Fatty acid & Triglyceride Synthesis
Ketobody Metabolism

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Biosynthesis of Fatty acids

- Excess dietary ***Carbohydrates & Proteins***
- Converted to fatty acids & stored as Triacylglycerol
- **De-novo synthesis** of Fatty acids takes place in
  - **Liver**
  - **Kidney**
  - **Adipose tissue**
  - **Lactating Mammary glands.**
- **Site**: Cytoplasm of the cell
- ***Requirements:***
- *Acetyl CoA* – source of Carbon atoms
- *NADPH* – provides reducing equivalents
- *ATP* – energy

⇒ Fatty acid synthesis in 3 stages

(i) Production of **Acetyl CoA & NADPH**

(ii) Conversion of **Acetyl CoA to Malonyl CoA**

(iii) Reactions of **Fatty acid synthase complex**.

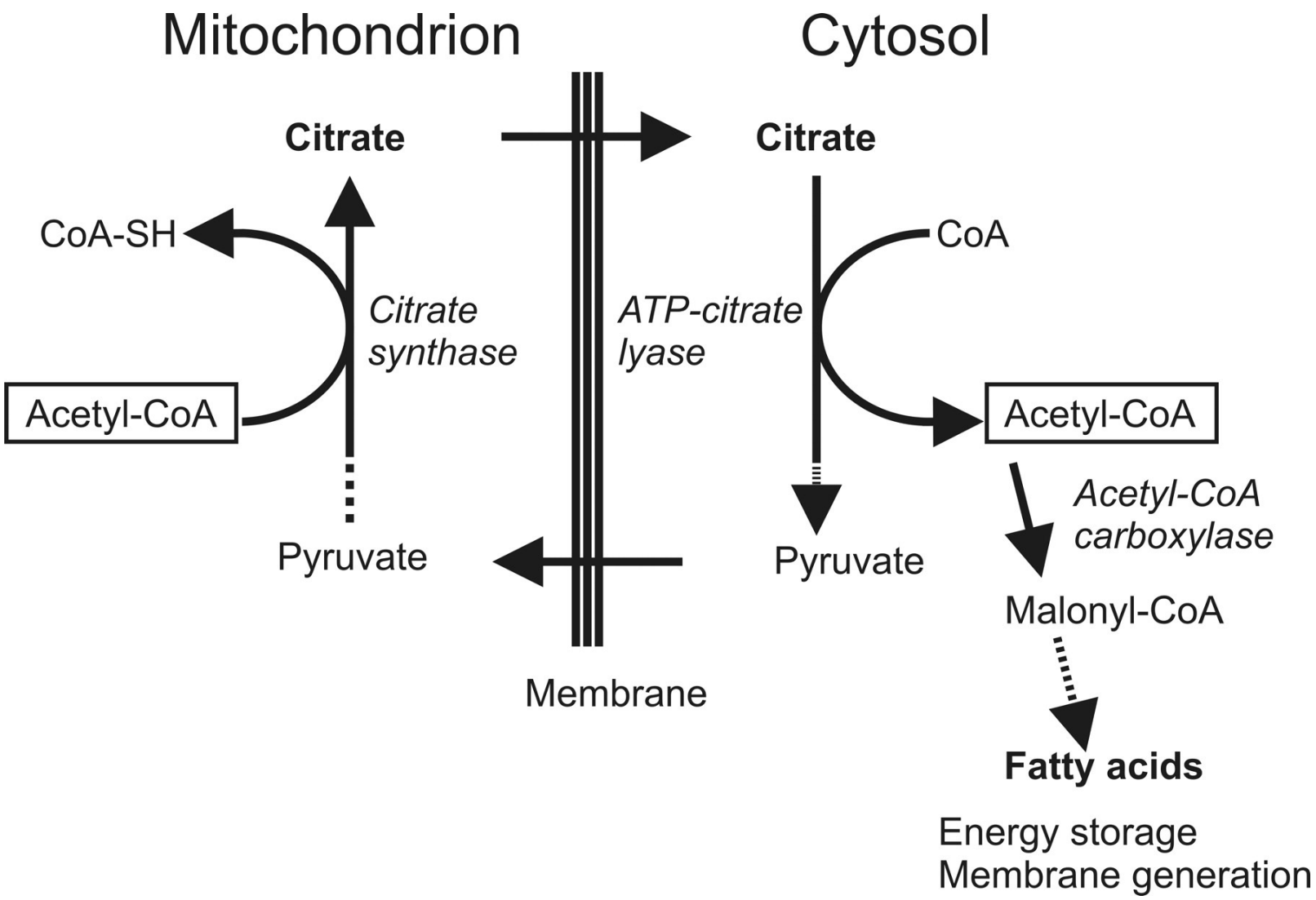
Production of Acetyl CoA & NADPH

Acetyl CoA is produced in mitochondria from oxidation of

- **Pyruvate**
- **Fatty acids**
- **Degradation of Amino acids**
- **Ketone bodies**

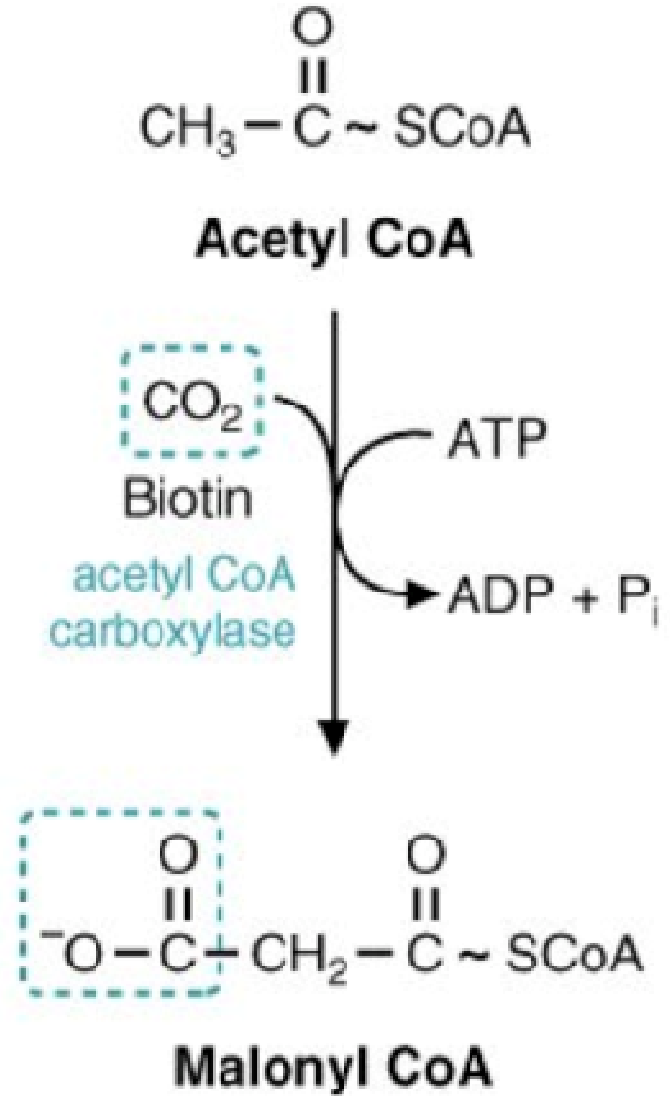
Mitochondrial membrane is impermeable to Acetyl CoA

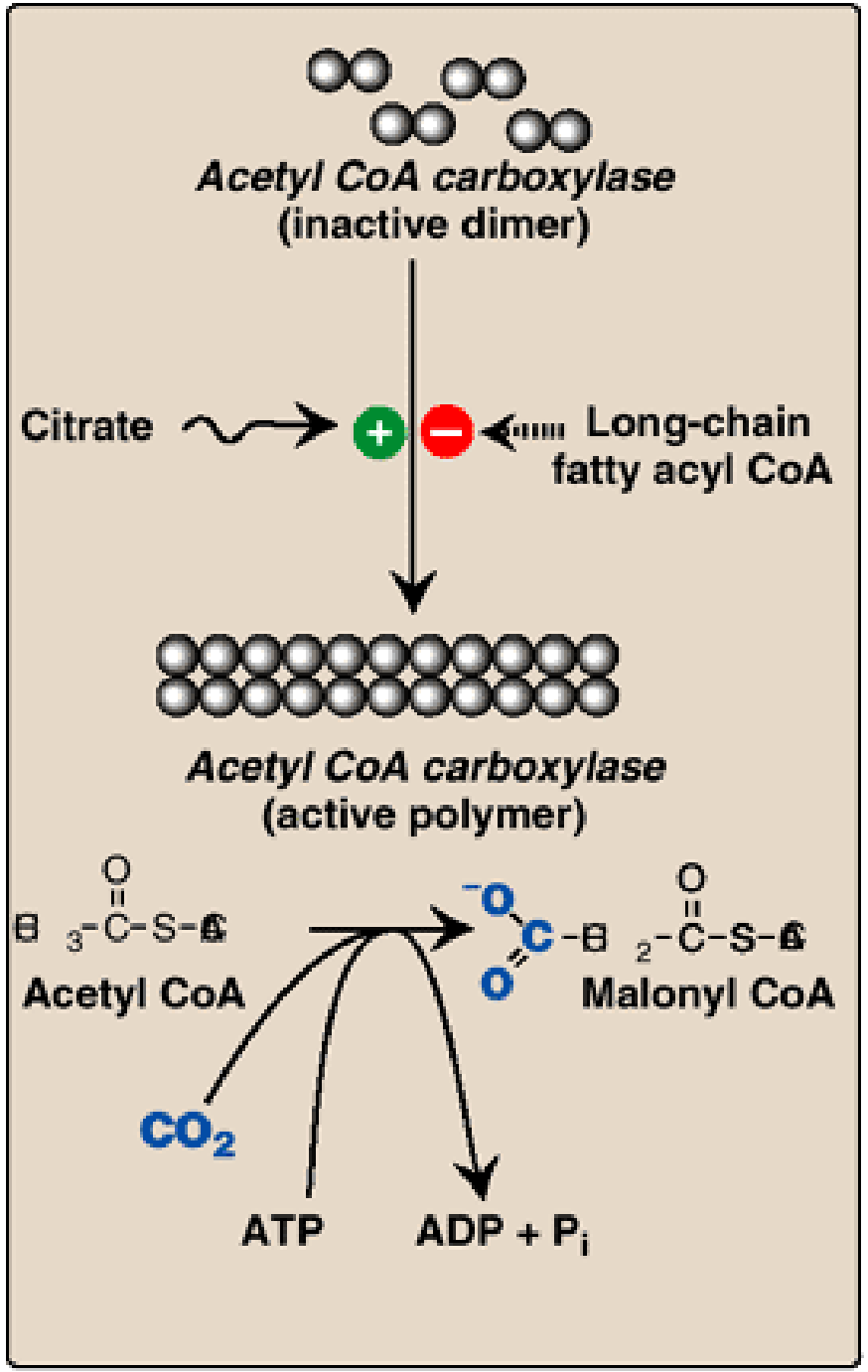
Transfer of Acetyl CoA from Mitochondria to Cytoplasm



