BCM 221 LECTURES

BY

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OUTLINE

- INTRODUCTION TO LIPID CHEMISTRY
- STORAGE OF ENERGY IN ADIPOCYTES
- MOBILIZATION OF ENERGY STORES IN ADIPOCYTES
- KETONE BODIES AND KETOSIS
- PYRUVATE DEHYDROGENASE COMPLEX AND ALPHA KETOGLUTARATE DEHYDROGENASE COMPLEXES
- TRICARBOXYLIC ACID CYCLE
- INTERRELATIONSHIP OF FAT AND CARBOHYDRATE METABOLISM

INTRODUCTION TO LIPID CHEMISTRY

- **LIPIDS:** Lipids are compounds which are insoluble in water but soluble in non polar organic solvents such as benzene, chloroform, ether.

- ADIPOCYTES: Adipocytes are also known as fat cells, they are specialized in storing energy as fats.

CLASSIFICATION OF LIPIDS

FATTY ACIDS: They are the simplest classes of lipids.

- Saturated fatty acids have single bonds. Examples are Lauric acid, myristic acid and palmitic acid.

- Unsaturated fatty acids have one or more double bonds. Examples are Oleic acid, Linoleic acid, Linolenic acid.

- Essential fatty acids: These are fatty acids that cannot be synthesized by the body and must be obtained from food. They include linoleic acid and linolenic acid.

TRIACYLGLYCEROL (TAG): These are fats and oils. They are made up of three molecules of fatty acids esterified to glycerol backbone.

- PHOSPHOLIPIDS: Are composed of glycerol, fatty acids, phosphate group. The phosphate group can be modified by with simple arganic molecules such as choline, ethanolamine.

- SPHINGOLIPIDS: They are composed of 18 carbon amino alcohol called sphingosine and fatty acid. Examples are ceramide and sphingomyelin.

- STEROIDS: They have steroid nucleus which is made up of three cyclohexane rings and one cyclopentane ring fused together. Example is cholesterol.

Assignment: write notes on structures and examples of

- Phospholipids
- Sphingolipids
- Steroids

STORAGE OF ENERGY IN ADIPOCYTES

- Fat (TAG) is used for energy production in most tissues. However, if energy (ATP) levels are high, fat is transported to adipose tissue for storage.

- Sources of fat:

  - From diet
  - Fat is produced in liver and adipose tissue from excess carbohydrate and protein.

- Production of fats from proteins: Proteins are degraded to amino acids. Ketogenic amino acids yields acetyl CoA when degraded. Acetyl CoA is a precursor of fats.

- Proteins → Amino acids → Acetyl CoA

  (ketogenic)

  ↓

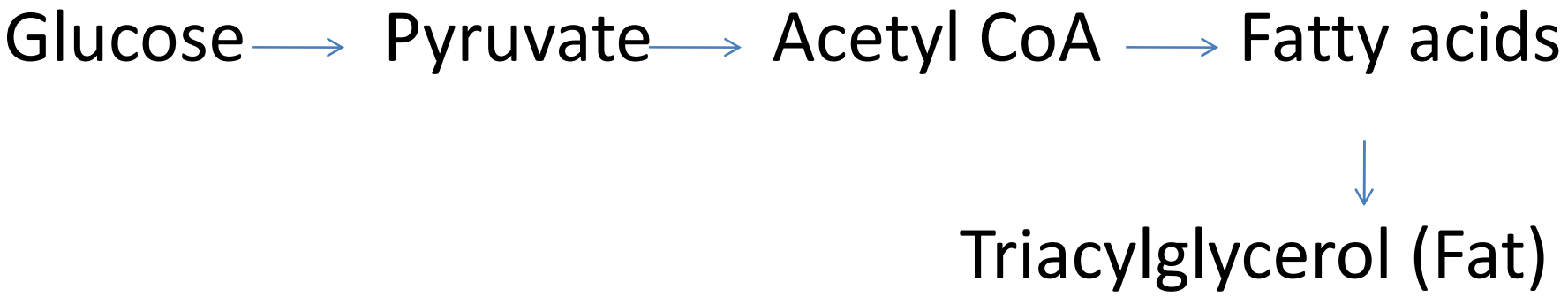
  Fatty acids

  ↓ + Glycerol

  Triacylglycerol (Fat)

- **Production of fats from carbohydrates**:

  Glucose is converted to pyruvate via glycolysis. Pyruvate dehydrogenase complex converts pyruvate to acetyl coA, which is used for fat biosynthesis.



