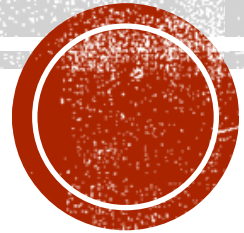
# Adipose tissue metabolism
# I. Lipogenesis & FA Synthesis



# LIPOGENESIS

1. **Definition**
2. **Site**
3. **Process**
   - A. Synthesis of glycerol 3 phosphate (active glycerol).
   - B. Synthesis & activation of long chain fatty acids (active FAs).
   - C. Synthesis of the triacylglycerol

# Lipogenesis

## Definition of lipogenesis:

It is the biosynthesis of triacylglycerols (TGs) principally from excess glucose to be stored after a carbohydrate rich meal.

## Site

Cytoplasm of most tissues especially:

- Adipose tissue,
- Liver,
- lactating mammary gland
- Brain.

# Lipogenesis

## Processes for lipogenesis:

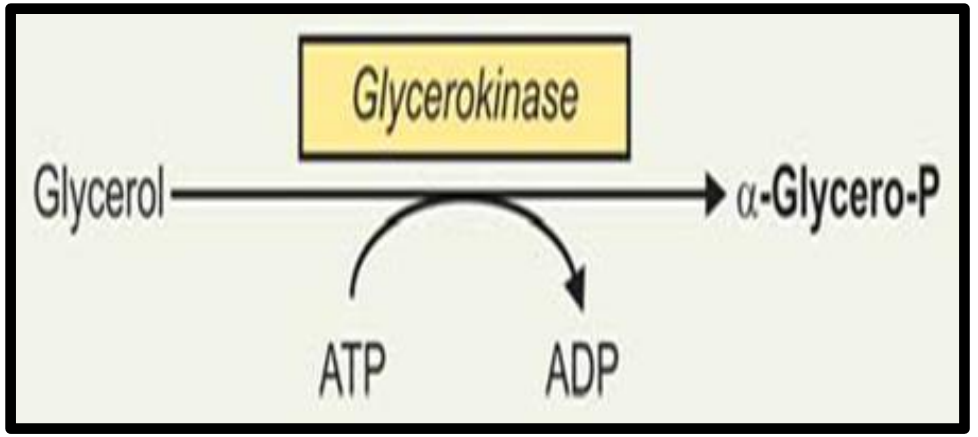
- **Lipogenesis can be divided into 3 processes:**
  - **A. Synthesis of glycerol 3 phosphate (active glycerol).**
  - **B. Synthesis & activation of long chain fatty acids (active FAs).**
  - **C. Synthesis of the triacylglycerol (esterification of both active glycerol & active FA).**

# A. Synthesis of Glycerol-3-P

# Synthesis of Glycerol-3-P (active glycerol)

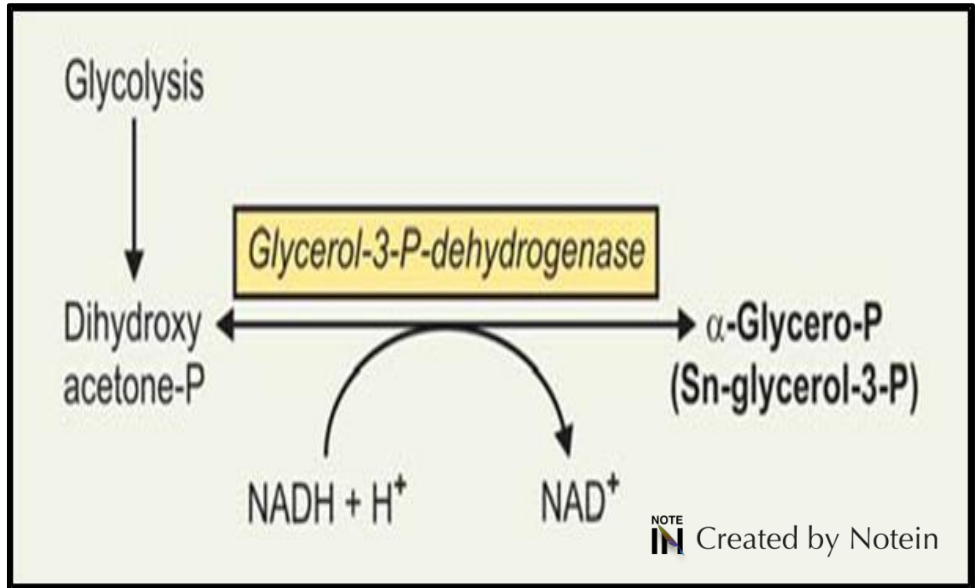
## A) In tissues (except adipose tissue)

- Glycerol is activated by **glycerokinase** to glycerol-3-P (active glycerol)
- **Need ATP**




## A) In Adipose tissue

- **No glycerokinase** is present in adipose tissue.
- Instead, glucose→ glycolysis→ **DHAP**(di-hydroxy-acetone-phosphate) Which gives glycerol 3 P by **dehydrogenase** enzyme



# B. Synthesis of fatty acids

## Cytoplasmic (Extramitochondrial) FA synthesis Pathway

- Definition, site & building block
- Sources of acetyl CoA
- Translocation of acetyl CoA to cytoplasm
- Enzyme of extramitochondrial Pathway
- Steps of extramitochondrial Pathway
- Fate of palmitate

