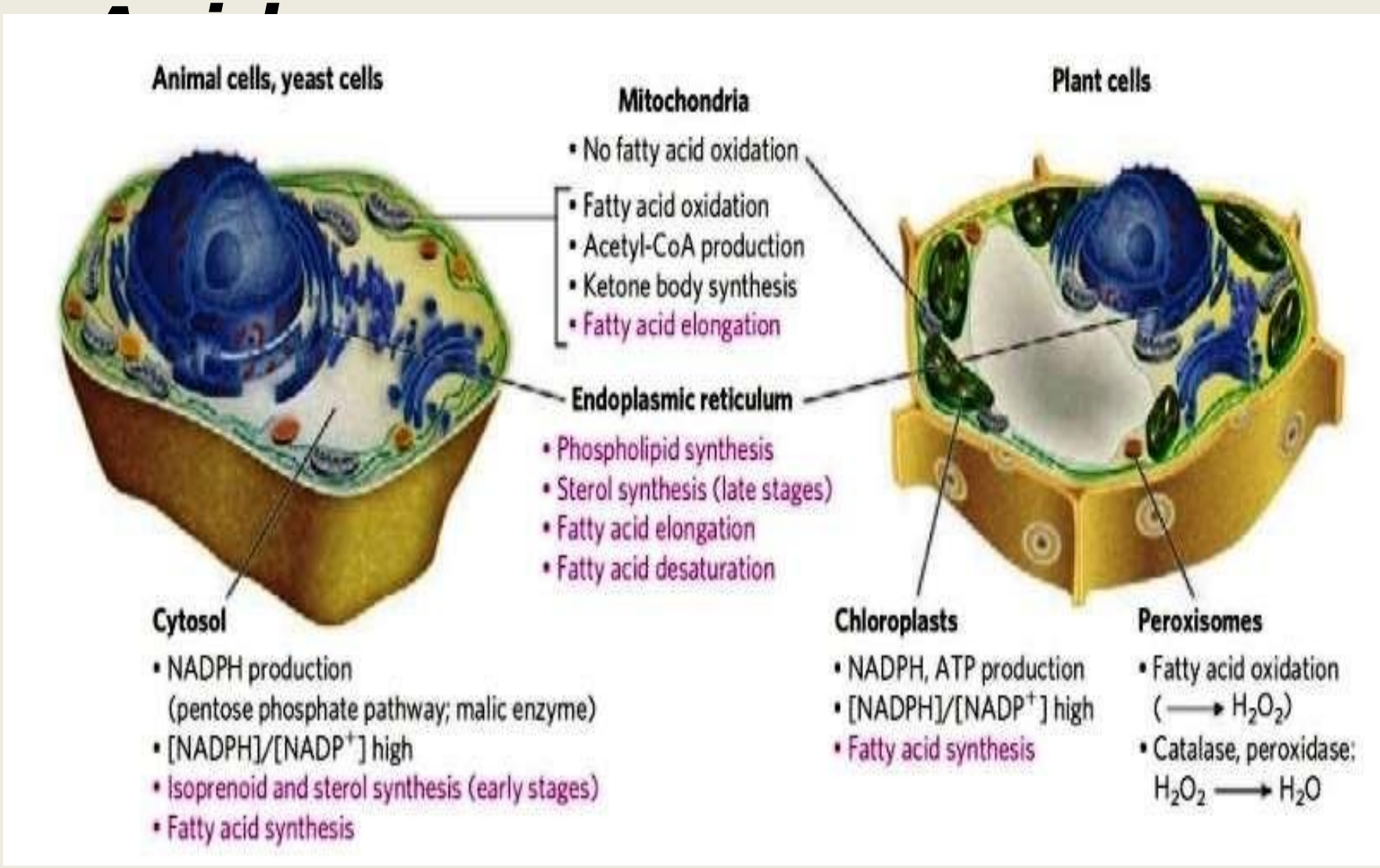
FATTY ACIDS SYNTHESIS

Dr. D. Balakrishna
Assistant Professor

De novo Synthesis of Fatty



Learning Objectives

- Sources of substrates required for Fatty acid synthesis.
- Synthesis of palmitic acid on FAS complex.
- Elongation of palmitic acid.
- Desaturation.
- Regulation of fatty acid synthesis.
- β oxidation v/s fatty acid synthesis.
- Recent advances

Introduction

- ***In the body:***

Major :

Liver, lactating mammary gland

Minor:

Brain, renal cortex, adipose tissue, lungs

- ***In the cell:*** **Cytoplasm**
- ***End product:*** **Palmitic acid (mostly)**
- ***Substrates:*** **Acetyl-CoA and HCO_3^-**
- ***Energy source:*** **ATP**
- ***Electron donor:*** **NADPH**

SOURCES OF ACETYL CoA:

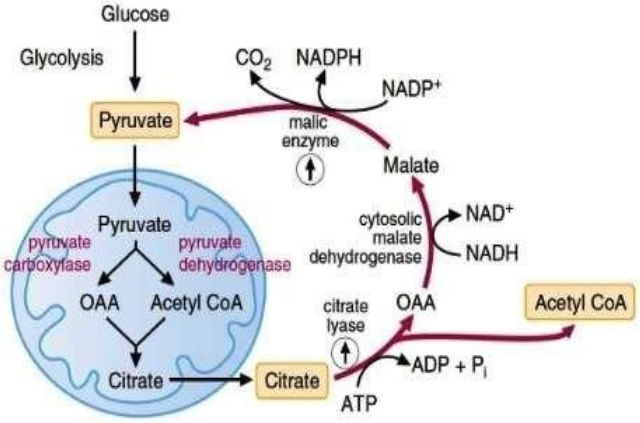
- Provides all the C atoms to FA as Malonyl CoA
- Located in Mitoc

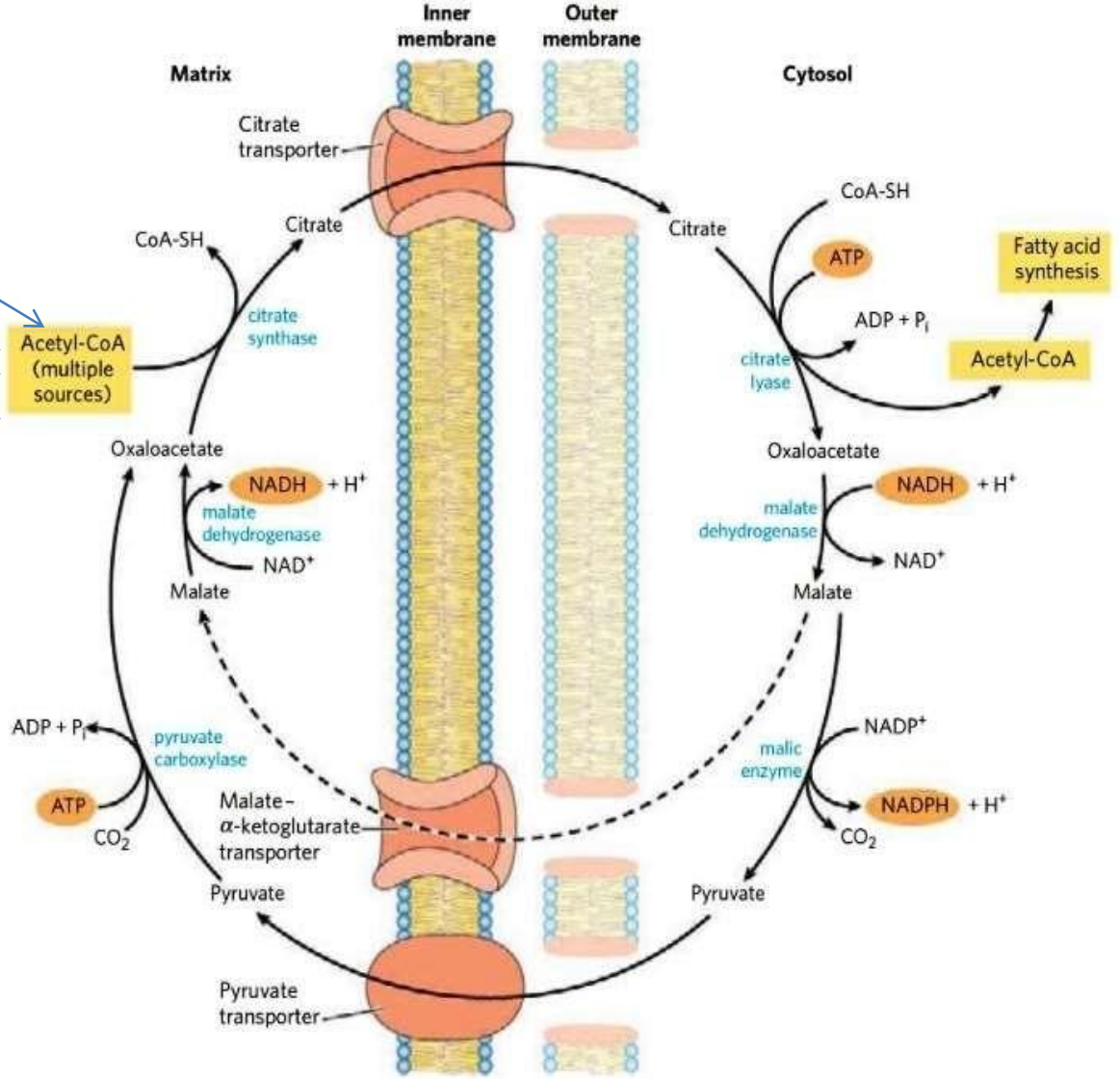
Oxidation of Pyruvate

Degradation of C skeleton of Amino acids

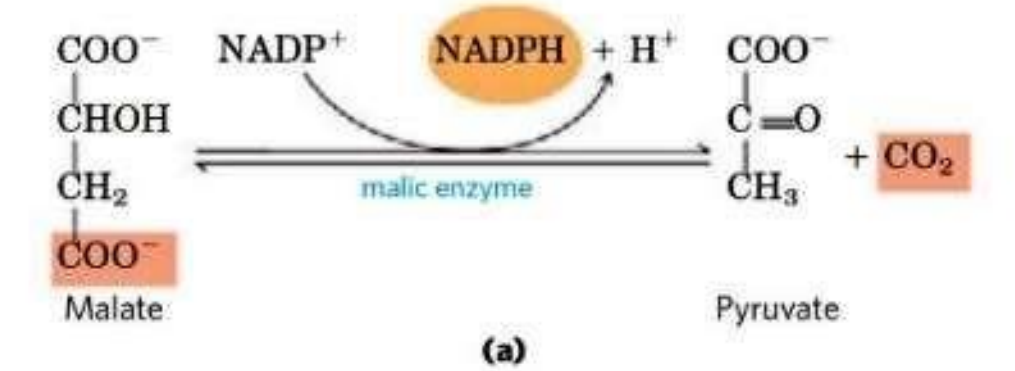
Oxidation of FA

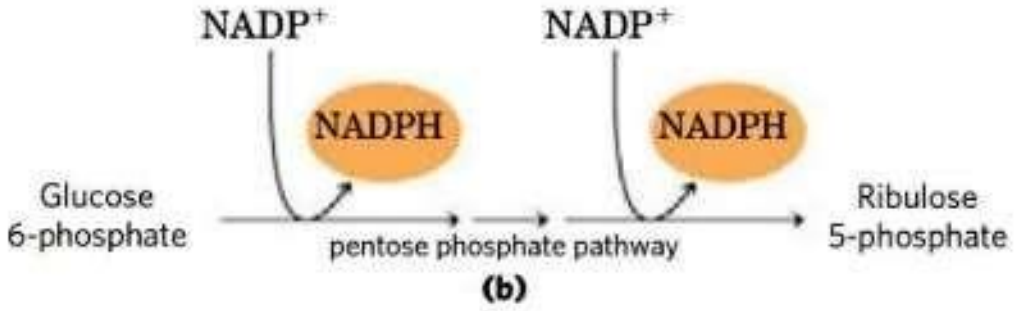
Degradation of ketone bodies





SOURCES OF NADPH:





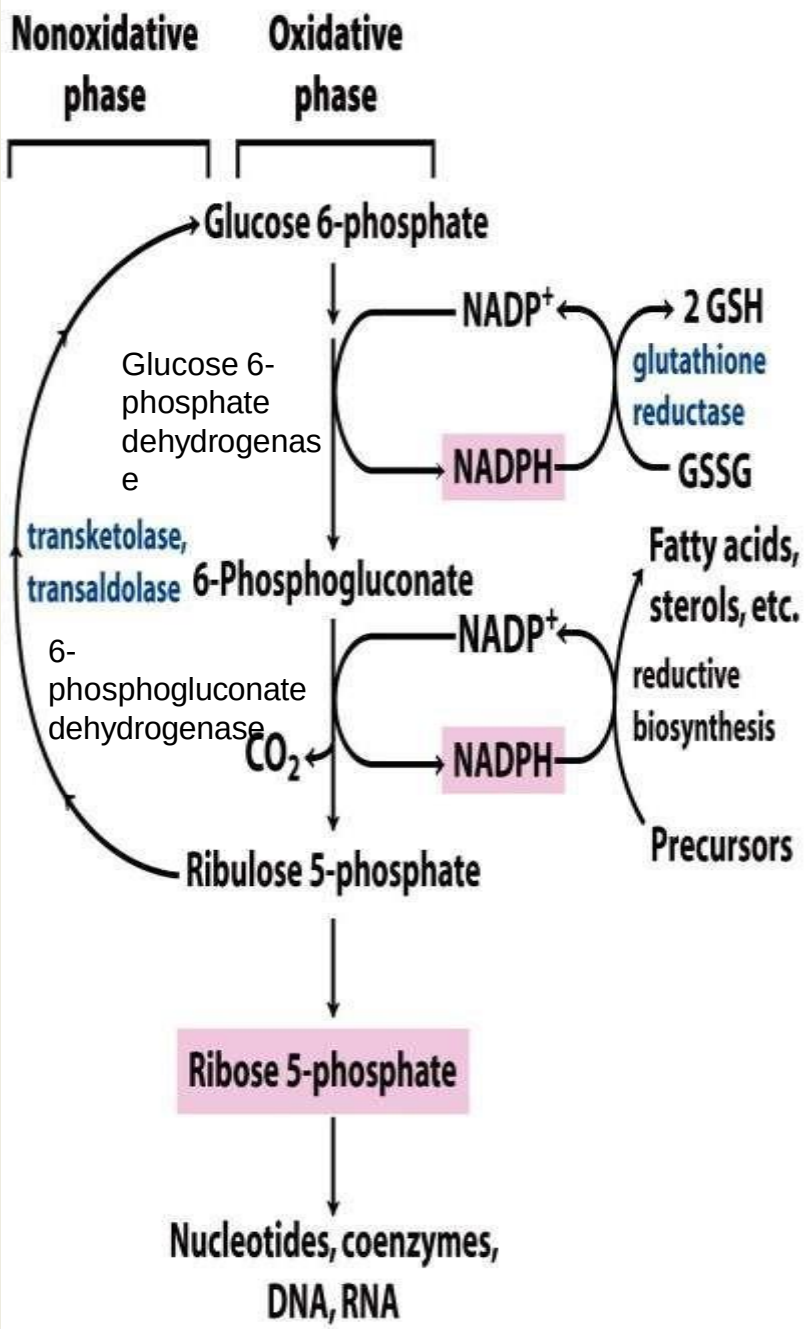
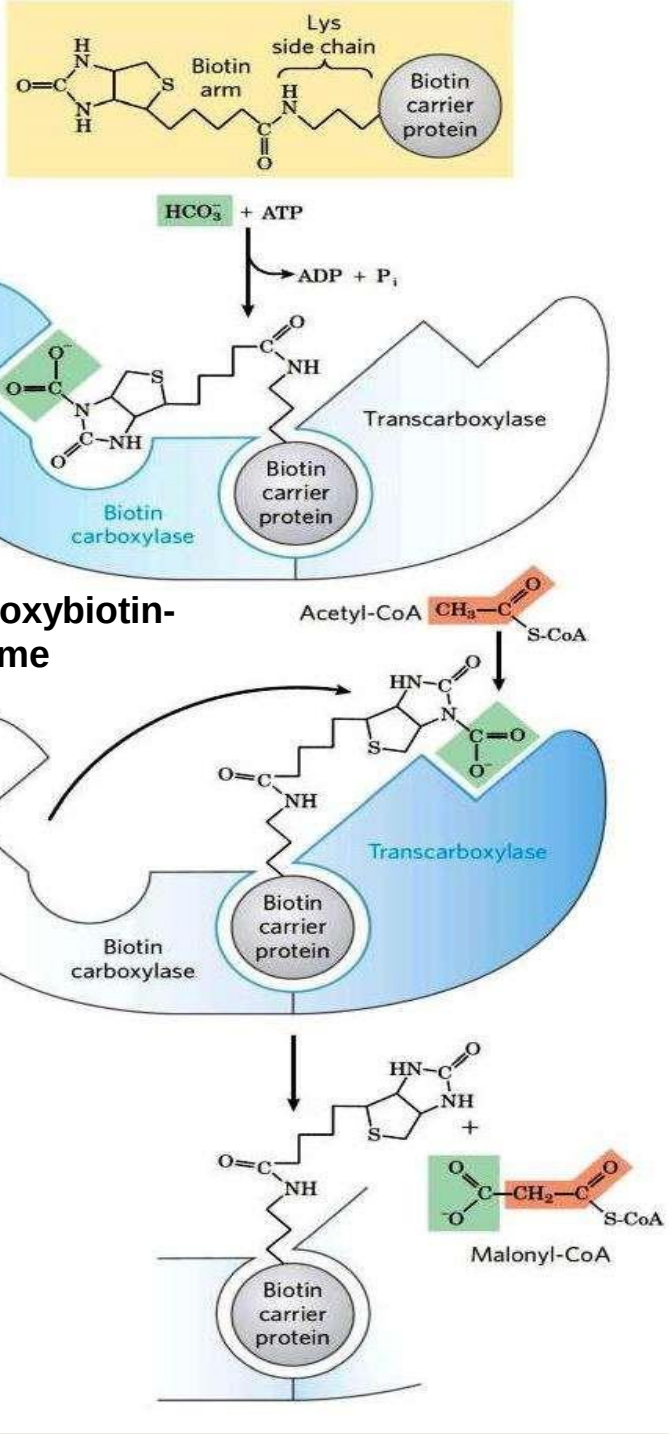