Formation of Malonyl CoA

- Acetyl CoA is carboxylated to Malonyl CoA by
- **Acetyl CoA Carboxylase**
- **This step is the regulating step for Fatty acid synthesis**



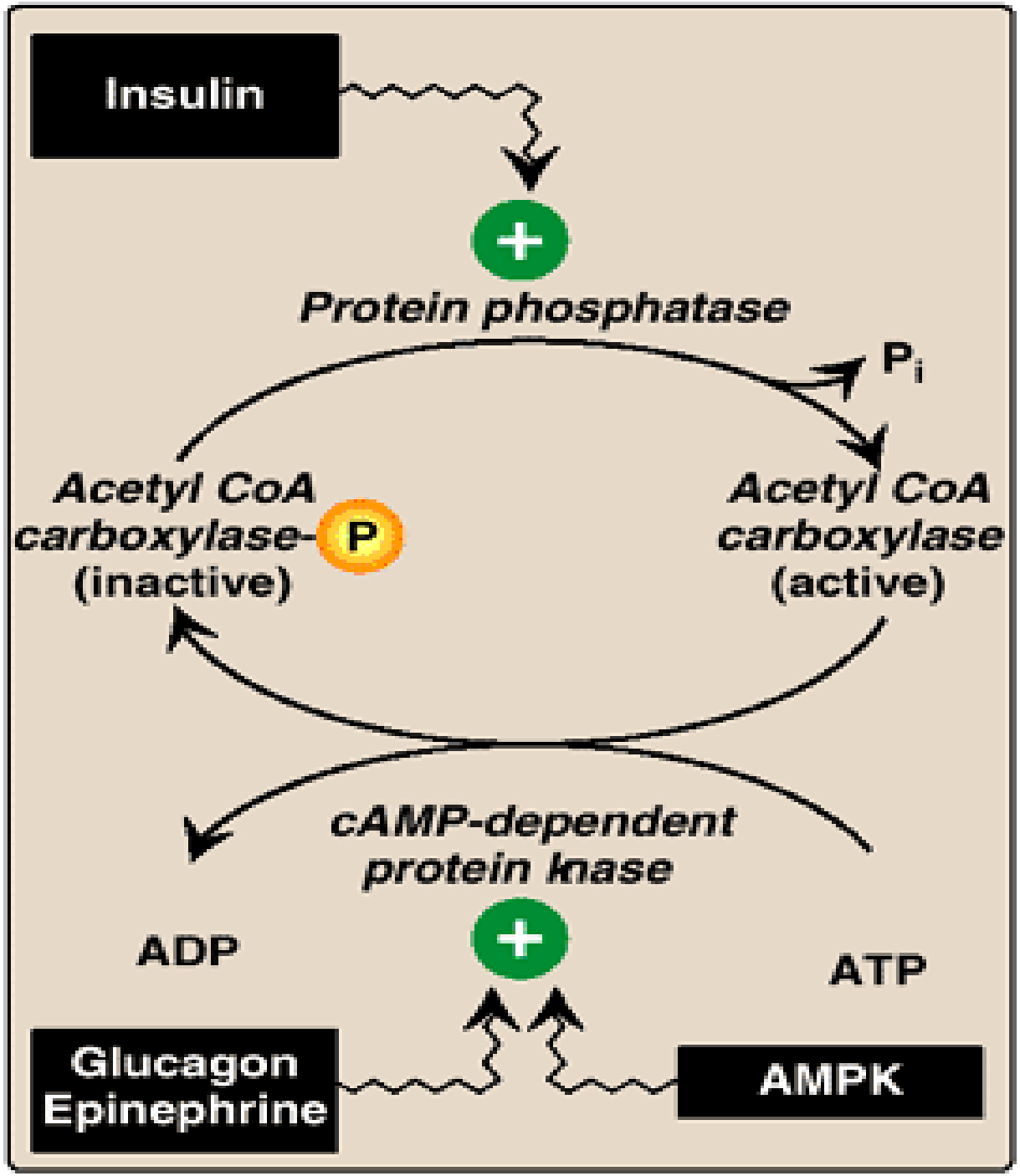

Acetyl CoA carboxylase
(inactive dimer)
Citrate
Long-chain
fatty acyl CoA
Acetyl CoA carboxylase
(active polymer)
Acetyl CoA
Malonyl CoA
CO2
ATP
ADP + Pi

Short term regulation

- Activated by
  - Citrate
  - Insulin
- Inactivated by
  - long-chain fatty acyl CoA
  - Epinephrine & Glucagon

Long term regulation

- Increase
  - Prolonged consumption of a diet containing excess calories
  - High-carbohydrate diets
- Decrease
  - Low-calorie diet and Fasting


Insulin
+
Protein phosphatase
P_i
Acetyl CoA carboxylase-P (inactive)
Acetyl CoA carboxylase (active)
cAMP-dependent protein kinase
+
ADP
ATP
Glucagon Epinephrine
AMPK

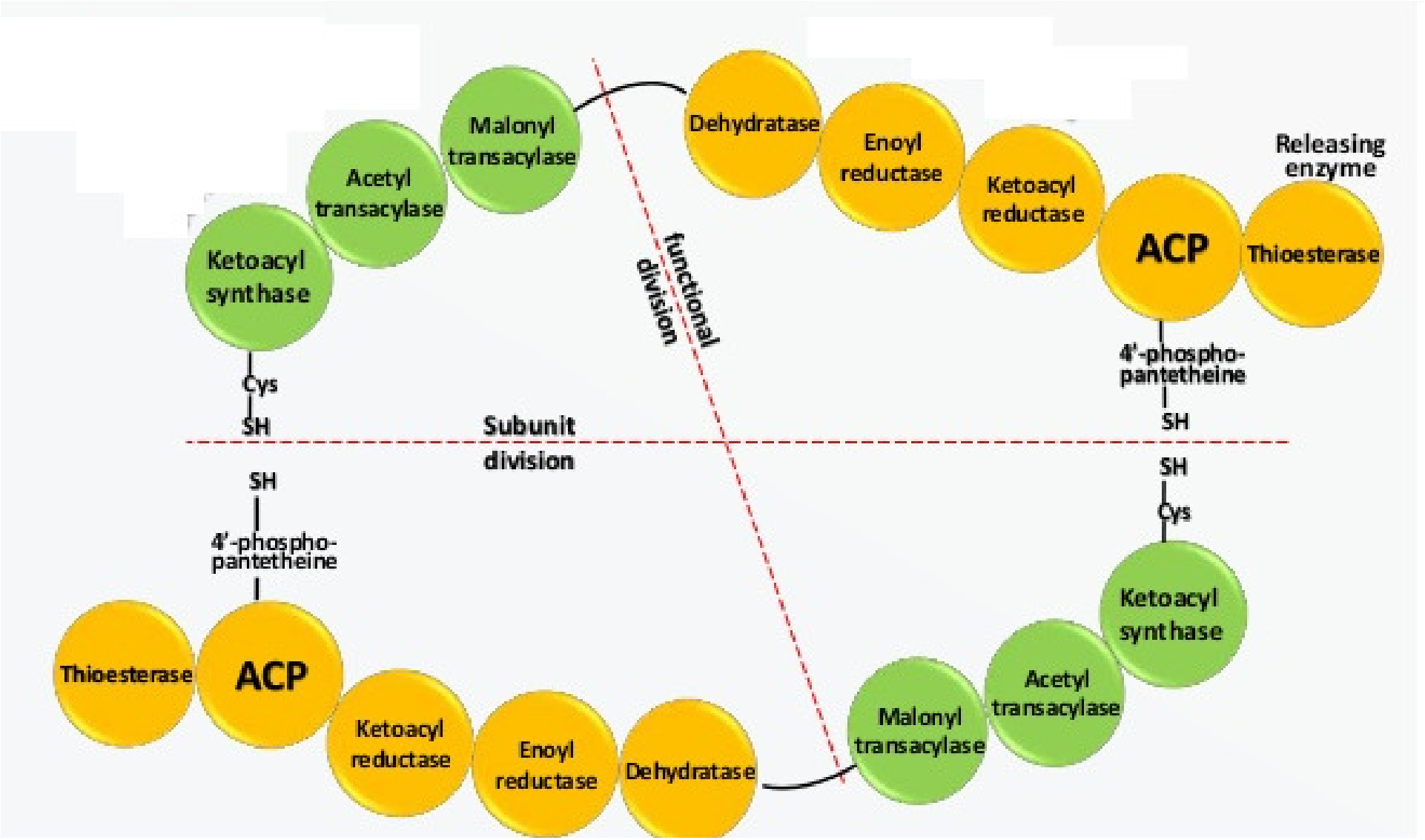
Fatty acid synthase complex:

Fatty acid synthase is a ***Multi enzyme complex***.

Dimer with two identical units.

