
بسم الله الرحمن الرحيم

LIPID METABOLISM

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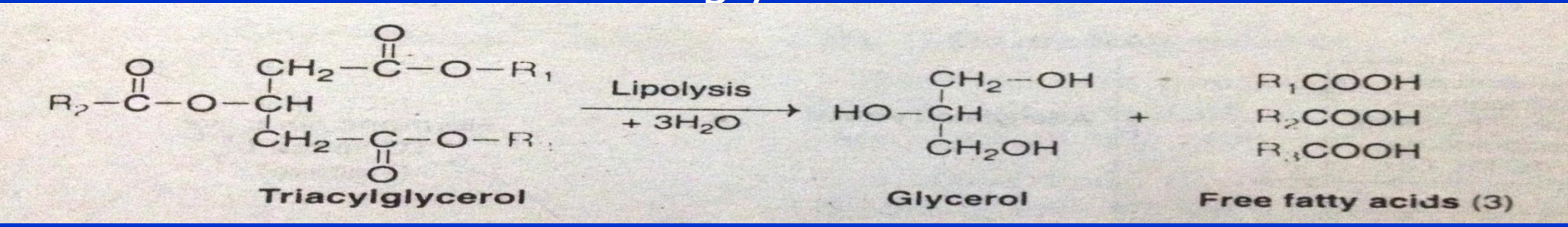
FATTY ACIDS

$CH3(CH\ 2)_n\ CH2\ CH2\ COO\text{-}$

SOURCESES of FATTY CIDS

- Lypolysis of adipose tissues

  TG -Lipase→ FFA + glycerol



- Degradation of chylomicrons and VLDL by enzyme lipoprotein lipase
- Small and medium chain FA from diet
- **FFA synthesis(de novo) from acetyl-Co A in liver.**

De Novo Synthesis of Fatty Acids "LIPOGENESIS"

Fatty acid synthesis

There are three systems for fatty acid synthesis.

- A. Extramitochondrial system
- B. 1. Microsomal chain elongation system

  2. Mitochondrial chain elongation system

LIPOGENESIS (Extra mitochondrial system)

- The dietary carbohydrate and proteins when consumed in excess can be converted to fatty acids.
- FA are synthesized by an extra mitochondrial system in the form of Palmitate from acetyl co-A in the **cytosol** of liver, kidney, brain, lungs, mammary gland and adipose tissue.

De Novo Synthesis of Fatty Acids LIPOGENESIS

1. Acetyl CoA is the source of carbon atom.
2. $NADPH^{+}+H^{+}$, provides the reducing equivalents
3. Mn^{++} , biotin and $HCO3^{-}$ as cofactors.
4. ATP as source of energy.

Acetyl-CoA is the substrate and palmatic acid is the end product.

De Novo Synthesis of Fatty Acids LIPOGENESIS

1- Production of Acetyl CoA

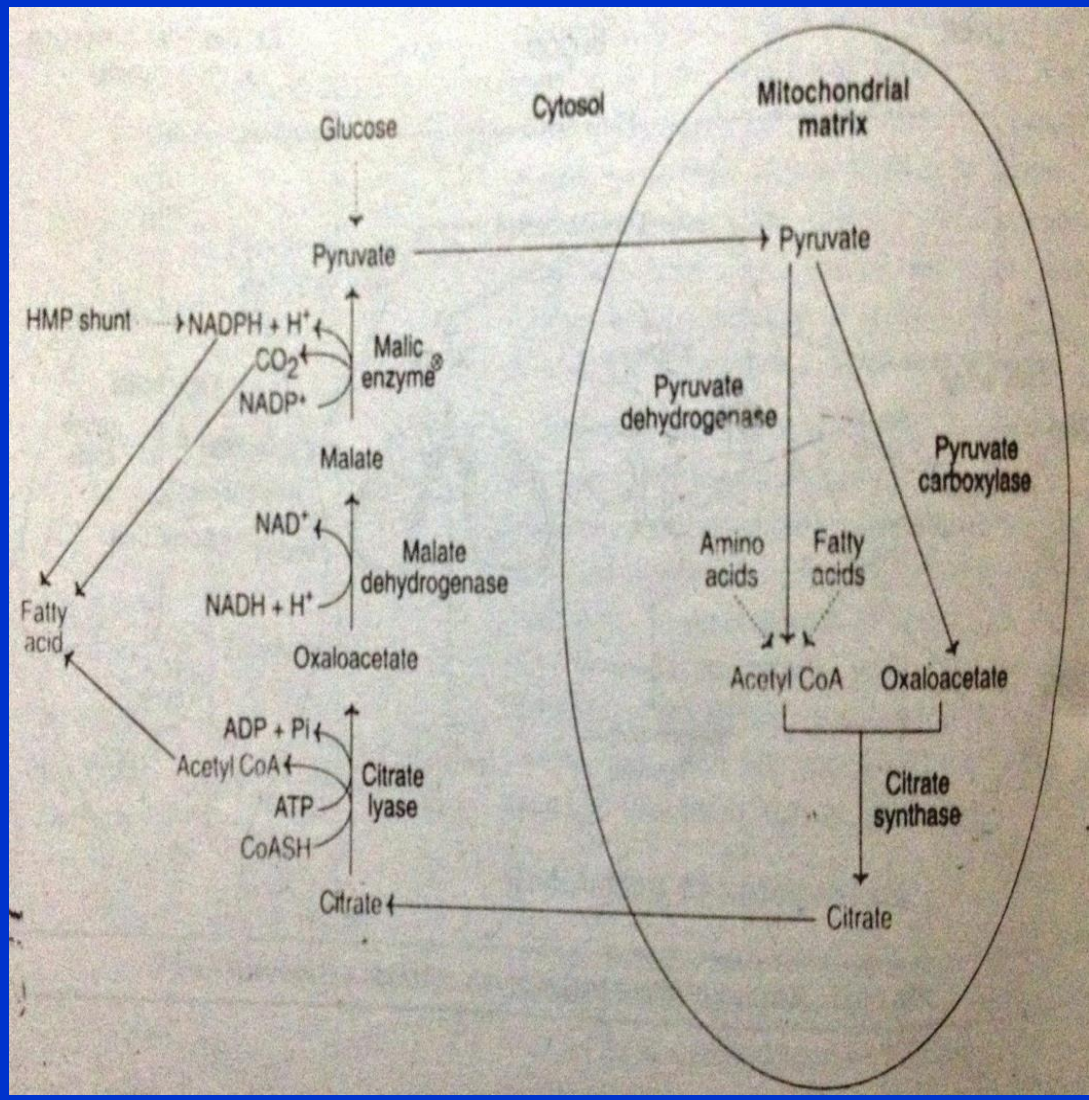
2- Formation of Malonyl CoA (controlling step of FA synthesis)

3- Reaction of Fatty acid synthase complex

De Novo Synthesis of Fatty Acids

Production of cytosolic Acetyl CoA

- Translocation of mitochondrial Acetyl coA to cytosol.
- mitochondrial Acetyl coA is converted to citrate by condensation of oxaloacetate and libration of CoA by citrate synthase.
- Conversion of citrate to Acetyl CoA + oxaloacetate by citrate lyase in cytosol



De Novo Synthesis of Fatty Acids

Carboxylation of acetyl CoA to malonyl CoA

- **Enzyme acetyl CoA carboxylase**
  - **Activators: insulin, CHO intake, fat-free diet**
  - **Inhibitors: malonyl CoA, palmitate, epinephrine, fasting, high fat diet**
- Rate limiting step in fatty acid synthesis
- Coenzyme: Biotin
- ATP Utilized
- $HCO3^-$ as source of CO2