Figure 14-20
Lehninger Principles of Biochemistry, Fifth Edition

Formation of Malonyl CoA

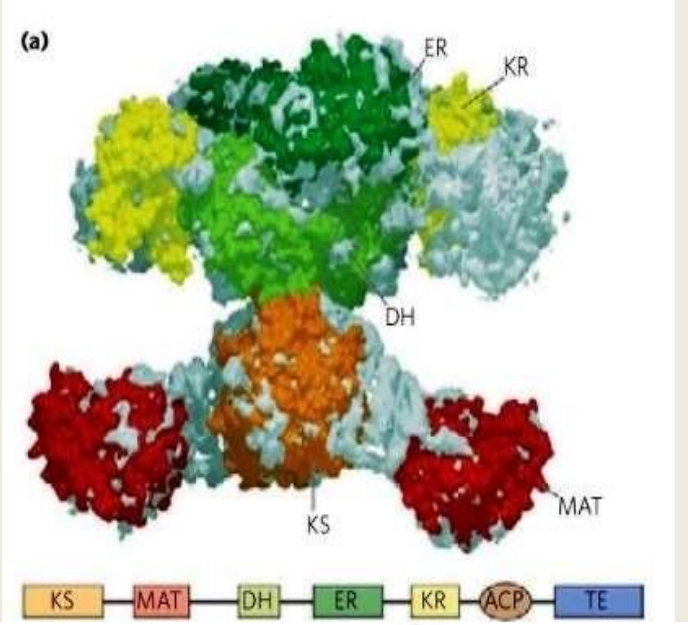
- Carboxylated acetyl CoA

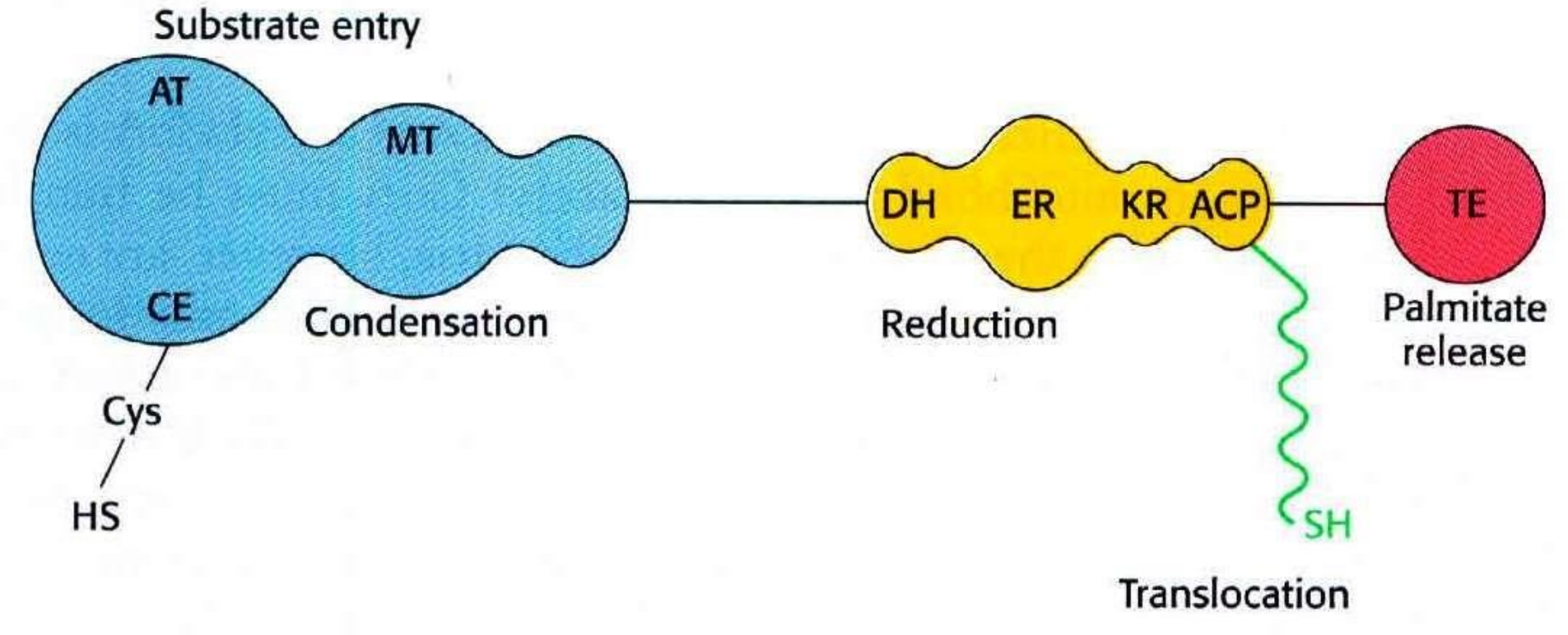
- Committed step
- Acetyl CoA Carboxylase :
  - ❑ Biotin
  - ❑ Biotin carrier protein
  - ❑ Biotin carboxylase
  - ❑ Transcarboxylase
- Rate-limiting step
- Regulatory enzyme

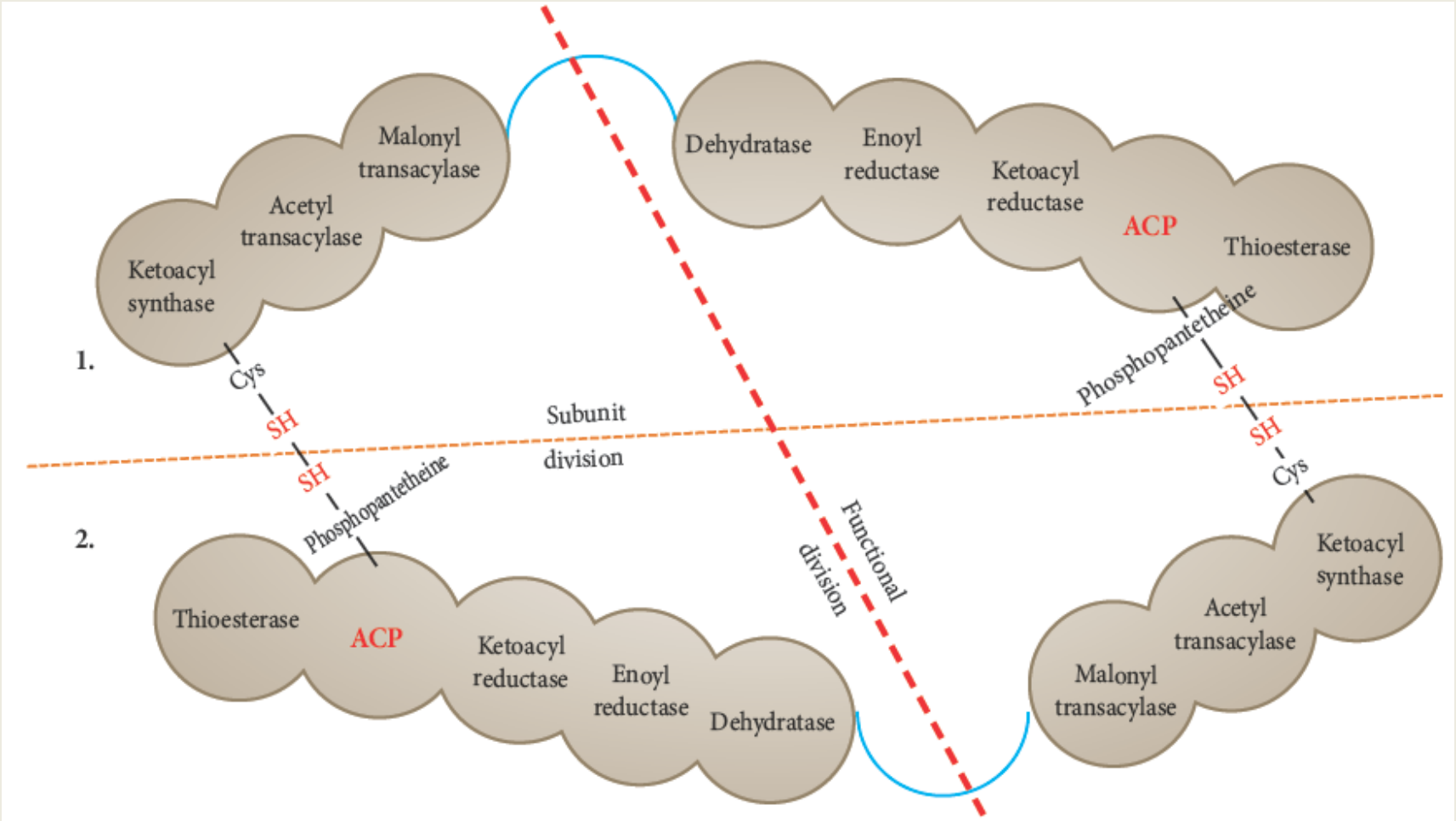


FATTY ACID SYNTHASE COMPLEX

- Cytoplasmic Multienzyme complex
- 7 enzymes ; 1 Acyl carrier Protein (ACP)
- Homodimer







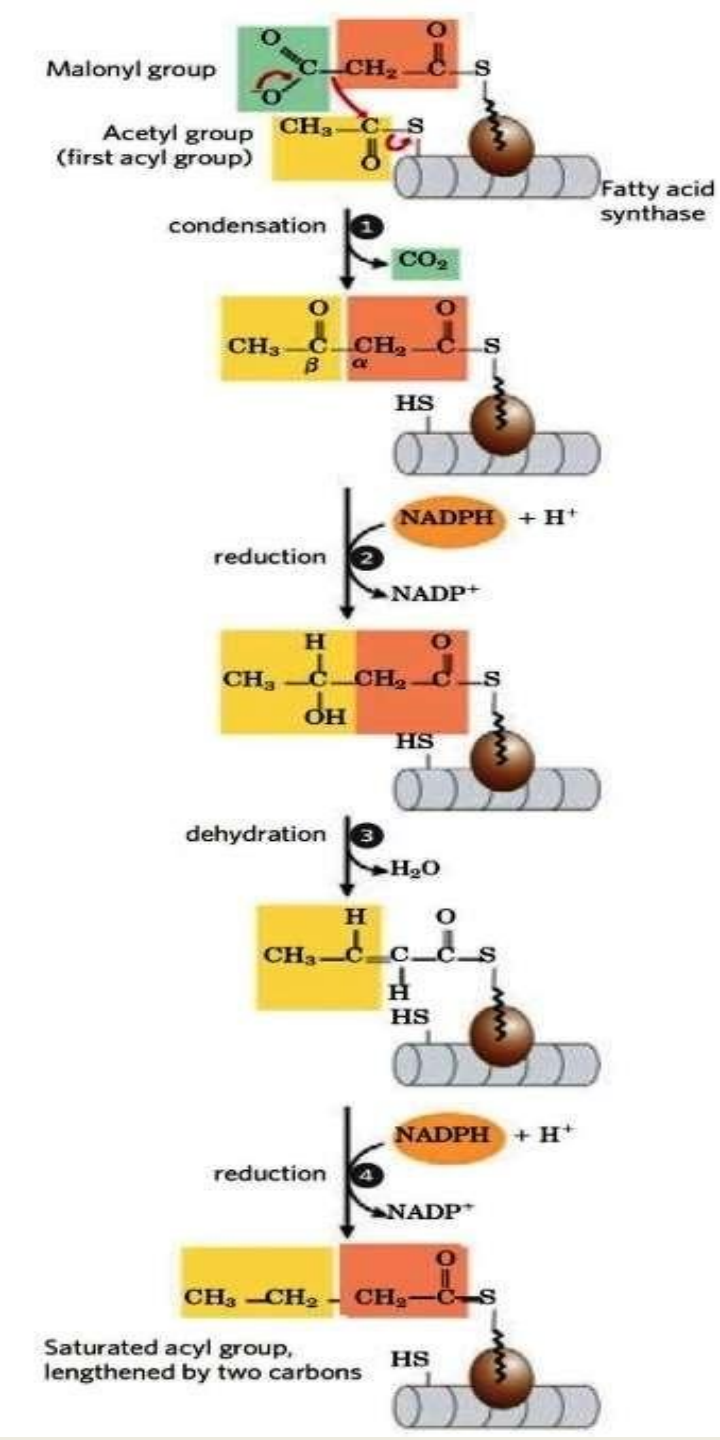
Fatty acid synthase multienzyme complex (The complex is a dimer with two identical polypeptides 1 and 2 running antiparallel to each other, each consisting of seven enzyme activitites and an acyl carrier protein – ACP).