Each unit contains ***7 enzymes*** and A***cyl Carrier Protein***

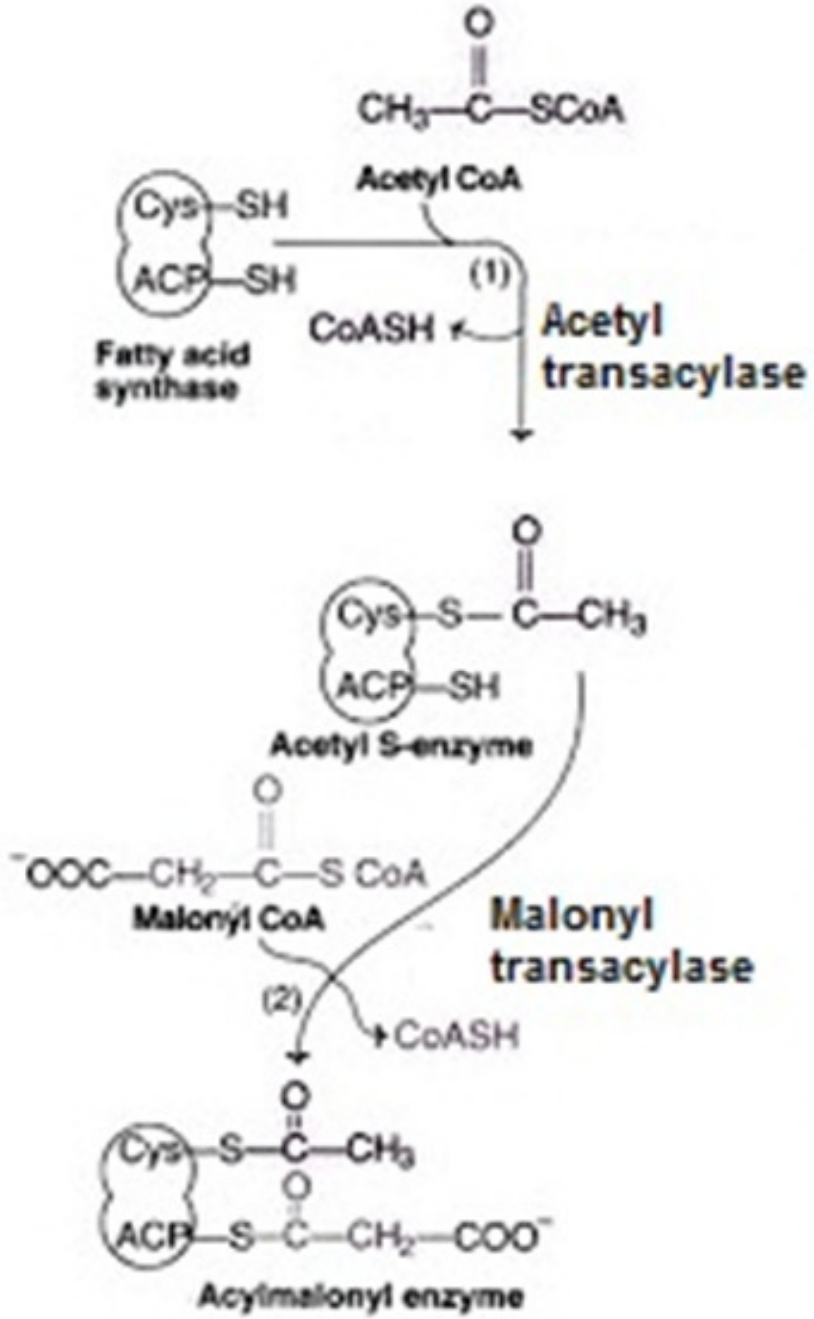
Fatty Acid Synthase Complex



Fatty Acid Synthase Complex

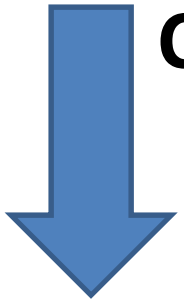
1. Acetyl transacylase
2. Malonyl transacylase
3. Ketoacyl synthase
4. Dehydratase
5. Enonyl reductase
6. Ketoacyl reductase
7. Thioesterase

- **Acyl Carrier Protein**


CH3—C—SCoA
Acetyl CoA
Cys—SH
ACP—SH
(1)
CoASH
Acetyl transacylase
Fatty acid synthase
Cys—S—C—CH3
ACP—SH
Acetyl S-enzyme
⁻OOC—CH2—C—S CoA
Malonyl CoA
Malonyl transacylase
(2)
CoASH
Cys—S—C—CH3
ACP—S—C—CH2—COO⁻
Acylmalonyl enzyme

(Unit-1) FA Synthase – KS – Cys – SH – Acetyl CoA

(Unit-2) FA Synthase – ACP – SH – Malonyl CoA

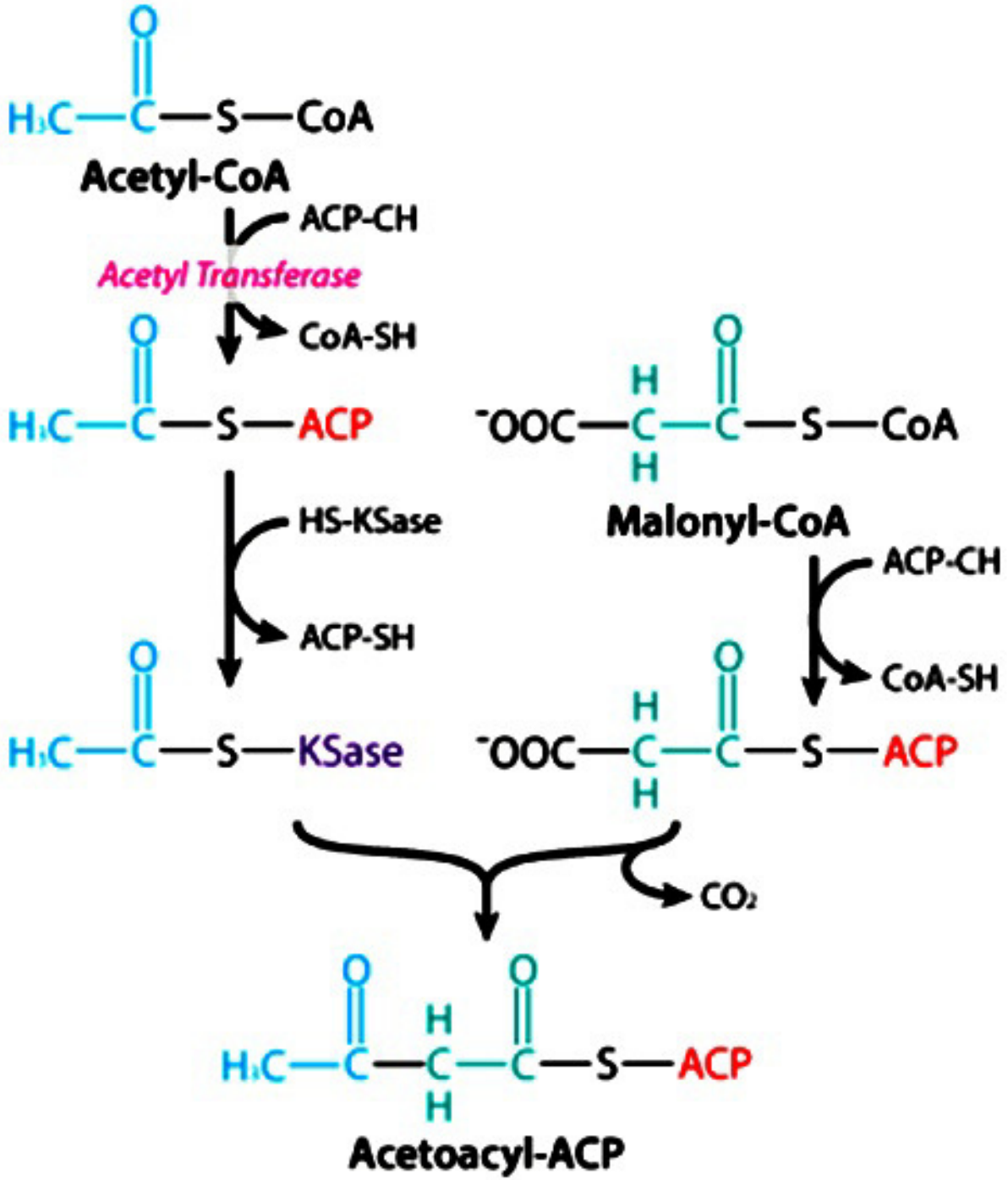


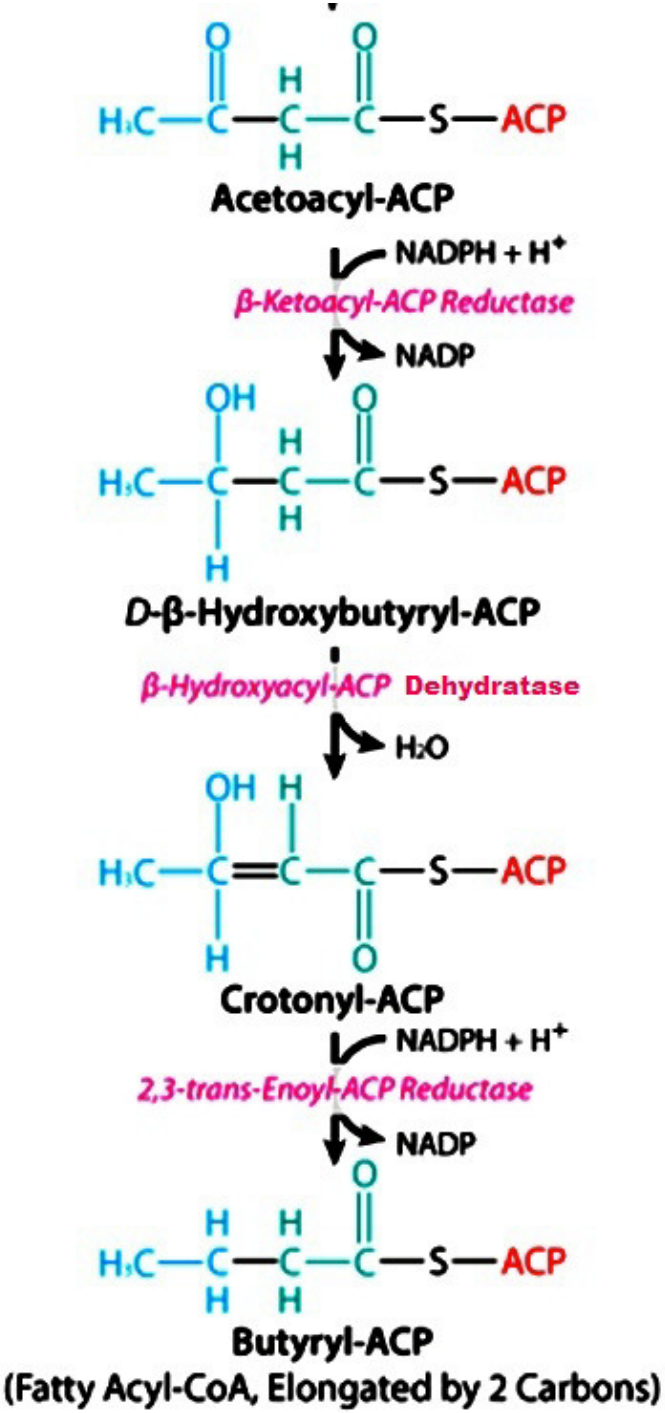
Condensing Enzyme

(Ketoacyl Synthase)

