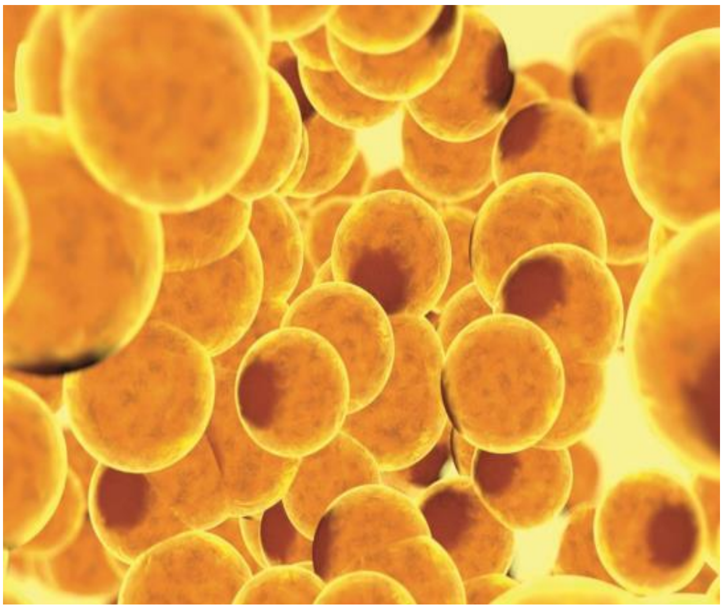
Lipolysis

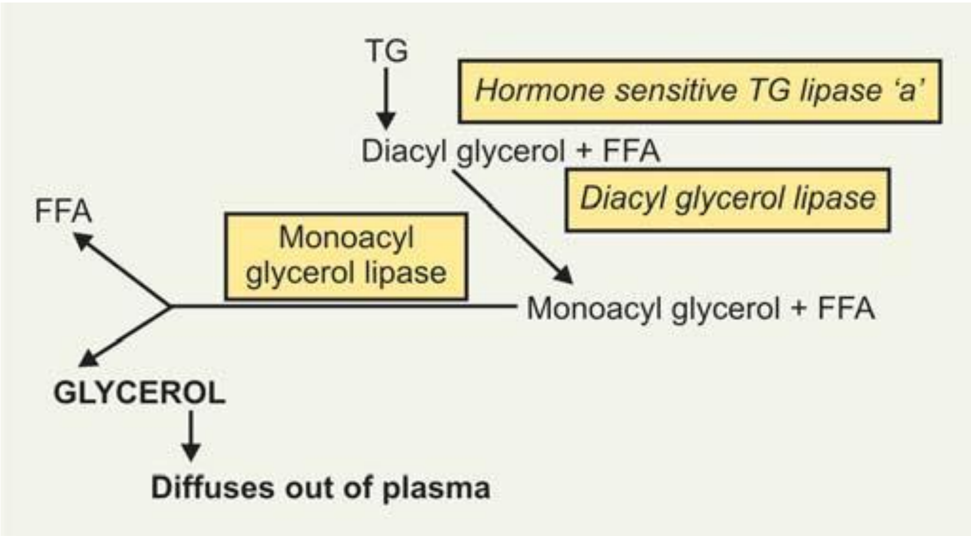
Adipose tissue metabolism

Forms of lipid:	• ***The lipids in the body physiologically exist in two forms:*** 1- ***Element constant or structural lipids*** *(as cytoplasm and cell membranes).* 2- ***Element variable or stored lipids*** *(serves as a storage site for excess calories ingested mainly in the form of triglyceraides TG).*
Dynamic state of adipose tissue:	• *Adipose tissue is* ***not just*** *a static lump of fats; it* ***is in dynamic state****; breakdown of fats and synthesis take place all the time.* • *TG stores are* ***continually undergoing*** *esterification (synthesis) and lipolysis (breakdown).* • *These two processes* ***determine*** *the level of free fatty acid (FFA) pool in adipose tissue and this, in turn, will determine the level of FFA circulating in the blood.*



Lipolysis

Def:	• *Breakdown of **TG** in adipose tissue by a hormone-sensitive TG lipase enzyme.*
Adipolytic lipases are three:	***1) Hormone sensitive triacylglycerol lipase** (Key regulating enzyme).* ***2) Two others are not hormone-sensitive:*** ➢ *Diacyl glycerol lipase* ➢ *Monoacyl glycerol lipase.*