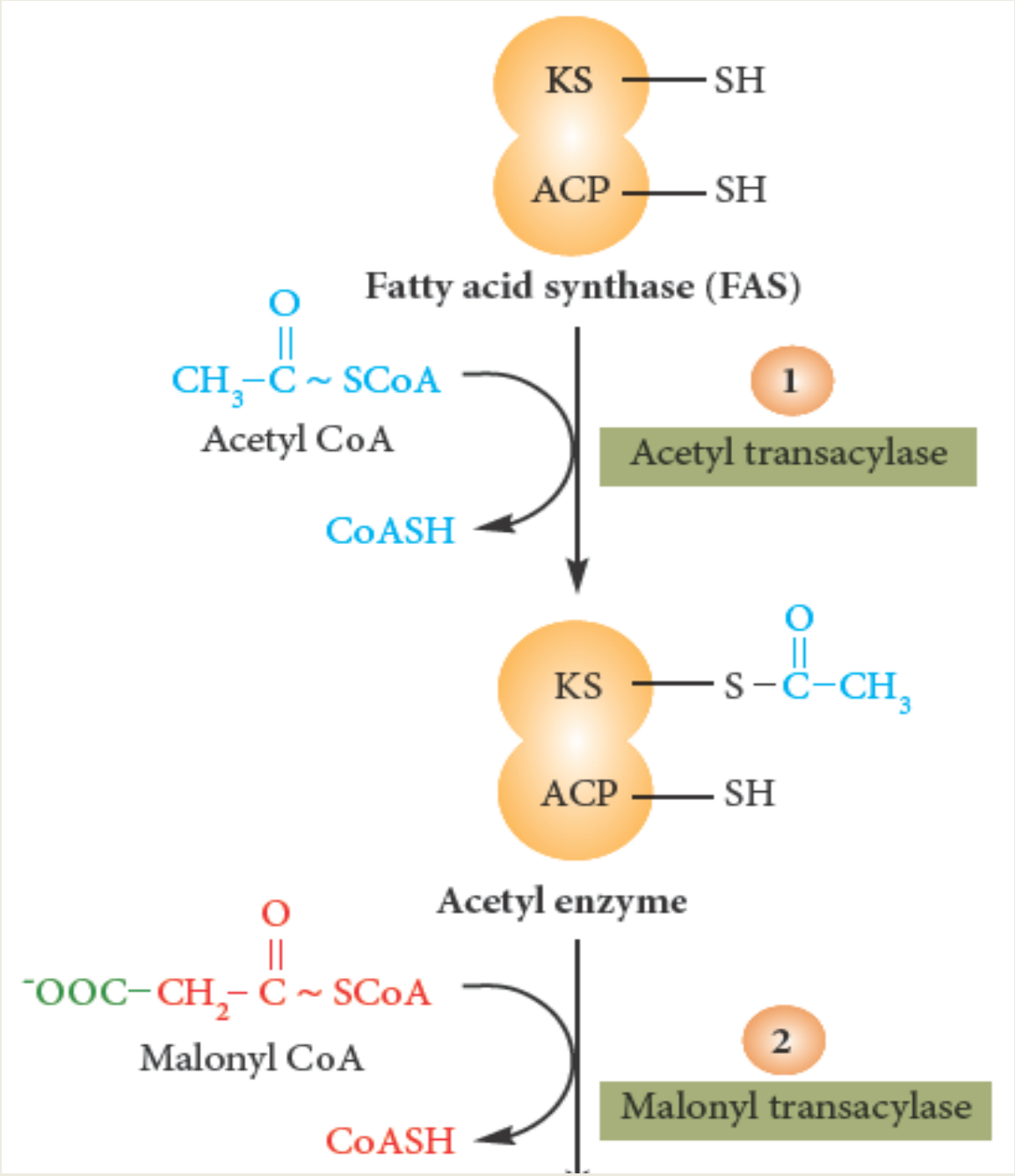
STEPS INVOLVED

- Addition of 2C at a time
- Goes through CYCLES (Lynen's spiral)

  Nobel laureate – Feodor Lynenin 1964.

- One cycle goes through 4 steps. 1st step: Condensation
  3rd Step: Dehydration
  4th Step: 2nd reduction with NADPH
  2nd Step: 1st reduction with NADPH




KS — SH
ACP — SH
Fatty acid synthase (FAS)
O
CH3–C ~ SCoA
Acetyl CoA
CoASH
1
Acetyl transacylase
KS — S – C – CH3
ACP — SH
Acetyl enzyme
O
-OOC–CH2– C ~ SCoA
Malonyl CoA
CoASH
2
Malonyl transacylase

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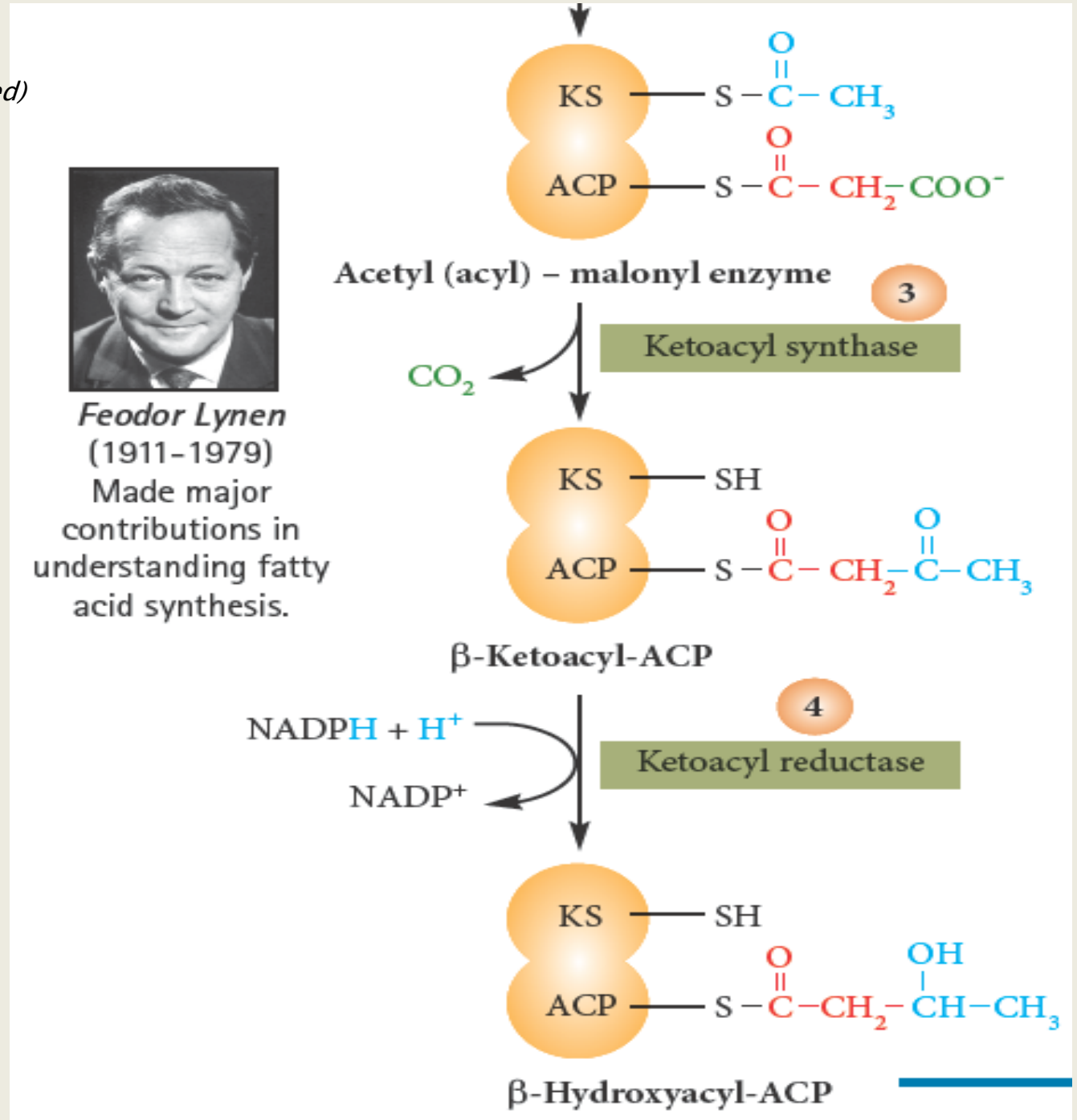
Feodor Lynen
(1911–1979)
Made major contributions in understanding fatty acid synthesis.



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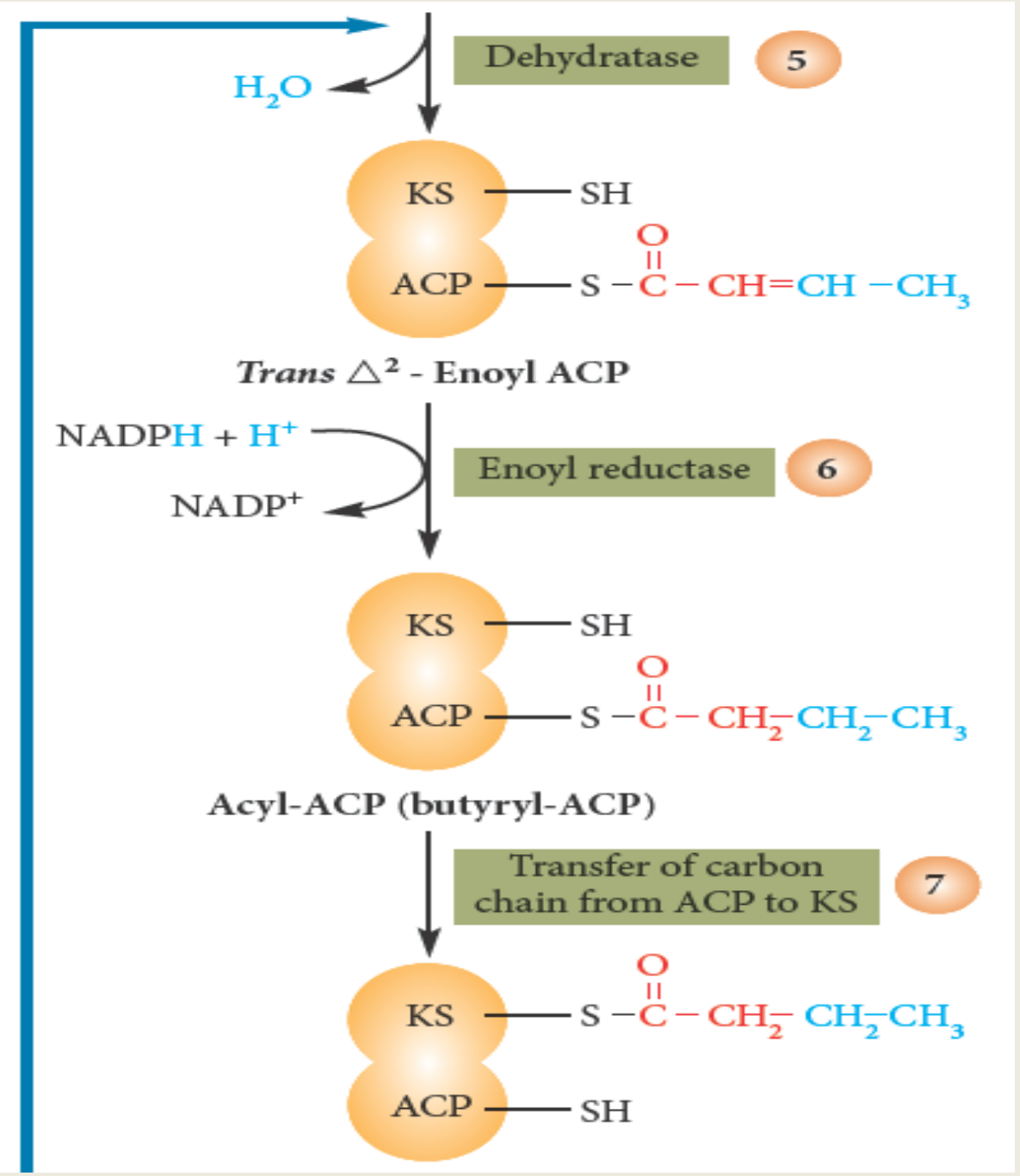

