), the hydrophobic portion is predominant. These molecules are highly water-insoluble, and must be transported in the circulation in association with protein.



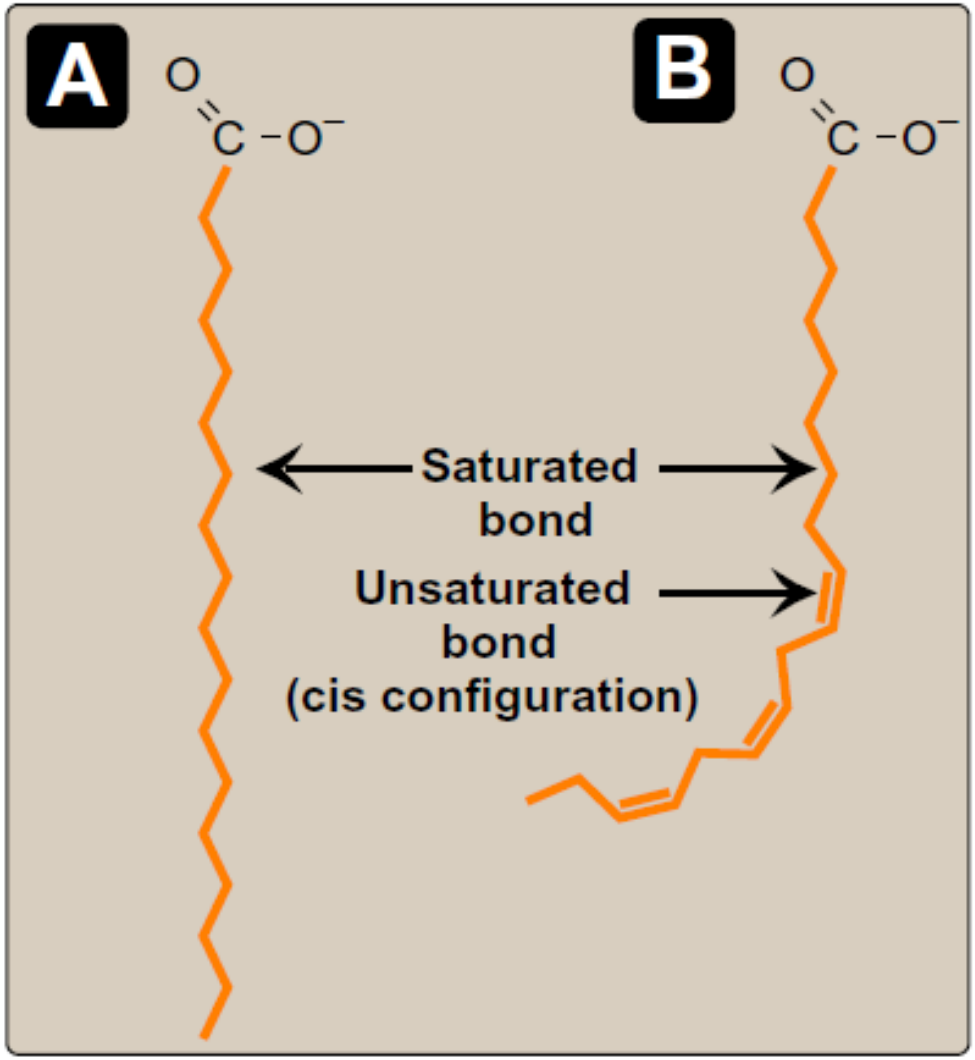
Structure of a fatty acid.

- More than 90% of the fatty acids found in plasma are in the form of fatty acid esters (primarily triacylglycerol, cholesteryl esters, and phospholipids) contained in circulating lipoprotein particles.
- Unesterified (free) fatty acids are transported in the circulation in association with albumin.

A. Saturation of fatty acids

- Fatty acid chains may contain no double bonds—that is, be saturated—or contain one or more double bonds—that is, be mono- or polyunsaturated.
- When double bonds are present, they are nearly always in the cis rather than in the trans configuration.
- The introduction of a cis double bond causes the fatty acid to bend or “kink” at that position.

- If the fatty acid has two or more double bonds, they are always spaced at three-carbon intervals.
- Note: In general, addition of double bonds decreases the melting temperature (Tm) of a fatty acid, whereas increasing the chain length increases the Tm. Because membrane lipids typically contain LCFA, the presence of double bonds in some fatty acids helps maintain the fluid nature of those lipids.]



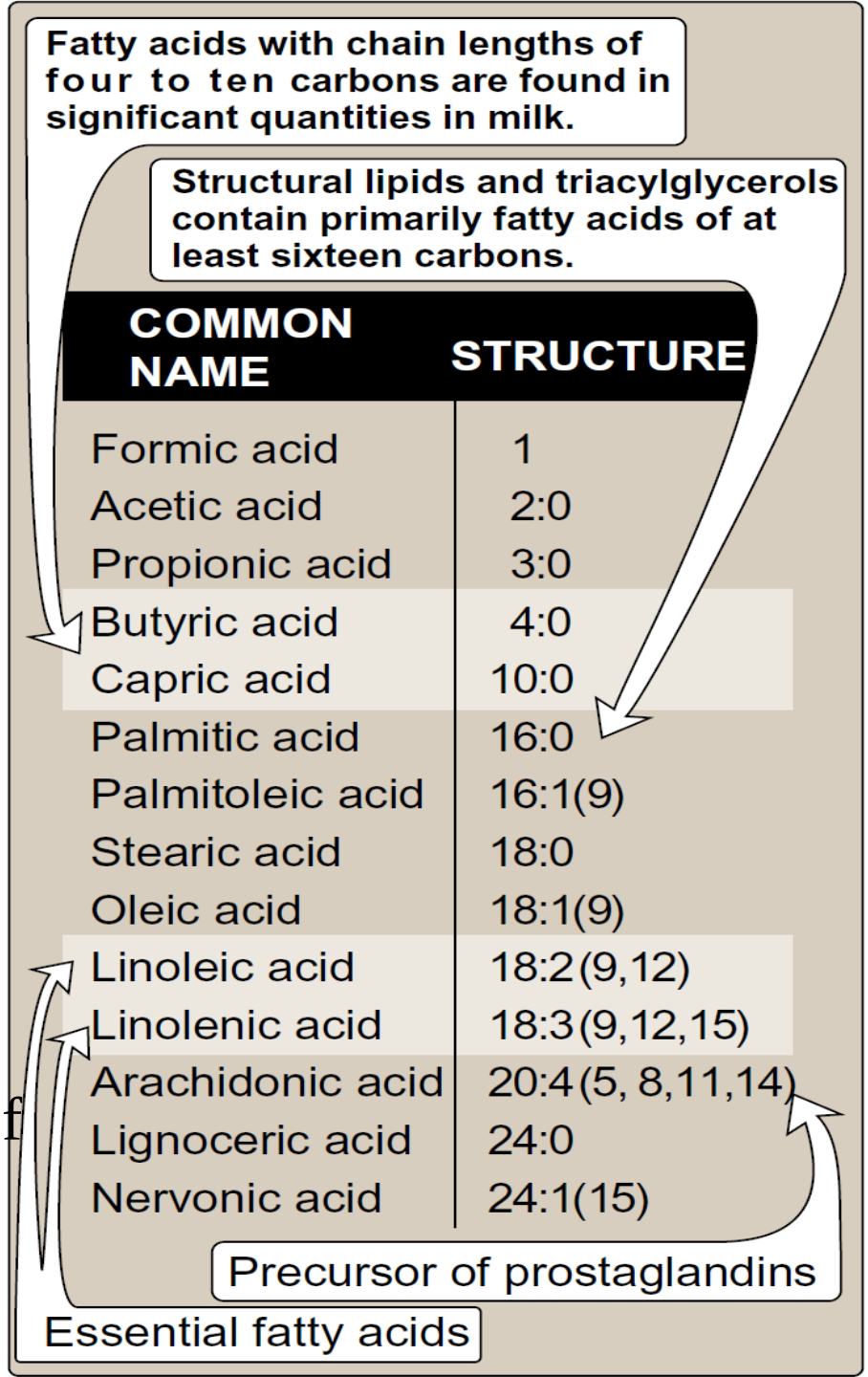
A saturated (A) and an unsaturated (B) fatty acid. [Note: Cis double bonds
cause a fatty acid to "kink."]