- ***Hormone sensitive triacylglycerol lipase:***

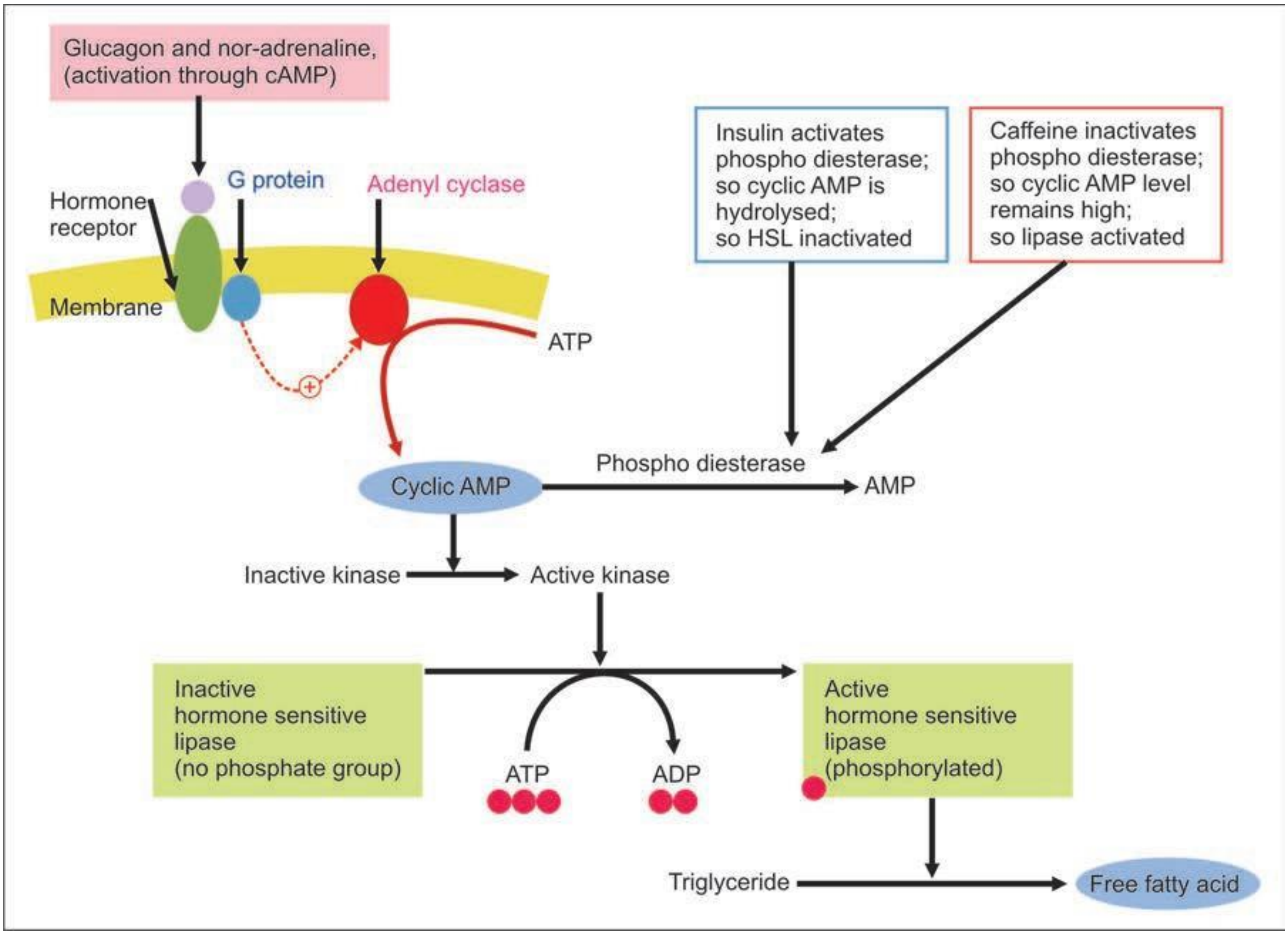
➢ ***The hormone-sensitive triacylglycerol lipase may exist in one of two forms:***