FATTY ACID BIOSYNTHESIS

- Fatty acid biosynthesis occurs in cytosol. The steps are below:
- Step 1: Carboxylation of acetyl coA to produce malonyl coA. This is the committed step.

NOTE: Fatty acid synthase complex has seven enzyme components that catalyze subsequent reactions of the pathway.

- Step 2: Step 2 involves formation of acetyl- CE from acetyl CoA and malonyl ACP from malonyl CoA

- **STEP 3: CONDENSATION STEP:** Acetyl group and malonyl ACP condenses to form acetoacetyl ACP.

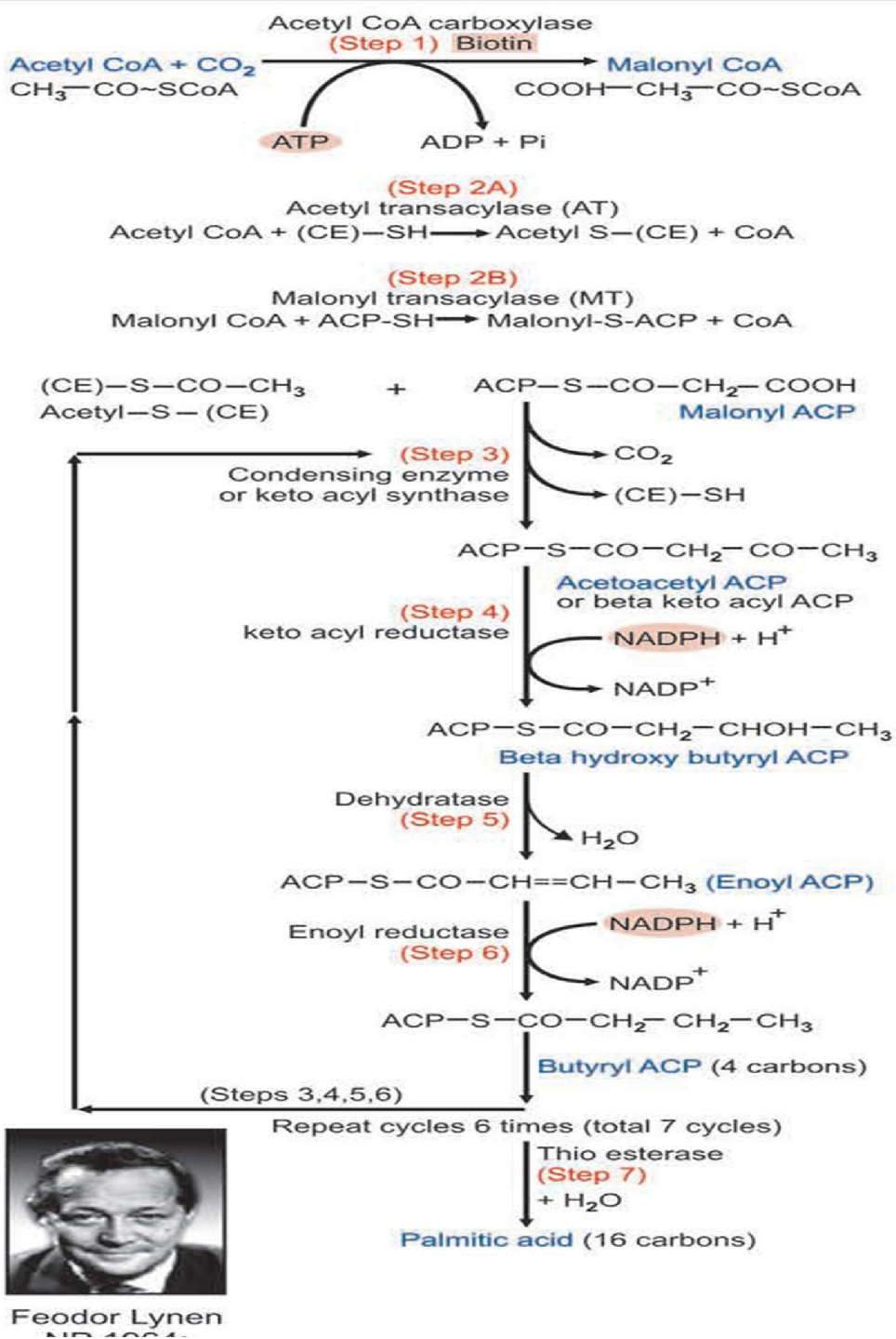
- **STEP 4: REDUCTION:** Acetoacetyl ACP is reduced by NADPH dependent β-ketoacyl ACP reductase to form β-hydroxybutyryl ACP.

