

De novo synthesis of fatty acids

Fatty acids are synthesised by adding 2 C units (Acetyl CoA)

Sites

Liver

Adipose tissue

Mammary gland

Adrenal gland etc

Organelle

Occurs in cytoplasm

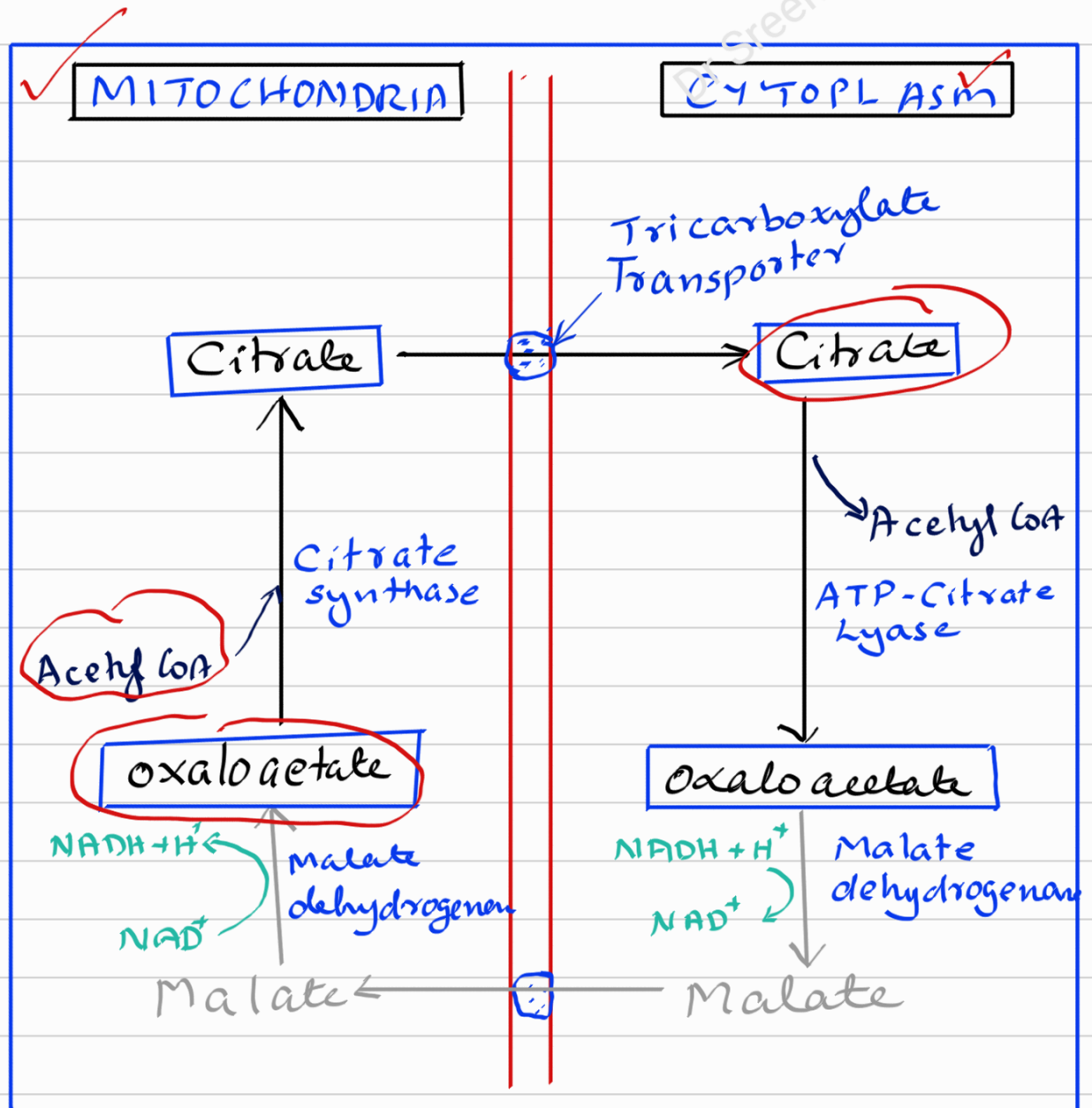
Dr. Sreekumar B
Acetyl CoA is usually produced in mitochondria.