*a) An inactive (dephosphorylated) form by **phosphatase***

*b) An active (phosphorylated) form by **cAMP dependent protein kinase.***

➢ ***cAMP is:***

- *Formed from **ATP** by adenyl cyclase enzyme*
- *Degraded by **phosphodiestrase enzyme.***



▪ Fate of lipolysis products:

1. Glycerol:	• *Adipose tissue and muscles lacks* ***Glycerol kinase enzyme****, so the glycerol passes into the blood.* • *It is taken by liver, kidney and other tissues which have* ***Glycerol kinase enzyme*** *in significant amounts.*
2. Free fatty acid (FFA):	• *FFA can be reconverted in adipose tissue to* ***acyl-CoA*** *by acyl-CoA synthetase and re-esterified to form* ***TG.*** • *However, when the rate of re-esterification is* ***not sufficient*** *to match the rate of lipolysis, FFA diffuse into the plasma, where they bind to* ***albumin*** *and uptake into tissues where they are* ***oxidized to obtain energy or re-esterified.***

Regulation of lipolysis:

- ***Nutritional and Metabolic state:***

In presence of glucose:	• ↑ *Utilization of Glucose by adipose tissue so* ↑ *Glycerol-3-P.* • ***Re-esterification > lipolysis*** *so plasma FFA* ↓.
In diabetes mellitus and in starvation:	• ↓ *glucose availability in adipose tissue so* ↓ *Glycerol-3-P.* • ***Re-esterification < Lipolysis*** *so* ↑ *plasma FFA level.*

- ***Hormonal state:***

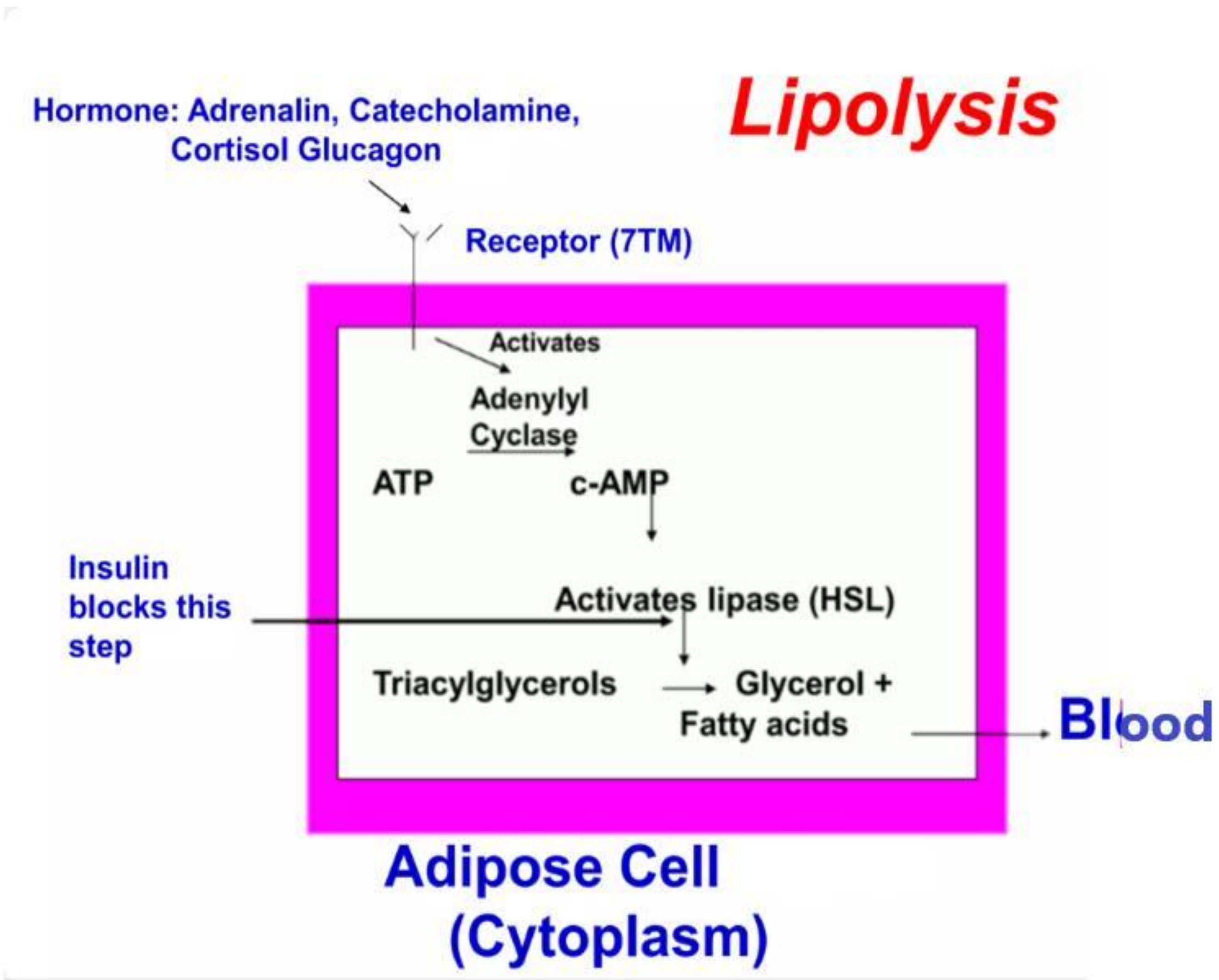
A) Insulin (the principal hormone):