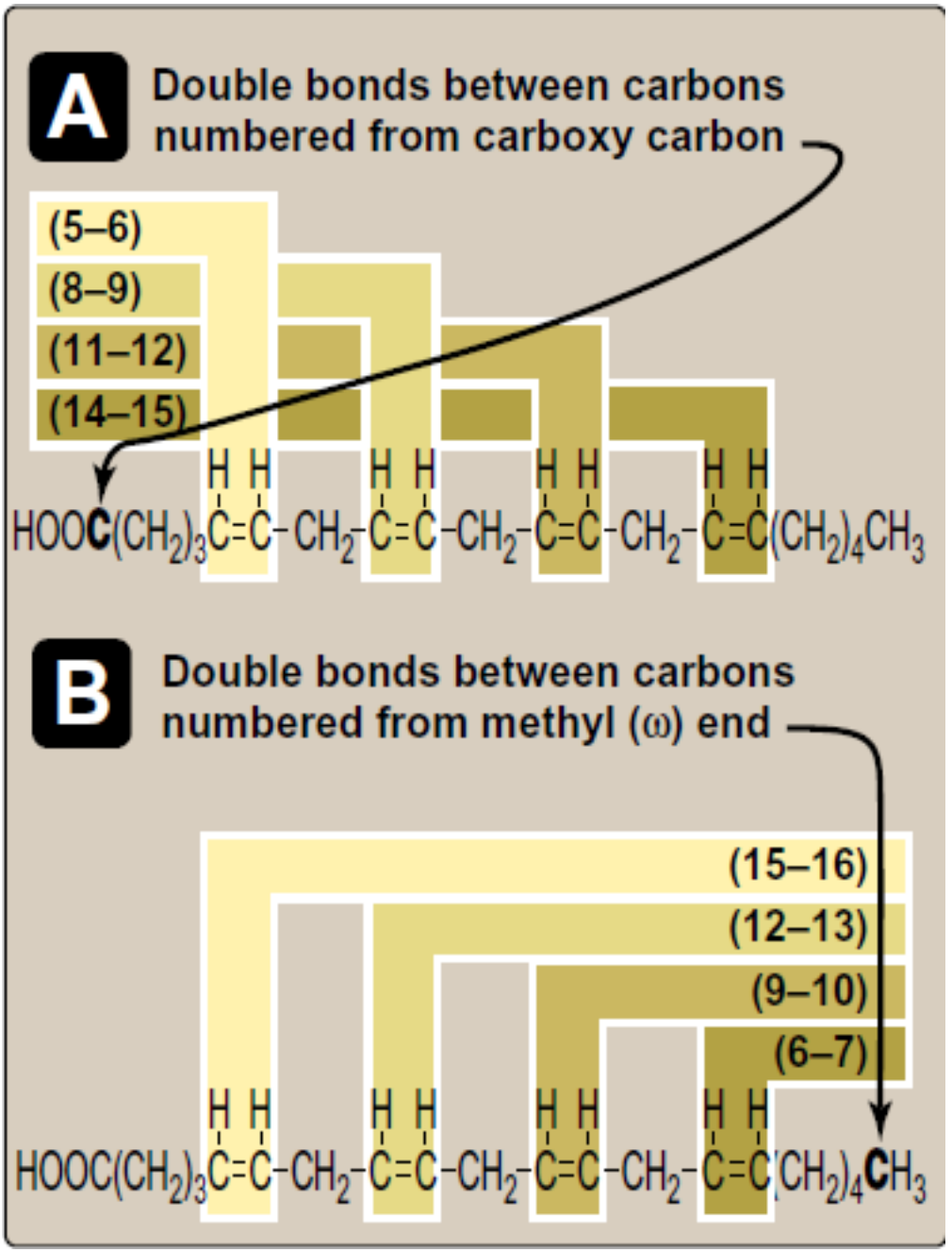
B. Chain lengths of fatty acids

- The common names and structures of some fatty acids of physiologic importance are given below. Note, the carbon atoms are numbered, beginning with the carboxyl carbon as carbon 1.
- The number before the colon indicates the number of carbons in the chain, and those after the colon indicate the numbers and positions of double bonds. E.g., arachidonic acid, 20:4 (5,8,11,14), is 20 carbons long and has 4 double bonds (between carbons 5–6, 8–9, 11–12, and 14–15).
- [Note: Carbon 2, the carbon to which the carboxyl group is attached, is also called the α-carbon, carbon 3 is the β-carbon, and carbon 4 is the γ-carbon.

- The carbon of the terminal methyl group is called the ω-carbon regardless of the chain length.] The carbons in a fatty acid can also be counted beginning at the ω (or methyl-terminal) end of the chain.
- Arachidonic acid is referred to as an ω-6 fatty acid because the closest double bond to the ω end begins six carbons from that end.
- Another ω-6 fatty acid is the essential linoleic acid, 18:2(9,12).
- In contrast, α-linolenic acid, 18:3(9,12,15), is an ω-3 fatty acid.

Some fatty acids of physiologic importance





Arachidonic acid, illustrating position of double bonds.

Essential fatty acids

- Two fatty acids are dietary essentials in humans: linoleic acid, which is the precursor of arachidonic acid, the substrate for prostaglandin synthesis, and α-linolenic acid, the precursor of other ω-3 fatty acids important for growth and development.
- Arachidonic acid becomes essential if linoleic acid is deficient in the diet.
- Essential fatty acid deficiency can result in a scaly dermatitis, as well as visual and neurologic abnormalities. Essential fatty acid deficiency, however, is rare.

Digestion and Absorption of Lipids

Diet contains triglycerides, cholesterol and its ester, phospholipids, fattyacids etc.Mouth and gastric juice has got lipase. It can hydrolyse fats without emulsification with bile salts.Milk fat and butter fat is digested by the enzyme.

Major part of fats are digested by pancreatic lipase. It acts on emulsified lipids only. The products are monoglyceride and 2 fatty acids. Monoglyceride is further hydrolyzed by another lipase. Thus 3 fatty acids and one glycerol molecule is produced from the digestion of dietary triglyceride

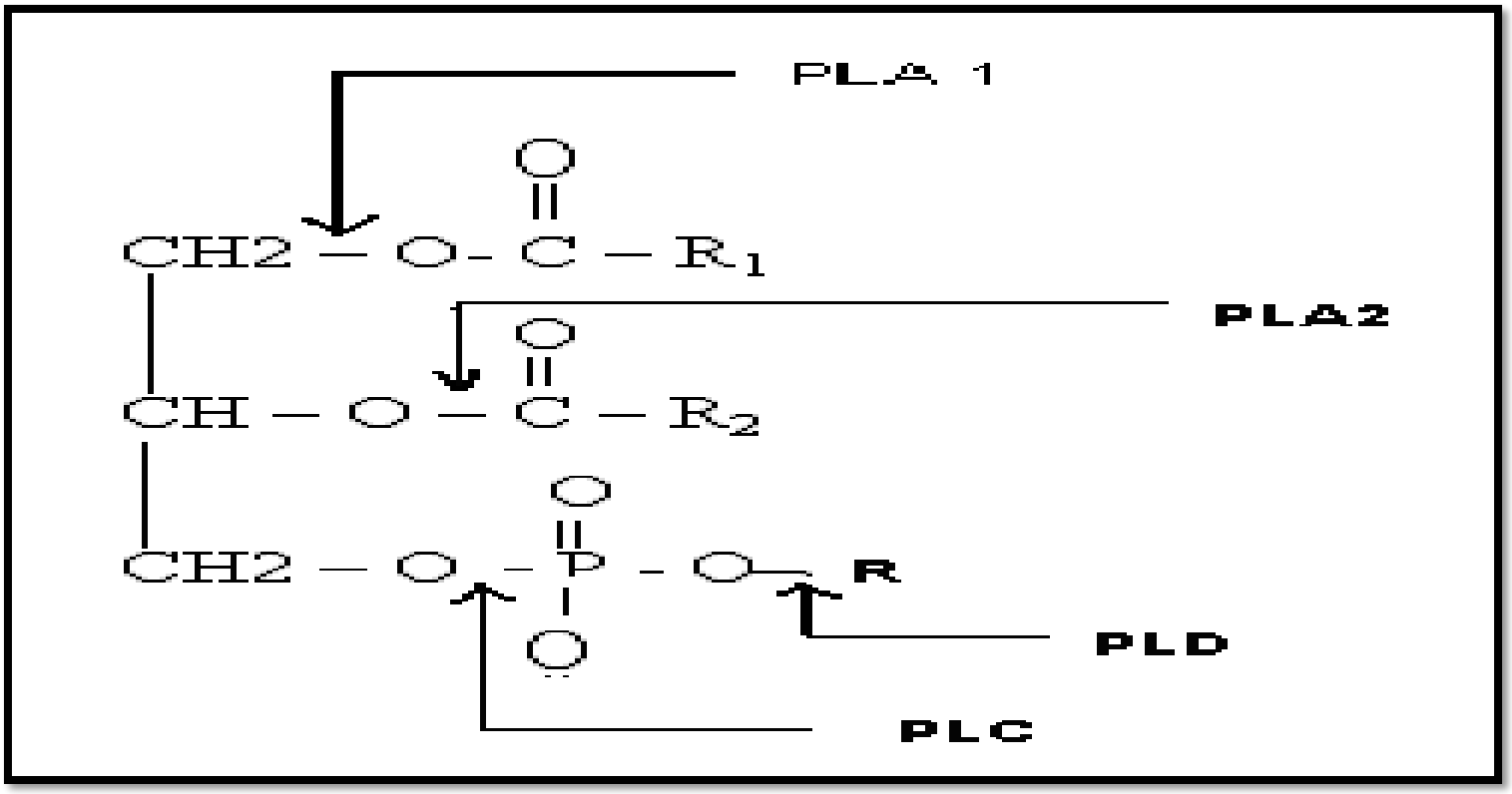
pospholipids are digested by phospholipases, secreted by pancreas and intestines.

They are four in number, A (A1, A2) B, C, and D. The action of these enzymes are shown down

below.

R=Alcohol, R1 and R2 are fatty acids

Fig 4.5:



Transport of Fatty Acids to the Mitochondria

The fatty acids transported to the different tissue cells must first be activated or primed by reaction with CoenzymeA at the expense of ATP. The reaction is catalyzed by AcylCoA synthetase or also called thiokinase, found in the cytosol and mitochondria of cells. The pyrophosphate generated from ATP favors more Acyl CoA formation by further hydrolysis. In order to undergo β-oxidation, the fatty acids must enter the mitochondria. But they cannot easily cross it as such by passive diffusion.

There are two fatty acid sources, those coming from absorption of FA and those from
hydrolysis of triacylglycerols from adipose tissue. The transport of acyl derivatives across the
mitochondrial membrane needs three acyltransferases (shuttles).

1. Specific for short chain acyl groups, does not require carnitine
2. Specific for the long chain acyl groups. The shuttles for long chain acyl groups are
carnitine acyltransferase I and II. Therefore, long chain acyl groups cross the mitochondrial
membrane in combination with carnitine.

Acyl-CoA + Carnitine---------- Acyl carnitine + CoASH

The carnitine pools are in the cytosol and mitochondria, abundant in muscle and it is synthesized
from the amino acids lysine and methionine in the liver and kidney. The other name of carnitine is
β-hydroxy-γ- trimethyl ammonium butyrate. Carnitine acyl transferase I, found in the surface of
the outer mitochondrial membrane, catalyzes the acyl transferase reaction from acylCoA to the
carnitine. It passes through the outer membrane to the inner membrane of mitochondrion.

I n the final stage of the transport, the fatty acyl group is released from the carnitine to the intramitochodrial CoASH by carnitine acyltransferase II, which is found in internal surface of the inner mitochondrial membrane. The regenerated acyl CoA is released to the matrix. It is worth noting that acyltransferase I is a regulatory enzyme in β-oxidation. The acyl CoA present in the matrix of the mitochondrion is now ready for β-oxidation.

β-oxidation of Fatty Acids

The successive oxidative removal of two carbons in the form of acetyl–CoA beginning from the carboxyl end is called β-oxidation.It requires a set of enzymes. The oxidation is so called because the β carbon is oxidized during the oxidation process. It takes place in the matrix of mitochondria.

Energy needs of tissues are met by the oxidation of free fatty acids, released by adipose tissue.

Fatty acids are activated with the help of thiokinase, prior to transport to mitochondria. Overall activation of fatty acid requires hydrolysis of two phosphodiester bonds.

Biomedical important

- Increase F.A oxidation occur in:

1.Starvation and diabetes mellitus, leading to ketone body formation by the liver and gives ketosis.

2. Impairment F.A oxidation leads to hypoglycemia,

Fatty acid oxidation

- As in the metabolism of glucose, FA must be first converted to an active form by reaction with COASH in the presence of ATP.