Eg: Pyruvate $\xrightarrow{\text{PDH}}$ Acetyl CoA

Fatty acids $\xrightarrow{\beta \text{ oxidation}}$ Acetyl CoA

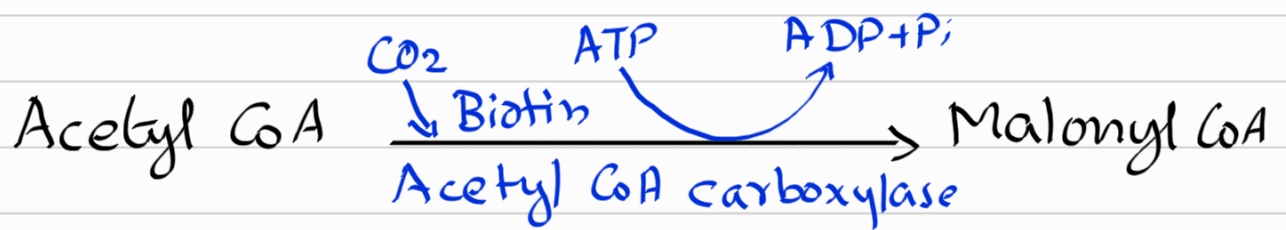
Dr. Sreekumar B
It has to be transported to cytoplasm.

Transport of acetyl CoA to cytoplasm



STEPS

First step is carboxylation of acetyl CoA to produce malonyl CoA. This is the key step (rate limiting step)



Remaining steps are catalyzed by a multienzyme complex called fatty acid synthase complex