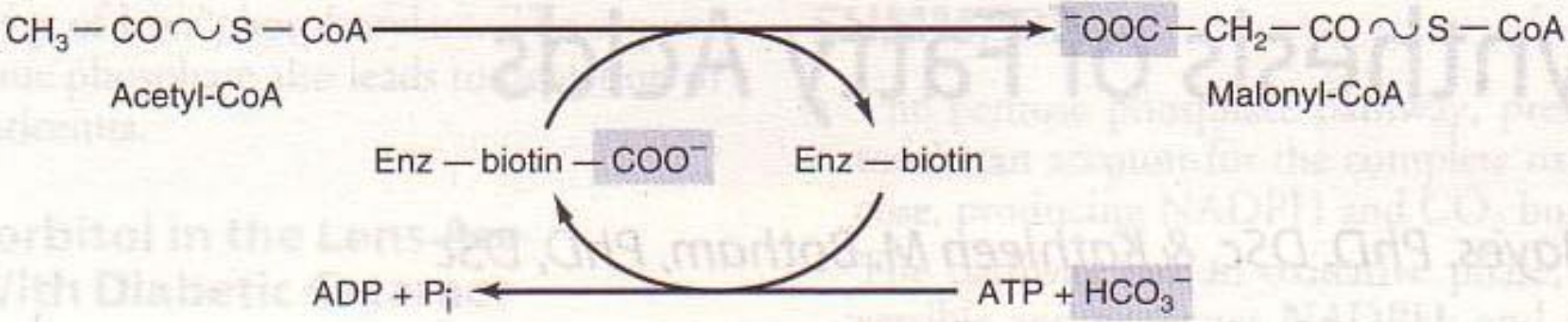
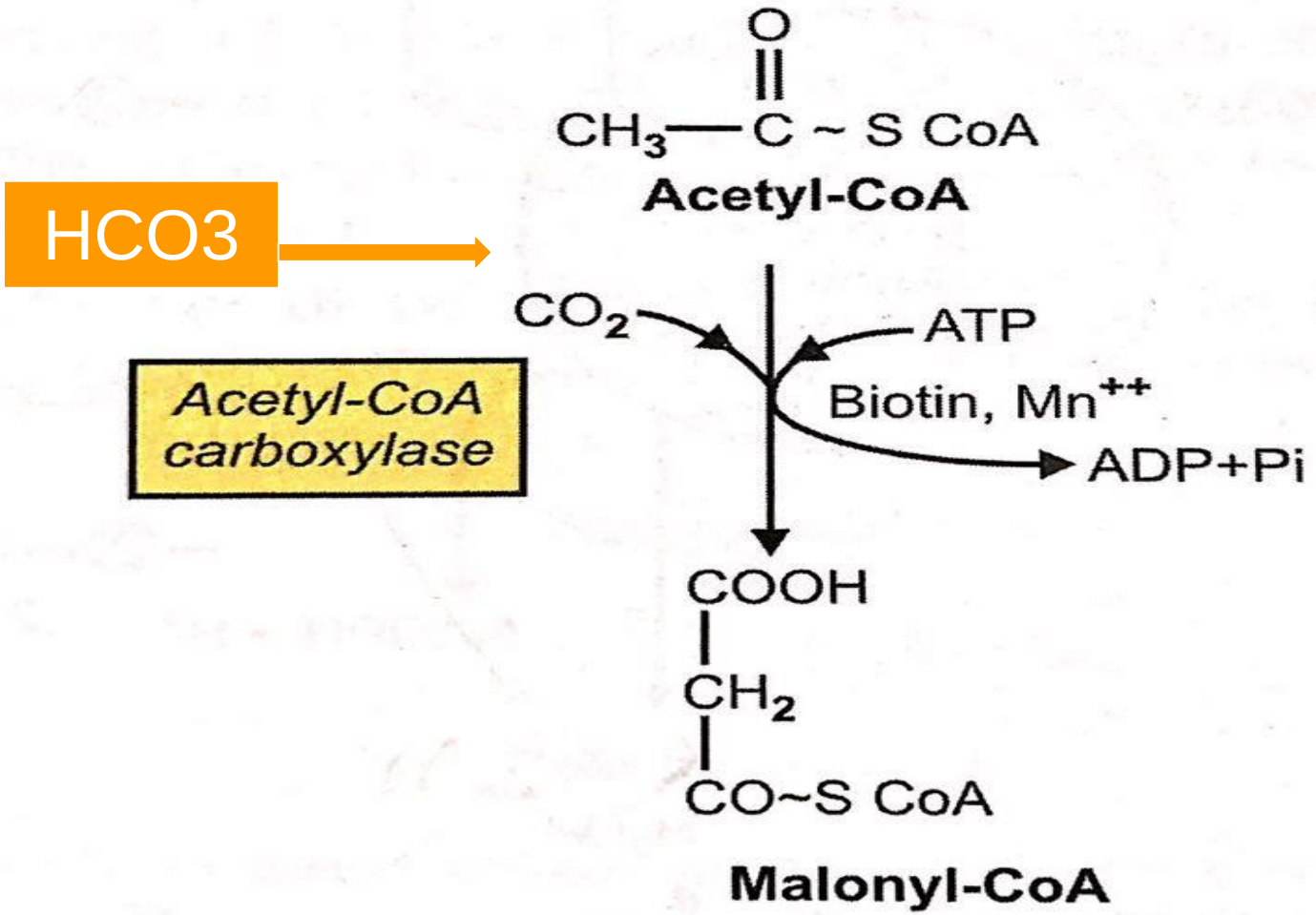


Figure 21–1. Biosynthesis of malonyl-CoA. (Enz, acetyl-CoA carboxylase.)

Malonyl-CoA Production

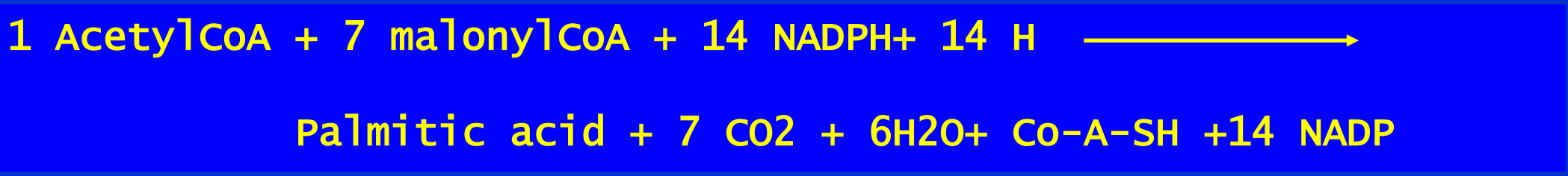


Rate-limiting enzyme: Acetyl CoA carboxylase

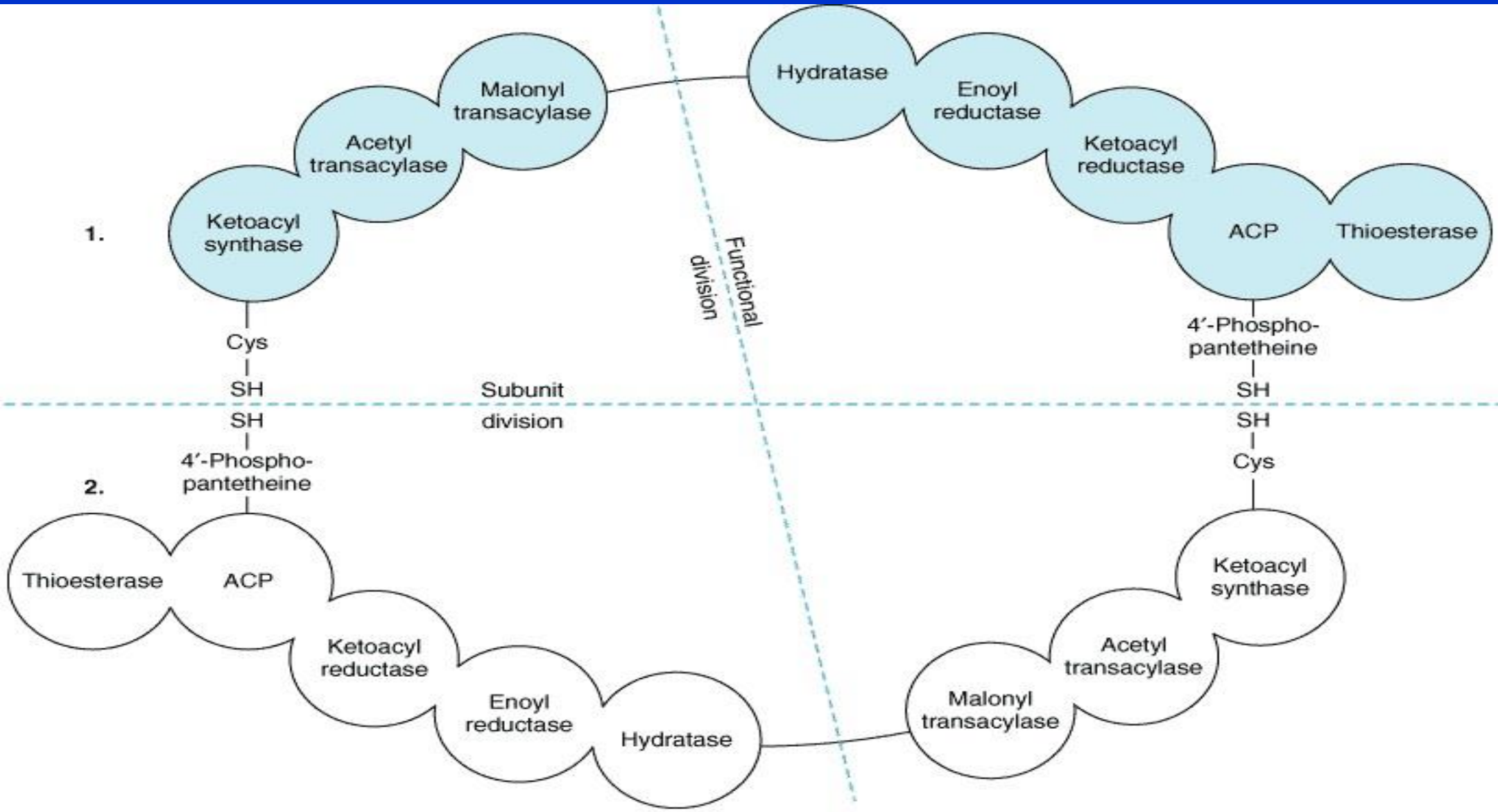
De Novo Synthesis of Fatty Acids

3. Reaction of Fatty acid synthase: a multienzyme complex

- Substrate: Acetyl CoA and Malonyl CoA
- End Product: Palmitic acid
- Site: Cytosol
- Enzyme: Fatty acid synthase
- NADPH + H+ are from HMP-Shunt and malic enzyme