(Unit-1) FA Synthase – KS – Cys – SH

(Unit-2) FA Synthase – ACP – SH – Malonyl – Acetyl CoA


H3C—C—S—CoA
Acetyl-CoA
ACP-CH
Acetyl Transferase
CoA-SH
H3C—C—S—ACP
HS-KSase
ACP-SH
H3C—C—S—KSase
-OOC—C(H)—C—S—CoA
Malonyl-CoA
ACP-CH
CoA-SH
-OOC—C(H)—C—S—ACP
CO2
H3C—C—C(H)—C—S—ACP
Acetoacyl-ACP


Acetoacyl-ACP
NADPH + H+
β-Ketoacyl-ACP Reductase
NADP
D-β-Hydroxybutyryl-ACP
β-Hydroxyacyl-ACP Dehydratase
H2O
Crotonyl-ACP
NADPH + H+
2,3-trans-Enoyl-ACP Reductase
NADP
Butyryl-ACP
(Fatty Acyl-CoA, Elongated by 2 Carbons)

(Unit-1) FA Synthase – KS – Cys – SH

(Unit-2) FA Synthase – ACP – SH – Butyryl CoA

(Unit-1) FA Synthase – KS – Cys – SH – Butyryl CoA

(Unit-2) FA Synthase – ACP – SH

(Unit-1) FA Synthase – KS – Cys – SH – Butyryl CoA

(Unit-2) FA Synthase – ACP – SH – Malonyl CoA

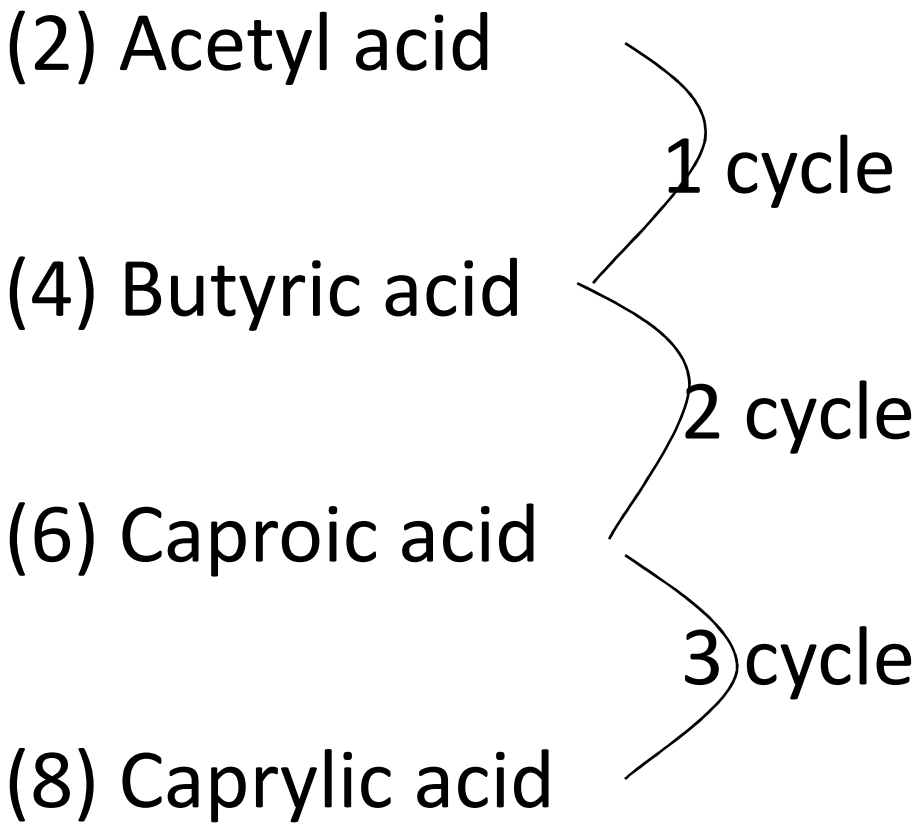
Condensing Enzyme (Ketoacyl Synthase)

(Unit-1) FA Synthase – KS – Cys – SH

(Unit-2) FA Synthase – ACP – SH – Malonyl-Butyryl CoA

Repeat Cycle

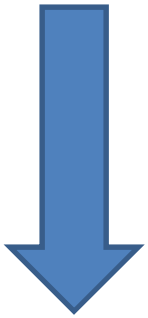
- For 1 cycle carbon chain length increase by 2 carbons



Termnation of Fatty Acid Synthasis

(Unit-1) FA Synthase – **KS – Cys – SH**

(Unit-2) FA Synthase – **ACP – SH –** Fatty Acyl CoA



Thioesterase

(Unit-1) FA Synthase – **KS – Cys – SH**

(Unit-2) FA Synthase – **ACP – SH**

+

Newly Synthesized Fatty Acid

Palmatic acid Synthesis:

It is a 16 carbon compound.

It requires 8 Acetyl CoA

Requires 7 cycles.

1 step acetyl CoA is added directly,

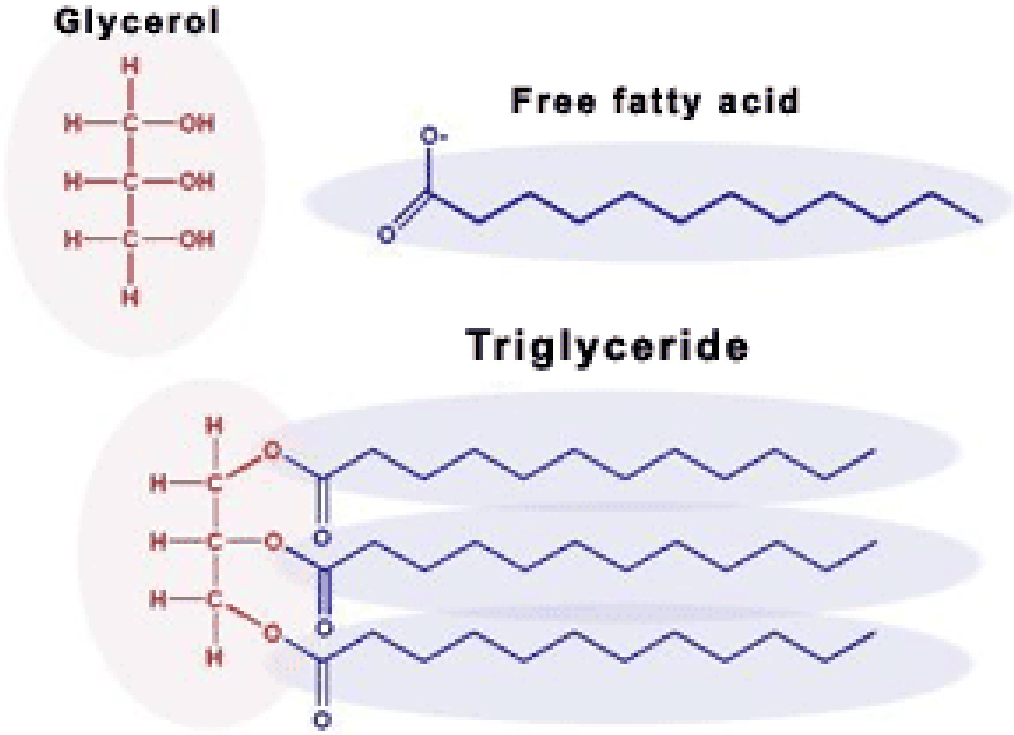
Than, in **Each cycle 2 Carbons** are added in the **form of Malonyl CoA**

8 Acetyl CoA + 7 ATP + 14 NADPH H^+ ⟶

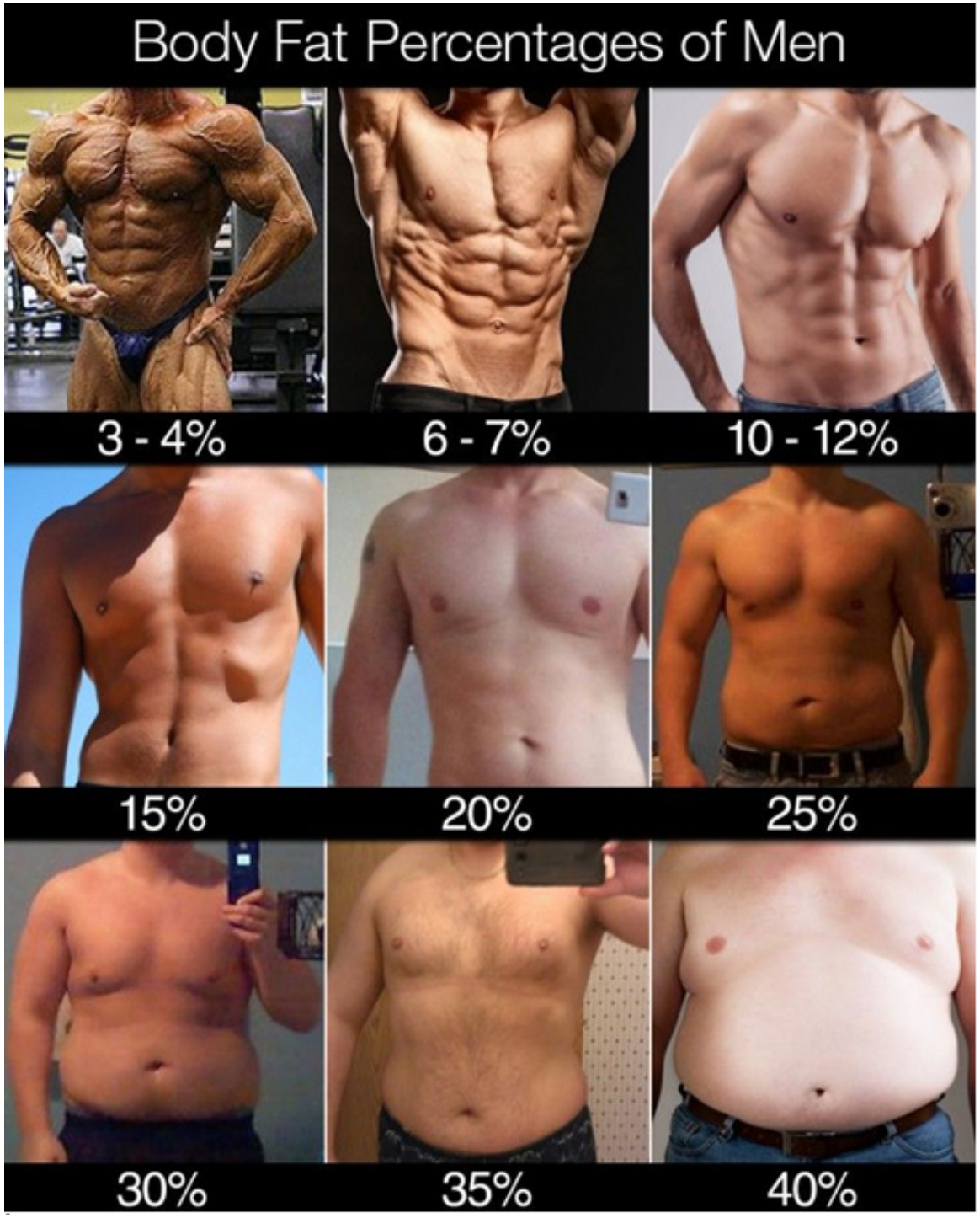
Palmitic acid + 8 CoA + 7 ADP + Pi + 7 H_2o

Triglyceride (TG) Synthesis

- Store form of Fat
- TG is store in adipose tissue



Body Fat Percentages of Men



Does TG have direct relation with obesity ?