Fatty acid synthase

Multienzyme complex in cytoplasm

It is a dimer

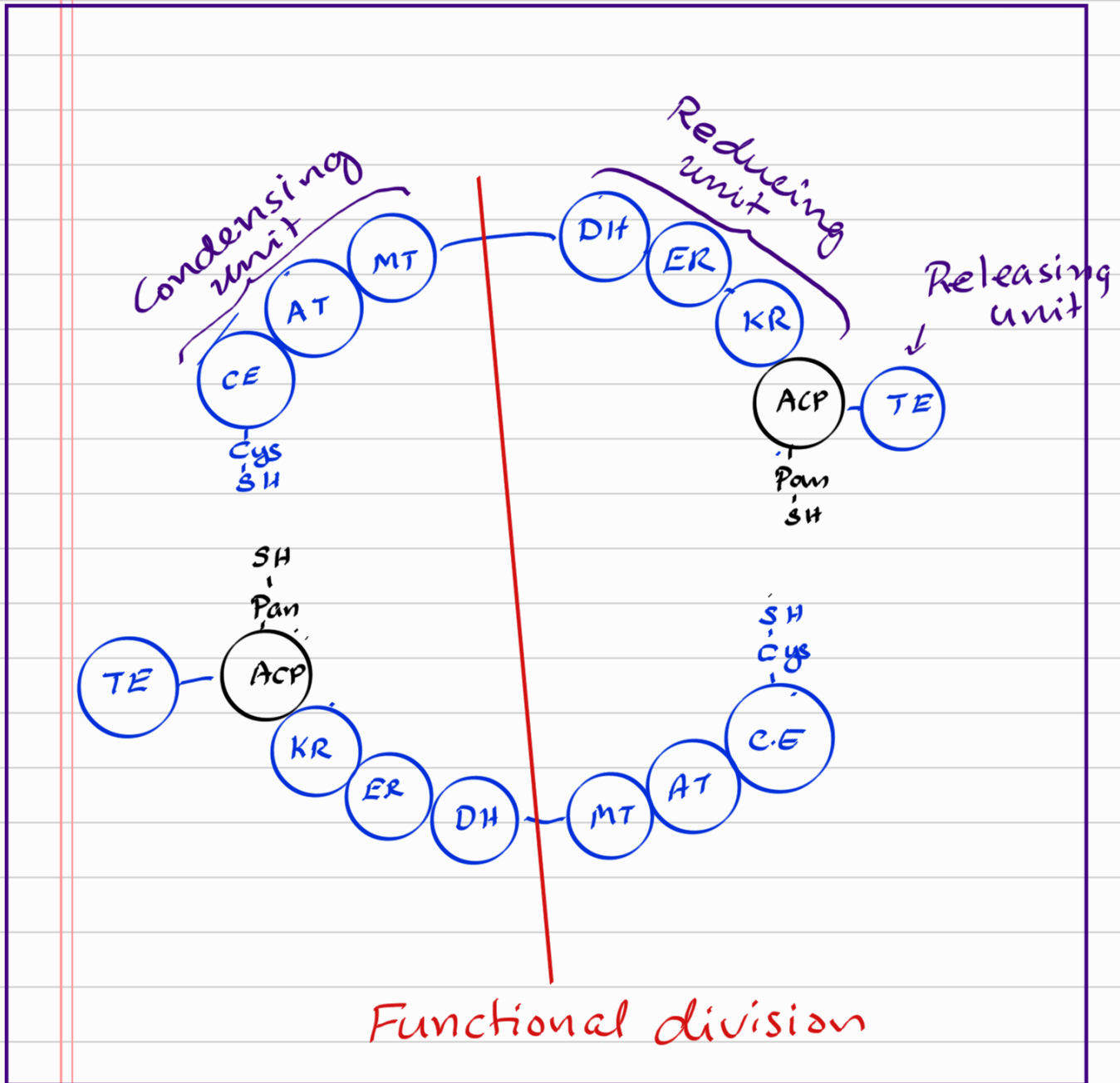
Each subunit has 7 enzymes and ACP (Acyl Carrier Protein)

Enzymes are :

- ① Ketoacyl Synthase (KAS)
(Condensing enzyme)
- ② Acetyl Trans Acylase
- ③ Malonyl Trans Acylase
- ④ Dehydratase
- ⑤ Enoyl Reductase
- ⑥ Ketoacyl Reductase
- ⑦ Thioesterase

Each subunit is connected to the other by -SH groups of condensing enzyme and ACP

Fatty acid synthase (Lynen spiral)



Cys residue of condensing enzyme and pantothenic acid of ACP carries -SH groups. These -SH groups are the sites where acetyl CoA and malonyl CoA get attached.

STEPS

① Attachment of priming molecule of acetyl CoA

Initially one acetyl CoA gets attached to the -SH group of Condensing enzyme - catalyzed by acetyl trans acylase