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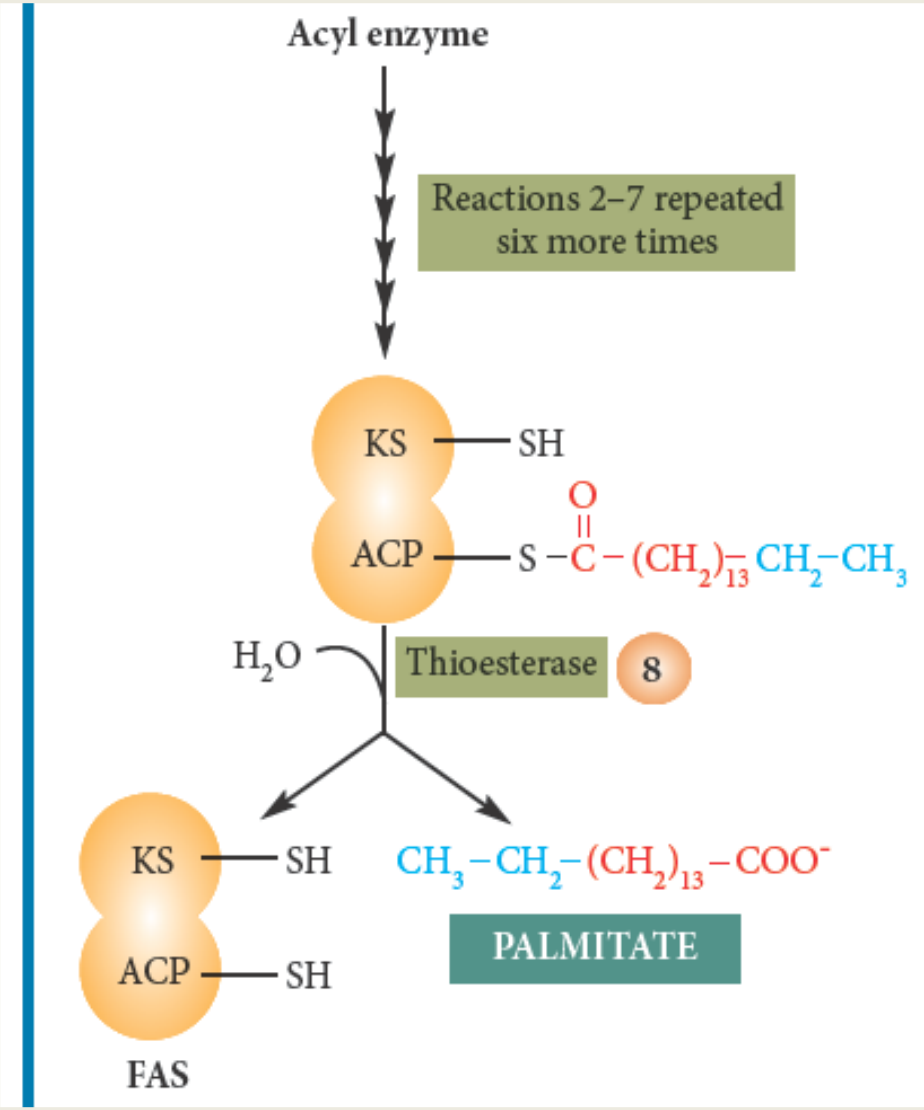


Biosynthesis of fatty acids (KS = Ketoacyl synthase; ACP = Acyl carrier protein).

Stoichometry:

the formation of seven malonyl-CoA molecules:

$$7\ \text{Acetyl-CoA} + 7CO_2 + 7ATP \rightarrow 7\ \text{malonyl-CoA} + 7ADP + 7P_i$$

then seven cycles of condensation and reduction:

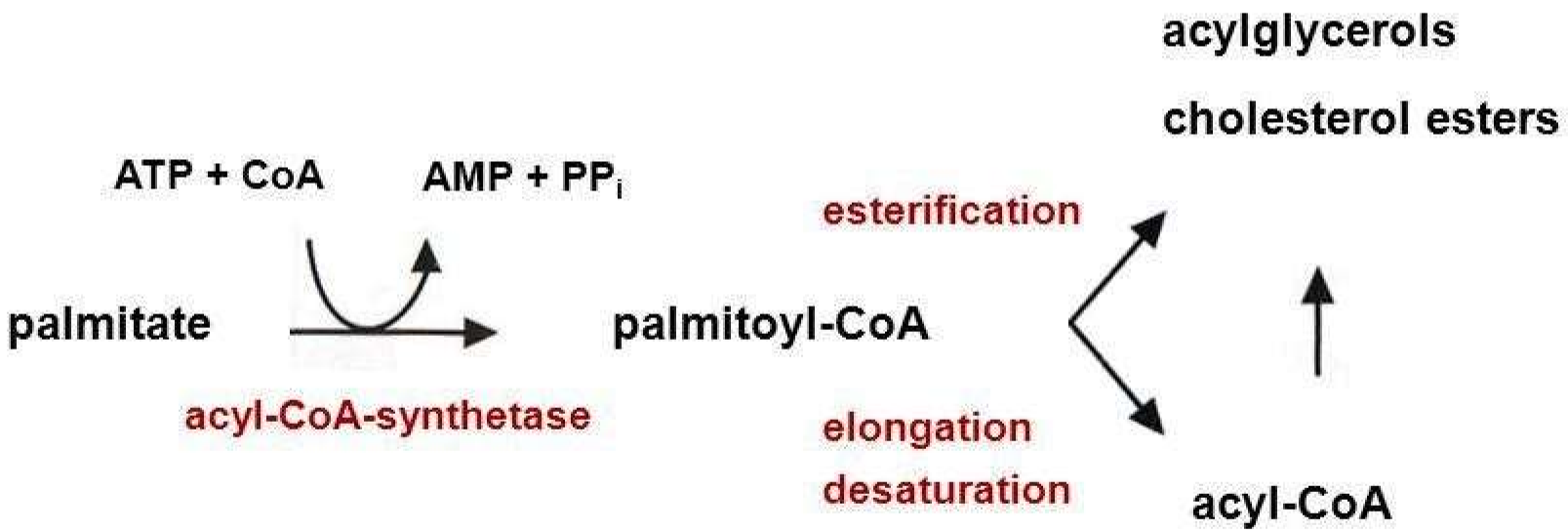
$$\text{Acetyl-CoA} + 7\ \text{malonyl-CoA} + 14NADPH + 14H^+ \rightarrow \text{palmitate} + 7CO_2 + 8\ \text{CoA} + 14NADP^+ + 6H_2O$$

The overall process is

$$8\ \text{Acetyl-CoA} + 7ATP + 14NADPH + 14H^+ \rightarrow \text{palmitate} + 8\ \text{CoA} + 7ADP + 7P_i + 14NADP^+ + 6H_2O$$