Fatty acid synthase: a multienzyme complex



Functional significance of FAS complex

1. Great efficiency
2. No permeability barriers
3. good coordination coded by single gene.

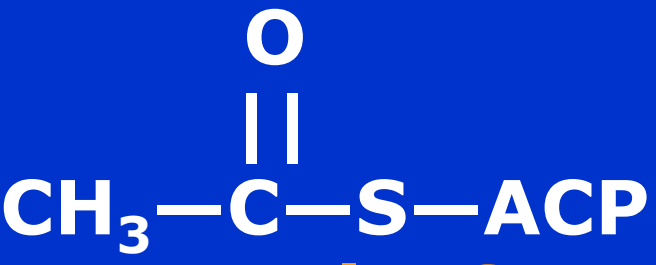
Lipogenesis: Fatty Acid Synthesis

Lipogenesis:

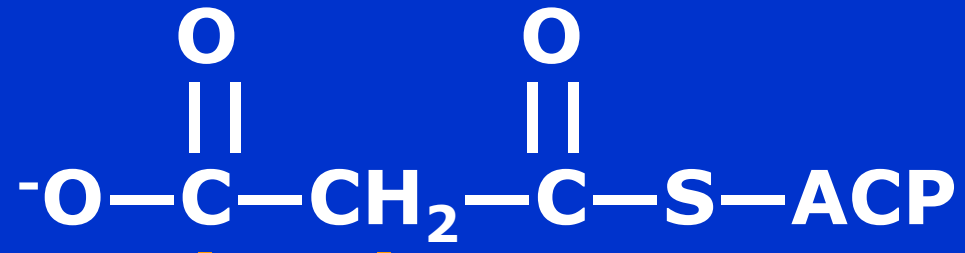
- **Is the synthesis of fatty acids from acetyl CoA.**
- **Occurs in the cytosol.**
- **Requires an acyl carrier protein (ACP).**

Formation of Acetyl and Malonyl ACP

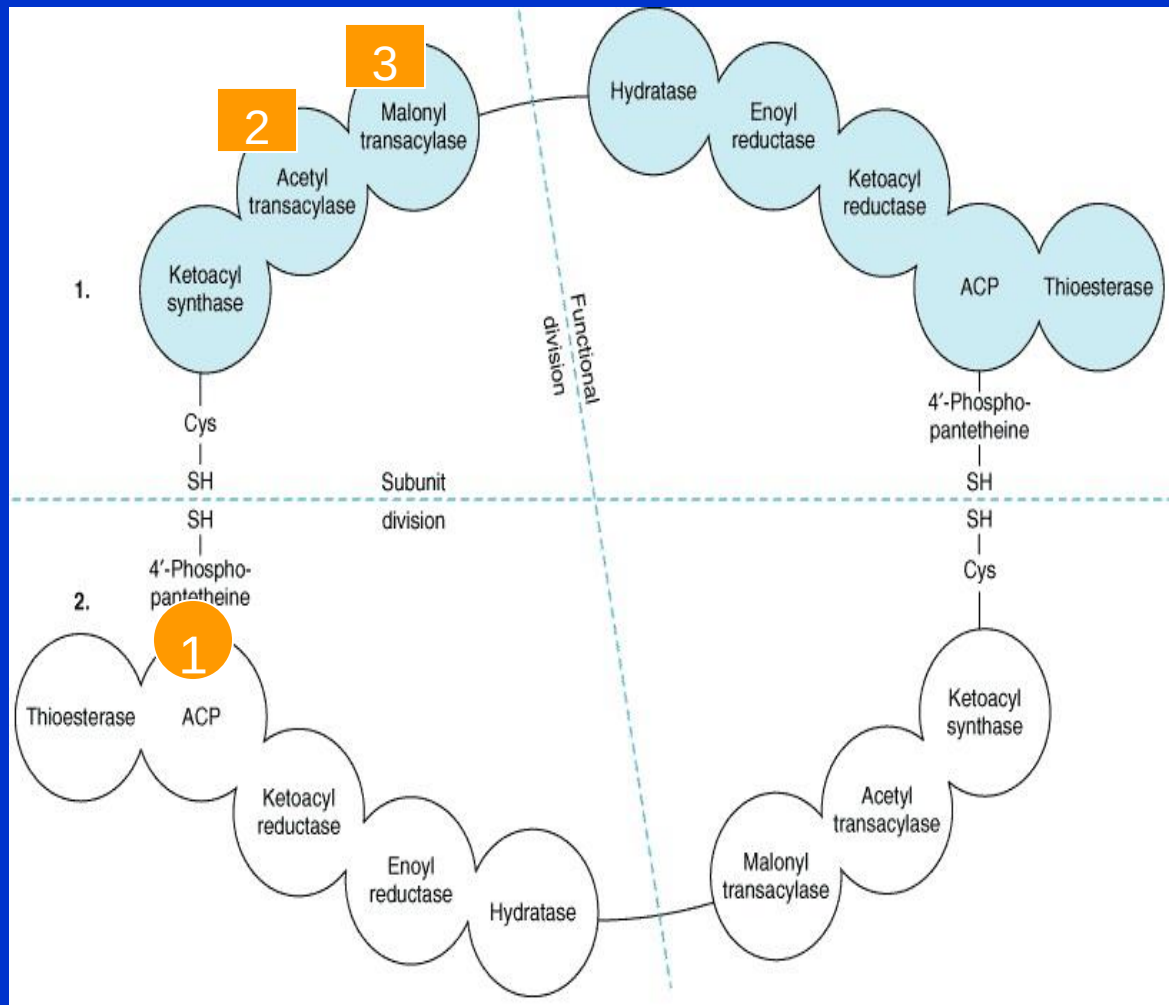
Acetyl CoA and malonyl CoA combine with acyl carrier protein(ACP)to form acetyl-ACP (acetyl transacylase)and malonyl-ACP(malonyl transacylase):