Does TG have direct relation with obesity ?

- Increase Triglyceride in Blood
  - Increase circulating TG / Chylomicron
  - May remain high for few hours after food ingestion
  - Some metabolic disorder related to TG metabolism
  - **HIGH BLOOD TG DOES NOT MEAN , IT IS OBESITY**
- Obesity – More Body fat (adipose tissue) %
  - Increase storage form of fat (TG)
  - Circulating TG may be normal.
  - **OBESITY DOES NOT MEAN, THERE MUST BE HIGH BLOOD TG.**

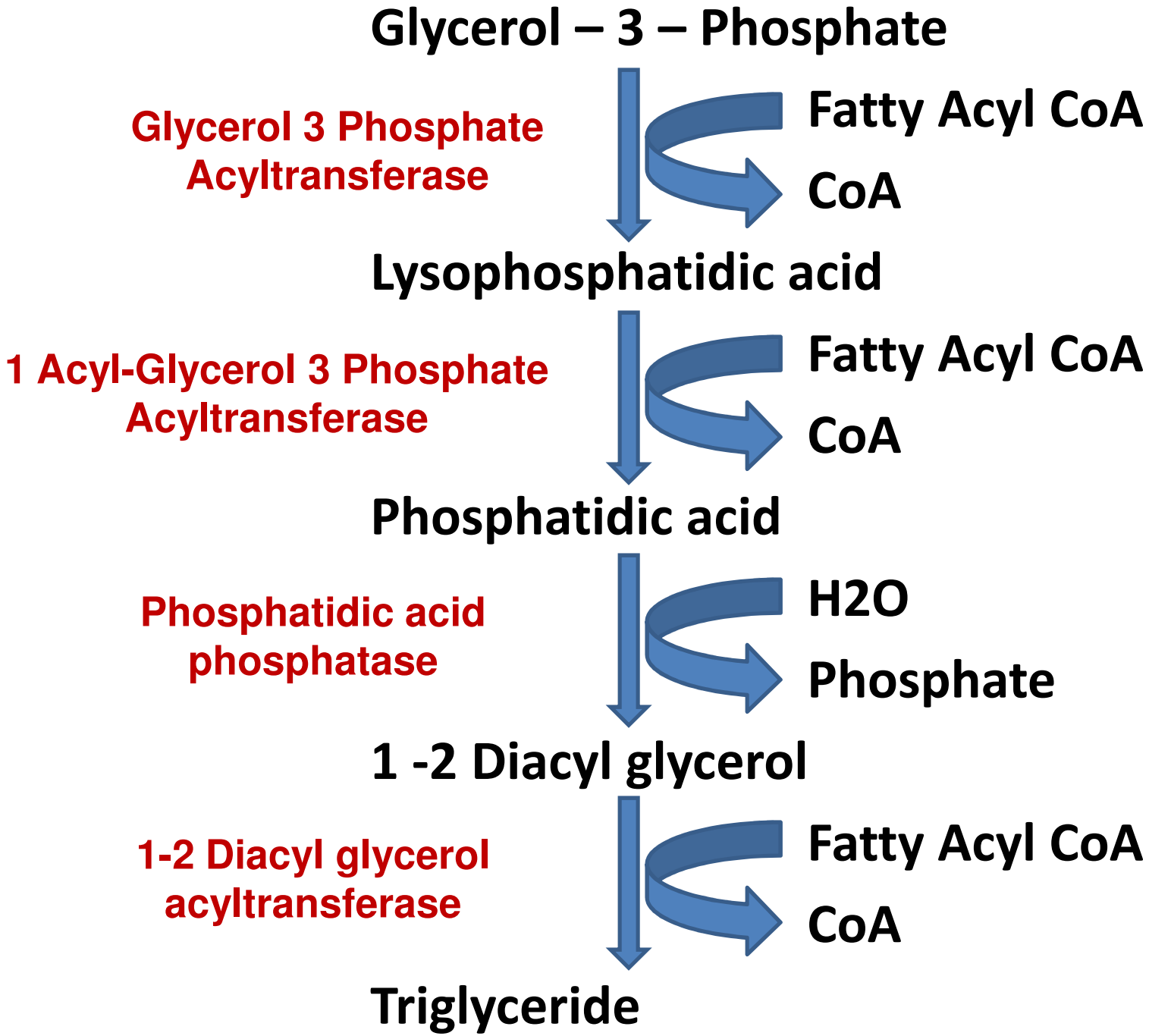
Triglyceride Synthesis

- **Precursor for Triglyceride synthesis**
  - **Glycerol – 3 – phosphate**
    - Derived from Glucose
  - **Dihydroxyacetone phosphate**
    - In liver & adipose tissue, from Glycolysis ,Dihydroxy Acetone Phosphate (DHAP) is provided
  - **Monoacylglycerol**
    - Most of our food has TG as fat
    - After digestion, major portion of TG is converted to monoacylglycerol

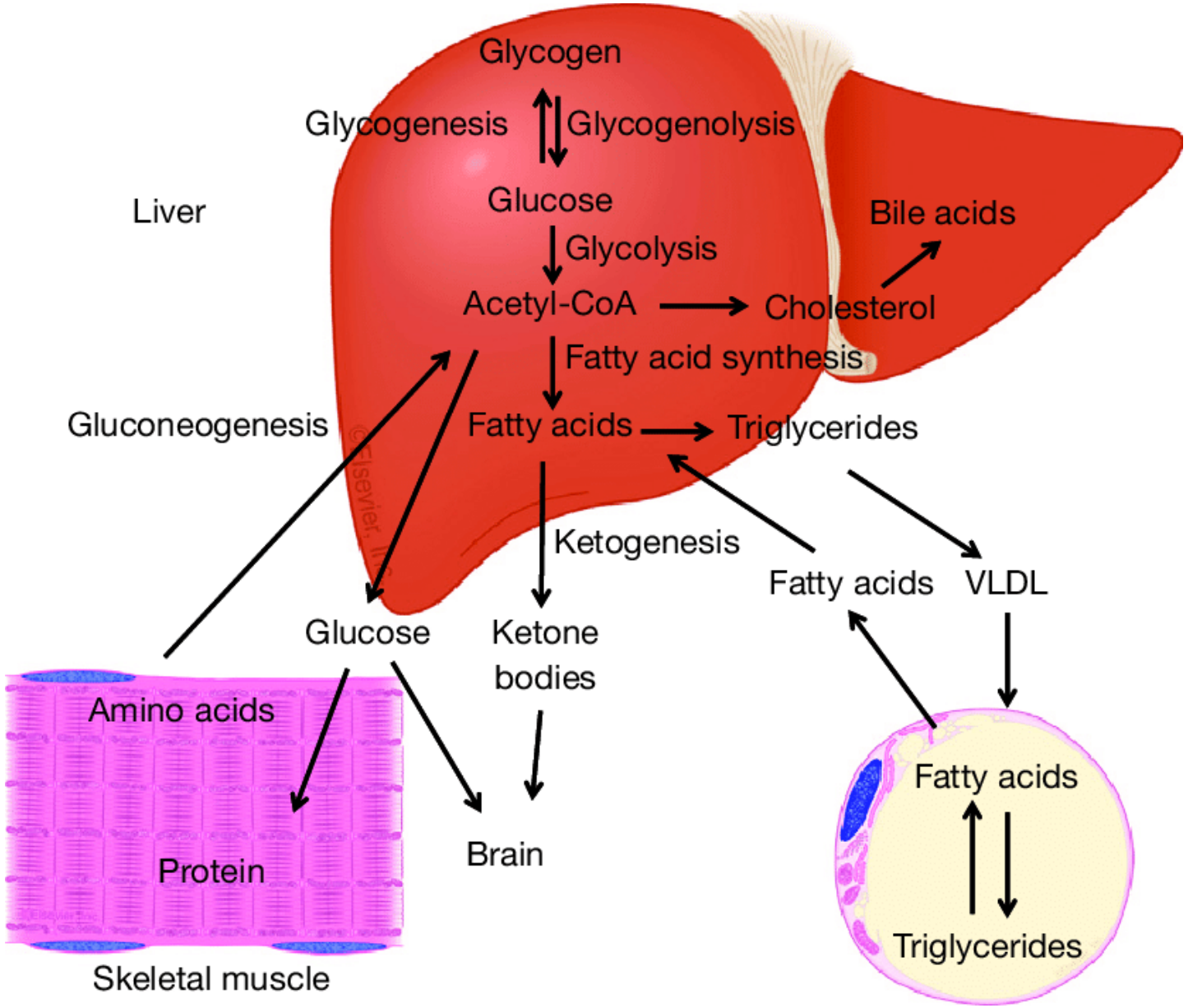
Triglyceride Synthesis

Synthesis of Glycerol – 3 – phosphate

- **Glycerol kinase**
  - **Absent in Adipose tissue**
    - **Major source DHAP from glucose**
  - **Active in Liver**


Glycerol – 3 – Phosphate
Glycerol 3 Phosphate Acyltransferase
Fatty Acyl CoA
CoA
Lysophosphatidic acid
1 Acyl-Glycerol 3 Phosphate Acyltransferase
Fatty Acyl CoA
CoA
Phosphatidic acid
Phosphatidic acid phosphatase
H2O
Phosphate
1 -2 Diacyl glycerol
1-2 Diacyl glycerol acyltransferase
Fatty Acyl CoA
CoA
Triglyceride

Effect of Well fed state & Fasting on TG synthesis



TG Synthesis in DM

- Type – 1 Diabetes Mellitus
  - Deficiency of insulin
  - Increase mobilization of TG from adipose tissue
  - Increase free fatty acid level
  - Insulin deficient , so triglyceride synthesis is also remain inhibited.