1. F.A + ATP + CoASH $\xrightarrow[\text{throkinase}]{\text{acyl CoA Synthetase}}$ Acyl CoA + PPi + AMP -1Mole ATP

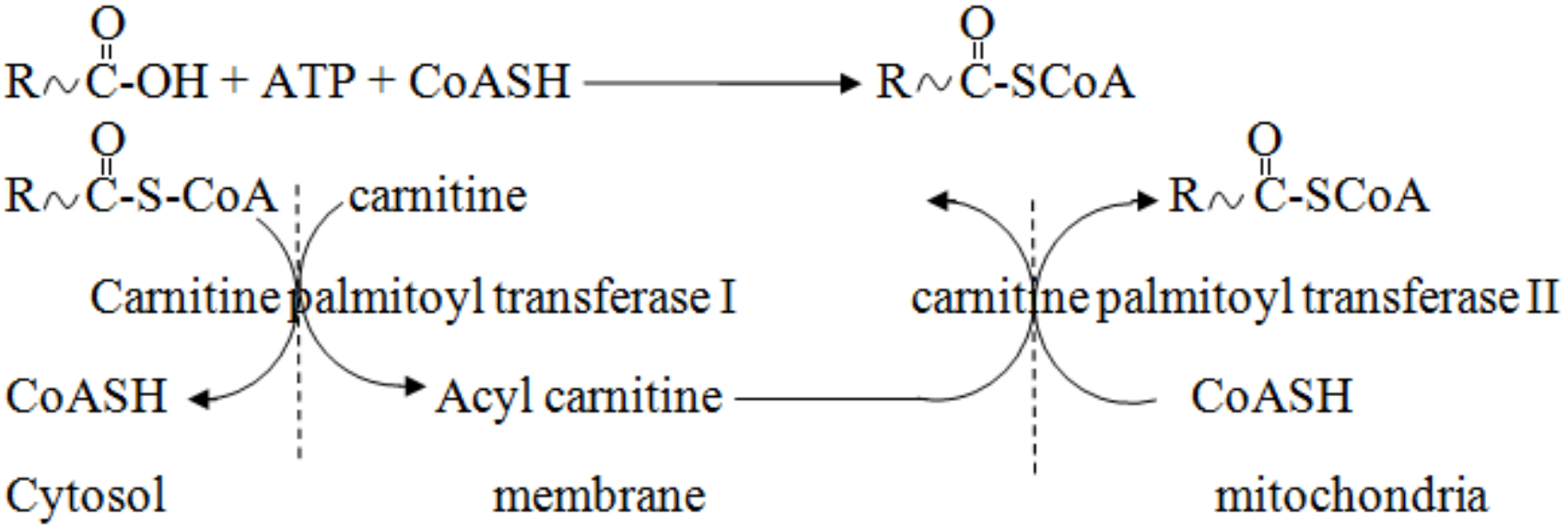
2. PPi + H_2O $\xrightarrow{\text{inorganic phosphatase}}$ 2Pi ≈ -1 M of ATP

Role of carnitine

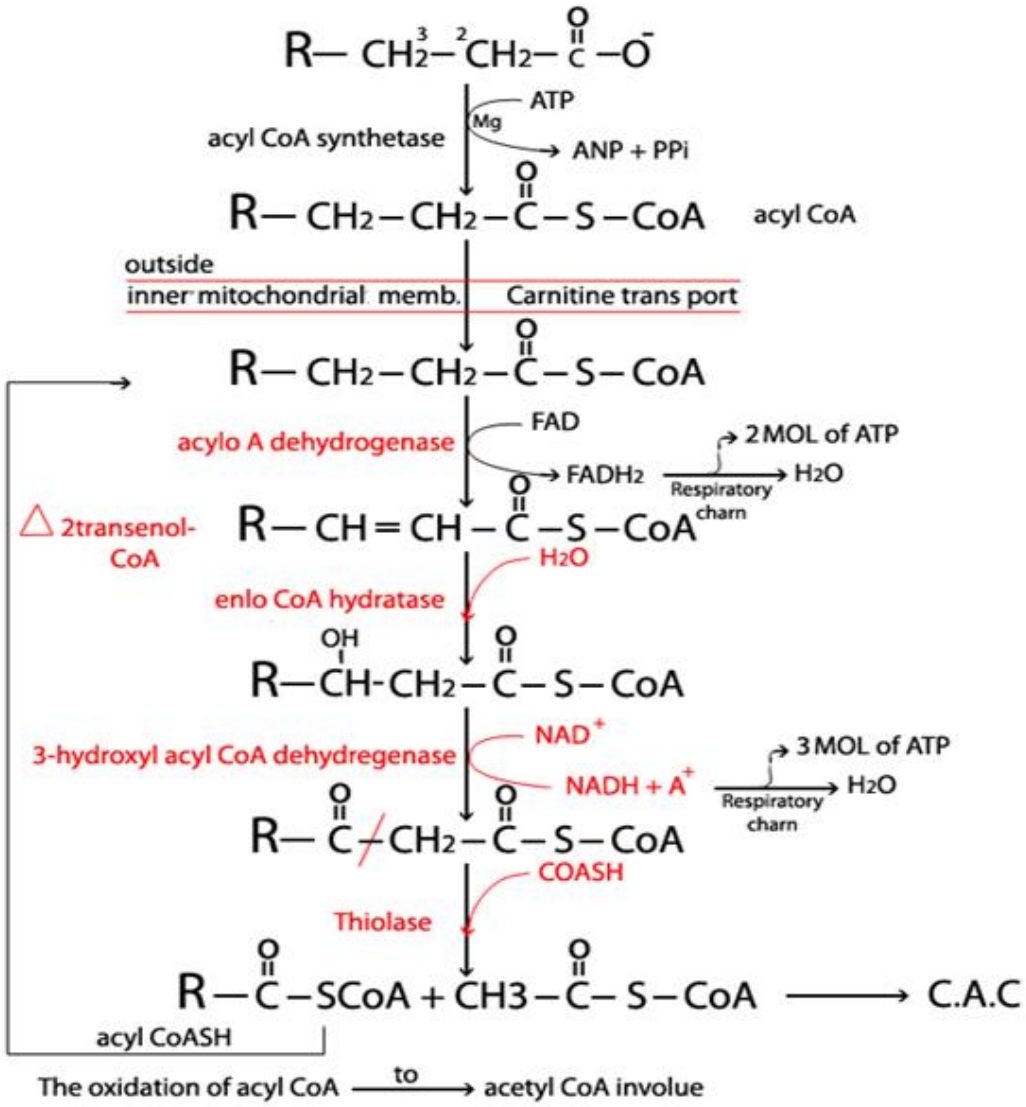
- Carnitine (β-hydroxy – γ – trimethyl ammonium butyrate), Widely distributed in tissue and abundant in muscle.
- It is synthesized from lysine and methionine in liver and kidny .

Role of carnitine

- Fatty acids are activated on the outer mitochondrial membrane,whereas they are oxidized in the mitochondrial matrix.
- A special transport mechanism is needed to carry long – chain acyl CoA molecules across the inner mitochondrial membrane . Activated long – chain fatty acids are transported across the membrane by conjogating them to carnitine.


R∼C-OH + ATP + CoASH
R∼C-SCoA
R∼C-S-CoA
carnitine
Carnitine palmitoyl transferase I
CoASH
Acyl carnitine
carnitine palmitoyl transferase II
R∼C-SCoA
CoASH
Cytosol
membrane
mitochondria

- In the membrane of mitochondria : carnitine acyl transferase acts as inner memberane carnitine transport.
- Another enzyme carnitine acyl transferase, is present and used to transfer short chain acyl group between CoASH and carnitine.


R— CH2 — CH2 — C — O
ATP
Mg
acyl CoA synthetase
ANP + PPi
R— CH2 — CH2 — C — S — CoA
acyl CoA
outside
inner mitochondrial memb.
Carnitine trans port
R— CH2 — CH2 — C — S — CoA
FAD
acylo A dehydrogenase
2 MOL of ATP
FADH2
H2O
Respiratory charn
2transenol-CoA
R— CH = CH — C — S — CoA
H2O
enlo CoA hydratase
OH
R— CH - CH2 — C — S — CoA
NAD+
3-hydroxyl acyl CoA dehydregenase
3 MOL of ATP
NADH + A+
H2O
Respiratory charn
R— C — CH2 — C — S — CoA
COASH
Thiolase
R — C — SCoA + CH3 — C — S — CoA
C.A.C
acyl CoASH
The oxidation of acyl CoA
to
acetyl CoA involue

1- Dehydration: by enzyme acyl dehydrogenase.

2- Hydration: by enolyl CoA hydratase.

3- Oxidation: by hydroxy acyl CoA dehydrogenase.

4-Cleaving: by thiolase.

The product of this reaction are acetyl CoA and acyl CoA containing 2carbon less than the original acyl CoA molecule.