- **STEP 5: DEHYDRATION:** β- hydroxybutyryl ACP is dehydrated to yield enoyl ACP.

- **STEP 6: ANOTHER REDUCTION:** Enoyl ACP is reduced to butyryl ACP

- **NOTE:** For synthesis of a 16 carbon palmitic acid, reactions 3,4,5,6 are repeated six times to produce **palmitoyl ACP** .

- **STEP 7: RELEASE OF PALMITIC ACID: Thioesterase catalyzes conversion of palmitoyl ACP to palmitic acid**


Acetyl CoA carboxylase
(Step 1) Biotin
Acetyl CoA + CO_2
CH_3—CO~SCoA
Malonyl CoA
COOH—CH_3—CO~SCoA
ATP
ADP + Pi
(Step 2A)
Acetyl transacylase (AT)
Acetyl CoA + (CE)—SH → Acetyl S—(CE) + CoA
(Step 2B)
Malonyl transacylase (MT)
Malonyl CoA + ACP-SH → Malonyl-S-ACP + CoA
(CE)—S—CO—CH_3
Acetyl—S—(CE)
+
ACP—S—CO—CH_2—COOH
Malonyl ACP
(Step 3)
Condensing enzyme
or keto acyl synthase
CO_2
(CE)—SH
ACP—S—CO—CH_2—CO—CH_3
Acetoacetyl ACP
or beta keto acyl ACP
(Step 4)
keto acyl reductase
NADPH + H^+
$NADP^+$
ACP—S—CO—CH_2—CHOH—CH_3
Beta hydroxy butyryl ACP
Dehydratase
(Step 5)
H_2O
ACP—S—CO—CH==CH—CH_3 (Enoyl ACP)
Enoyl reductase
(Step 6)
NADPH + H^+
$NADP^+$
ACP—S—CO—CH_2—CH_2—CH_3
Butyryl ACP (4 carbons)
(Steps 3,4,5,6)
Repeat cycles 6 times (total 7 cycles)
Thio esterase
(Step 7)
+ H_2O
Palmitic acid (16 carbons)
Feodor Lynen

BIOSYNTHESIS OF TRIACYLGLYCEROL

- Triacylglycerol (TAG) is synthesized by esterification of fatty acyl CoA with glycerol-3- phosphate.

- Majority of the glycerol-3- phosphate used for TAG synthesis is derived from Dihydroxyacetone phosphate (DHAP), which is a glycolytic intermediate.

- In the liver, a small amount of glycerol-3- phosphate is formed from glycerol by the action of glycerol kinase.

- Glycerol kinase is absent in the adipose tissues, hence it relies on DHAP for TAG synthesis.

- The first step involves the synthesis of glycerol 3-phosphate as described above