# Cytoplasmic (Extramitochondrial) De novo Synthesis of long chain FA synthesis

- **Definition**: It is the only system responsible for de novo synthesis of long chain FA from active acetate (acetyl CoA).
- **Site**: cytoplasm of many tissues especially adipose tissue , liver, brain, lactating mammary gland.
- **Building block for FA synthesis**: Acetyl CoA
- **Product of FA synthesis**: long chain FA **Palmitic acid** (16 carbons)

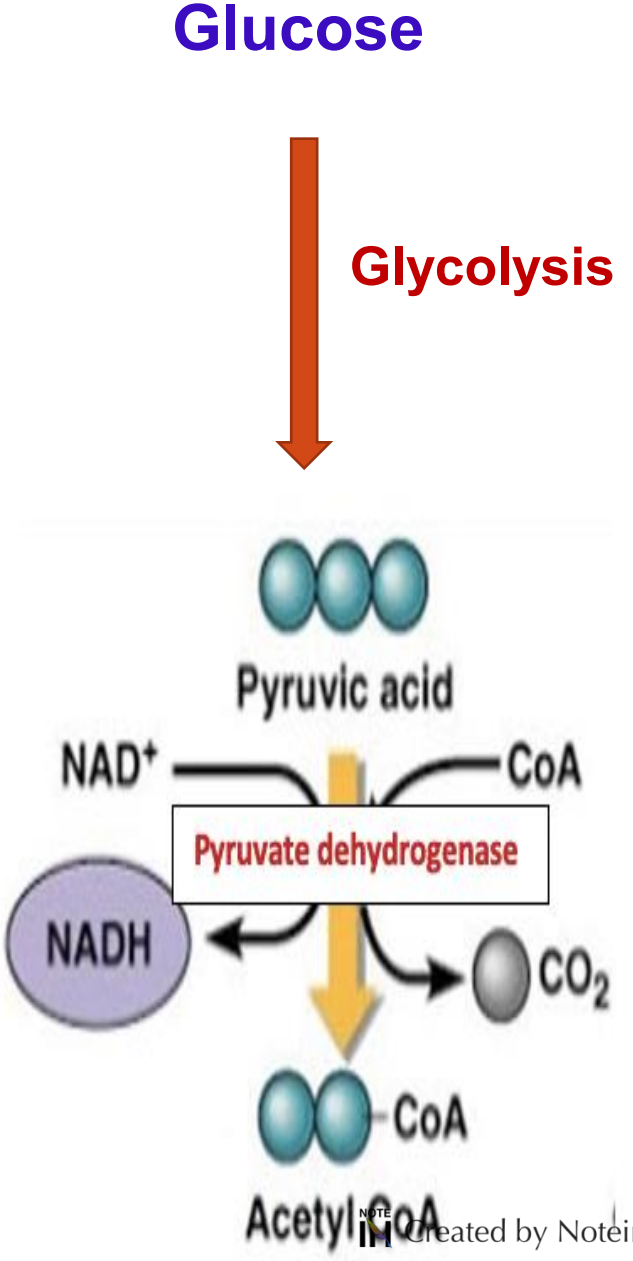
# ❖ Steps

## 1.Source of acetyl-CoA for FA synthesis:

- ***Mainly from Glucose*** ( **carbohydrates**):
(glucose→ glycolysis→ pyruvate→ oxidative decarboxylation by **pyruvate dehydrogenase** enzyme in the **mitochondria**→ acetyl CoA)

- ***To less extent from ketogenic amino*** acids ( **proteins**).

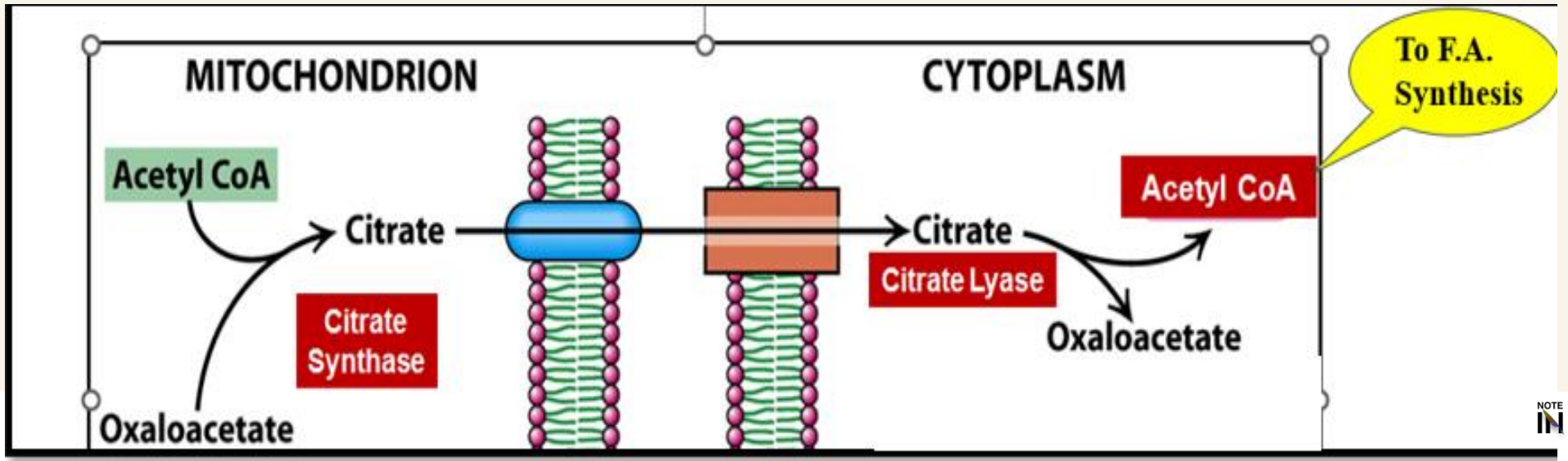
- ***Never*** **from fats**)