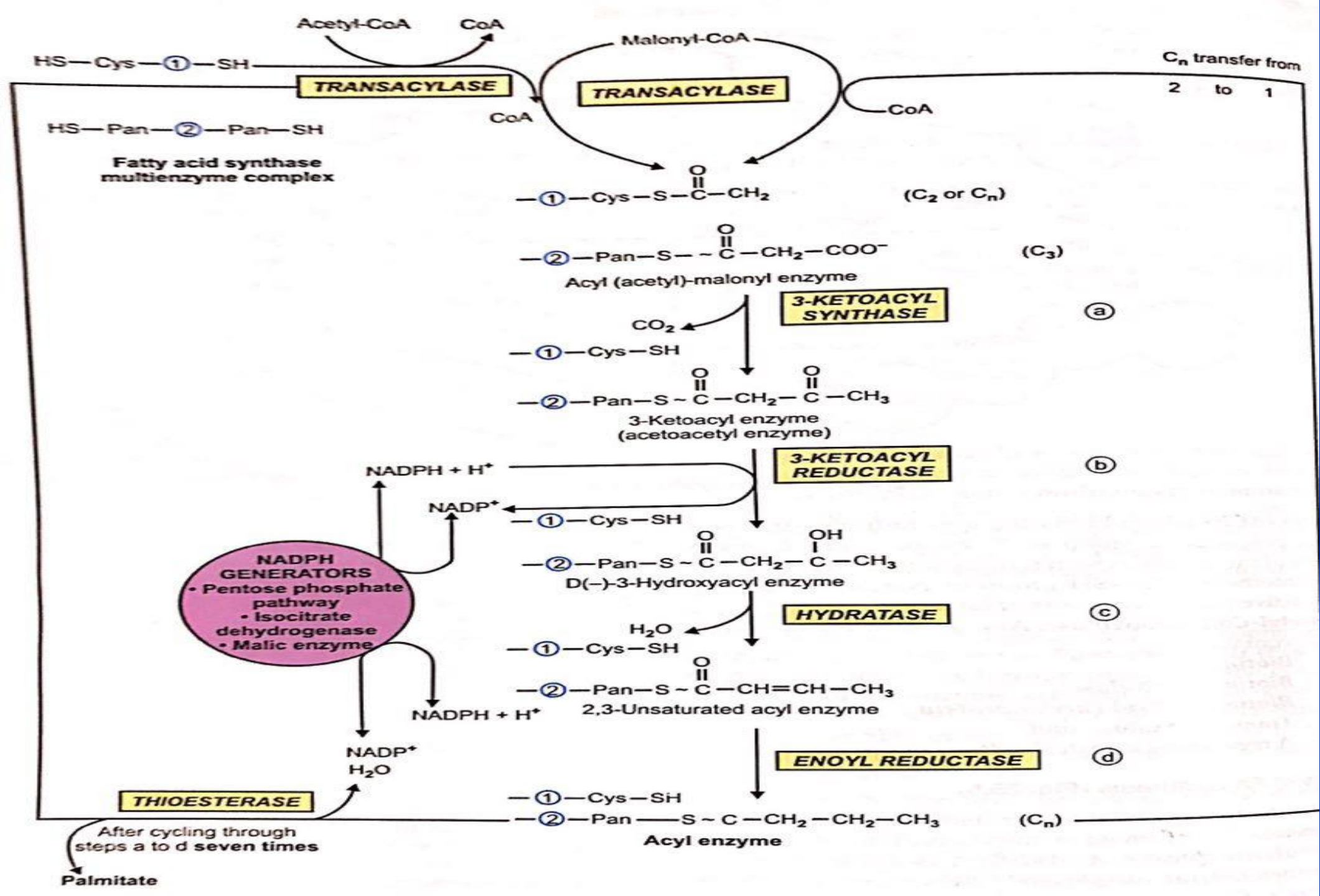


Acetyl-ACP



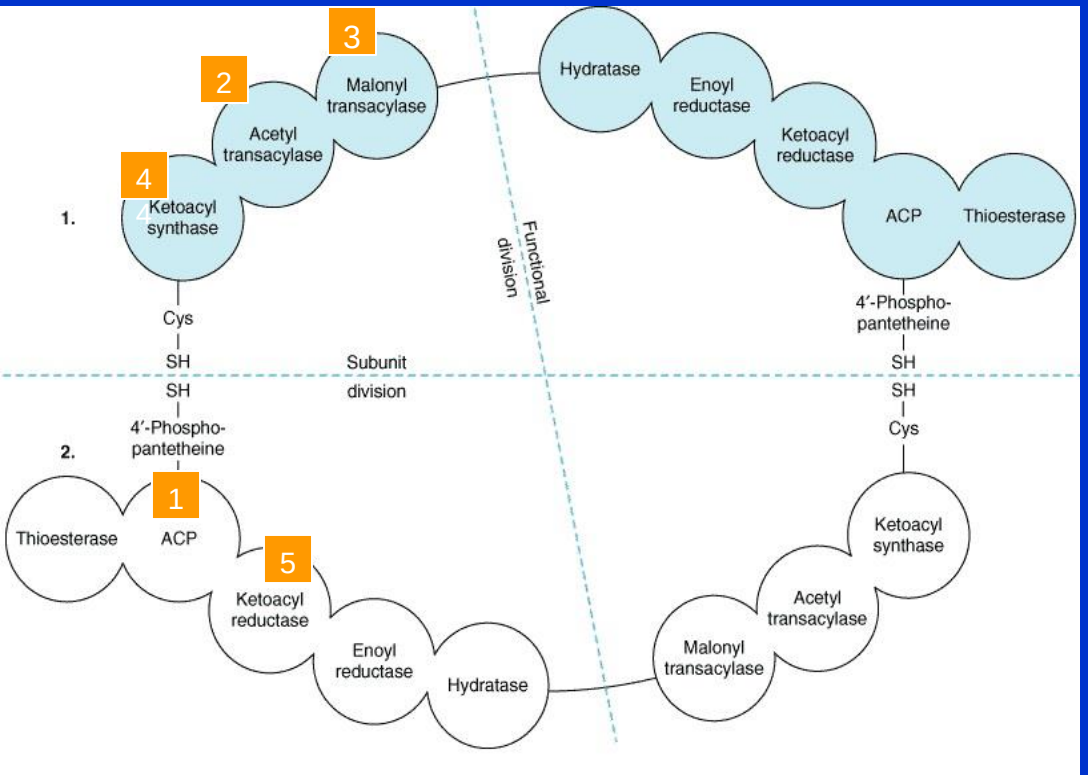
Malonyl-ACP

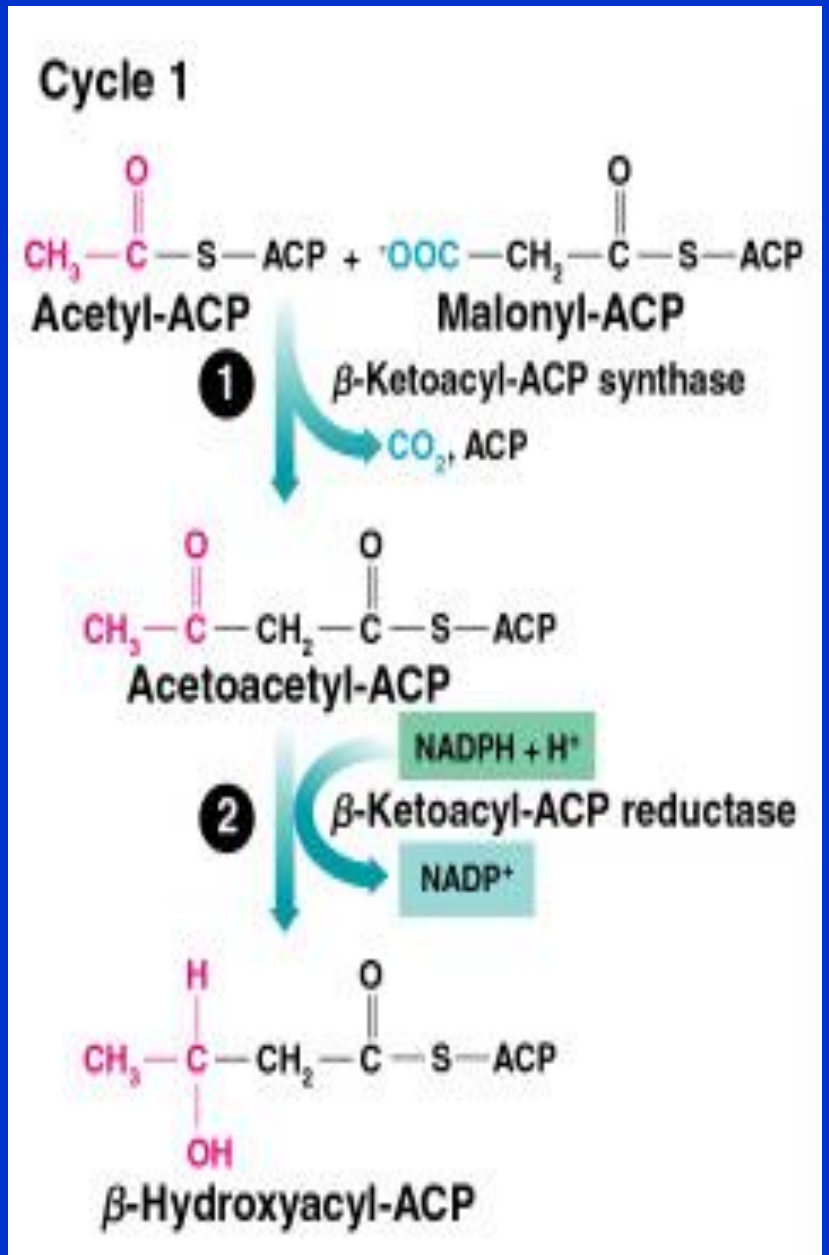



Acetyl-CoA
CoA
HS—Cys—①—SH
TRANSACYLASE
HS—Pan—②—Pan—SH
Fatty acid synthase multienzyme complex
Malonyl-CoA
TRANSACYLASE
CoA
C_n transfer from 2 to 1
—①—Cys—S—C(=O)—CH_2 (C_2 or C_n)
—②—Pan—S—~C(=O)—CH_2—COO^- (C_3)
Acyl (acetyl)-malonyl enzyme
3-KETOACYL SYNTHASE
a
CO_2
—①—Cys—SH
—②—Pan—S—~C(=O)—CH_2—C(=O)—CH_3
3-Ketoacyl enzyme (acetoacetyl enzyme)
3-KETOACYL REDUCTASE
b
NADPH + H^+
$NADP^+$
—①—Cys—SH
—②—Pan—S—~C(=O)—CH_2—C(OH)—CH_3
D(−)-3-Hydroxyacyl enzyme
NADPH GENERATORS
• Pentose phosphate pathway
• Isocitrate dehydrogenase
• Malic enzyme
HYDRATASE
c
H_2O
—①—Cys—SH
—②—Pan—S—~C(=O)—CH=CH—CH_3
2,3-Unsaturated acyl enzyme
NADPH + H^+
$NADP^+$
H_2O
ENOYL REDUCTASE
d
THIOESTERASE
—①—Cys—SH
—②—Pan—S—~C(=O)—CH_2—CH_2—CH_3 (C_n)
Acyl enzyme
After cycling through steps a to d seven times
Palmitate