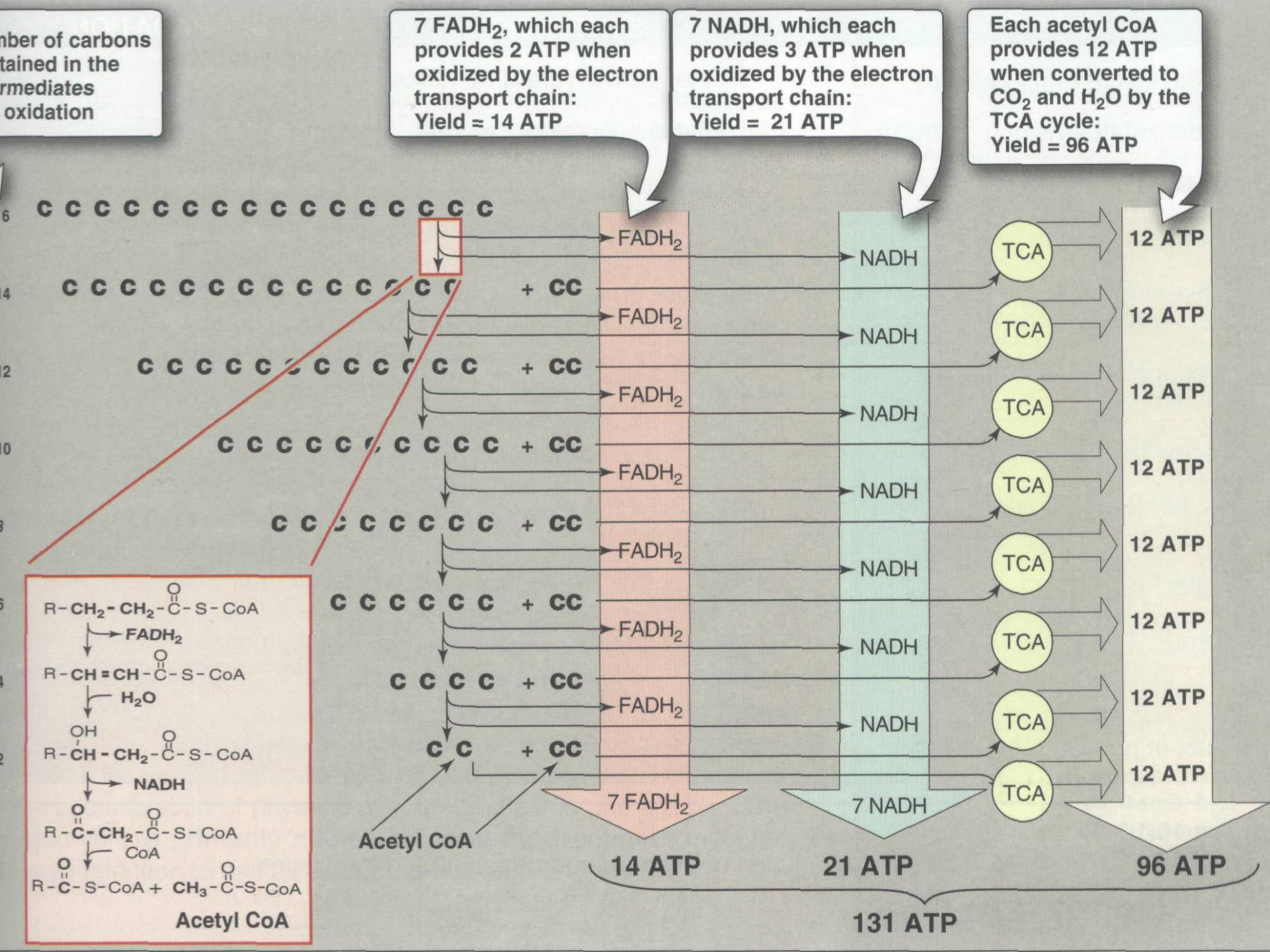
Degradation of FA to acetyl CoA

Reaction	ATP
1. Activation ,FA ⟶ acyl CoASH	-2
2. Dehydration: acyl CoA ⟶ α, β, unsat. acyl CoA	+2
3. Hydration: α, β, unsat. acyl CoA ⟶ 3-hydroxy acyl CoA	0.0
4. Oxidation: 3 hydroxy acyl CoA ⟶ β-ketoacyl CoA	+3
5. β, ketoacyl CoA: cleaving ⟶ acylCoA + acetyl CoA	0.0
	+5mole

- EX: stearic acid C18 ⟶ 9 mole acetyl CoASH

  Repeating seq. 8 times ⟶ produce 8x5 =40 mole of ATP

  -2 mole of energy expanded = 38 mole of ATP
- Complete of oxidation of acetyl CoASH in C.A.C each unit give 12 mole of ATP
- Then 9x12 = 108 mole of ATP + 38 mole / 146 mole of ATP


mber of carbons
tained in the
rmediates
oxidation
7 FADH2, which each provides 2 ATP when oxidized by the electron transport chain: Yield = 14 ATP
7 NADH, which each provides 3 ATP when oxidized by the electron transport chain: Yield = 21 ATP
Each acetyl CoA provides 12 ATP when converted to CO2 and H2O by the TCA cycle: Yield = 96 ATP
FADH2
NADH
TCA
12 ATP
Acetyl CoA
7 FADH2
7 NADH
14 ATP
21 ATP
96 ATP
131 ATP
Acetyl CoA

Oxidation of Fatty Acids with Odd Number of Carbons

Ruminant animals can oxidize them by B- oxidation producing acetylCoAs until a three carbon propionylCoA residue is left.The acetylCoAs produced are funneled to the Krebs cycle but the propionylCoA produced is converted to succinylCoA by three enzymatic steps. SuccinylCoA is an intermediate in the Kreb's cycle and it can be metabolized.

Oxidation of fatty acid with an odd number of carbon

- F.A with odd number oxidize by β oxidation pathway to produce acetyl CoA + 3 carbon unit (propinayl CoA), which is converted to methyl malonyl CoA D, then L, and by isomerase it is converted to succinyl CoASH, thus the propinayl CoA residue is the only part of F.A is glycogenic.
- Peroxisomes oxidize very long chain F.A, by modification of β-oxidation, and leads to formation of acetyl CoA and, H2O2 from FAD dehydrogenase which is break down by catalogs, C20,C22 applied.
- α- oxidation: removal one carbon at time from carboxyl and molecule found in brain and not require CoA intermediate, and does not generate high energy.

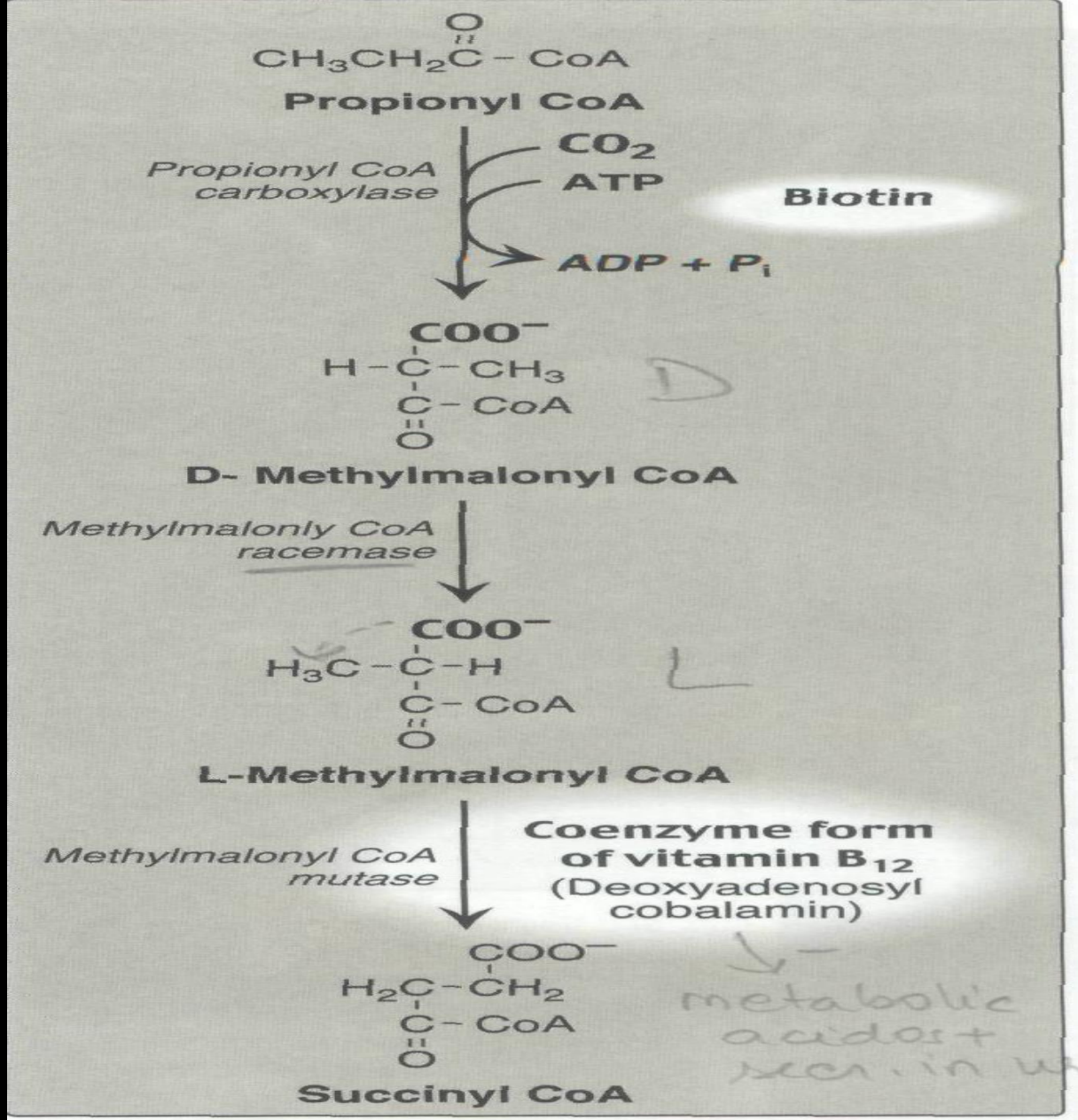
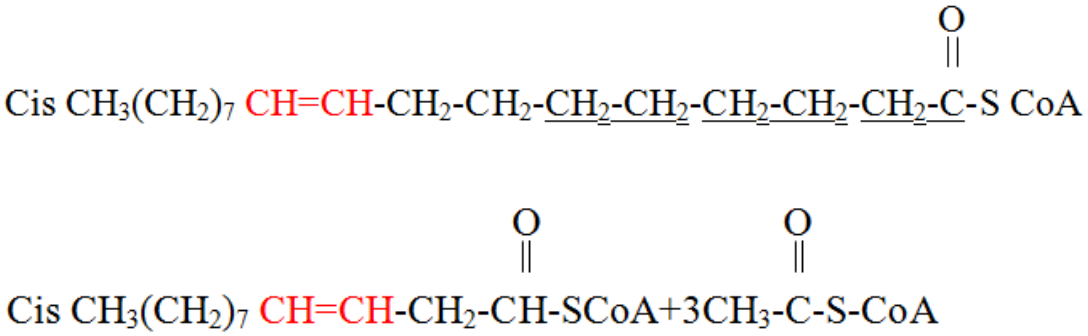
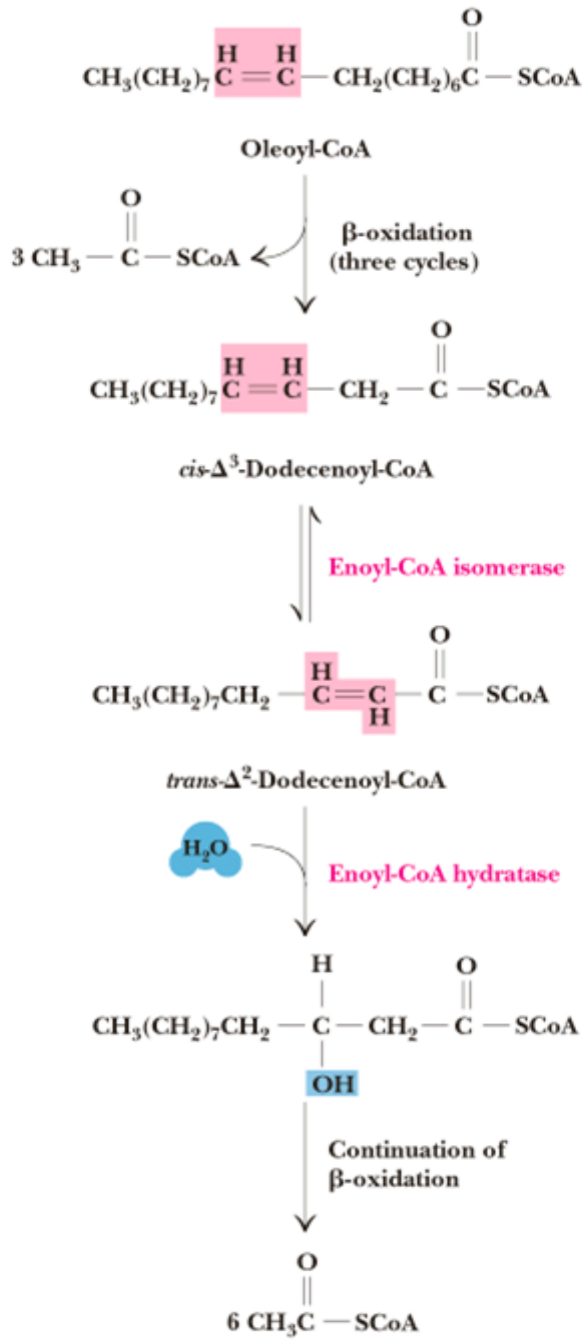


Figure 16.20
Metabolism of propionyl CoA.