# 2. Translocation of Acetyl-CoA from mitochondria to cytoplasm

# (Citrate shuttle)

- Acetyl-CoA, formed within mitochondria, does not penetrate the mitochondrial membrane to cytoplasm.1st it must condense with oxaloacetate to form citrate, which can pass out mitochondrial membrane **(Citrate shuttle).**
- In cytoplasm citrate splits again by **citrate lyase** enzyme into
  - **a) Acetyl-CoA and**
  - **b) oxaloacetate.**



# 3. Enzymes of cytoplasmic Fatty acid synthesis:

## 2 Enzymes are needed for this process:

### 1-Acetyl CoA carboxylase

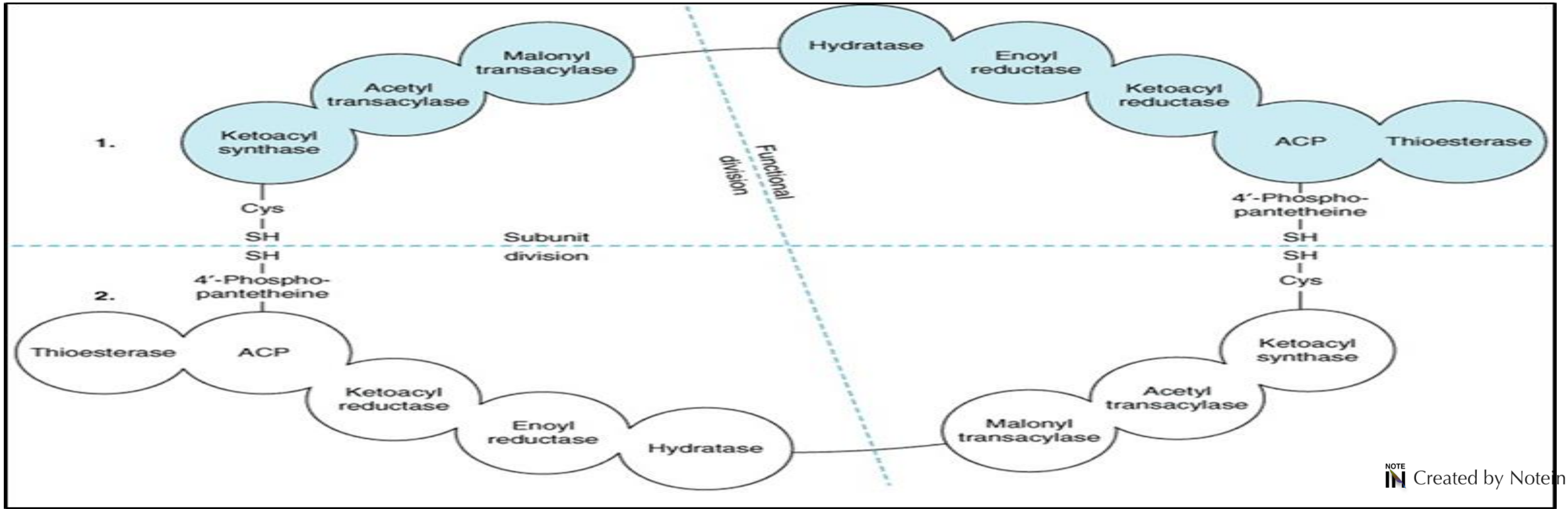
- **(The key regulatory enzyme for Lipogenesis)**
- This enzyme is responsible of synthesis of **malonyl Co A from** the acetyl CoA

### 2- The fatty acid synthase complex

- It is a multi-enzyme complex, formed of **2 subunits** ( dimers)
- Each subunit contains all **7 enzymes** of FA synthase & **2 SH groups**
- This enzyme is responsible of adding **malonyl Co A** to the acetyl CoA in **7 cycles** to form the **palmitic acid** (16 Carbons FA).