Condensation and Reduction

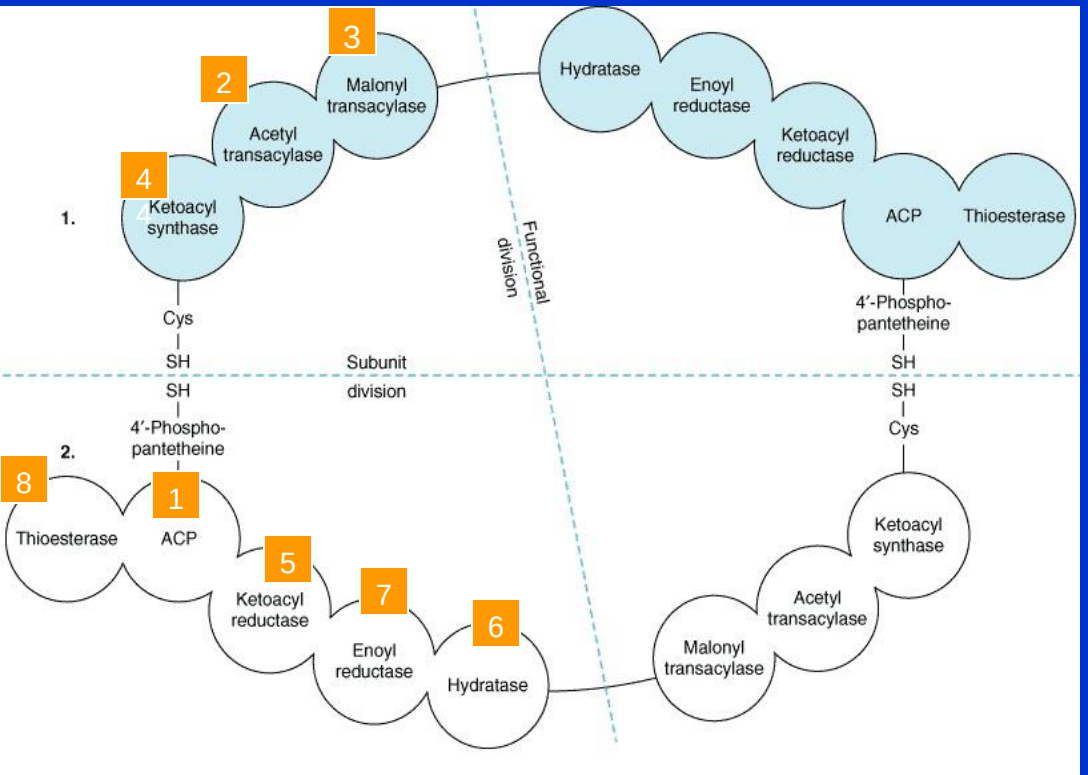
- **Condensation** by a Ketoacyl synthase acetyl-ACP combines with malonyl-ACP to form acetoacetyl-ACP (4C) and CO_2 (reaction 1).
- **Reduction** converts a ketone to an alcohol using NADPH (reaction 2).