1. inhibits lipolysis by:	• *Inhibiting* ***adenyl cyclase*** *and increasing the* ***phosphodiesterase*** *activity so* ↓ ***cAMP*** *so Protein kinase not activated so hormone-sensitive TG* ***lipase not activated.***
2. Increases glucose metabolism in adipose tissue by:	• ↑ ***Glucose uptake*** *by translocation of glucose transporters to the plasma membrane.* • ***Stimulation of glycolysis*** *provides Glycero-3-P.* • ***Stimulation of HMP pathway*** *provides NADPH.*
3. Enhances FA synthesis and TG synthesis by:	• ***Increasing the activity of:*** a) ***Pyruvate dehydrogenase*** *so* ↑ *acetyl CoA.* b) ***acetyl-CoA carboxylase*** *so* ↑ *malonyl CoA so* ↑ *FA synthesis.* c) ***Glycerol-P-acyl transferase*** *so* ↑ *TG synthesis.*

B) Lipolytic hormones (increase lipolysis):

- *Catecholamines (epinephrine and norepinephrine)*
- *Glucagon*
- *Growth hormone*
- *Glucocorticoids*

Most of them act by activating ***adenyl cyclase****, so ↑* ***cAMP*** *resulting in ++ Protein kinase which ++* ***hormone-sensitive TG lipase.***



Fatty Acid Oxidation

Methods of fatty acids oxidation:

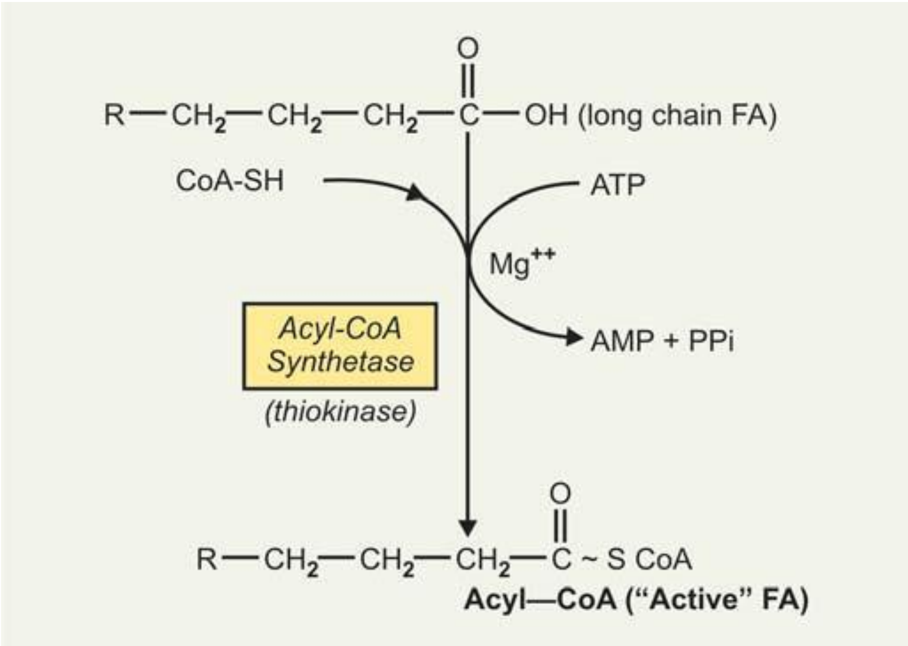
Principal method	Other methods
• It is **β-oxidation.**	• α and **omega (ω) oxidation** • Peroxisomal FA oxidation.