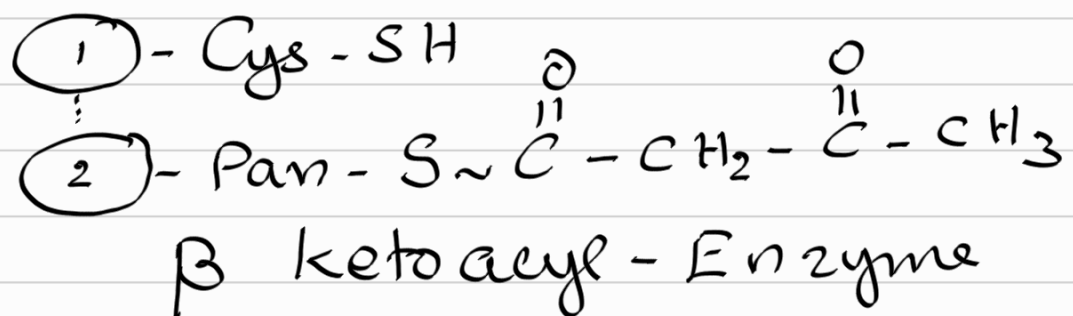
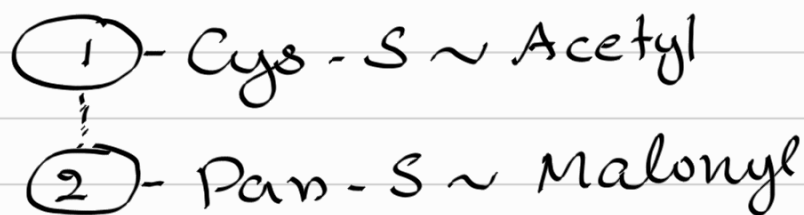
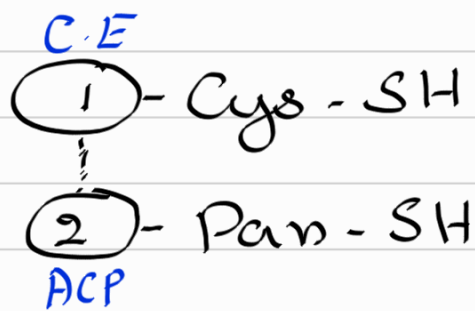
② Attachment of malonyl CoA

Malonyl CoA attaches to -SH group of ACP of the other monomer - catalyzed by malonyl trans acylase