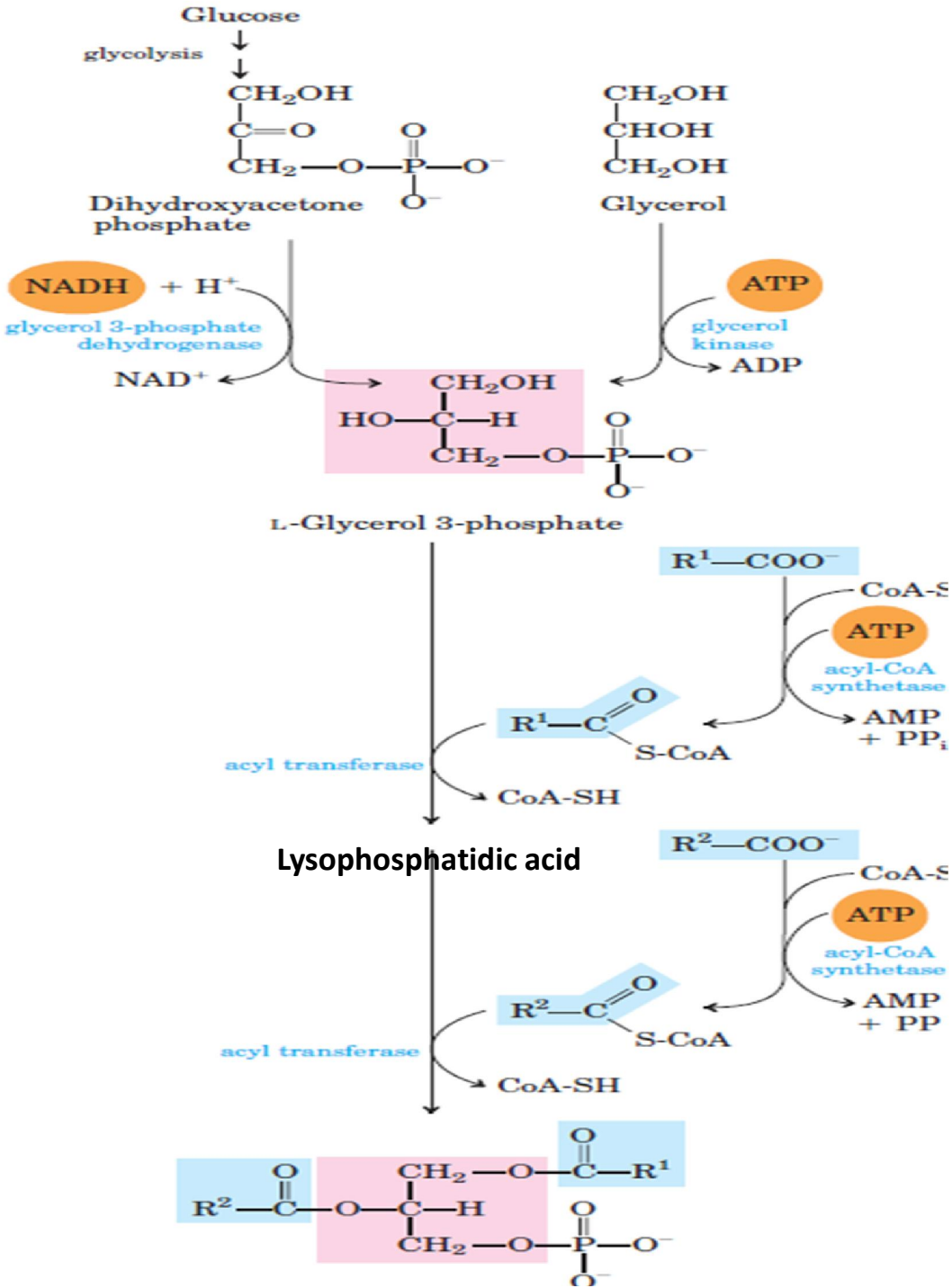
- The second step is the attachment of acylgroup (i.e acylation) to free hydroxyl group of glycerol 3- phosphate to form lysophosphatidic acid

- Acylation of lysophosphatidic acid yields phosphatidic acid

- Phosphatidic acid is then converted to 1,2- diacylglycerol

- Finally diacylglycerol is acylated to triacylglycerol

Note: insulin stimulates TAG synthesis by activating glycerolphosphate acyltransferase.