# 2- The fatty acid synthase complex

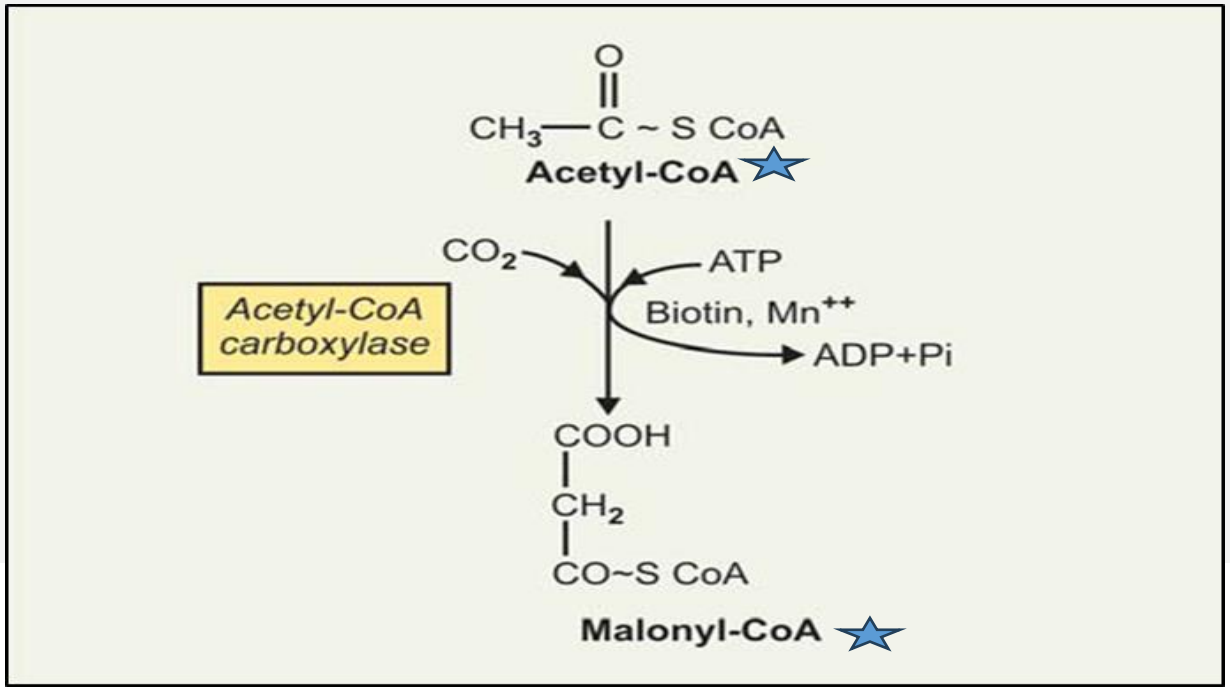
- **2 subunits** ( dimers), **lie in head to tail configuration.**
- Each subunit contains all **7 enzymes** of FA synthase & **2 SH groups**



# 4. Steps of Extra-mitochondrial synthesis of palmitic acid (16 carbon FA)

## 1. Synthesis of malonyl CoA (3C):

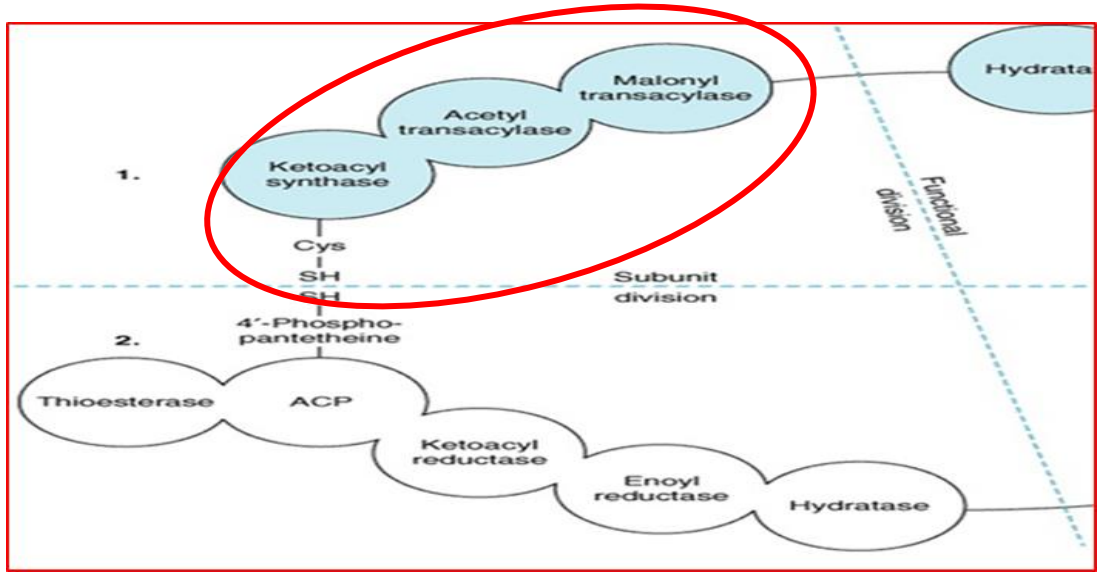
- It is synthesized from acetyl CoA by **acetyl CoA carboxylase**
- In presence of **ATP, biotin and bicarbonate** as a source of CO2.