TG Synthesis in DM

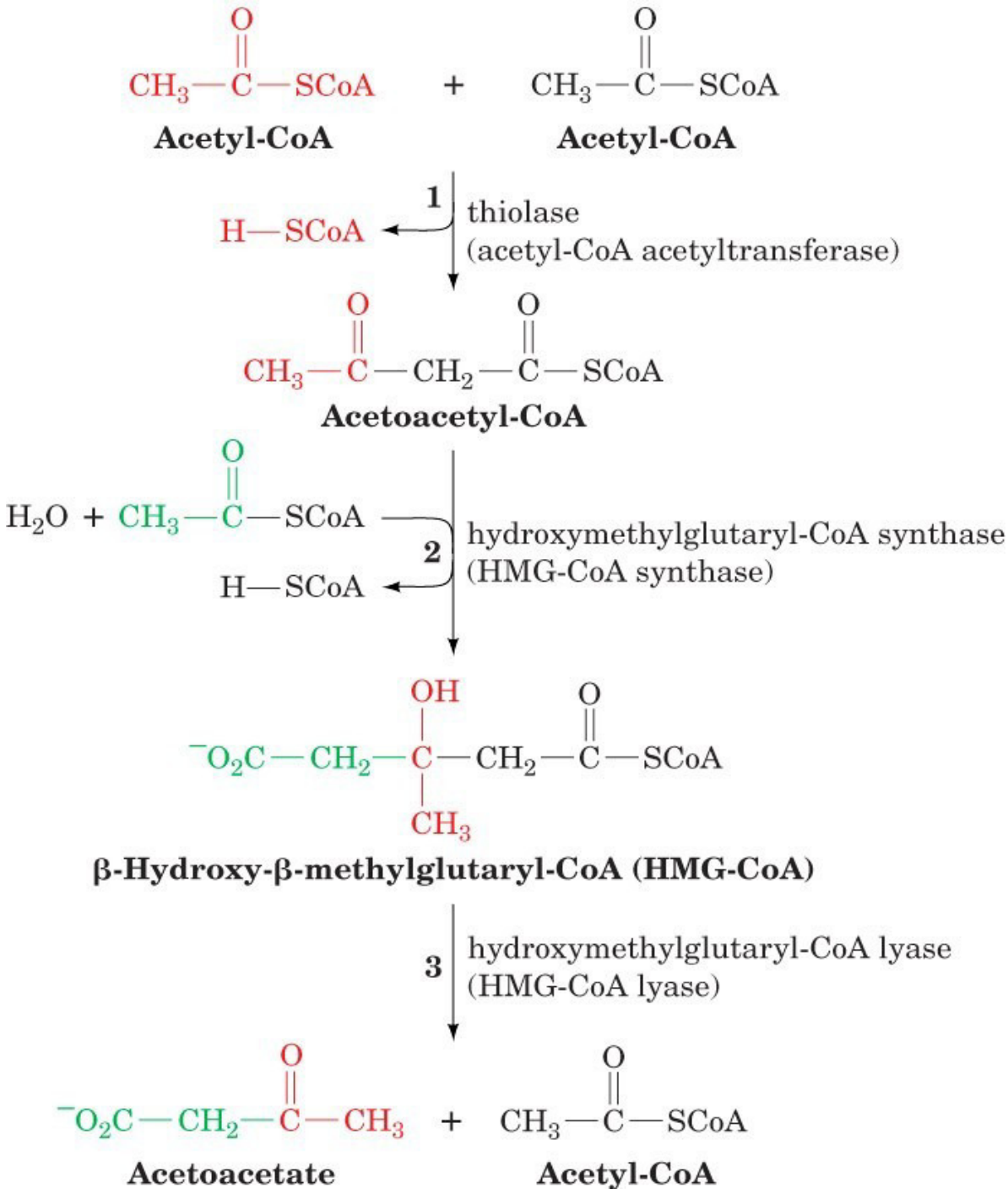
- Type – 2 Diabetes Mellitus
  - High level insulin & Insulin receptor resistance
  - Increase mobilization of TG from adipose tissue
  - Increase Free Fatty acid level – Reaches to Liver
  - Because of high Insulin and high free fatty acid ,
  - Increase Triglyceride synthesis & it’s level.
  - Hyper-triglyceridemia
  - Increase VLDL synthesis
  - Increase transport of TG to adipose tissue through VLDL
  - Increase obesity

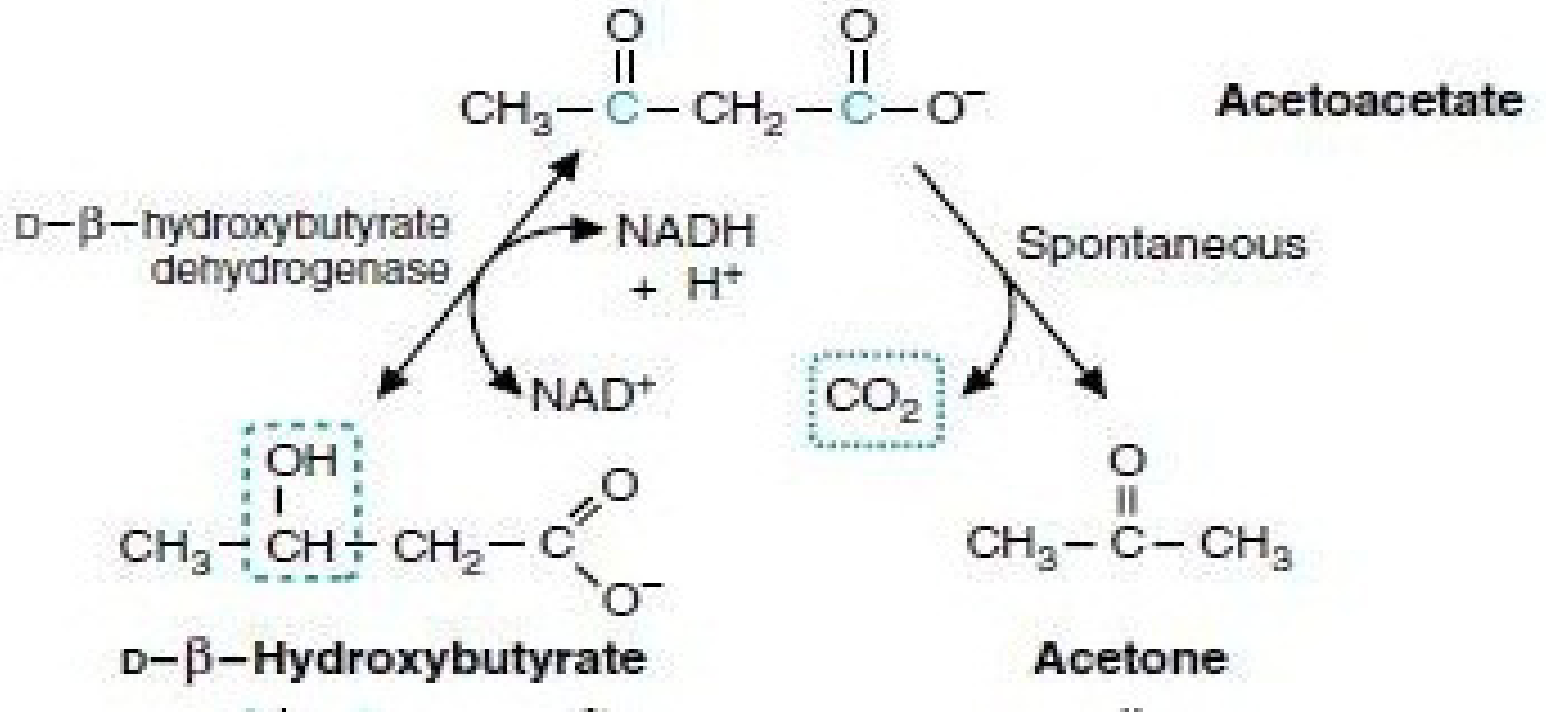
Ketone Body

- **Three Ketobodies**
  - Acetoacetate
  - Beta Hydroxybutyrate
  - Acetone
- Blood Level < 1 mg %
- It utilized by tissue through Ketolysis
  - Cardiac muscle & Renal Cortex **(prefer as fuel)**
  - Skeletal muscle & Brain **(as alternate source of energy)**