Glucose
glycolysis
Dihydroxyacetone phosphate
Glycerol
NADH + H+
glycerol 3-phosphate dehydrogenase
NAD+
ATP
glycerol kinase
ADP
L-Glycerol 3-phosphate
R1—COO−
CoA-S
ATP
acyl-CoA synthetase
AMP + PPi
acyl transferase
S-CoA
CoA-SH
Lysophosphatidic acid
R2—COO−
CoA-S
ATP
acyl-CoA synthetase
AMP + PP
acyl transferase
S-CoA
CoA-SH

Phosphatidic acid

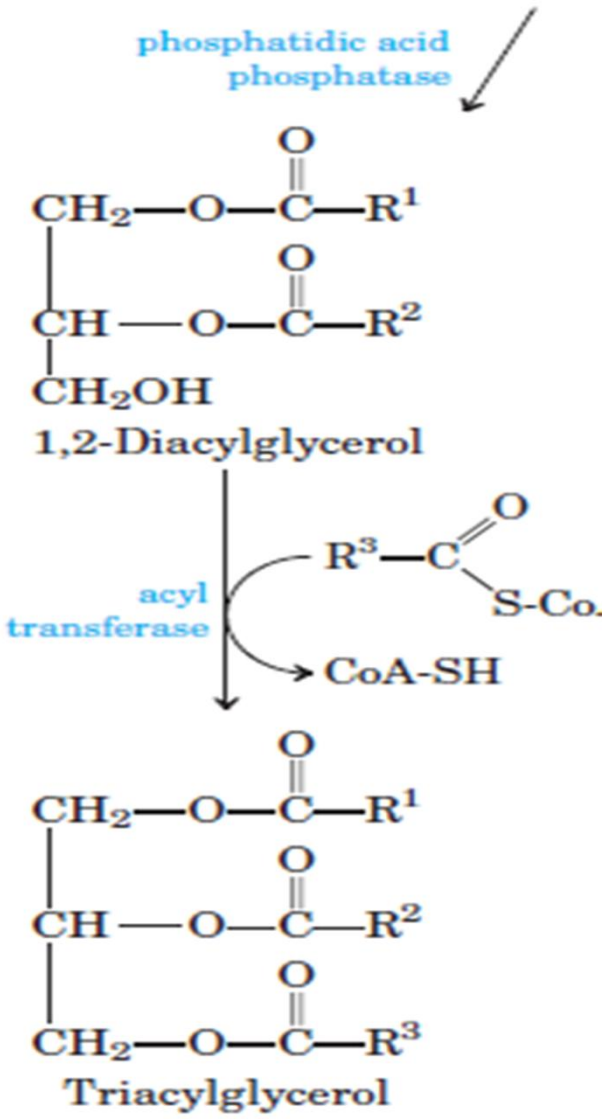


Fig: BIOSYNTHESIS OF TAG

MOBILIZATION OF ENERGY STORES IN ADIPOCYTES

- During fasting (lack of food), stored fat is used for ATP production, this is called ‘mobilization of energy stores in adipocytes’.

- The initial step is the hydrolysis of TAG by lipase, a process called lipolysis.

- Lipolysis occurs via enzyme cascade mechanism as follows:

LIPOLYSIS

- During fasting, hormones such as glucagon, epinephrine bind to receptors on adipose cells, this causes activation of G protein. (Guanine nucleotide binding protein).

- Active G protein activates adenylate cyclase, which converts ATP to cyclic AMP (cAMP).

- cAMP activates Protein kinase A which in turns activates hormone sensitive lipase by phosphorylating it.

- Thus, glucagon, epinephrine and norepinephrine stimulate lipolysis. In contrast, insulin inbibits lipolysis by activating phosphodiesterase (an enzyme that reduces levels of cAMP)