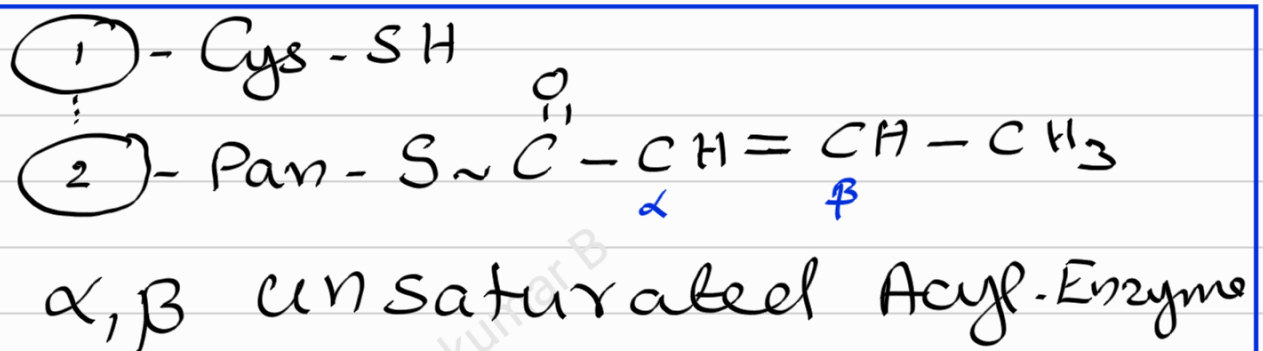
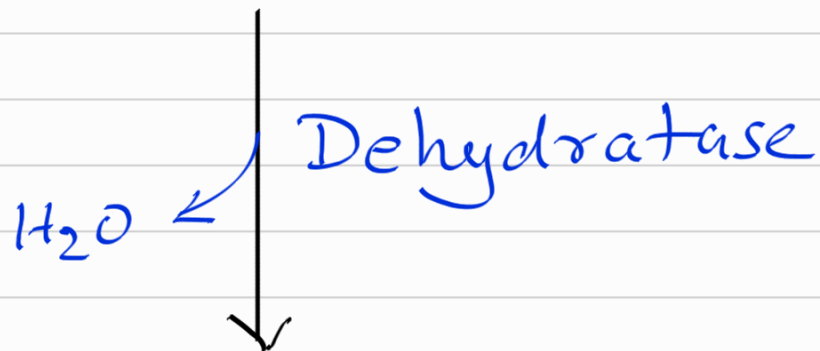
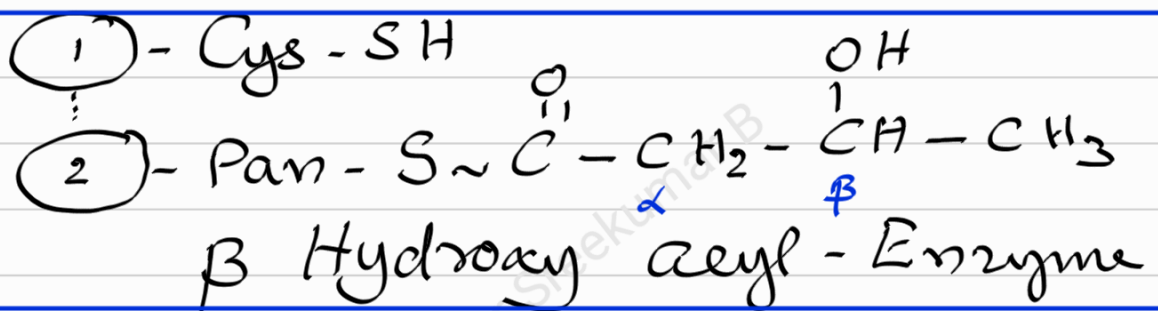
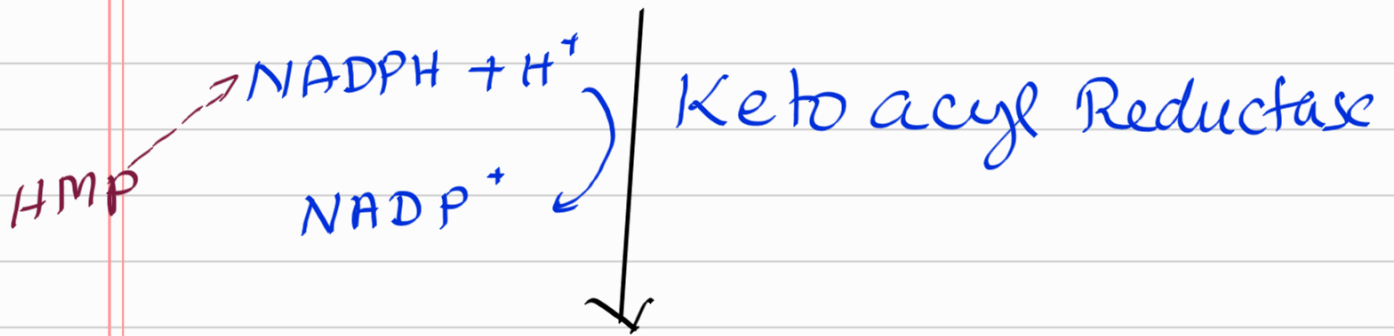
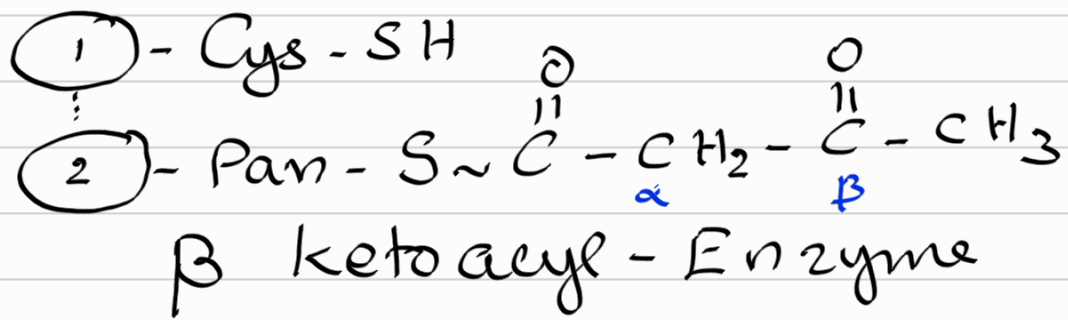
③ Condensation of 2 Acetyl groups to form β ketoacyl enzyme