Oxidation of unsaturated Fatty acid

- Unsaturated F.A undergo degradative similar to those of sat. F.A.
- EX: C18 oleic converted to oleyl-CoA and oxidize until the double bound C12 when unsat. between carbon 3 and 4 is obtained.

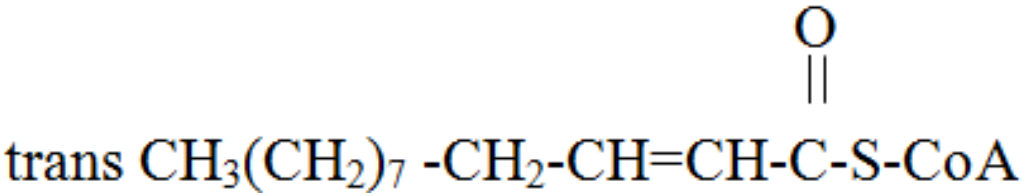



Oleoyl-CoA
β-oxidation
(three cycles)
cis-Δ3-Dodecenoyl-CoA
Enoyl-CoA isomerase
trans-Δ2-Dodecenoyl-CoA
H2O
Enoyl-CoA hydratase
Continuation of
β-oxidation

Two reactions not required with saturated oxidation

1- The double bond migrate to α, β position between C2, and C3.

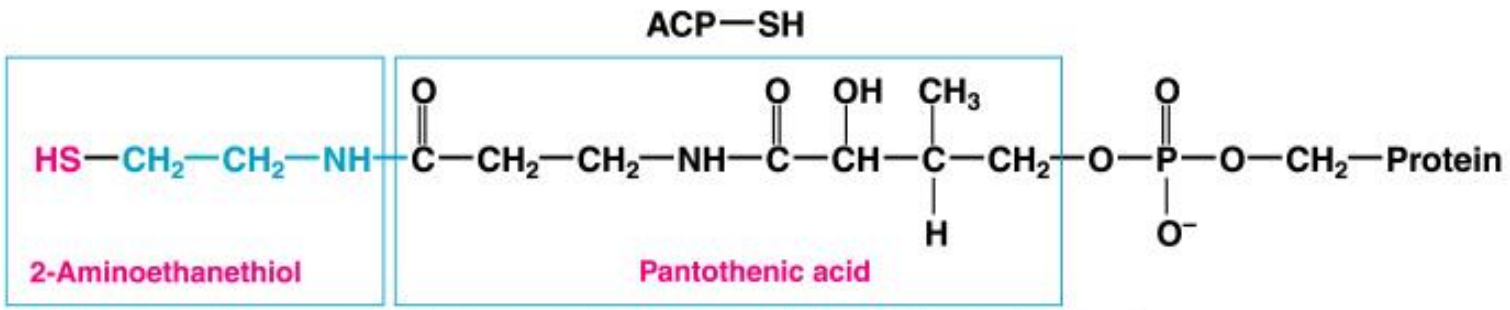
2- The origin C is configuration transferred to trans isomers.



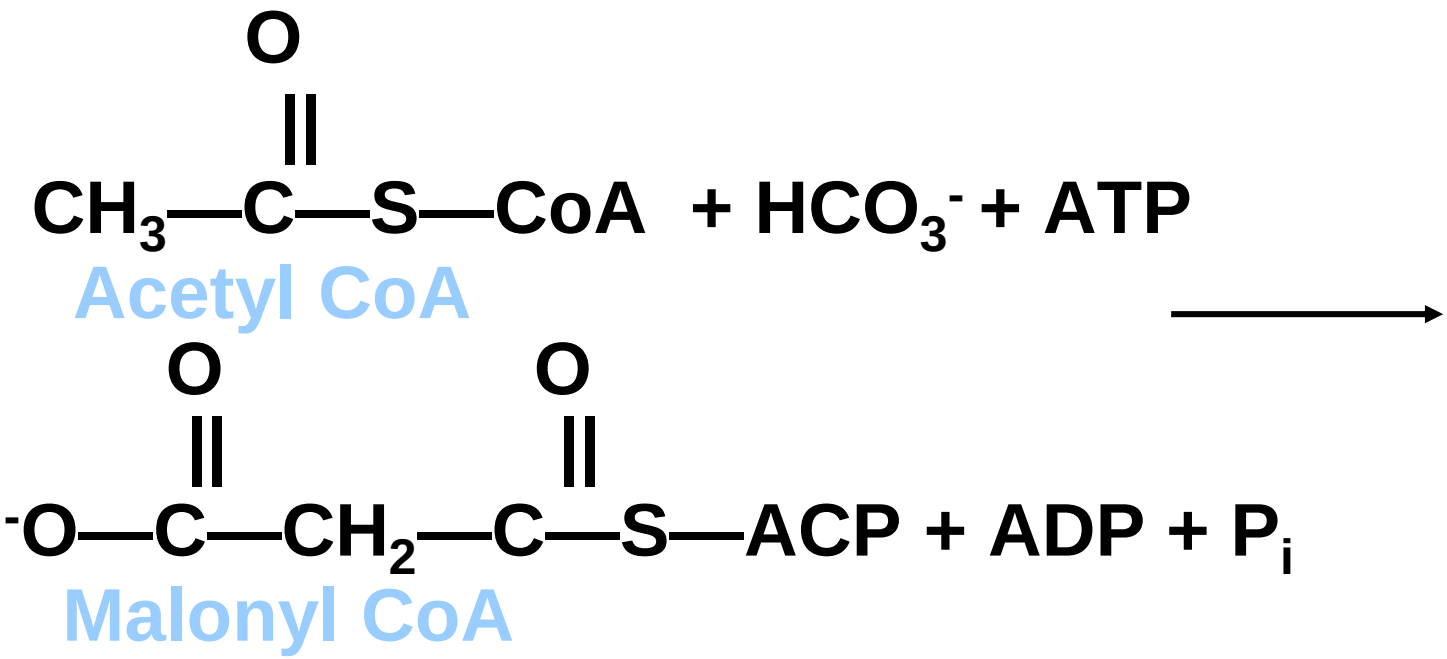
- This compound may hydrate, dehydrogenated and cleaving as the same process for sat.
- The same reaction and process applied for poly unsaturated F.A.

Lipogenesis:

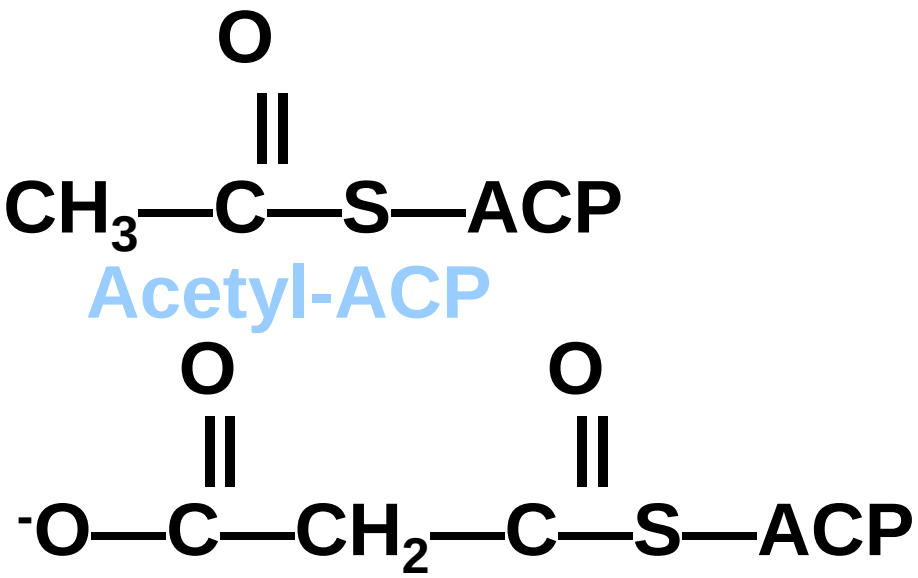
- **Is the synthesis of fatty acids from acetyl CoA.**
- **Occurs in the cytosol.**
- **Uses reduced coenzyme NADPH (NADH with a phosphate group).**
- **Requires an acyl carrier protein (ACP).**



In lipogenesis, acetyl CoA combines with bicarbonate to form malonyl CoA. ATP hydrolysis provides energy.

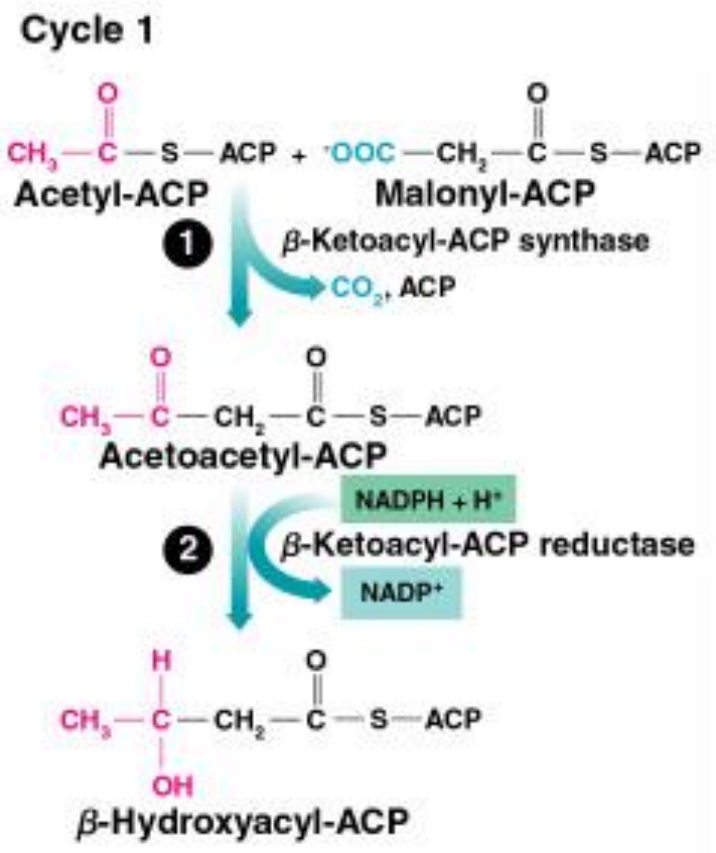


Acetyl CoA and malonyl CoA combine with acyl carrier protein (ACP) to form acetyl-ACP and malonyl-ACP:



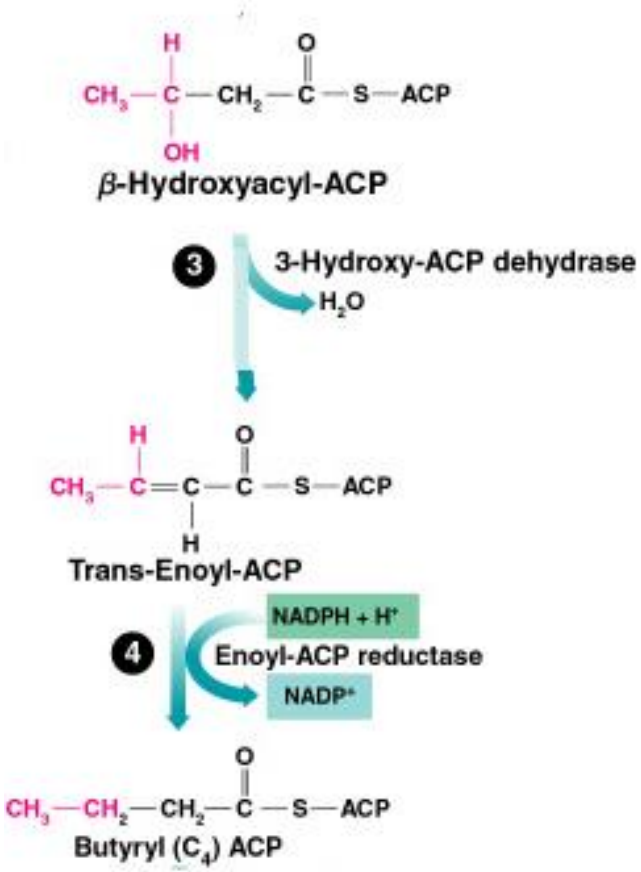
In reactions 1 and 2 of fatty acid synthesis:

- **Condensation by a synthase combines acetyl-ACP with malonyl-ACP to form acetoacetyl-ACP (4C) and CO_2 (reaction 1).**
- **Reduction converts a ketone to an alcohol using NADPH (reaction 2).**



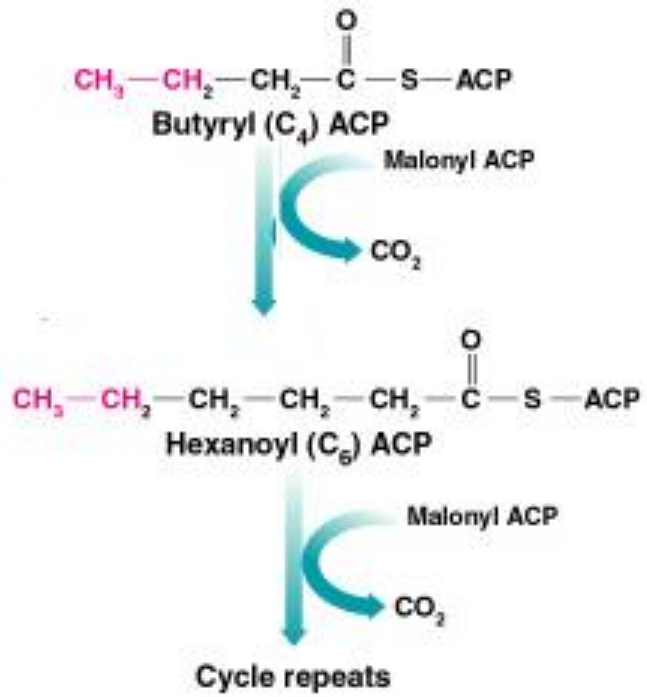
In reactions 3 and 4 of fatty acid synthesis:

- **Dehydration forms a trans double bond (reaction 3).**
- **Reduction converts the double bond to a single bond using NADPH (Reaction 4).**

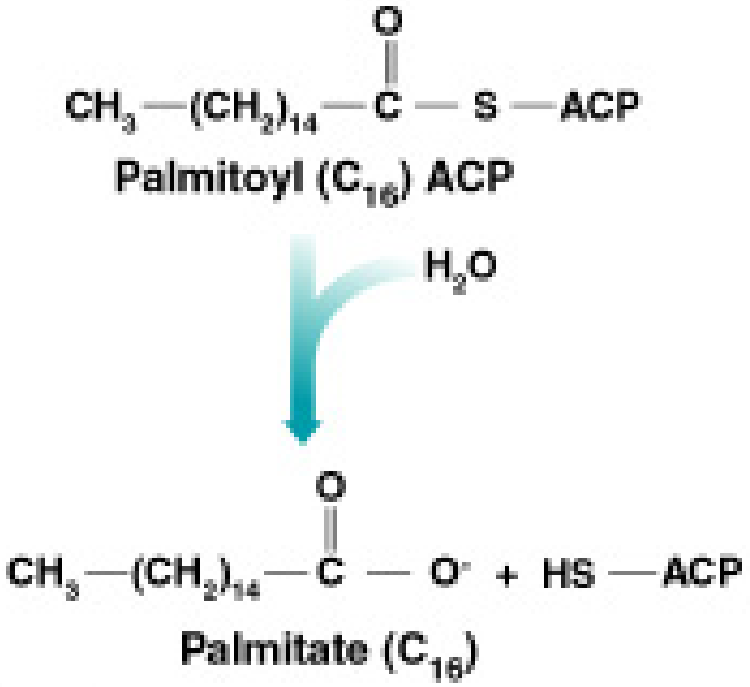


Fatty acid synthesis continues:

- **Malonyl-ACP combines with the four-carbon butyryl-ACP to form a six-carbon-ACP.**
- **The carbon chain lengthens by two carbons each cycle.**



- **Fatty acid synthesis is completed when palmitoyl ACP reacts with water to give palmitate (C_{16}) and free ACP.**



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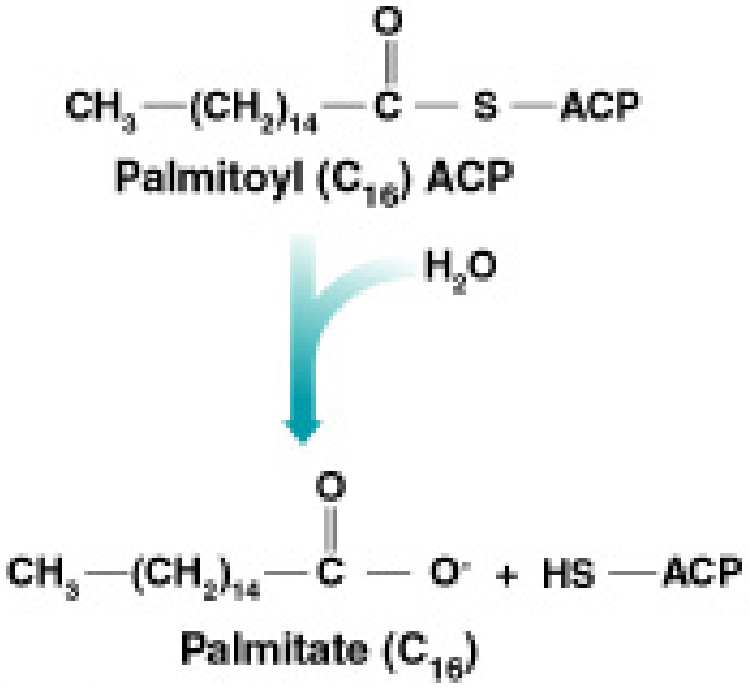
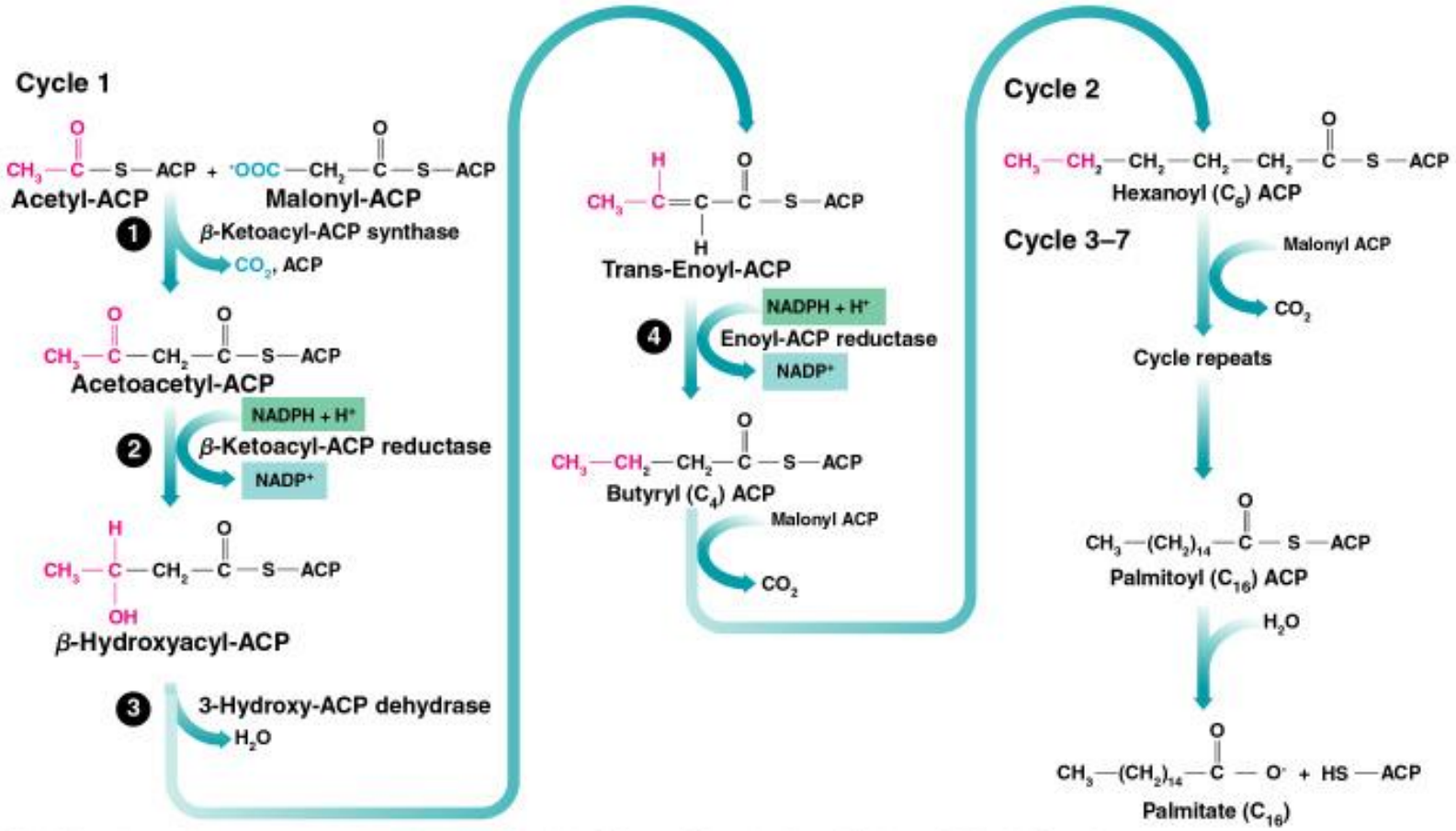