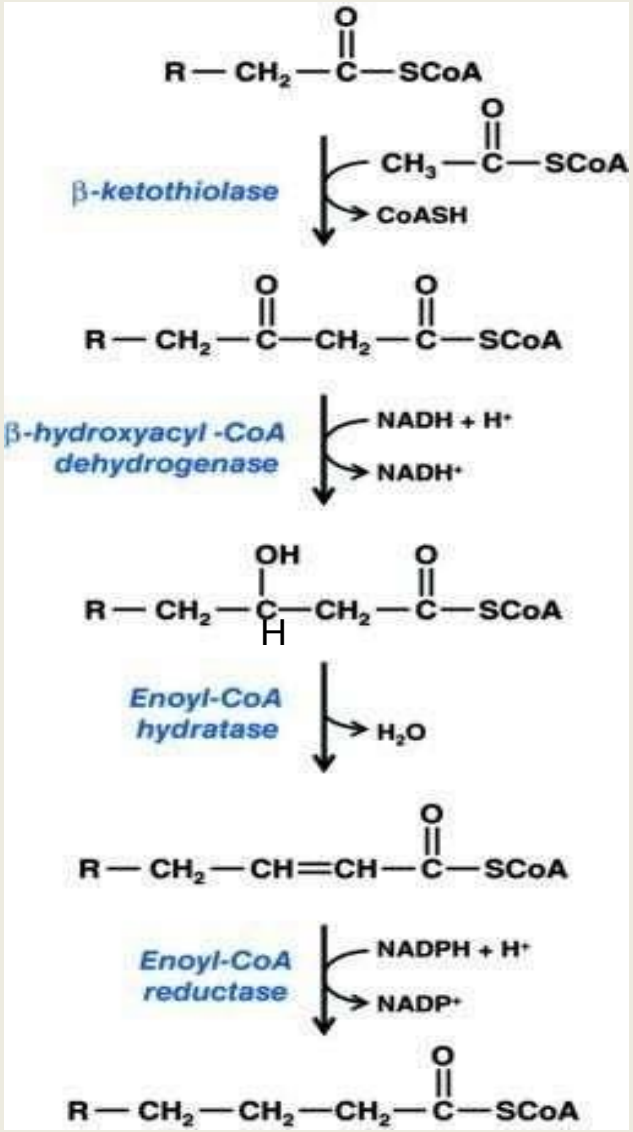
FA biosynthesis

The fate of palmitate after FA biosynthesis

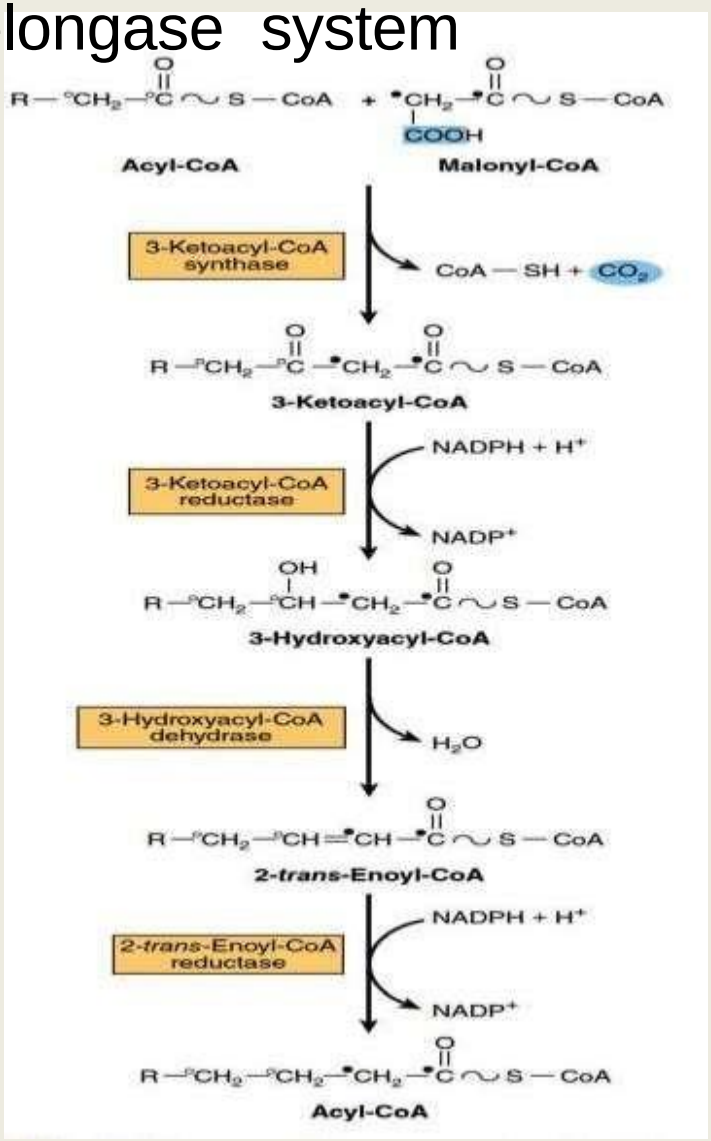


Elongation of fatty acids

- Mitochondrial: Acetyl CoA

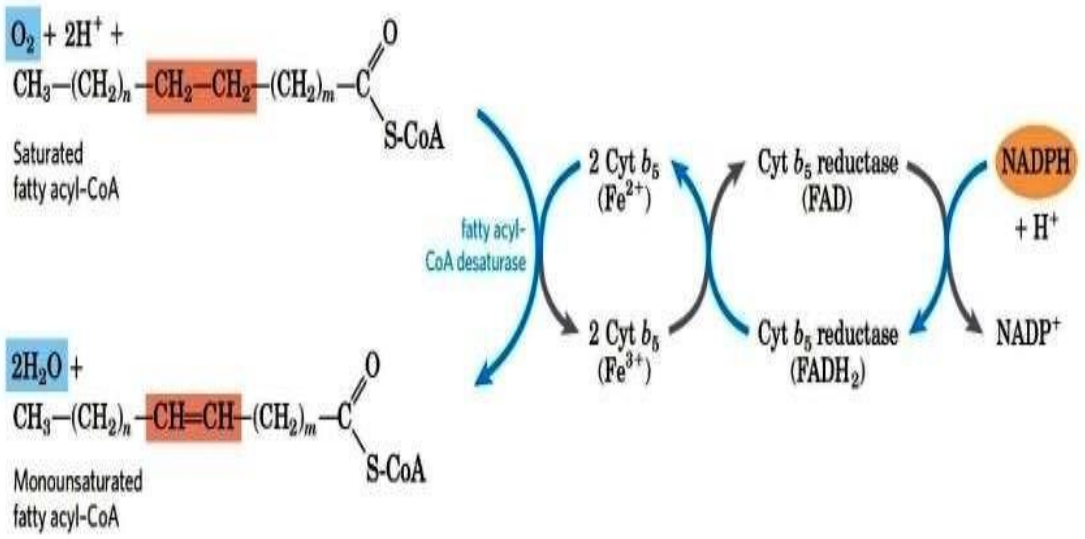


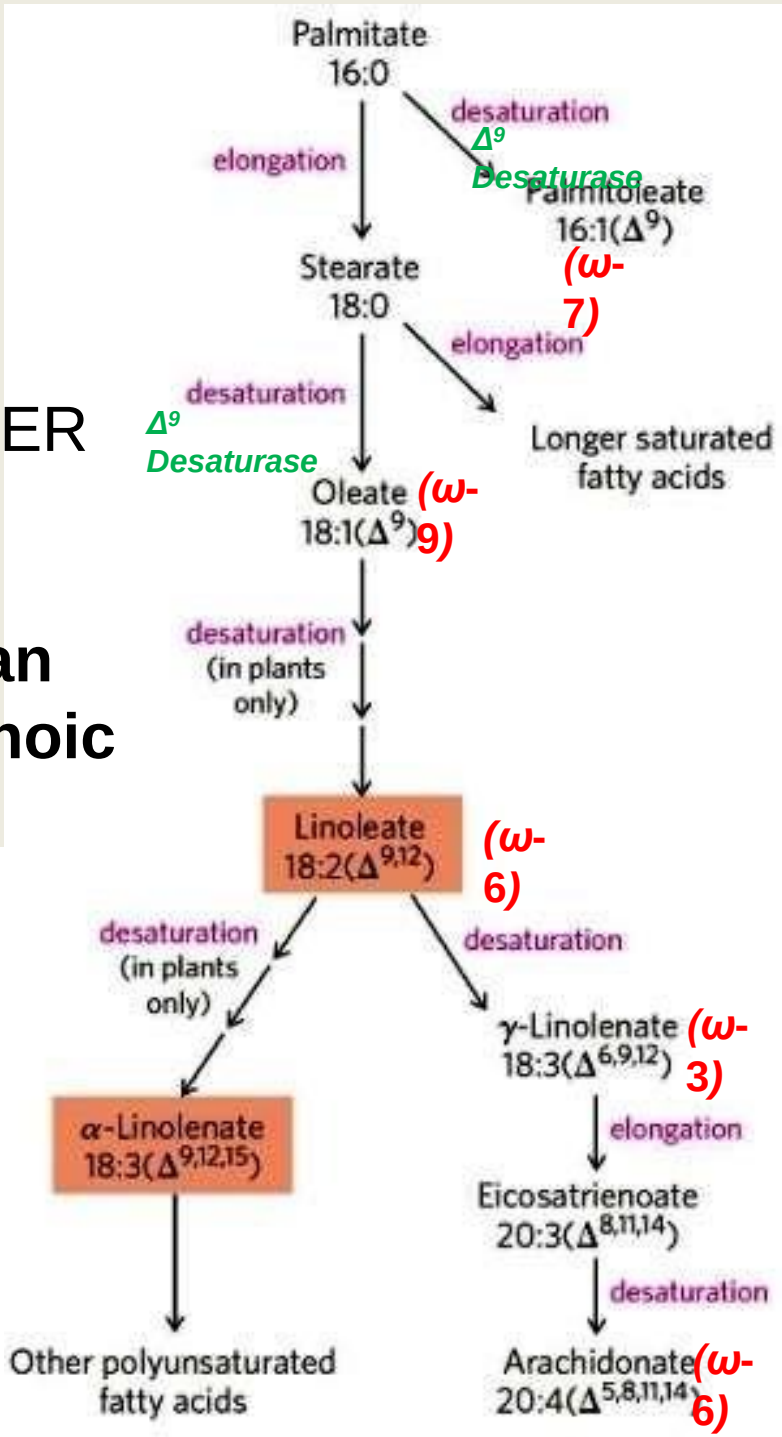
- Microsomal fatty acid elongase system



Synthesis of Unsaturated Fatty acids

- Microsomal desaturase system
- Electron transport chain on smooth ER
- Mixed function oxidases
- Δ^9 ,Δ^6 ,Δ^5 & Δ^4 positional specificity
- **Δ^6 ,Δ^5 & Δ^4 : at C-terminal side: can never produce *ω*-3 or *ω*-6 polyenoic acids (Essential fatty acids)**





Regulation of FA synthesis

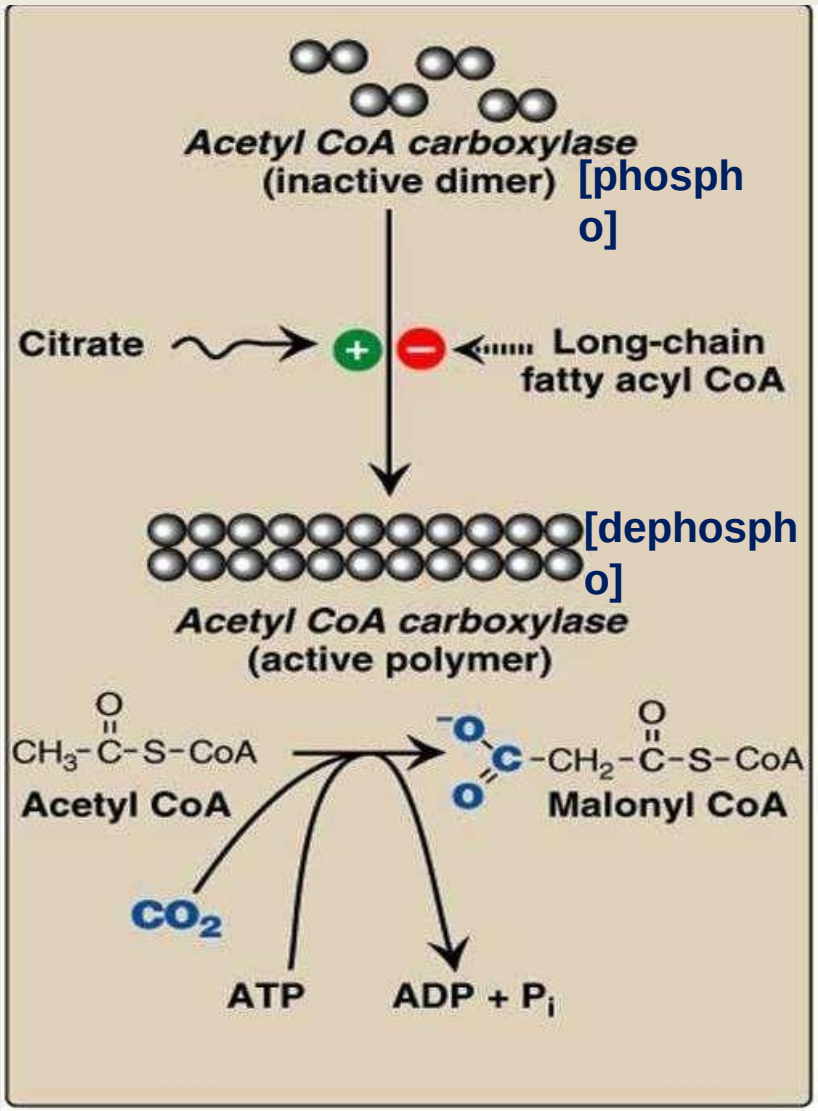
1. Regulation of Acetyl CoA Carboxylase:
   - Allosteric regulation
   - Feedback inhibition
   - Covalent modification