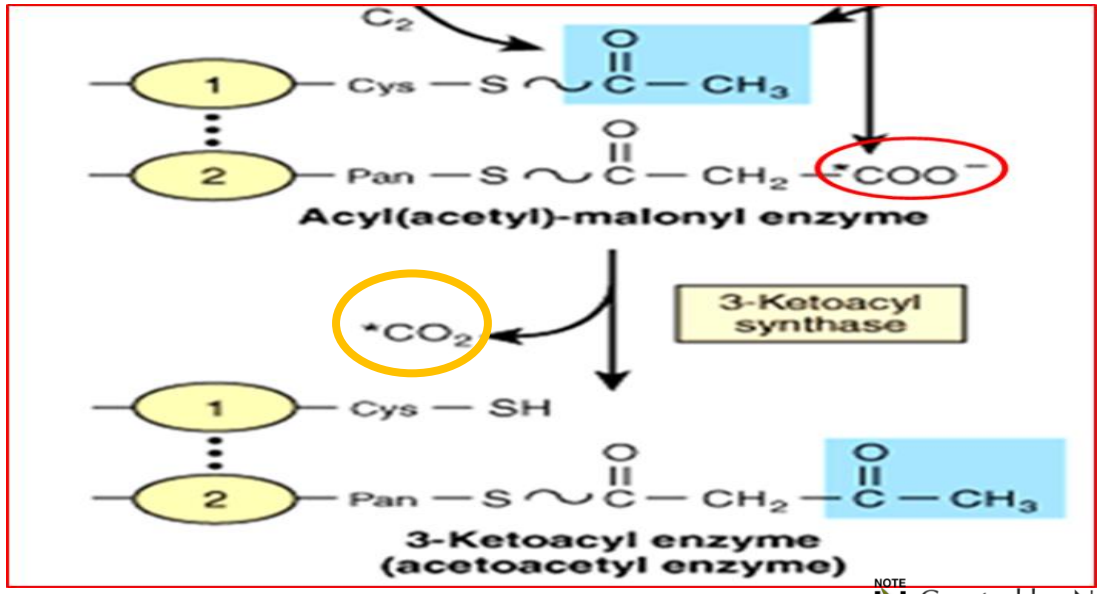


# 2. Synthesis of palmitate by the fatty acid synthase complex:

**The first 3 steps involves 3 enzyme actions:**

- 1st step is addition of an **acetyl CoA** to SH group at position 1
- 2nd step is addition of a **malonyl CoA** to SH group at position 2
- 3rd step is **condensation** of the acetyl CoA in position 1 with the malonyl CoA in position 2 with the release of one CO2.