- **Shorter fatty acids undergo fewer cycles.**
- **Longer fatty acids are produced from palmitate using special enzymes.**
- **Unsaturated cis bonds are incorporated into a 10-carbon fatty acid that is elongated further.**
- **When blood glucose is high, insulin stimulates glycolysis and pyruvate oxidation to obtain acetyl CoA to form fatty acids.**

Table 25.1 A Comparison of β Oxidation and Fatty Acid Synthesis

	β Oxidation	Fatty Acid Synthesis (lipogenesis)
Site	Mitochondrial matrix	Cytosol
Activated by	Glucagon Low blood glucose	Insulin High blood glucose
Activator	Coenzyme A (CoA)	Acyl carrier protein (ACP)
Initial subtrate	Fatty acid	Acetyl CoA ⟶ Malonyl CoA
Coenzymes	FAD, NAD^+	NADPH, $NADP^+$
Types of Reaction	Oxidation Hydration Cleavage	Reduction Dehydration Condensation
Function	Cleaves two-carbon acyl group	Adds two-carbon acyl group
Final product	Acetyl CoA units	Palmitate (C_{16}) and other fatty acids

The synthesis of F.A by multi enzyme system

- Multi enzyme complex called fatty acid synthetase system, used to produce long chain acyl derivative from acetyl unit. the enzyme complex bound to each other so the step that, they catalyze is efficient and regulated. for this we requires acyl carries protein ACP, which is low m.wt protein link via the hydroxyl oxygen of serine residue to phosphate pantothenic acid, and also mercapto ethylamine.

- ACP takes the role of CoA. Two advantages of single multi enzyme system.

1- The enzyme is efficient and freedom from interference competing reaction.

2- The synthesis of all enzyme is coordinated , since it is encoded by single gene.

- The enzyme is dimer, containing 7 enzyme activity of F.A synthesis with ACP with 4-phosphopantetheine – SH.

1. Reaction of acetyl CoA + Acp-SH $\xrightarrow{acetyl\ transacylase}$ $CH_3\text{-}\overset{\overset{O}{\|}}{C}\text{-Acp}$ + CoASH

2. Malonyl CoASH + Acp $\xrightarrow{malonyl\ transacylase}$ Malonyl-Acp + CoASH

3. The acetate gro transfer from Acp to snifhyolryl groof cystine resiolue on enzyme complex by β-Keto acyl-Acp synthetase.

$CH_3\text{-}\overset{\overset{O}{\|}}{C}\text{-S-Acp} + \text{En-SH} \longrightarrow CH_3\text{-}\overset{\overset{O}{\|}}{C}\text{-S-En} + \text{AcpSH}$

4. $CH_3\text{-}\overset{\overset{O}{\|}}{C}\text{-S-En} + COO^{-}CH_2\text{-}\overset{\overset{O}{\|}}{C}\text{-Acp} \xrightarrow[synthetase]{3\ Ketoacyl} CH_3\text{-}\overset{\overset{O}{\|}}{C}\text{-}CH_2\text{-}\overset{\overset{O}{\|}}{C}\text{-S-Acp} + \text{EnSH} + CO_2$

The CO_2 incorporated in synthesis of malonyl CoA is not incorporated in the carbon chain of fatty acid.

5. $CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-S-Acp} + NADPH + H^+ \xrightarrow[reductase]{B-Ketoacyl\ Acp} CH_3\text{-}\overset{OH}{\overset{|}{C}}H\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-S-Acp} + NADP^+$

This β-hydroxy butyrl differ from β-hydroxy bulyrl, D- β-hydroxy butyrl Acp which is formed during olegraolation of fatty acid (L), while this is D confrgration.

6. $CH_3\text{-}\overset{OH}{\overset{|}{C}}H\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-S-Acp} \xrightarrow[hydratase]{enoyl-Acp} CH_3\text{-}CH{=}CH\text{-}\overset{O}{\overset{\|}{C}}\text{-S-Acp} + H_2O$

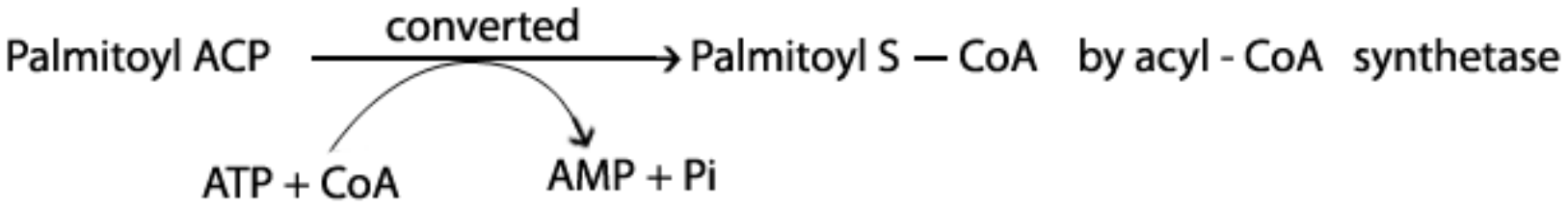
The product has a trans configuration at the double bond.

7. $CH_3\text{-}CH{=}CH\text{-}\overset{O}{\overset{\|}{C}}\text{-S-Acp} \xrightarrow{Enol\ reductase} CH_3CH_2CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-S-Acp} + NADP^+$

Butyrl Acp

- Then the length increase by two unit. condensation of butyrl ACP + malonyl ACP followed by repeating reaction. The sequence repute unit from 16 C atom in palmitoyl ACP, the carbon chain drive from 1 unit of acetyl ACP and 7 unit of Malonyl ACP, the acetyl ACP is the a carbon at 15 and 16.

Elongation of fatty acid



- To system for elongation:
- 1- using microsomal enzyme (endoplasmic reticulum): using Malonyl CoA as acetyldoner. And NADPH as a reductant catalyzed by F.A elongase. then hydratase and reductase.

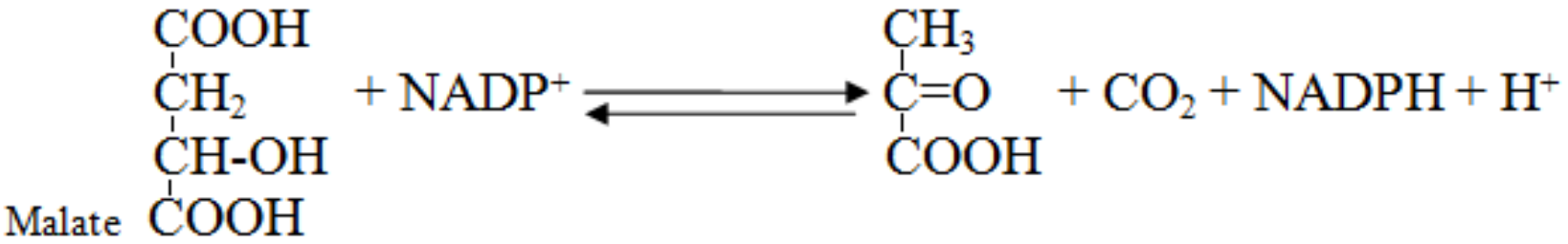
- 2- Mitochondrial: by addition acetyl CoA instead of malonyl CoA.

Source of NADPH

- 2 moles of NADPH required in each time length extended by 2 carbon. thus complete synthesis of palmitic acid required 14 mole of NADPH. It is source are from :

1- Oxidation of glucose via pentose phosphate pathway.

2- Conversion of malate to pyruvate by malic enzyme, NADP malate dehydrogenase.



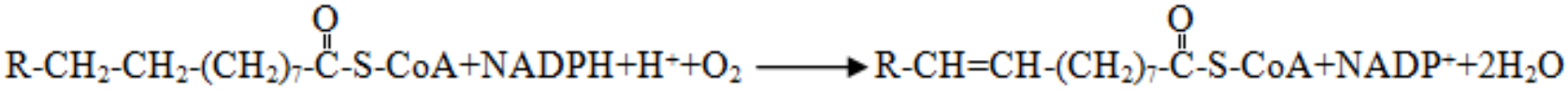
3. Oxidation of isocitrate by $NADP^+$ dependent isocitrate dehydrogenase

isocitrate + $NADP^+$ ⟶ α-Ketoglutarate + CO_2 + NADPH + H^+

- The amount of NADPH produce by these two way is much less than that derived from pentose pathway, and this give the reason why the tissue are active in synthesis F.A should metabolize glucose via pentose pathway.

Unsaturated Fatty acid

- Liver and adipose tissue having enzyme to converting palmitoyl CoA and stearyl CoA to the respective unsaturated product of patmitoleyl CoA **and** Oleyl CoA, this enzyme is "mixed function oxygenase".



- In mammals: de saturation of Fatty acyl CoA cannot occur between C12-C13, C15-C16, and for this reason we cannot synthesis linoleic $\Delta^{9,12}$ or linolenic $\Delta^{9,12,15}$
- Therefore these acids must be supplied in the diet, their deficiency in rats, inhibit growth and provide abnormal skin condition. Linoleic acid serve as a precursor in bio synthesis of prostaglandins, which is highly potent biologic activities and effecting in lowering blood pressure, and enhance contraction of certain smooth muscle.

The metabolism of Ketone Bodies

When the level of acetyl CoA from β-oxidation increases in excess of that required for entry into the citric acid cycle,
It undergoes ketogenesis in the mitochondria of liver (ketone body synthesis).
The three compounds viz., acetoacetate, β-hydroxybutyrate, and acetone are collectively known as ketone bodies.
The synthesis of ketone bodies takes place during severe starvation or severe diabetes mellitus.
During such conditions, the body totally depends on the metabolism of stored triacylglycerols to fulfill its energy demand.

In the synthesis, two molecules of acetyl CoA condense together to form acetoacetyl CoA, a reaction catalyzed by thoilase.
Another molecule of acetyl CoA reacts with the acetoacetyl CoA to form 3-Hydroxy-3-methyl glutaryl CoA (HMGCoA).
This step is the rate limiting step and the reaction is catalyzed by HMGCoA synthase enzyme.
Note that this compound is also an intermediate in the synthesis of cholesterol in the liver cell cytosol but the mitochondrial HMGCoA goes to ketone body synthesis.

The HMGCoA formed in the hepatocytes mitochondria by the action of the enzyme HMGCoA lyase is changed to acetoacetate.

The acetoacetate, when its concentration is very high in blood is spontaneously decarboxylated to acetone.

Acteoacetate can be converted to β-hydroxy butyrate by a dehydrogenase enzyme. It is areversible reaction.