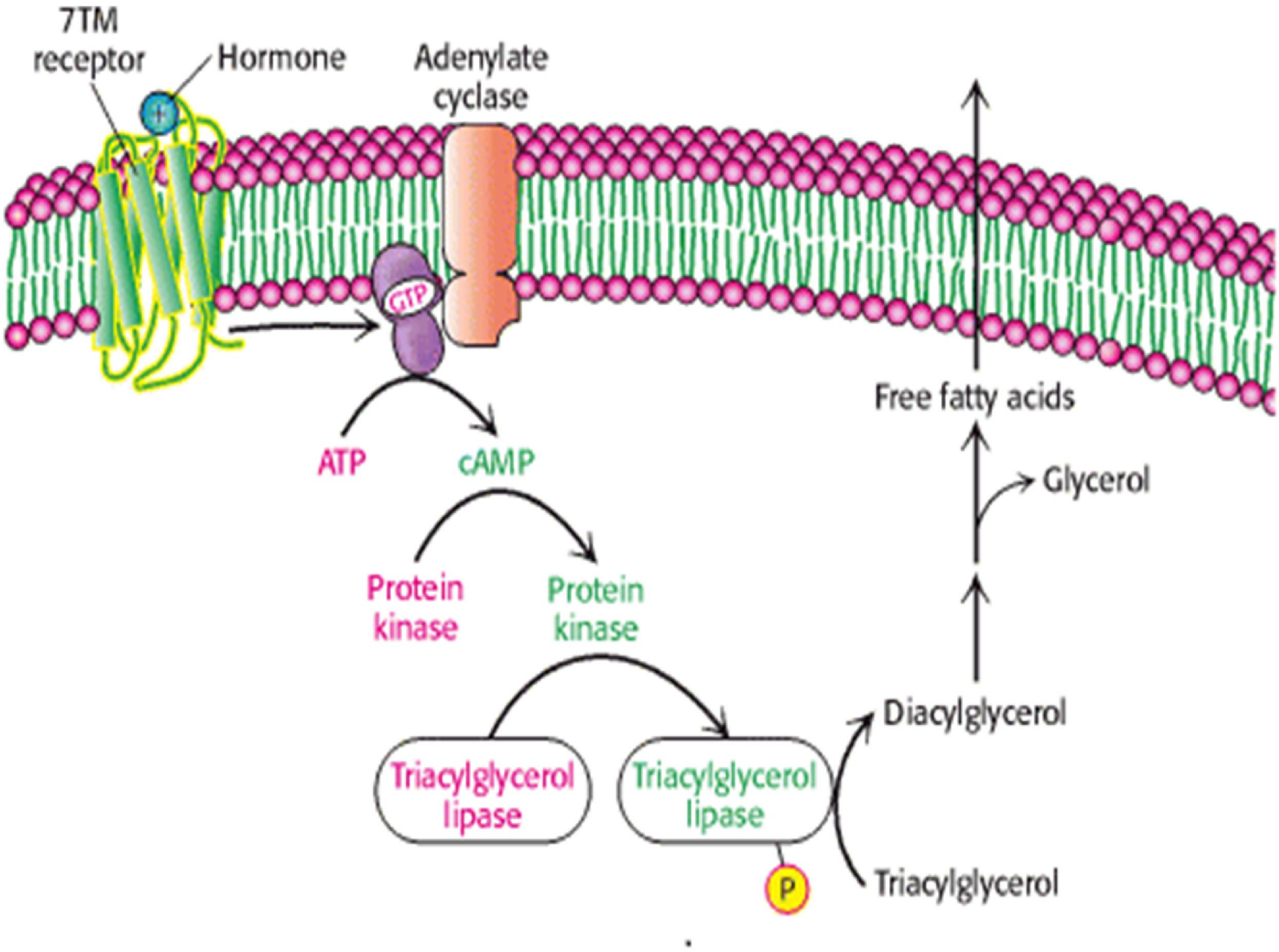


Fig: LIPOLYSIS

- Free fatty acids formed by lipolysis are used as fuel by other tissues via beta oxidation pathway.

- The glycerol formed is absorbed by liver and converted to glycerol 3- phosphate by glycerol kinase and then converted to Dihydroxyacetone phosphate (DHAP) by glycerol 3- phosphate dehydrogenase. DHAP is converted to glyceraldehyde 3-phosphate which enters glycolytic pathway

BETA OXIDATION OF FATTY ACIDS

- Beta oxidation is the cleavage of two carbon units at a time from fatty acyl CoA molecule, starting at the carbonyl end.

- The two carbon units formed are acetyl CoA which enter the TCA cycle for energy production when energy is low.

- Before beta oxidation, fatty acids are activated to form fatty acyl CoA in the cytosol. The resultant fatty acyl CoA is then transported to the mitochondria by means of a transporter called carnithine , since beta oxidation takes place in mitochondria.