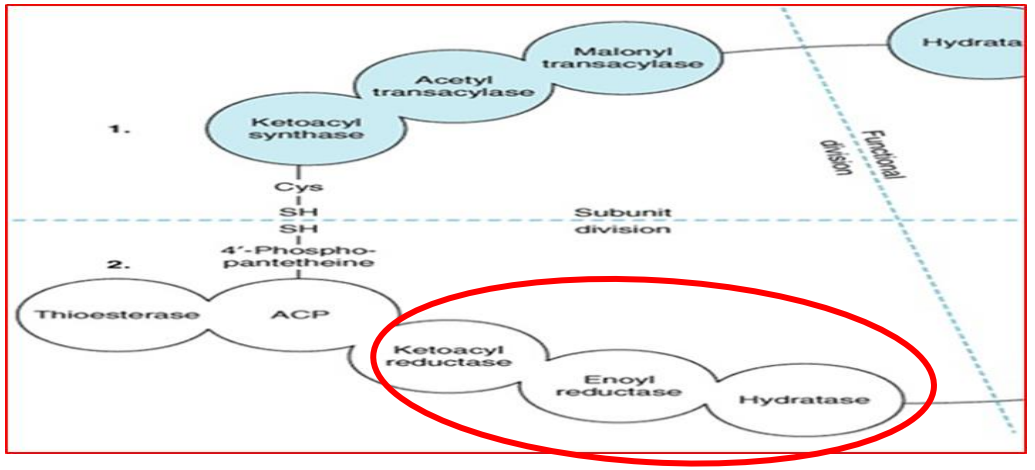


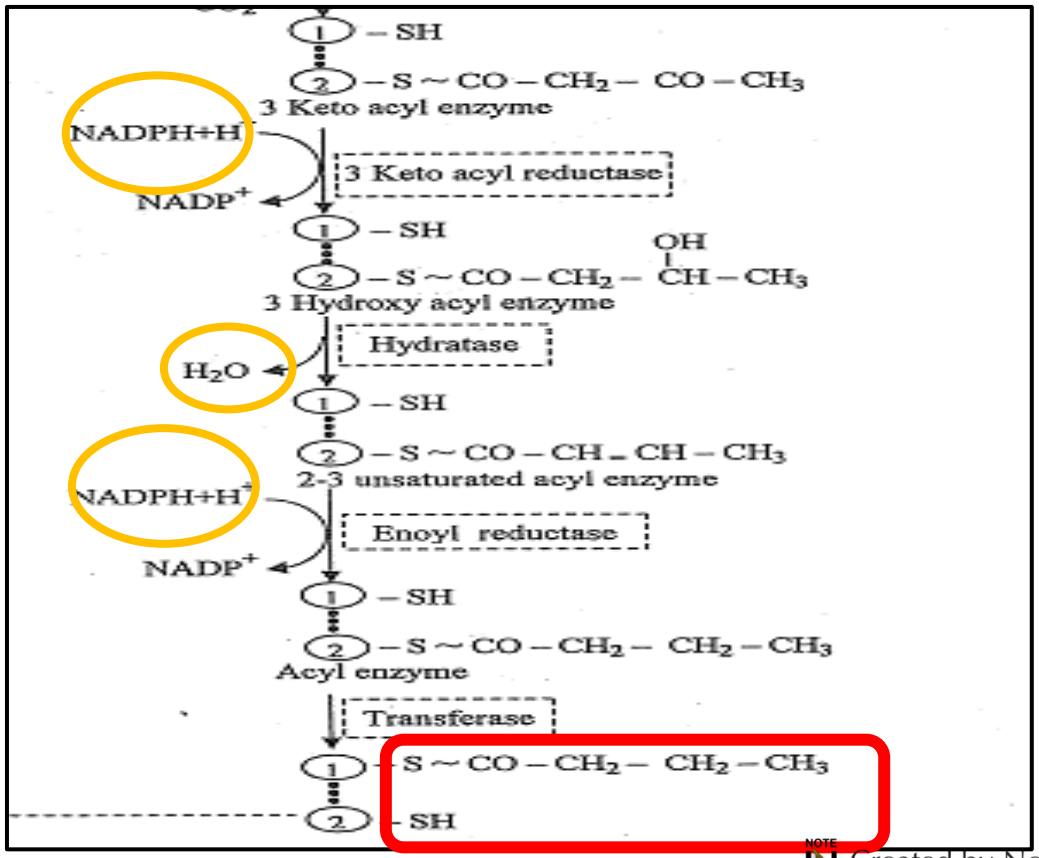



- **A next 4 steps process involves 3 enzyme actions:**

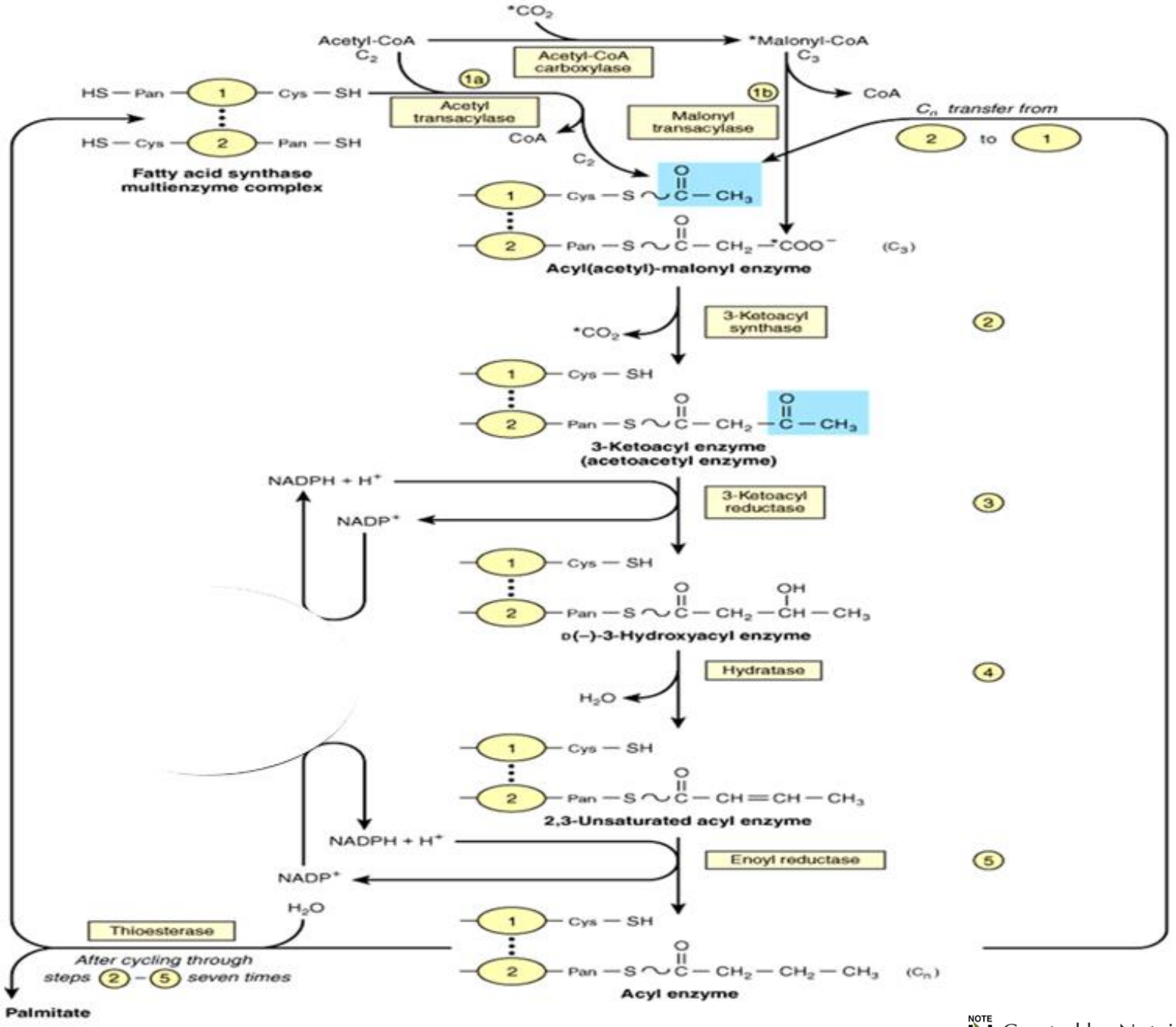
1. **Reduction** in the presence of NADPH+.
2. **Dehydration** by release of one H2O.
3. **Reduction** in the presence of NADPH+.
4. Transfer from position 2 to 1.

- **Now position 2 is free to accept a new malonyl CoA.**



- **The process is repeated 6 more times.**
- **At the end** of FA synthesis , **thioesterase** hydrolyzes the thioester bond to release palmitate from the enzyme complex.