2. Long term effects of Insulin

3. Coordinated regulation of Fatty acid oxidation and synthesis.

Regulation of Acetyl CoA Carboxylase:

1. Allosteric activation



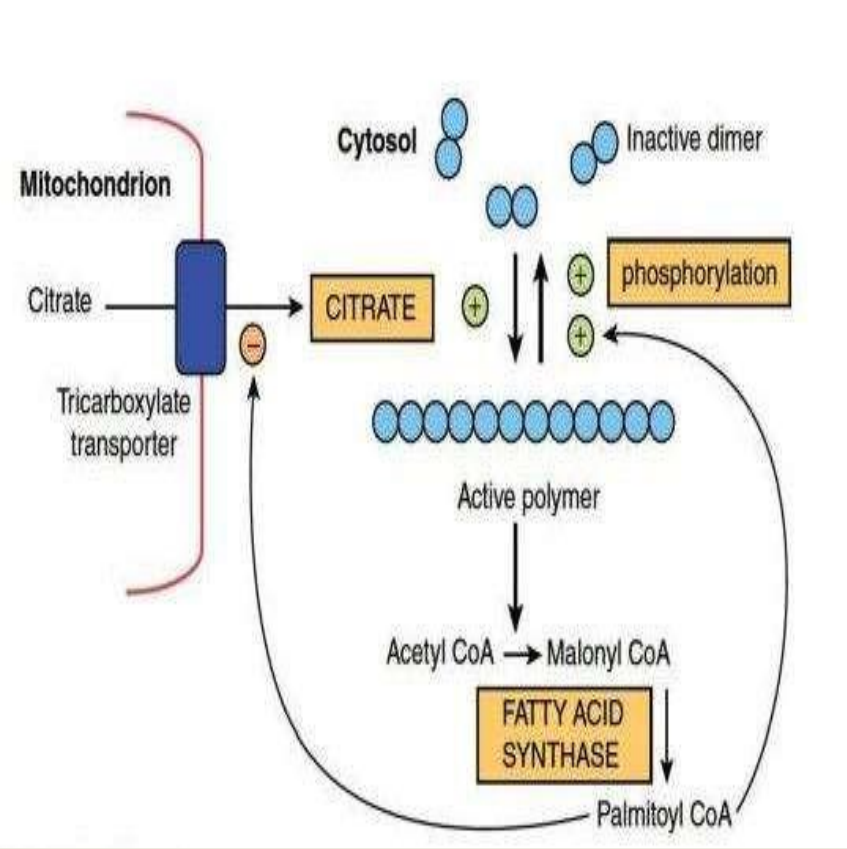
- ⬆ Carbohydrate oxidation (well fed state)

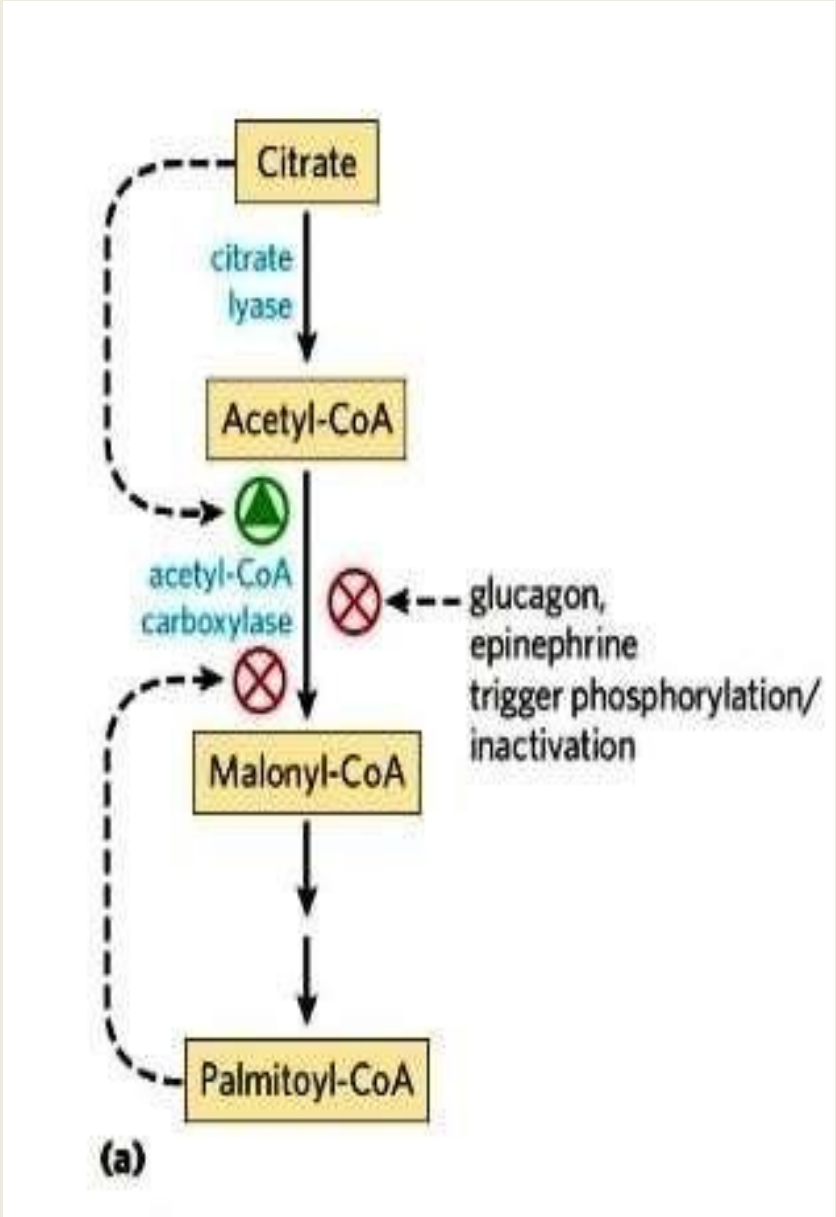
  ⬇

  ⬆ Citrate

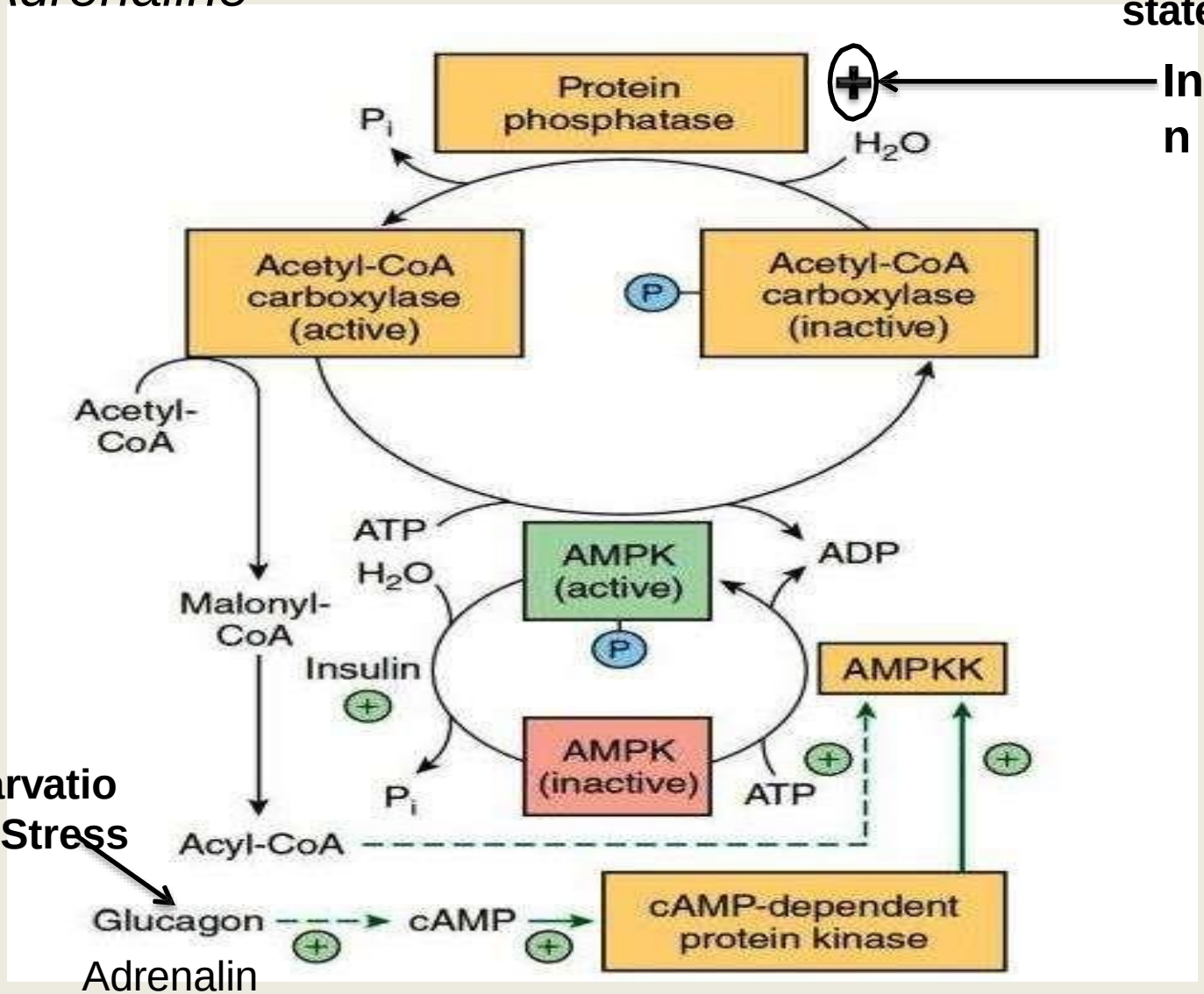
2. Feedback inhibition:

- By long chain fatty acyl-CoA
- Inhibits tricarboxylate (citrate) transporter

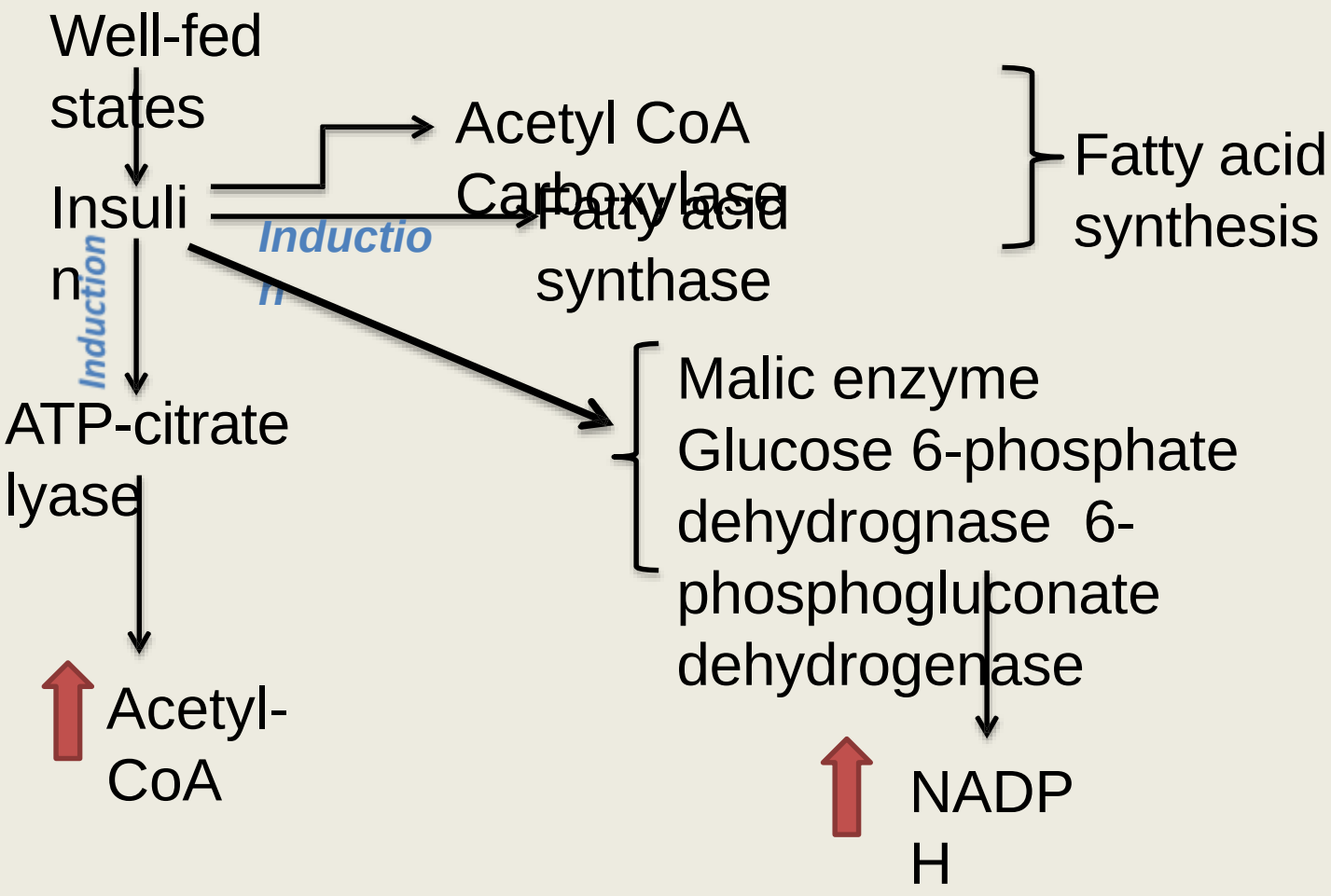




3. Covalent modification: Glucagon, Adrenaline



Long-term actions of insulin:



Fatty acid oxidation v/s

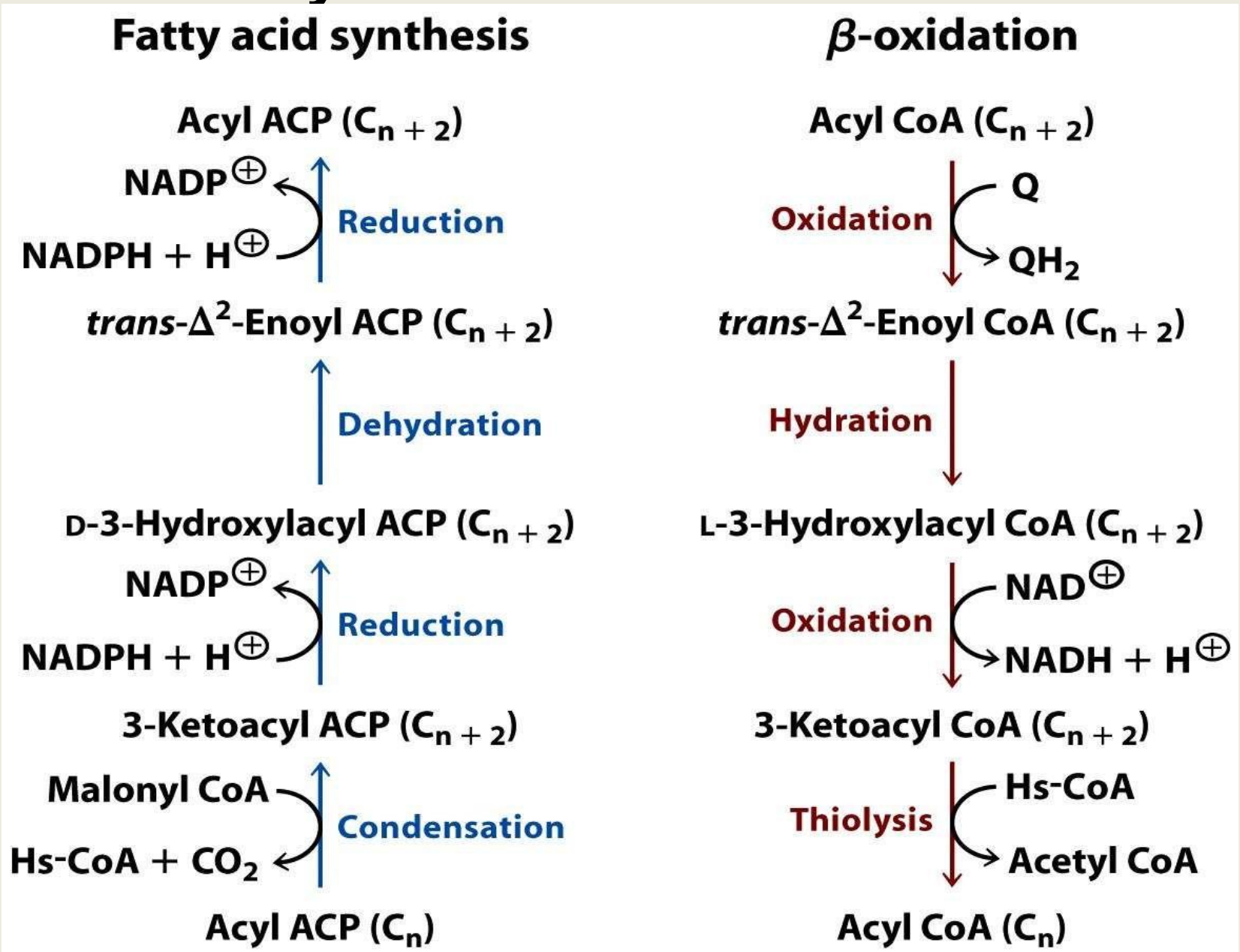


Figure 16-20 Principles of Biochemistry, 4/e

	β-Oxidation	FA Synthesis
SITE	Mitochondrial Matrix	Cytosol
Enzymes	4 distinct ,independent proteins	FAS is a Multi-enzyme complex
Process	2 C units Split off as acetyl CoA	2 C units added as 3C malonyl CoA
Transport system of Acetyl CoA	Carnitine shuttle (Cytosol to MC)	Citrate shuttle (MC to Cytosol)
Direction	Starts at carboxyl end	Starts at methyl end
Coenzymes	NAD, FAD (get reduced)	NADPH (Supplies reducing equivalents)
Acyl carrier	SH of CoA	SH of ACP
End Product	Acetyl CoA	Palmitic acid
Participation of CO	No	Yes

	β-Oxidation	FA Synthesis
Stereoisomeric form of 3-OH-acyl group	L	D
Increased operation of pathway	In starvation	After diet rich in CH /proteins

Recent

Fatty Acid Synthase Inhibitors May Be Useful Drugs

Fatty acid synthase is overexpressed in a number of cancers. Researchers intrigued by this observation have tested inhibitors of fatty acid synthase on mice to see if the inhibitors slow tumor growth. These inhibitors do indeed slow tumor growth, apparently by inducing apoptosis. However, another startling observation was made: *mice treated with inhibitors of the condensing enzyme showed remarkable weight loss* because they ate less. Thus, fatty acid synthase inhibitors are exciting candidates both as antitumor and as antiobesity drugs.

Fan, H., Liang, Y., Jiang, B., Li, X., Xun, H., Sun, J., He, W., Lau, H. T., Ma, X."*Curcumin inhibits intracellular fatty acid synthase and induces apoptosis in human breast cancer MDA-MB-231 cells*". Oncology Reports 35, no. 5 (2016): 2651-2656. http://dx.doi.org/10.3892/or.2016.4682

- **Curcumin** : one of the major active ingredients of Curcuma longa, which has been proven to inhibit the growth of cancer cells.
- In this study, potential activity of curcumin as a FAS inhibitor for chemoprevention of breast cancer was investigated.
- As a result, curcumin induced human breast cancer cell apoptosis ,blocked FAS activity, expression and mRNA level in a dose-dependent manner.
- Moreover, FAS knockdown showed similar effect as curcumin. All these results suggested that curcumin

Summary

- FA synthesis occurs in cytosol and uses Acetyl CoA as substrate.
- Formation of Malonyl CoA is committed step in FA synthesis .
- Acetyl CoA carboxylase is the regulatory enzyme.
- Occurs on Multifunctional enzyme complex.
- Elongation and unsaturation of FA are accomplished by accessory enzyme systems.
- FA synthethic and degradative pathways are distinct.

References

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