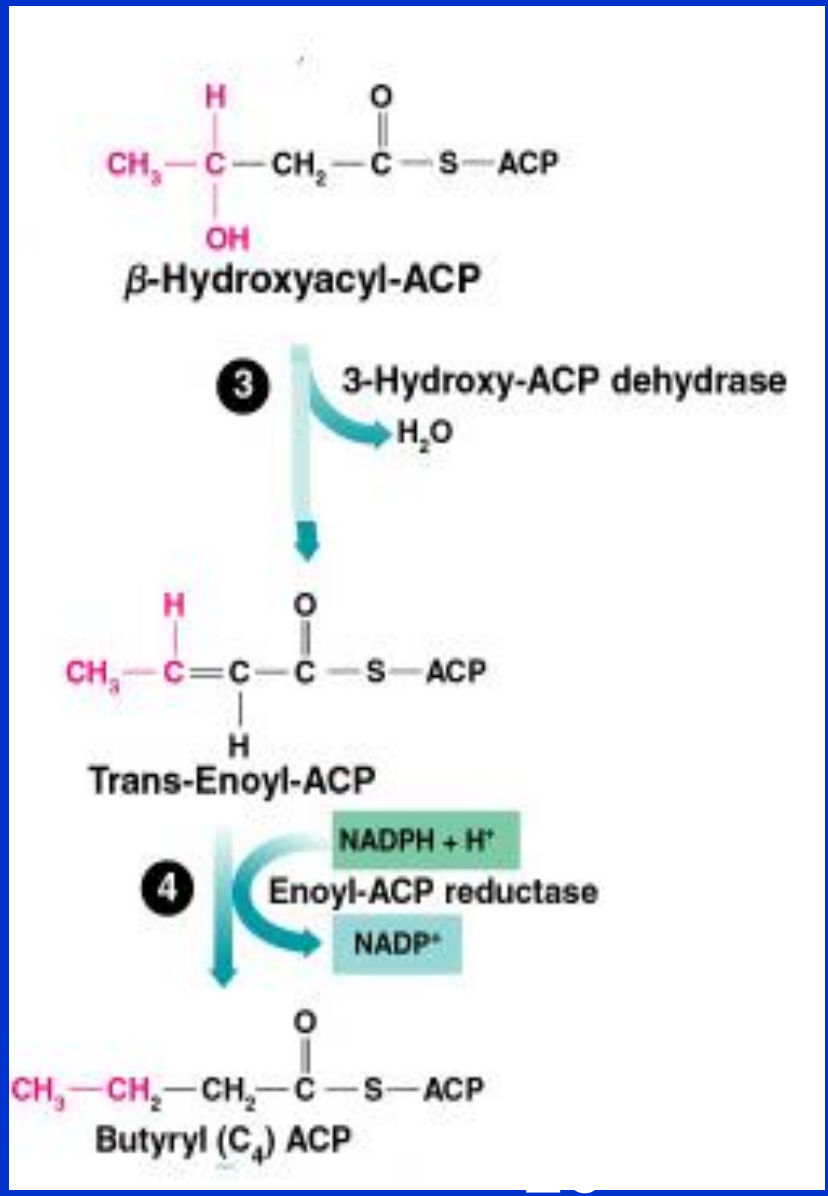


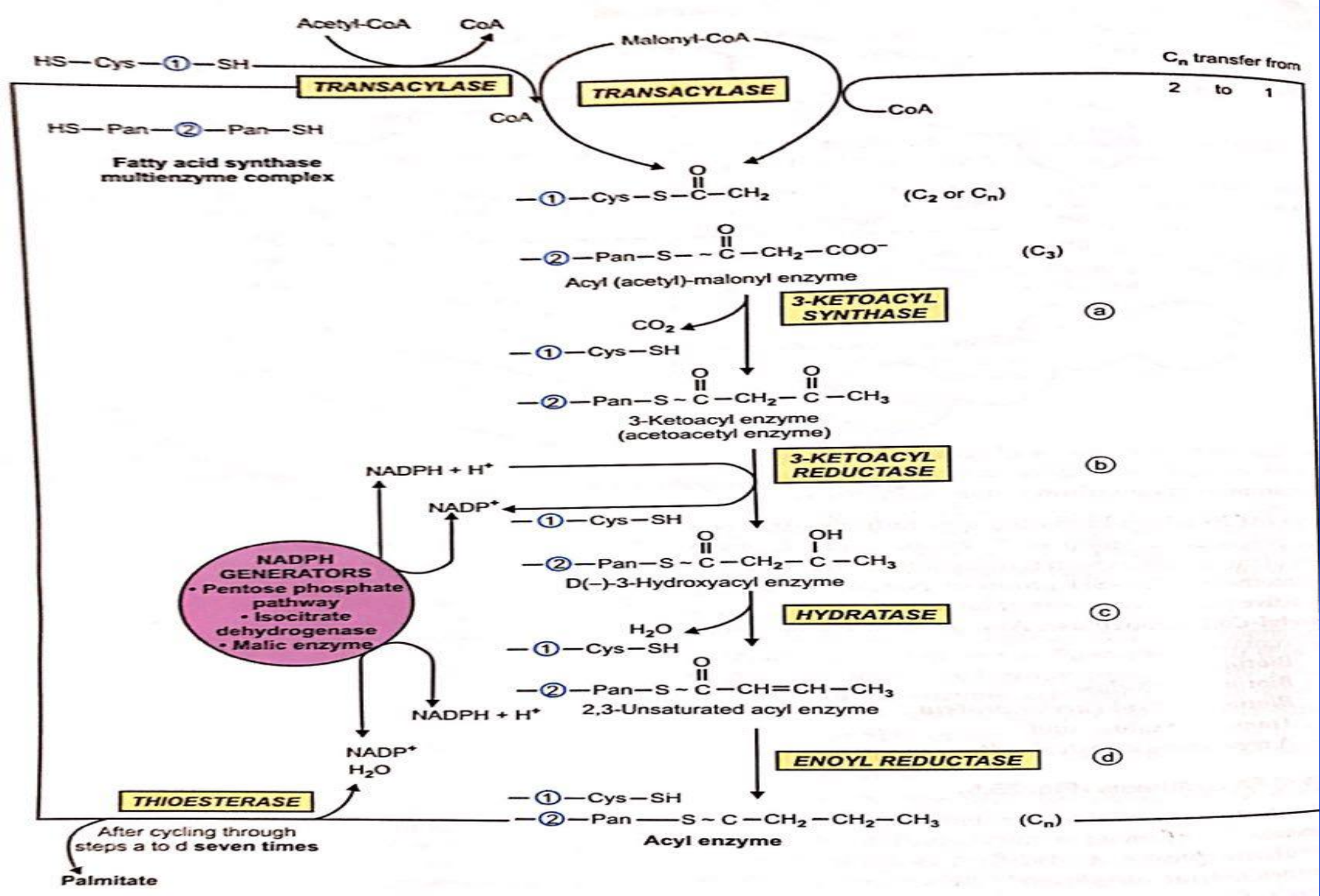


Dehydration and Reduction

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



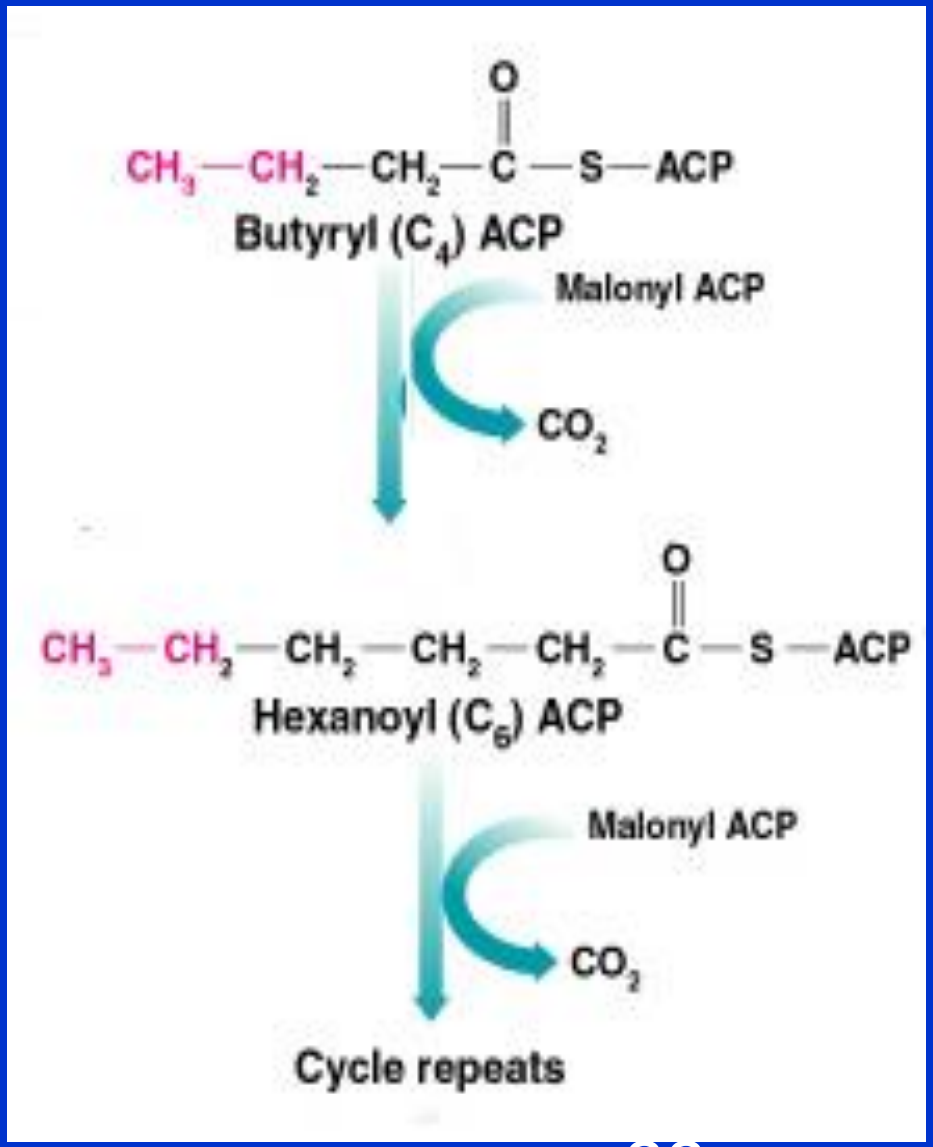



Acetyl-CoA
CoA
HS—Cys—①—SH
TRANSACYLASE
HS—Pan—②—Pan—SH
Fatty acid synthase multienzyme complex
Malonyl-CoA
TRANSACYLASE
CoA
C_n transfer from 2 to 1
—①—Cys—S—C(=O)—CH_2 (C_2 or C_n)
—②—Pan—S—~C(=O)—CH_2—COO^- (C_3)
Acyl (acetyl)-malonyl enzyme
3-KETOACYL SYNTHASE
a
CO_2
—①—Cys—SH
—②—Pan—S—~C(=O)—CH_2—C(=O)—CH_3
3-Ketoacyl enzyme (acetoacetyl enzyme)
3-KETOACYL REDUCTASE
b
NADPH + H^+
$NADP^+$
—①—Cys—SH
—②—Pan—S—~C(=O)—CH_2—C(OH)—CH_3
D(−)-3-Hydroxyacyl enzyme
NADPH GENERATORS
• Pentose phosphate pathway
• Isocitrate dehydrogenase
• Malic enzyme
HYDRATASE
c
H_2O
—①—Cys—SH
—②—Pan—S—~C(=O)—CH=CH—CH_3
2,3-Unsaturated acyl enzyme
NADPH + H^+
$NADP^+$
H_2O
ENOYL REDUCTASE
d
THIOESTERASE
—①—Cys—SH
—②—Pan—S—~C(=O)—CH_2—CH_2—CH_3 (C_n)
Acyl enzyme
After cycling through steps a to d seven times
Palmitate

Lipogenesis Cycle Repeats

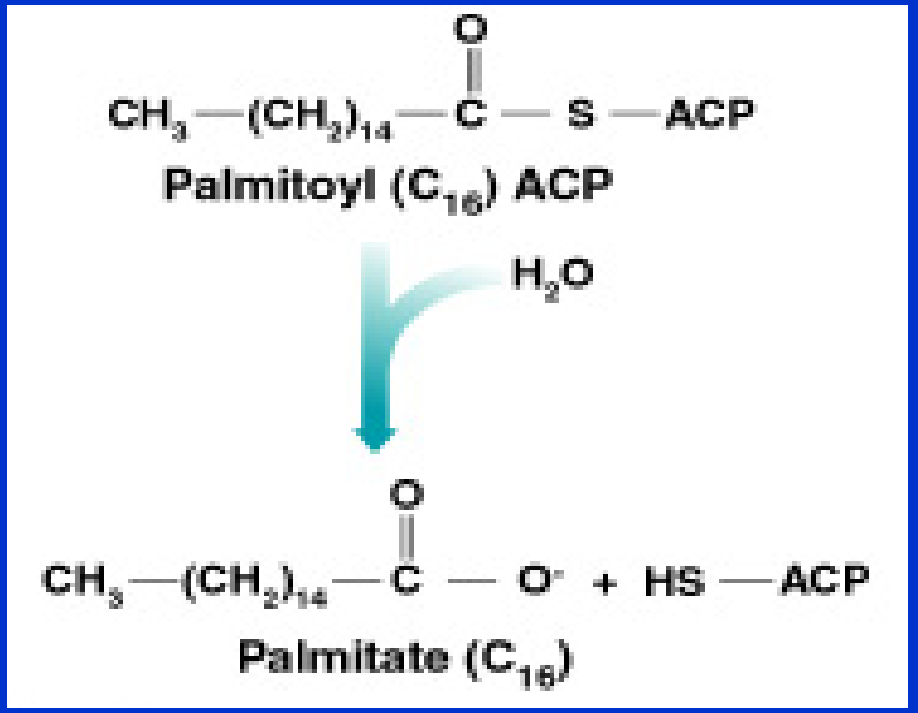
Fatty acid synthesis continues:

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

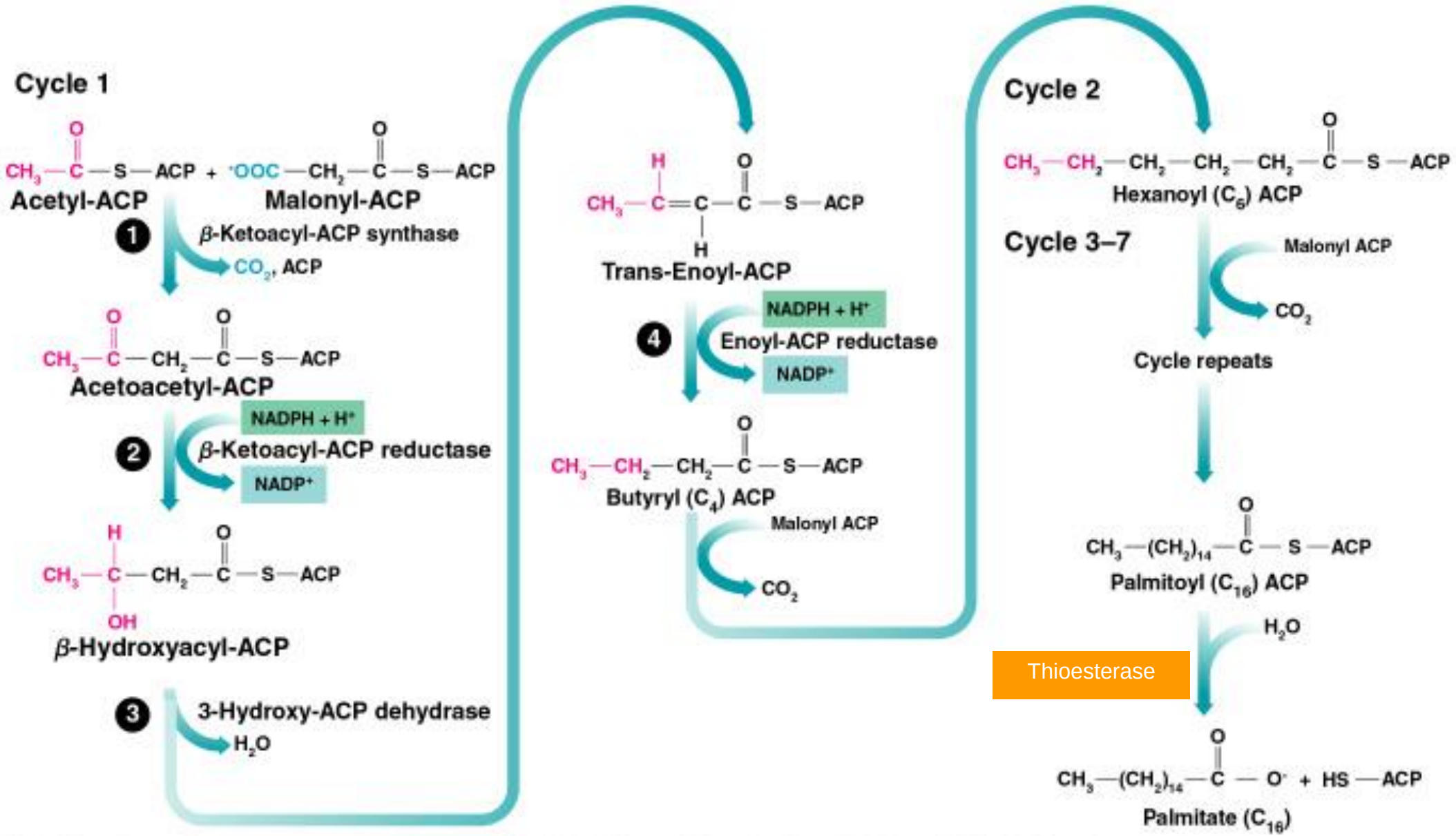


Lipogenesis Cycle Completed

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



Summary of Lipogenesis



Summary of palmitate synthesis

Acetyl CoA +7malonyl coA +14NADH +14H^+ 7ATPs ------→

Palmitate+ 14NADP+ 7CO2+ 7ADP + 6H2O

Fatty Acid Formation

- Shorter fatty acids undergo fewer cycles.
- Longer fatty acids are produced 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.

Synthesis of long chain FAs from Palmitate

- The end product of FA synthase system in cytosol is palmitate.
- Further elongation of FA chain in mitochondria or endoplasmic reticulum by **enzyme elongase**.

Elongation of FAs

- 1. mitochondrial chain elongation
- 2. microsomal chain elongation

Mitochondrial Chain Elongation

- **Reaction of Mitochondrial Elongase Enzyme**
  - **Substrate: Palmityl CoA .**
  - **End Product: Stearyl CoA etc**
  - **Site: MITOCHONDRIA.**
  - **NADPH from HMP shunt.**
  - **Pyridoxal-p as co-enzyme.**
  - **enzyme of synthesis: Mitochondrial elongase.**
  - **Up to 18 carbon chain FAs can be synthetized.**

Microsomal Chain Elongation

- **Reaction of Elongase Enzyme**
  - **Substrate: Palmitic acid**
  - **End Product: Stearic acid etc**
  - **Site: Smooth endoplasmic reticulum.**
  - **NADPH from HMP shunt.**
  - **enzyme of synthesis: elongase**
  - **Up to 24 carbon chain FAs can be synthesized.**

Desaturation of FA chains

- Enzyme system fatty acyl CoA desaturase, NADH and molecular O2.
- Mammals lacks the enzymes responsible for the synthesis of unsaturated FA beyond C 9 and C10.

Regulation of fatty acid synthesis

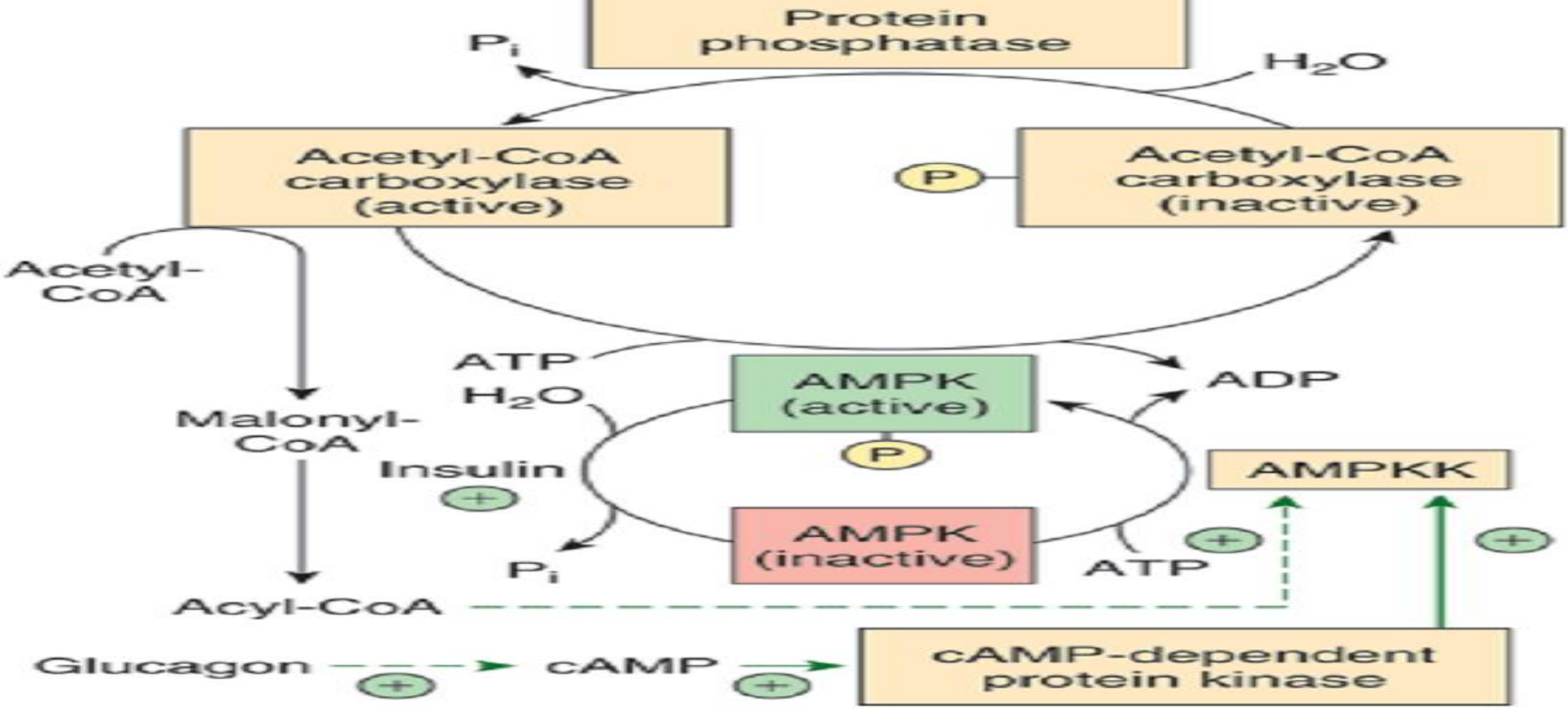
- 1. Acetyl CoA carboxylase
- 2. Hormonal influence
- 3. Dietary regulation
- 4. Availability of NADPH

Acetyl CoA carboxylase

- Control the formation of malonyl CoA.
- It exists as an inactive monomer or active polymer.
- Citrate promotes polymer formation, hence increase the FAs synthesis.
- Palmitoyl CoA cause depolymerization of enzyme and therefore inhibit FAs synthesis.