# ❖The overall reaction for palmitic acid synthesis:

**7 molecules of malonyl CoA** is added to **1 molecule of acetyl CoA** in 7 cycles by FA synthase enzyme complex to form **palmitic acid**

1 Acetyl CoA+ 7 Malonyl CoA+ 14 NADPH + 7ATP

**FA synthase complex**

1 Palmitate(16C)+ 8 CoA+ 14 NADP+ 7(ADP+Pi)+ 7 CO2+ 7 H2O

## 5. Main product of FA synthesis : free Palmitic acid (16 C)

### ❖ Fates of palmitic acid

**Free palmitic acid must be activated to palmitoyl CoA (by thiokinase= acyl CoA synthetase) to be used for:**

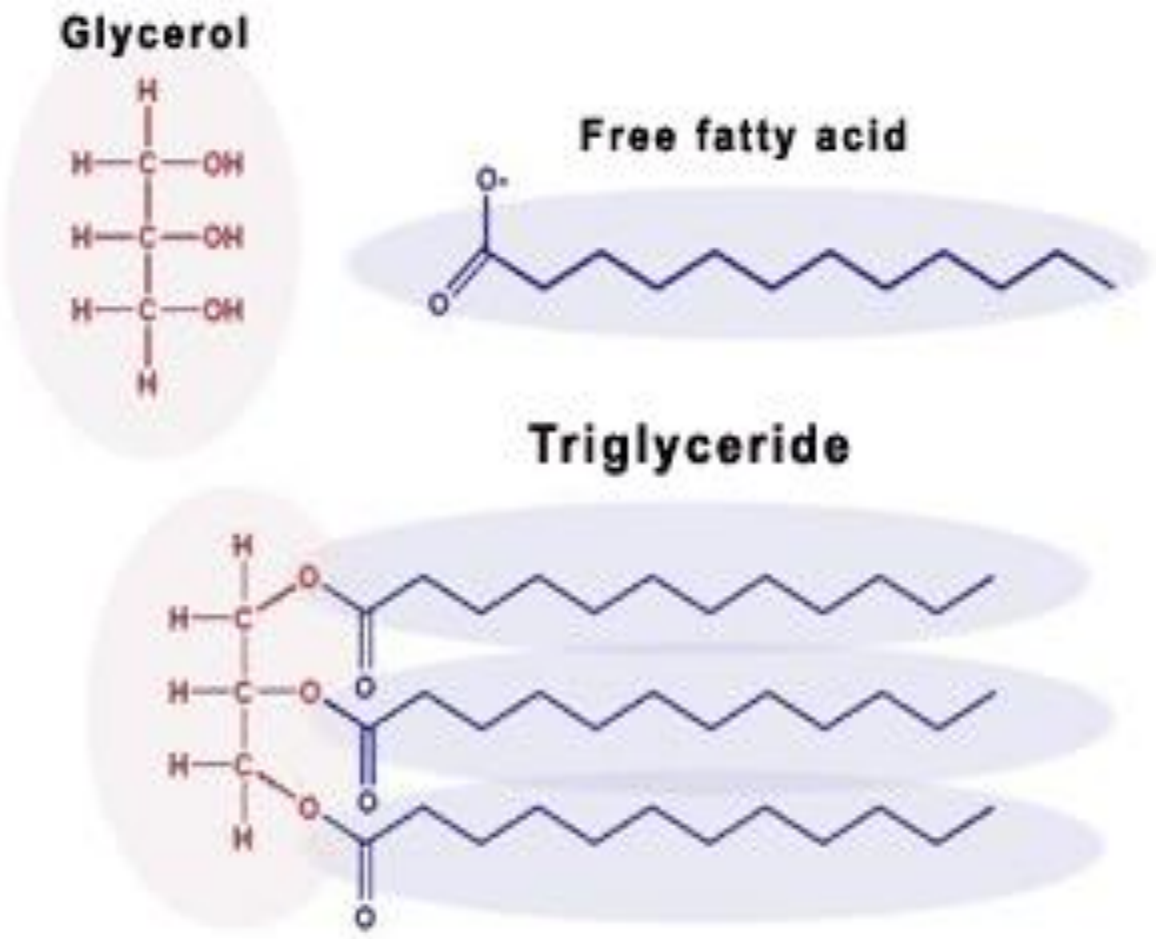
1. **Esterification** with glycerol (to form TG)**** or with cholesterol (to form cholesterol esters).
2. **Chain elongation**: For synthesis of longer chain F.A.
3. **Desaturation:** Synthesis of unsaturated FA.
4. **Sphingosine formation**: palmitoyl CoA + Serine