Ketone Body Synthesis

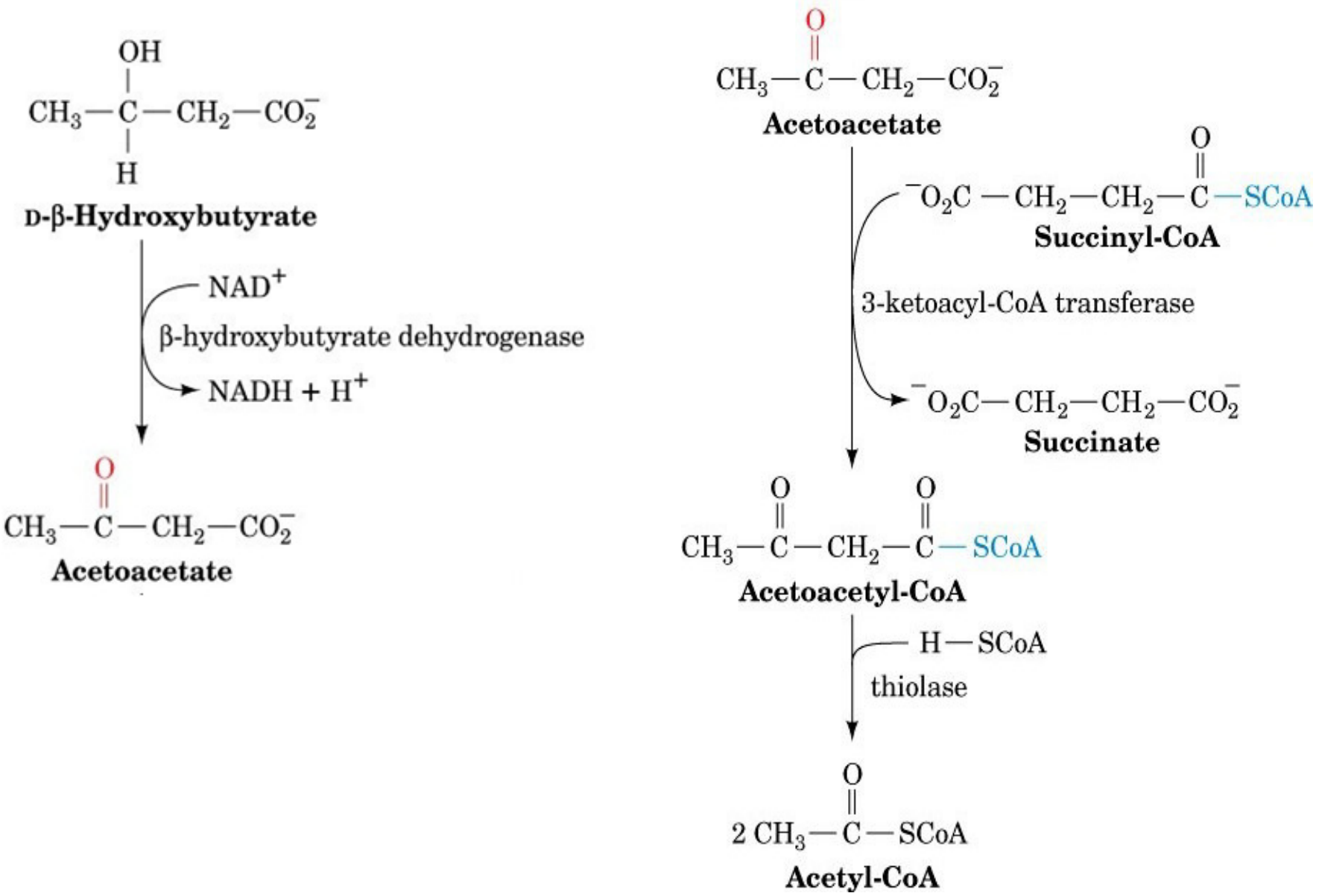
- Significant of Acetyl CoA
  - Enter into TCA Cycle and form Energy
  - Cholesterol synthesis
  - Fatty Acid synthesis
  - Ketone body synthesis
- **In Starvation and Diabetes mellitus, Acetyl CoA takes alternative pathway for ketone bodies synthesis.**
- Synthesized in **Liver Mitochondria**

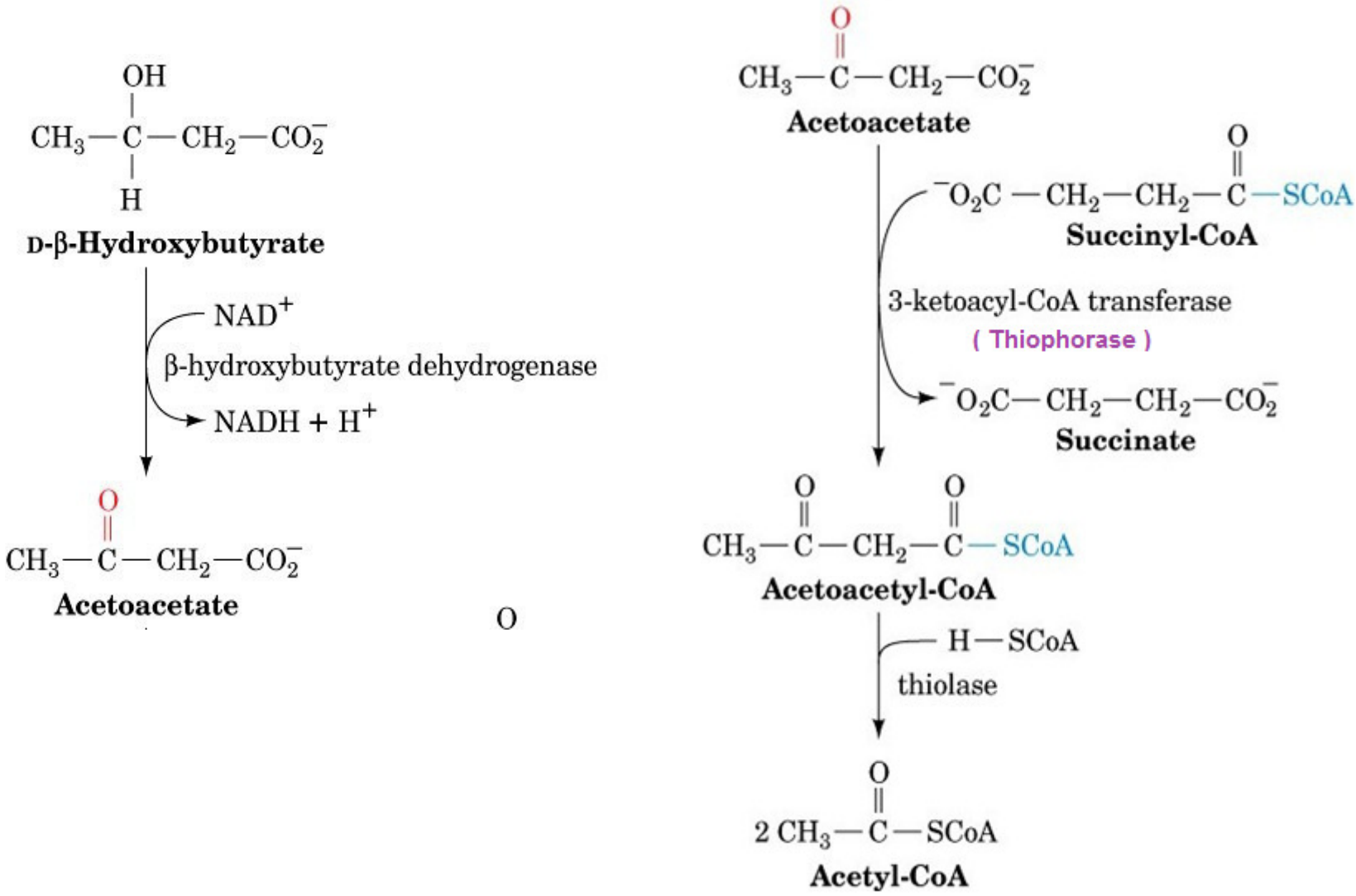

Acetyl-CoA
Acetyl-CoA
1
thiolase
(acetyl-CoA acetyltransferase)
H—SCoA
Acetoacetyl-CoA
2
hydroxymethylglutaryl-CoA synthase
(HMG-CoA synthase)
H—SCoA
β-Hydroxy-β-methylglutaryl-CoA (HMG-CoA)
3
hydroxymethylglutaryl-CoA lyase
(HMG-CoA lyase)
Acetoacetate
Acetyl-CoA



- Primary ketone body – Acetoacetate
- Secondary ketone body – Beta-hydroxybutyrate & Acetone

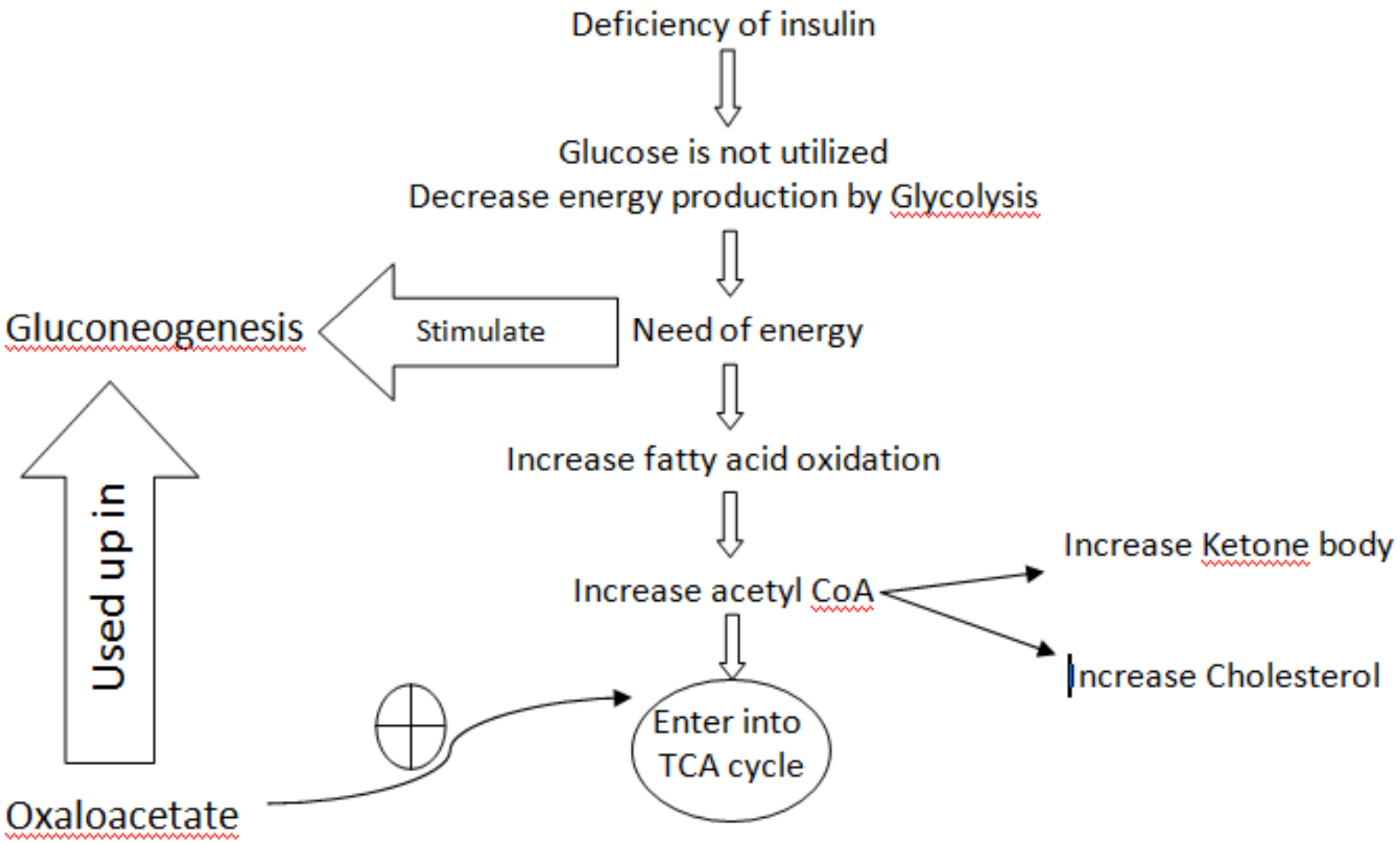
Ketolysis


D-β-Hydroxybutyrate
NAD+
β-hydroxybutyrate dehydrogenase
NADH + H+
Acetoacetate
Acetoacetate
Succinyl-CoA
3-ketoacyl-CoA transferase
Succinate
Acetoacetyl-CoA
H—SCoA
thiolase
Acetyl-CoA



- Liver lacks thiophorase (ketoacyl-CoA transferase)
- So Liver can not utilized ketone bodied.