The odor of acetone may be detected in the breath of a person who has a high level of acetoacetate, like diabetic patients.

During starvation and severe diabetes mellitus peripheral tissues fully depend on ketone bodies. Even tissues like the heart and brain depend mainly on

ketone bodies during such conditions to meet their energy demand.

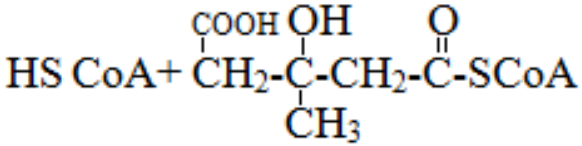
Ketone bodies

- Oxidation of F.A produce acetyl CoA, that is oxidize by TCA to give CO2+ H2O in the liver, when molecule of acetyl CoA condense, form, acetoacetyl CoA.

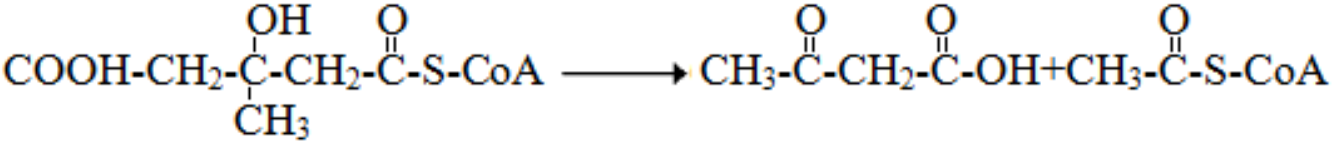
Then it is converted to free acetoacetate by two mechanism:

1. Less important,

2. More important:



β-hydroxy-β-methyl glutaryl CoA



This is the intermediate for cholesterol synthesis.

In extra hepatic tissue it is metabolize by either reduction or decarboxylation.

1. $CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}OH + NADH + H^+ \xrightarrow{dehydrogenase} CH_3\text{-}\overset{OH}{\overset{|}{C}}H\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}OH + NAD^+$

β-D-hydroxy butyrate.

2. $CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}OH \xrightarrow[Spontaneously]{decarboxylation} CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3 + CO_2$

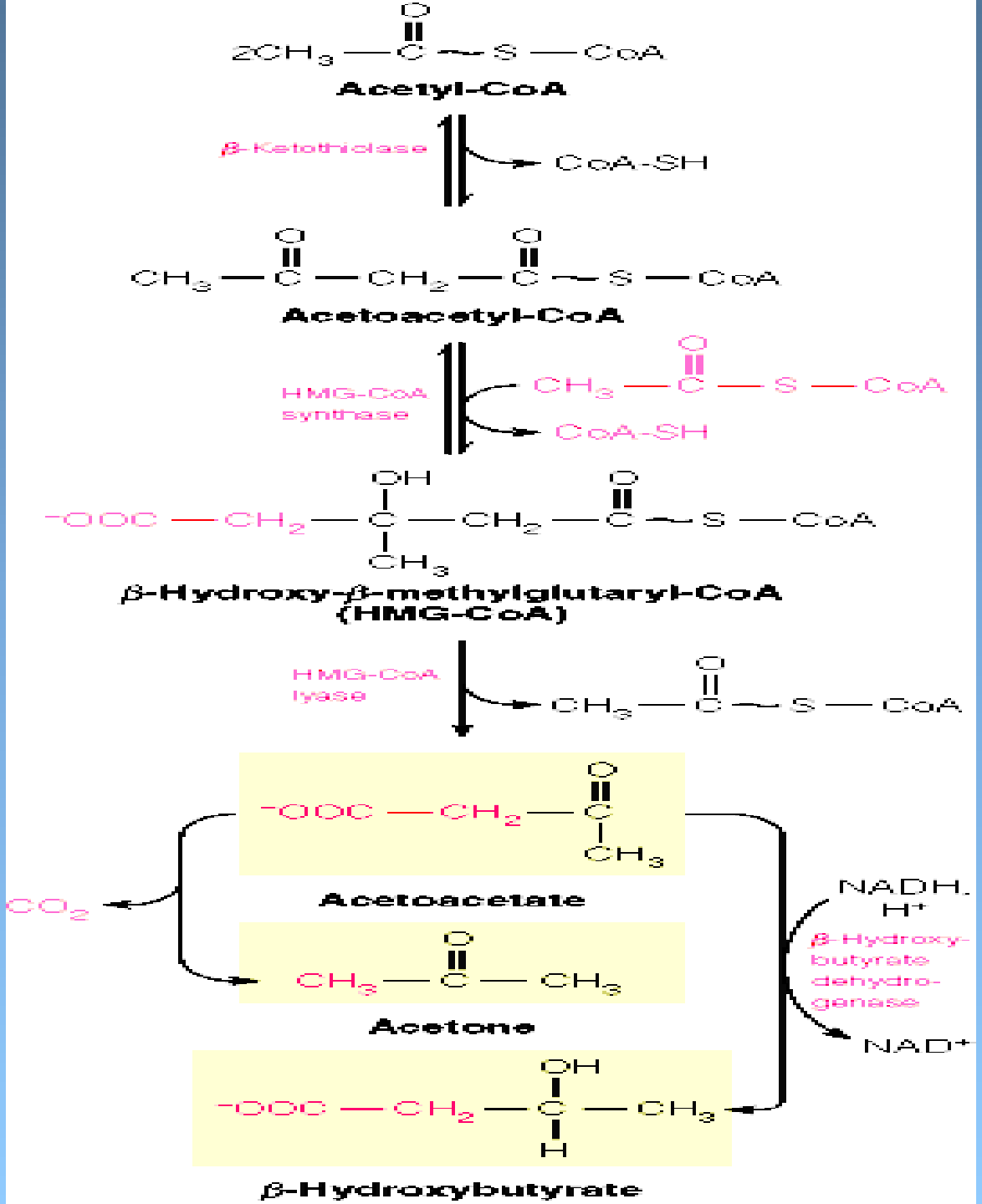
These three substance produce in the liver, known ketone bodies also called aceton bodies. The inter conversion acetoacetate to 3-H-butyrated depend on (NAD^+/NADH) that is redox state. The blood ratio [3.H-B]/[AB] is 1:1 to 10:1 normally not exceed 0.2mm/L, it is conce. In urine < 1mg/day.

The acetoacetate can not be metabolize by the liver, however it can be utilize for energy by skeletal and heart muscle and for alimited extent by brain.

In order to be utilize, it must be activated, and extra hepatic tissue, kidney, muscle, contain enzyme for the formation of activation to give acetoacetyl CoA including thiokinase and thiophorase.

1. $CH_3\text{-}\overset{\overset{O}{\|}}{C}\text{-}CH_2\text{-}\overset{\overset{O}{\|}}{C}\text{-}OH + ATP + HSCoA \xrightarrow{thiokinase} CH_3\text{-}\overset{\overset{O}{\|}}{C}\text{-}CH_2\text{-}\overset{\overset{O}{\|}}{C}\text{-}S\text{-}CoA + AMP + PPi$

2. $CH_3\text{-}\overset{\overset{O}{\|}}{C}\text{-}CH_2\text{-}\overset{\overset{O}{\|}}{C}\text{-}OH + \underset{\text{Succinyl CoA}}{\overset{\overset{COOH}{|}}{CH_2}\ CH_2\text{-}\overset{\overset{O}{\|}}{C}\text{-}S\text{-}CoA} \xrightarrow{thiophorase} CH_3\text{-}\overset{\overset{O}{\|}}{C}\text{-}CH_2\text{-}\overset{\overset{O}{\|}}{C}\text{-}SCoA + Succinate$


2CH3—C(=O)—S—CoA
Acetyl-CoA
β-Ketothiolase
CoA-SH
CH3—C(=O)—CH2—C(=O)—S—CoA
Acetoacetyl-CoA
HMG-CoA synthase
CH3—C(=O)—S—CoA
CoA-SH
⁻OOC—CH2—C(OH)(CH3)—CH2—C(=O)—S—CoA
β-Hydroxy-β-methylglutaryl-CoA (HMG-CoA)
HMG-CoA lyase
CH3—C(=O)—S—CoA
⁻OOC—CH2—C(=O)—CH3
Acetoacetate
CO2
CH3—C(=O)—CH3
Acetone
NADH, H+
β-Hydroxybutyrate dehydrogenase
NAD+
⁻OOC—CH2—C(OH)(H)—CH3
β-Hydroxybutyrate

Regulation of Ketone Body Synthesis

It is regulated by

- Rate of β-oxidation
- Availablity of substrates to enter TCA cycle
- Mobilization of carbohydrate stores

Utilization of Ketone Bodies

Ketone bodies are produced in the Liver and they are utilized in extrahepatic tissues.

Liver does not contain the enzyme required for activation of ketone bodies

Aceto acetate is activated by two processes for its utilization.

1. Aceto acetate + ATP + CoA → Acetoacetyl CoA + AMP.

The enzyme is Synthase

2. Aceto acetate + Succinyl CoA → Aceto acetyl CoA + Succinate.

The enzyme is Thiophorase(Absent in Liver)

Aceto acetyl CoA is broken down to two molecules of Acetyl CoA, which enters TCA cycle for the production of energy.
Aceto acetate and β-hydroxy butyrate are the normal substrates for respiration and important sources of energy .
Renal cortex and heart muscle use acetoacetate in preference to glucose .
Brain switches over to utilization of ketone bodies for energy during starvation and in uncontrolled diabetes.
Acetone is exhaled out .It does not produce energy. Normal level of ketone bodies in blood is 1mg %.
In ketonuria, the level increases.
Excretion of ketone bodies increases in urine, called ketonuria. If the patient suffers from both the signs, it is called ketosis.

Causes of Ketosis:

1. Prolonged starvation, depletion of carbohydrate stores results in increased fatty acid oxidation
and ketosis.
2. Lactating mothers develop ketosis, if the carbohydrate demands are not met with.
3. Diabetic patients with uncontrolled blood glucose, invariably suffer from ketosis, ketoacidosis.
Ketosis usually associated with sustained high levels of free fatty acids in blood. Lipolysis and
ketogenesis are regulated by hormones.

In Diabetes, there is lack of insulin, which brings about lipolysis and decreased utilization ofglucose.
Lipolysis increases free fatty acids in blood, which are oxidized to meet energy requirements. This causes increased production of acetyl CoA, NADH, ATP which in turn inhibits TCA cycle.
Acetyl CoA requires oxalo acetate to enter TCA cycle .Since oxaloacetate is not forming from glucose, acetyl CoA can't enter the cycle. It is diverted to ketone bodies synthesis.
Similarly in starvation, due to hypoglycemia, there is less insulin, lipolysis increases and ketogenesis increases .
Oxaloacetate is also diverted to gluconeogenesis, which further depletes TCA cycle .
So acetyl CoA can only be converted to ketone bodies.


Thank You