# C. Synthesis of Triglycerides (esterification of active glycerol and active FA)

1- Synthesis of glycerol-3-phsophate

2- Synthesis of fatty acyl CoA

# 3- Synthesis of TG

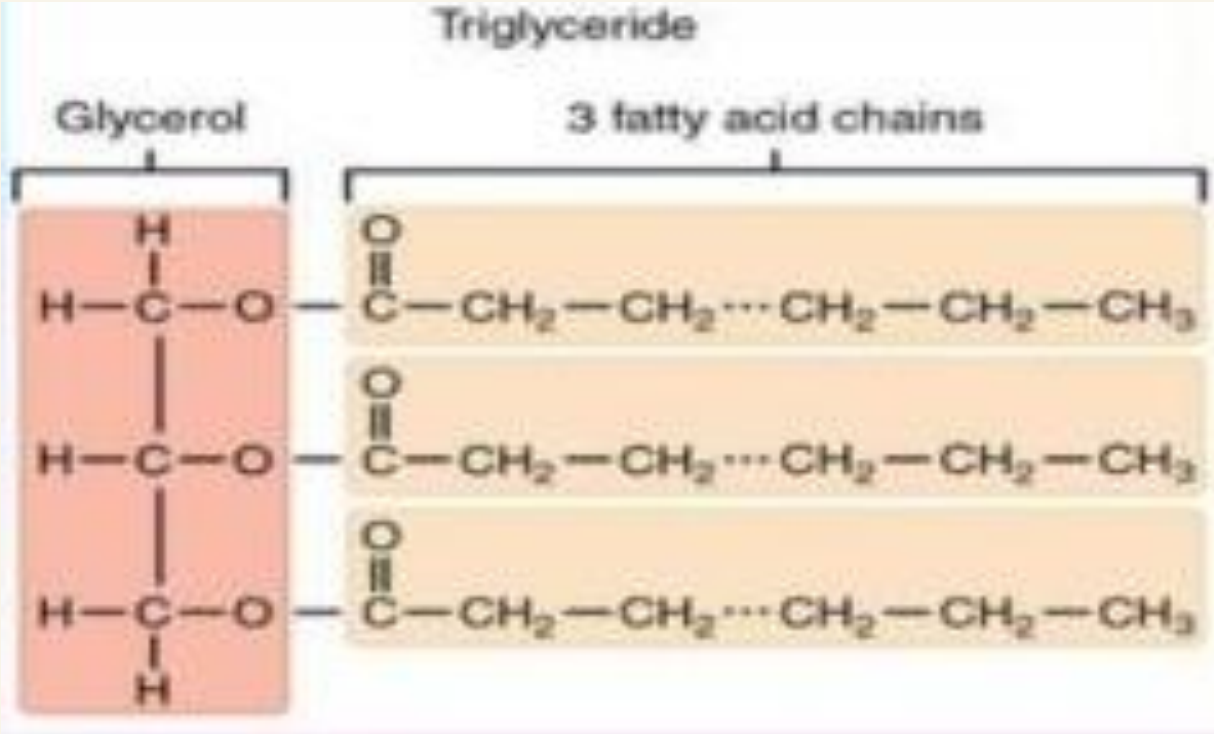


# Synthesis of Triglycerides

- The active FA then esterified to active glycerol forming triacylglycerol (TAG)

- TAG is formed of:
  - 1 glycerol
  - 3 FAs

  Attached by **ester bonds**




- TGs then stored **Mainly in adipocyte** to be ready for mobilization (utilization) if the body needs energy

# REGULATION OF ADIPOSE TISSUE METABOLISM

# 6. Regulation of adipose tissue metabolism

**Dietary, metabolic and hormonal factors regulate adipose tissue metabolism :**

## 1- Dietary factor:

- Excess glucose (↑ carbohydrate meal)→ ↑↑ **lipogenesis**
- Fasting→ ↑↑ **lipolysis**

## 2- Metabolic factor

- Uncontrolled Diabetes mellitus→↑↑ **lipolysis**

# 3- Hormonal factor regulation

## I. Rate limiting enzyme

- Rate limiting enzyme of **lipogenesis** is **Acetyl-CoA carboxylase** which present in 2 forms
  - **Active form**: Dephosphorylated
  - **Inactive form** Phosphorylated

- Rate limiting enzyme of **lipolysis** is **Hormone sensitive lipase** which present in 2 forms
  - **Active form**: Phosphorylated
  - **Inactive form:** Dephosphorylated

# 3- Hormonal factor regulation

## II. During fed state

❖ ↑ Blood glucose→ release of **insulin**→ **dephosphorylation** of the enzymes:

- **Dephosphorylate HSL**→ inactivate it→ ↓↓ **lipolysis**
- **Dephosphorylate acetyl CoA carboxylase**→ ↑↑ **lipogenesis**

## III. During fasting

❖ ↓ Blood glucose→ release of **anti-insulin hormones (glucagon & adrenalin)**→ **activate adenyl cyclase** enzyme→ **Phosphorylation** of the enzymes:

- **Phosphorylate HSL**→ activate it→ ↑↑ **lipolysis**
- **Phosphorylate acetyl CoA carboxylase**→ ↓↓ **lipogenesis**

# QUESTION 1

- **Which of the following cofactors or their derivatives must be present for the conversion of acetyl CoA to malonyl CoA in extra-mitochondrial fatty acid synthesis?**

(A) Biotin

(B) FAD

(C) FMN

(D) ACP

(E) $NAD^+$

# QUESTION 3

**Fatty acid synthase enzyme complex involves which of these vitamins:**

a) Vit B1

b) Vit B3

c) Vit B5

d) Vit B10

e) Vit B12

# QUESTION 2

**Acetyl CoA required for extra mitochondrial fatty acid synthesis is produced mainly by:**

(A) Pyruvate dehydrogenase complex

(B) Pyruvate carboxylase

(C) Citrate lyase

(D) Thiolase

(E) Carnitine-acyl transferase

# References