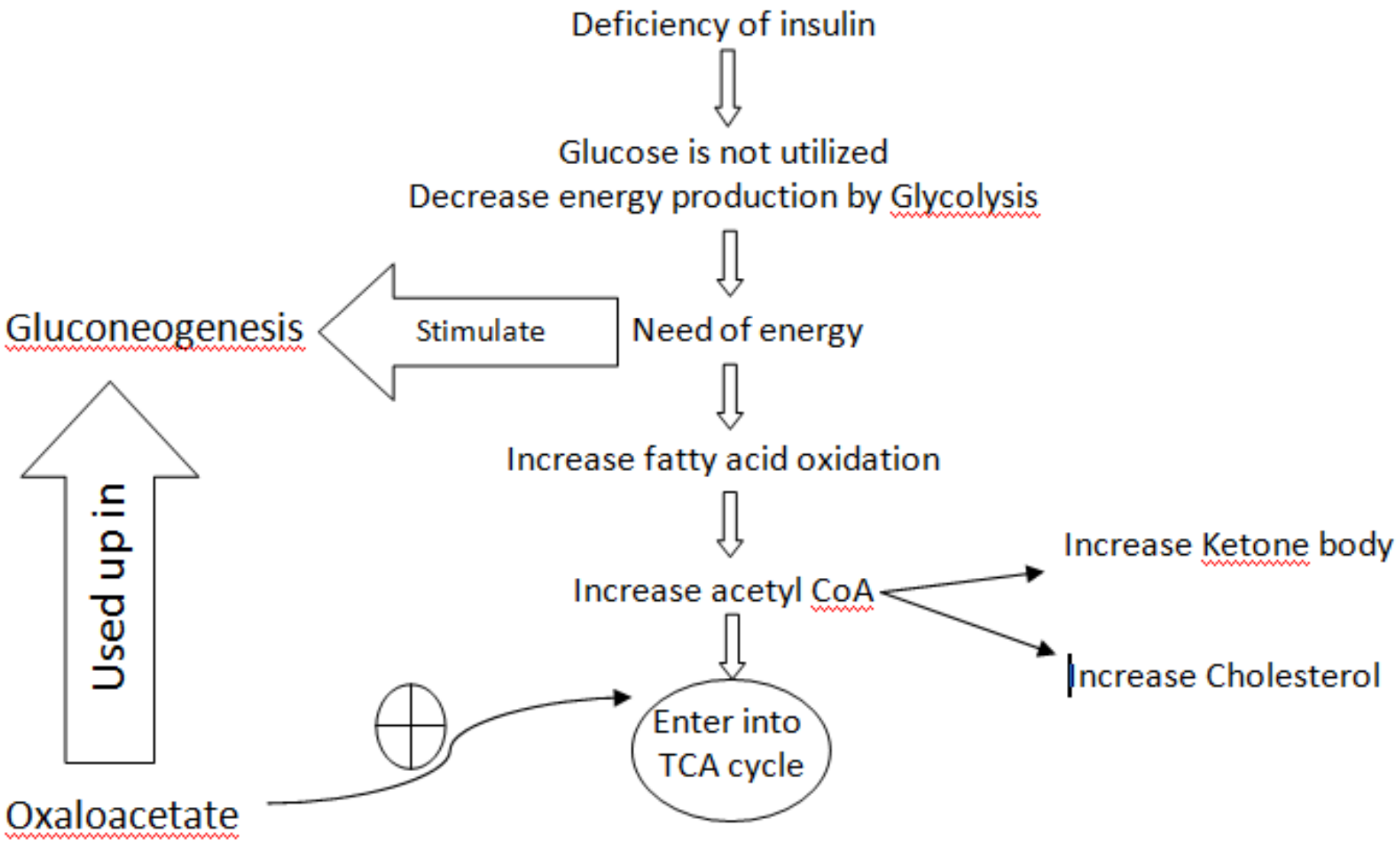
Patient of IDDM have more risk of diabetic ketocidosis than NIDDM.



Patient of IDDM have more risk of diabetic ketocidosis than NIDDM.

- **In type II diabetes mellitus**
  - High glucose level and High insulin level.
  - Decrease sensitivity of receptors
- **So, some amount of glucose can be utilized by cell. Which**
  - Prevent proteolysis – **less formation of Acetyl CoA.**
  - Prevent fatty acid oxidation - **less formation of Acetyl CoA.**
  - Less utilization of oxaloacetate by gluconeogenesis
  - **More Acetyl CoA utilized** into TCA cycle.
- **So less acetyl CoA will be available for ketone body synthesis**
- **So NIDDM have less risk of DKA than IDDM.**

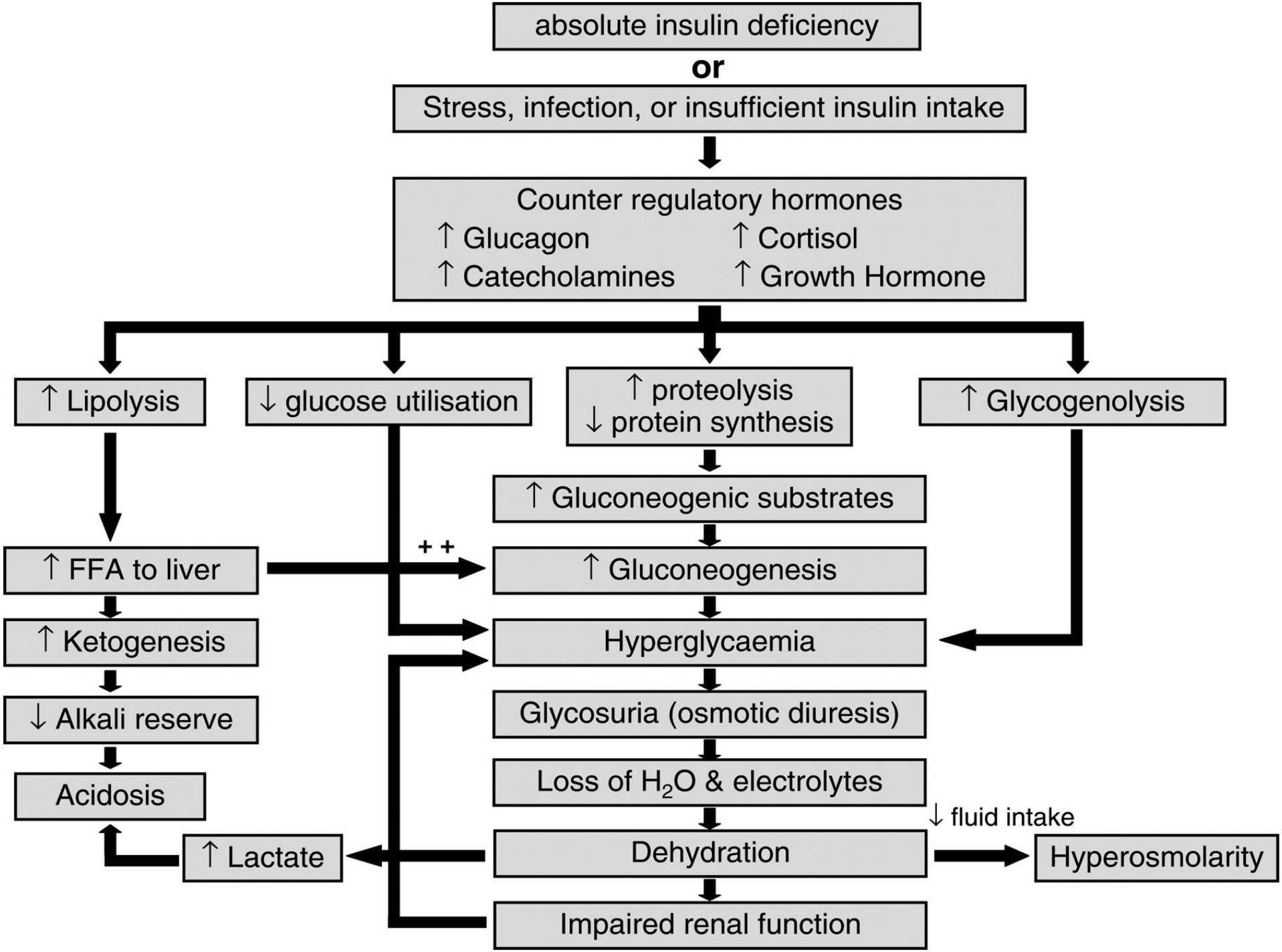
Uncontrolled diabetic mellitus patient has more risk of atherosclerosis.



Uncontrolled diabetic mellitus patient has more risk of atherosclerosis.

- **In Uncontrolled diabetes mellitus,**
  - Glucose can not utilized by Cell
  - More gluconeogenesis
  - More Proteolysis
  - More Fatty acid oxidation for energy production.
  - **So there will be more Acetyl CoA formation.**
- **Simultaneously, due to more to gluconeogenesis**
  - Less oxaloacetate available
  - **which decrease utilization of acetyl CoA into TCA cycle.**
- **That excess acetyl CoA make synthesis of**
  - More cholesterol & More ketone body formation
- **Increase risk of atherosclerosis in long term uncontrolled DM.**

Pathogenesis and consequences of Diabetes Ketoacidosis


absolute insulin deficiency
or
Stress, infection, or insufficient insulin intake
Counter regulatory hormones
↑ Glucagon
↑ Cortisol
↑ Catecholamines
↑ Growth Hormone
↑ Lipolysis
↓ glucose utilisation
↑ proteolysis
↓ protein synthesis
↑ Glycogenolysis
↑ Gluconeogenic substrates
↑ FFA to liver
+ +
↑ Gluconeogenesis
↑ Ketogenesis
Hyperglycaemia
↓ Alkali reserve
Glycosuria (osmotic diuresis)
Acidosis
Loss of H_2O & electrolytes
↓ fluid intake
↑ Lactate
Dehydration
Hyperosmolarity
Impaired renal function


THANK
YOU!