- For a 16 carbon palmitoyl CoA , eight acetyl CoA molecules are produced from seven rounds of beta oxidation.

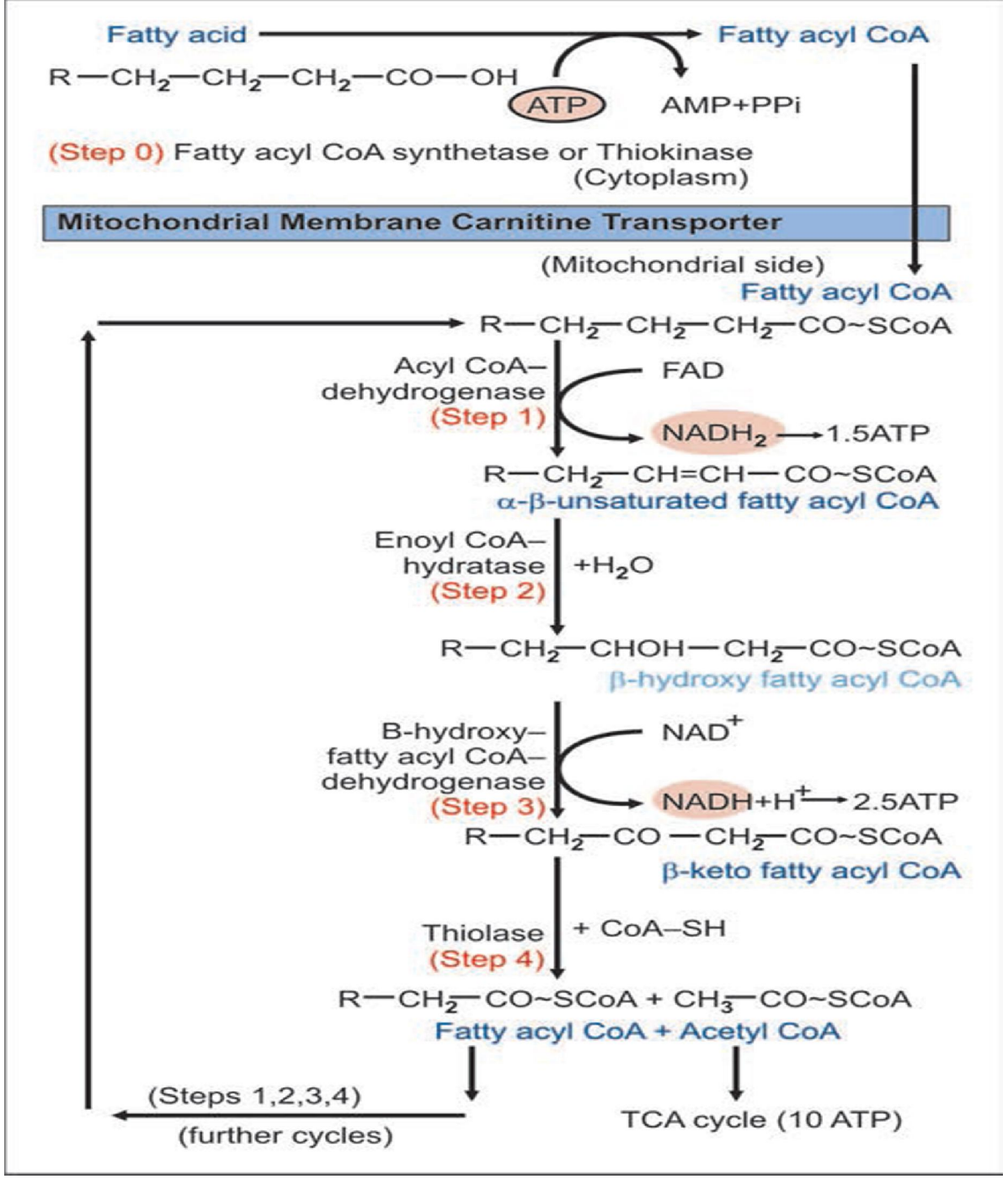


FIG: BETA OXIDATION PATHWAY