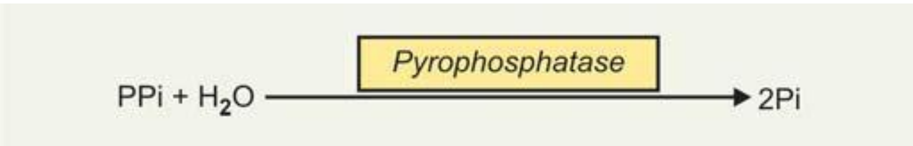
β-oxidation

Def:	• The oxidation and splitting of **two carbon** units occur at the beta-carbon atom.
Site:	• **Mitochondria.**
Function:	• The circulating free **fatty acids** (FFA) are taken up by the cells then oxidized to get **energy**.
Steps	1. **Preparing FA for Beta Oxidation by:** a. Activation of fatty acid. b. Transport of fatty acyl CoA from the cytosol into mitochondria. 2. **Beta oxidation steps.**

1) Activation of fatty acid:

- ***FA*** *must be first activated to an* ***acyl-CoA*** *so that they participate in metabolic pathway.*
- *This occurs in cytoplasm in presence of* ***ATP****, coenzyme A, and* ***acyl-CoA synthetase enzyme.***

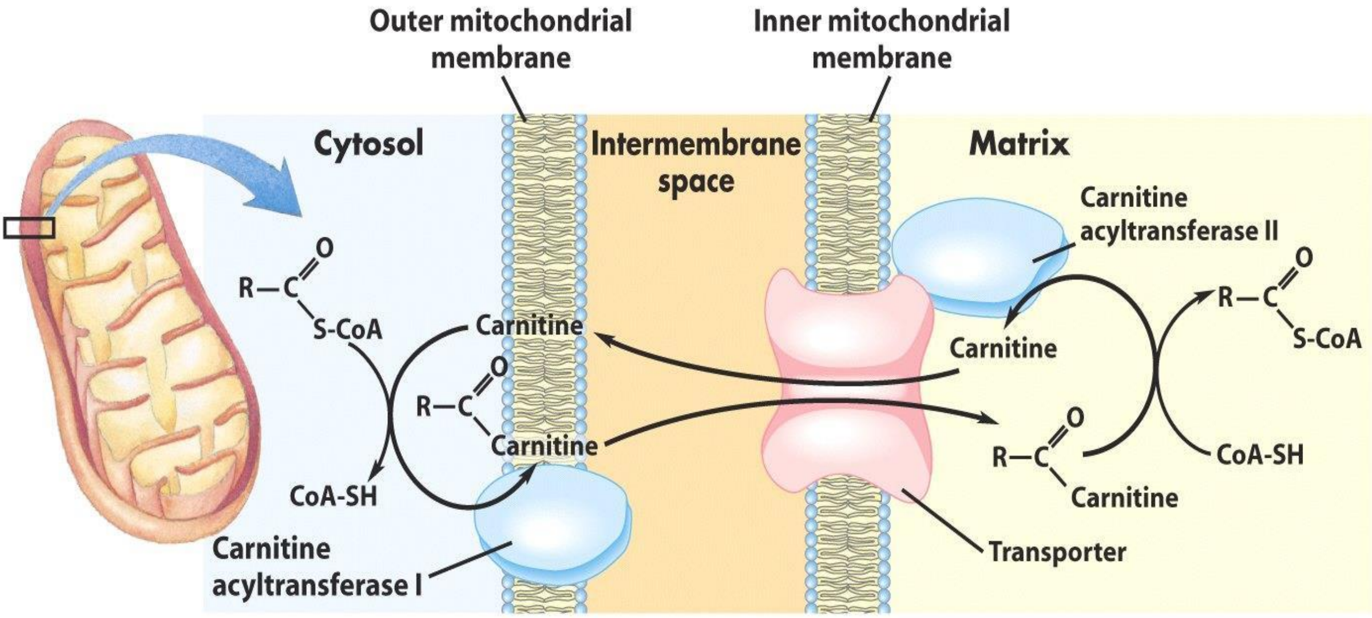


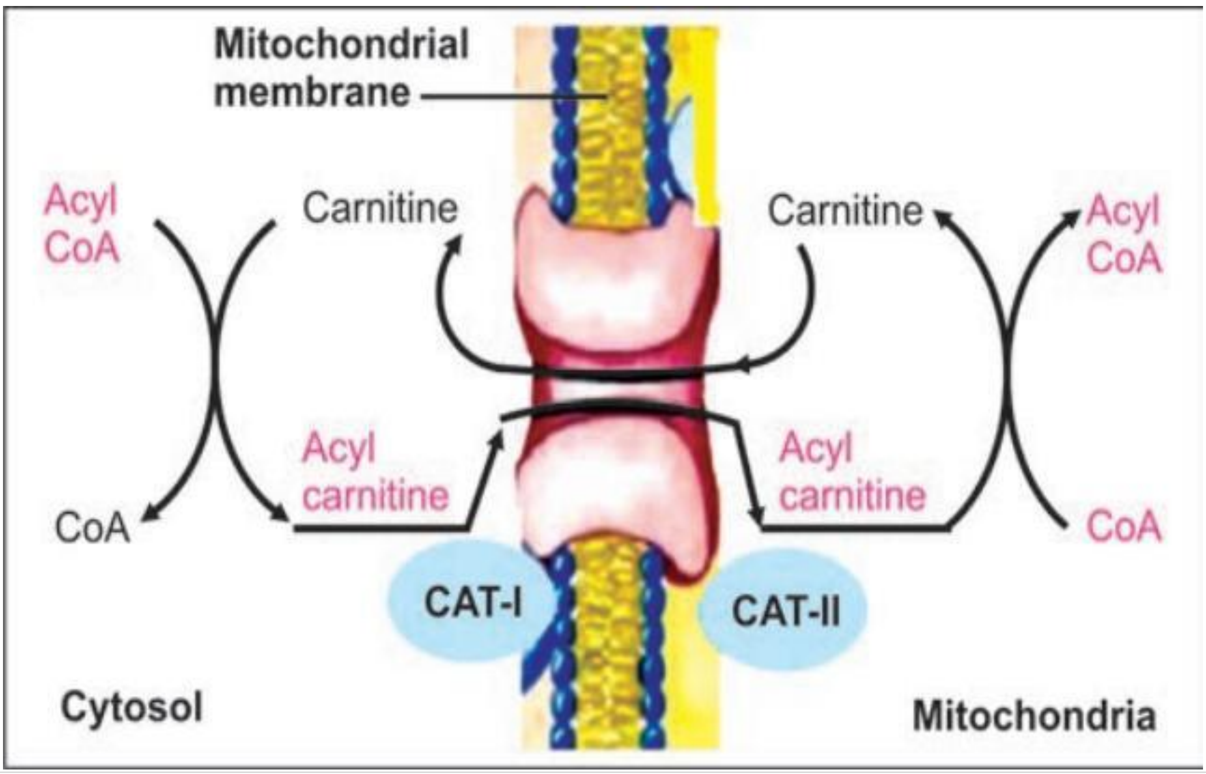


2) Transport of fatty acyl CoA into mitochondria:

- *Acyl-CoA are formed in* ***cytosol****, whereas Beta oxidation of FA occurs in* ***mitochondria.***
- *Acyl CoA are impermeable to mitochondrial membrane.*
- *Long chain activated FA penetrates the inner mitochondrial membrane only in combination with* ***carnitine****.*
- ***Carnitine:***
  - *It can be obtained from the* ***diet (meat products).***
  - *It is synthesized from* ***lysine and methionine*** *in liver and kidney.*