HORMONAL INFLUANCE

- Hormones regulate acetyl CoA carboxylase by phosphorylation (inactive form) and dephosphrylation (active form) of the enzyme.
- Glucagon , epinephrine and non epinephrine inactivate the enzyme by cAMP dependent phosphorylation and inhibits FA synthesis .
- Insulin dephosphorylate and activate the enzyme and promotes FA synthesis .



Regulation of acetyl-CoA carboxylase by phosphorylation/dephosphorylation. The enzyme is inactivated by phosphorylation by AMP-activated protein kinase (AMPK), which in turn is phosphorylated and activated by AMP-activated protein kinase kinase (AMPKK). Glucagon (and epinephrine) increase cAMP, and thus activate this latter enzyme via cAMP-dependent protein kinase. The kinase kinase enzyme is also believed to be activated by acyl-CoA. Insulin activates acetyl-CoA carboxylase via dephosphorylation of AMPK.

Dietary regulation

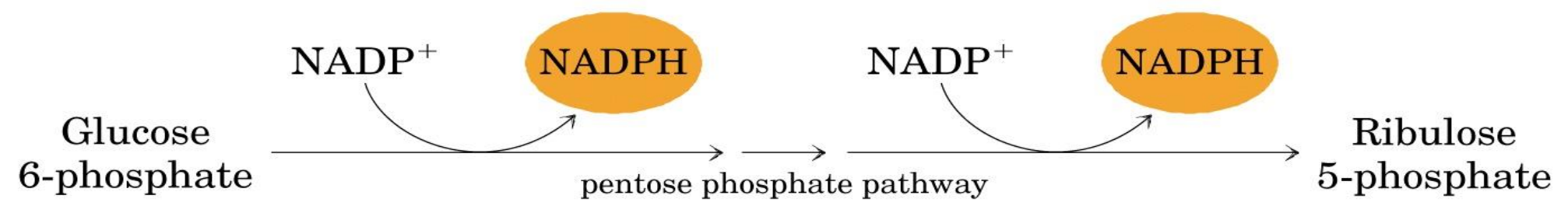
- High CHO or fat-free diet increases the synthesis of acetyl CoA carboxylase and FA synthase, which promotes FA formation.
- Fasting or high fat diet decreases FA production by reducing the synthesis of these two enzymes.

Availability of NADPH

- The reducing equivalents for FA synthesis are provided by the NADPH which comes from:

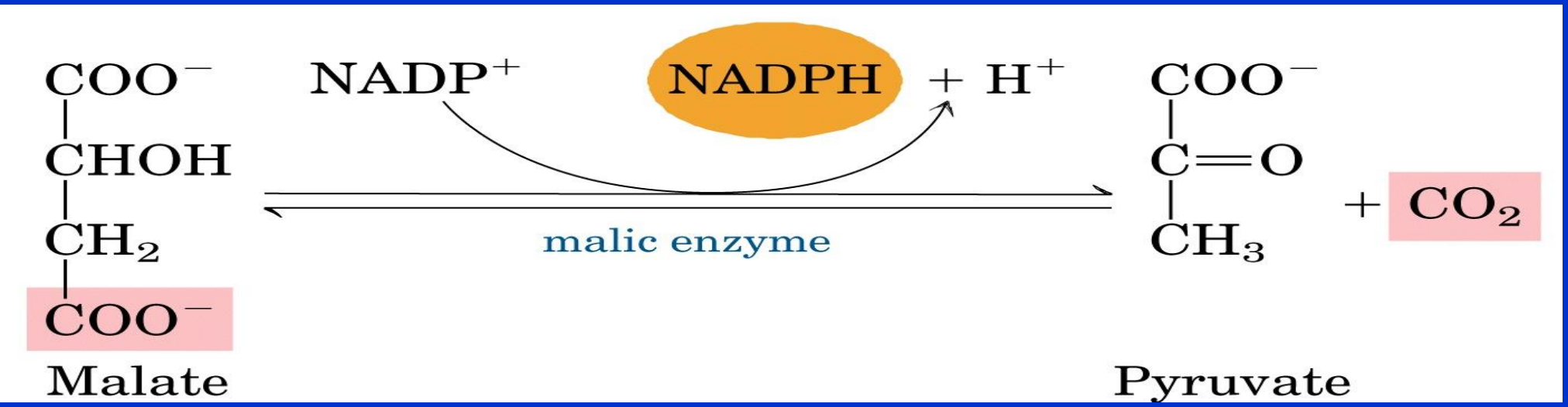
- The oxidative reactions of the **pentose phosphate pathway are the chief source** of the hydrogen required for the reductive synthesis of fatty acids.
- Other sources of NADPH include the reaction that converts **malate to pyruvate catalyzed by the "Malic enzyme"** (NADP malate dehydrogenase) and the **extra mitochondrial.**
- **Isocitrate dehydrogenase** reaction.

The pentose phosphate pathway/ HMP Pathway- Source of NADPH



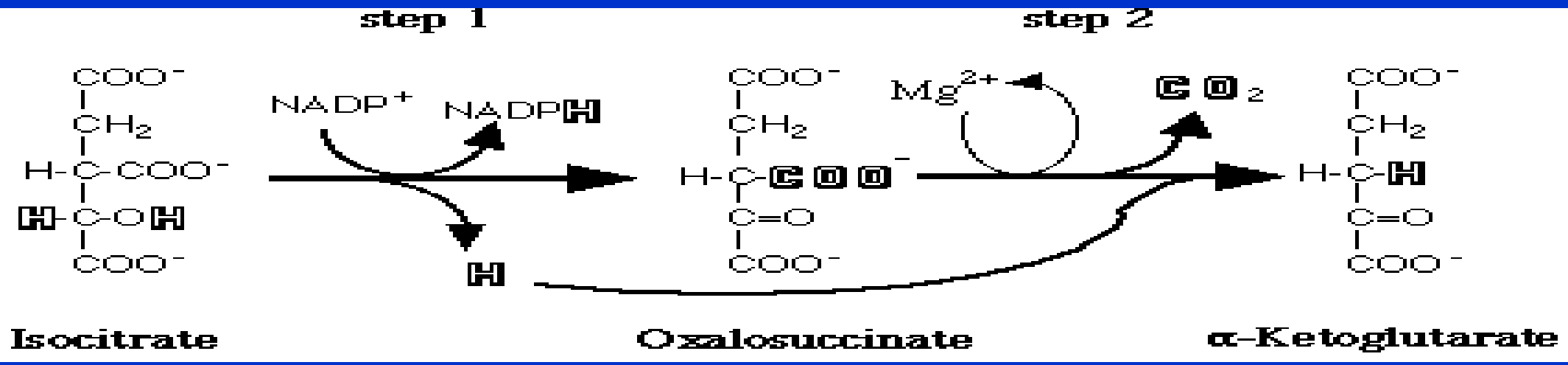
In hepatocytes, adipose tissue and the lactating mammary glands, the NADPH is supplied primarily by the pentose phosphate pathway.

The Malic enzyme- Source of NADPH



Reversible reaction, pyruvate produced in the reaction reenters the mitochondrion for further utilization.

Cytosolic Isocitrate Dehydrogenase- Source of NADPH



There are three isoenzymes of isocitrate dehydrogenase. One, which uses NAD^+, is found only in mitochondria. The other two use $NADP^+$ and are found in mitochondria and the cytosol.

Function and Utilization of FAs

- As building block: the building block of phospholipids and glycolipid (fluid mosaic of cell membrane).
- As targeting molecules: FAs are attached to many proteins and are directed to their appropriate place in membrane.
- As a fuel molecule: FAs are stored as TG.
- Messengers: FAs used to make ATPs.
- Assist in the absorption of fat soluble Vits

ANY QUESTION

- CHATTERJEA BIOCHEMISTRY
- LIPPINCOTT BIOCHEMISTRY
- HARPERS BIOCHEMISTRY
- SATYANARAYANA BIOCHEMISTRY
- INTERNET

Thank you