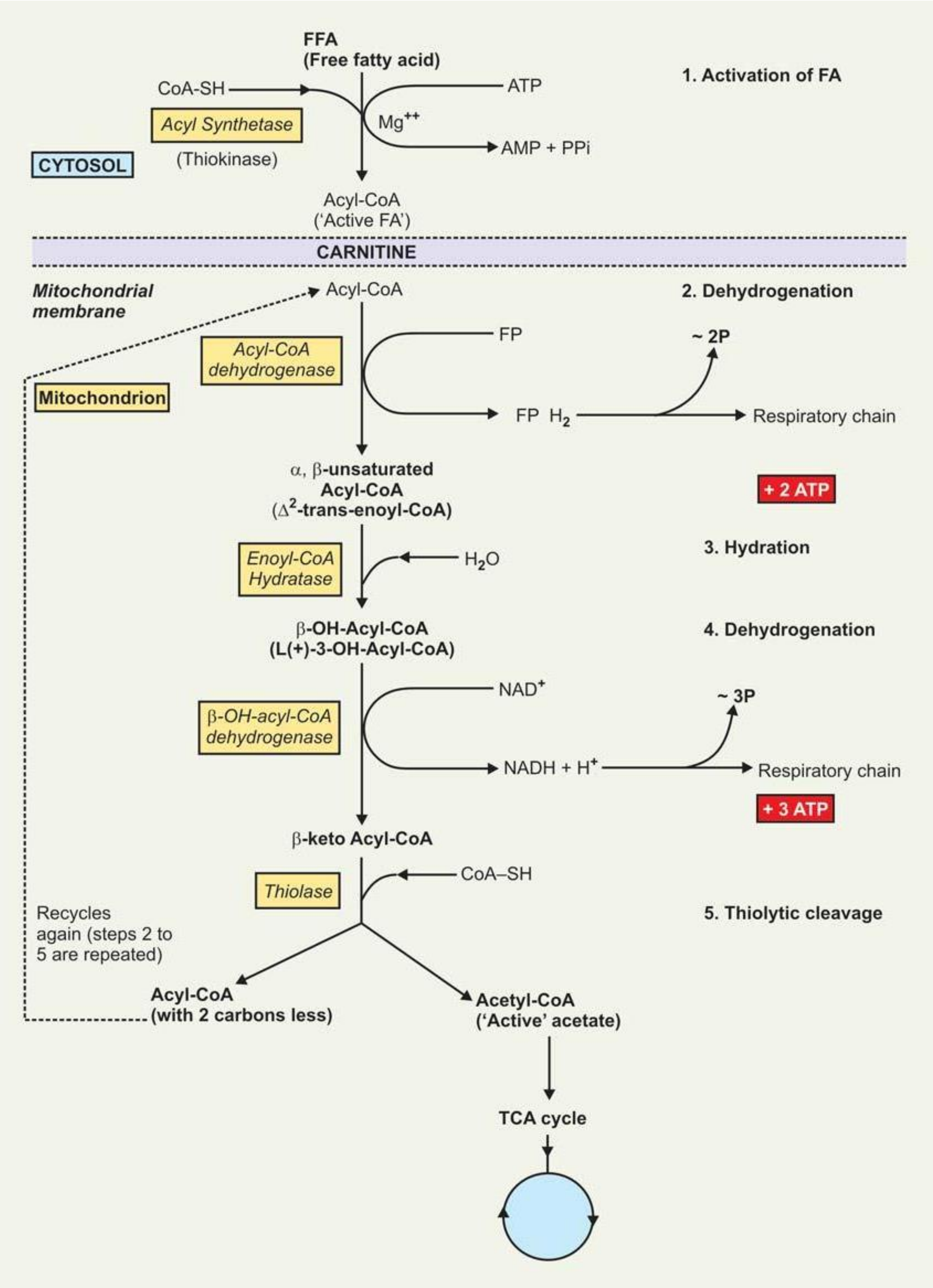
- <u>***Steps of transportation:***</u>
  - ***Carnitine acyl transferase-I (CAT-I)*** *transfer the fatty acyl group to carnitine to form acyl carnitine.*
  - *This occurs on the cytosolic side of inner mitochondrial membrane.*
  - ***Translocase*** *will carry the acyl carnitine across the membrane to the matrix of mitochondria.*
  - ***Carnitine acyl transferase-II (CAT-II)*** *transfer the acyl group back to co-enzyme A molecule.*





3) Beta oxidation steps:

Step	Enzyme	Mechanism
1. Dehydrogenation:	**Acyle COA dehydrogenase**	• *The acyl CoA is dehydrogenated to trans enoyl CoA (**also called α, β-unsaturated acyl-CoA**) with the **FAD** accepting the hydrogen atoms **by the enzyme acyl-CoA dehydrogenase.***
2. Hydration (addition of molecule of water):	**Hydratase**	• *One molecule of water is added to saturate the double bond to form **β-OH acyl-CoA** by the **enzyme enoyl – CoA hydratase.***
3. Dehydrogenation:	**β-OH-acyl-CoA dehydrogenase.**	• *β-OH acyl-CoA is dehydrogenated to- **ketoacyl-CoA** with the NAD accepting the hydrogen atoms **by the enzyme β–OH–acyl-CoA dehydrogenase.***
4. Cleavage:	**Thiolase enzyme.**	• *β-keto-acyl-CoA is split at the 2,3 positions by **thiolase** splitting off a molecule of **acetyl CoA** and leaving behind **a fatty acid with 2 carbon atoms less.*** • *Further Cycles of steps 1, 2, 3 and 4 **proceed until** the fatty acid is completely converted to acetyl CoA.*


FFA
(Free fatty acid)
CoA-SH
ATP
1. Activation of FA
Acyl Synthetase
Mg++
AMP + PPi
CYTOSOL
(Thiokinase)
Acyl-CoA
('Active FA')
CARNITINE
Mitochondrial membrane
Acyl-CoA
2. Dehydrogenation
FP
~ 2P
Acyl-CoA dehydrogenase
Mitochondrion
FP H2
Respiratory chain
α, β-unsaturated Acyl-CoA
(Δ2-trans-enoyl-CoA)
+ 2 ATP
Enoyl-CoA Hydratase
H2O
3. Hydration
β-OH-Acyl-CoA
(L(+)-3-OH-Acyl-CoA)
4. Dehydrogenation
NAD+
~ 3P
β-OH-acyl-CoA dehydrogenase
NADH + H+
Respiratory chain
+ 3 ATP
β-keto Acyl-CoA
Thiolase
CoA–SH
Recycles again (steps 2 to 5 are repeated)
5. Thiolytic cleavage
Acyl-CoA
(with 2 carbons less)
Acetyl-CoA
('Active' acetate)
TCA cycle

Energy production by beta oxidation

- **Example:** Palmitic acid (16 C).
  - **Oxidation of palmitic acid (C16) requires 7 cycles of β oxidation producing:**
    - 8 molecules of **acetyl-CoA**
    - 7 molecules of **FADH2**
    - 7 molecules of **NADH**
  - Electrons from **FADH2 and NADH** enter the respiratory chain:

NADH & FADH2	Acetyl-CoA
• NADH → **3 ATP.** • $FADH_2$ → **2 ATP.** ➢ So in every cycle → **5 ATP.** ➢ So 5 ATP x **7** cycles **= 35 ATP**	• Each Acetyl-CoA enters the citric acid cycle and is further oxidized → 12 ATP • So **8** Acetyl CoA x 12 ATP = **96 ATP**

- **2 ATP** are utilized in the Initial activation of FA (only once).

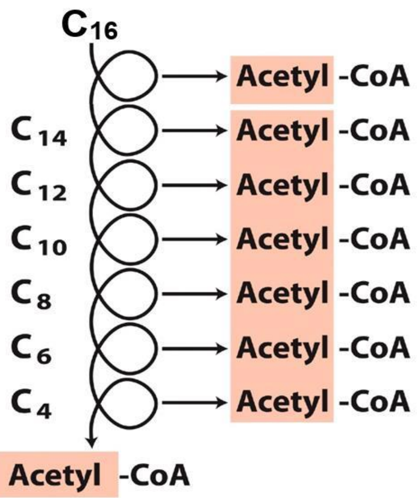
- **Total energy produced:**

  = 8 acetyl-CoA + 7 NADH + 7 FADH2

  = (35 + 96) = 131 ATP

- **Total energy production:**

  = 131 ATP - 2 ATP = 129 ATP



Regulation of Beta oxidation:

- ***The availability of free fatty acid (FFA):***
  - *The level of FFA regulates **the net utilization** through beta oxidation.*
  - *The level of FFA is controlled by **glucagon/insulin ratio.***
    - *Glucagon increases FFA level.*
    - *Insulin has the opposite effect.*

- ***CAT-I:***
  - ***CAT-1** is the regulator of entry of fatty acid into mitochondria.*
  - ***Malonyl CoA** inhibits CAT-I activity. Thus, during de novo synthesis of fatty acid, the beta oxidation is inhibited.*