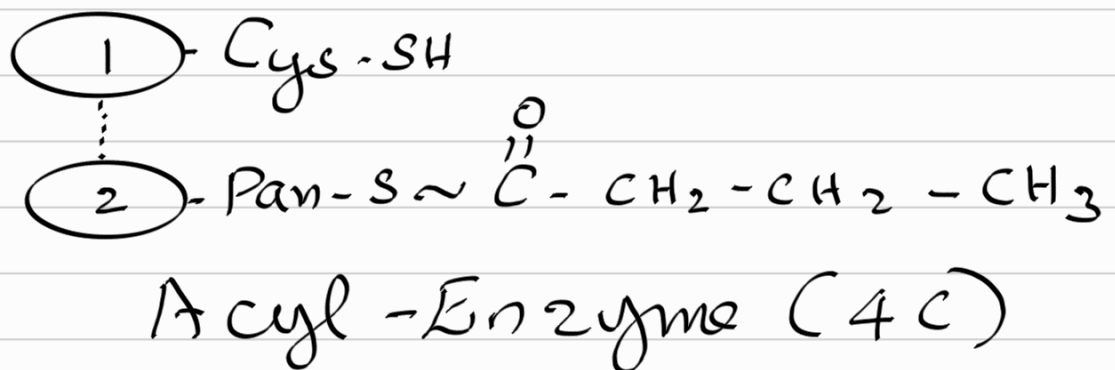
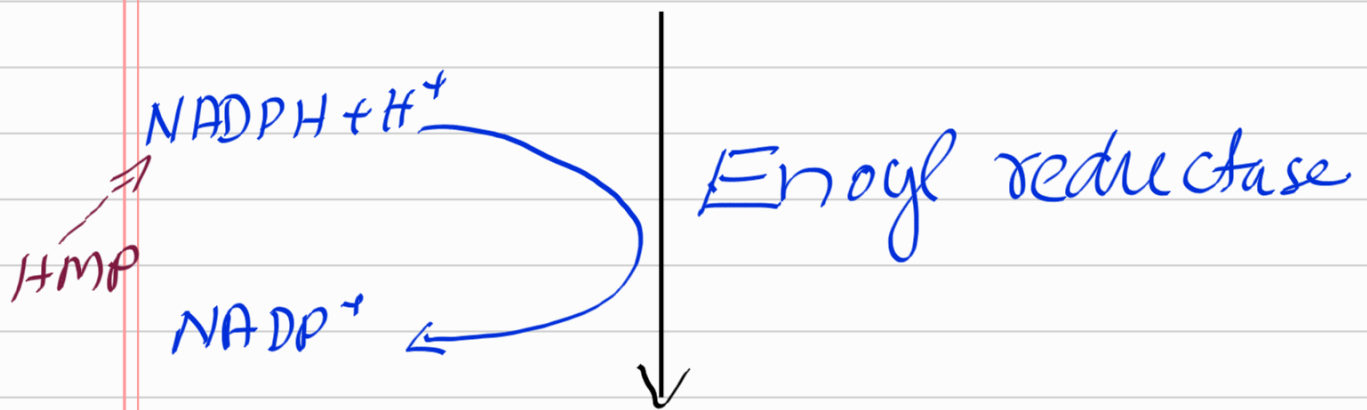
With the help of condensing enzyme, malonyl group is decarboxylated and acetyl group of primer condenses with it to form a 4C compound (Acetoacetyl - Enzyme)

or β -ketoacyl - Enzyme. This will remain attached to ACP.



β ketoacyl enzyme is
 reduced, dehydrated
 and reduced again to
 form γ C Acyl - Enzyme





Another malonyl CoA gets attached to ACP, displacing the acyl chain to Condensing enzyme.

Same reactions repeat till the acyl chain is of needed length - usually 16C

Then it is released by

Thioesterase (Deacylase)

Fate of palmitic acid

Activated to palmitoyl CoA

→ Esterification to acyl glycerols

→ Formation of Cholesteryl esters

→ Chain elongation

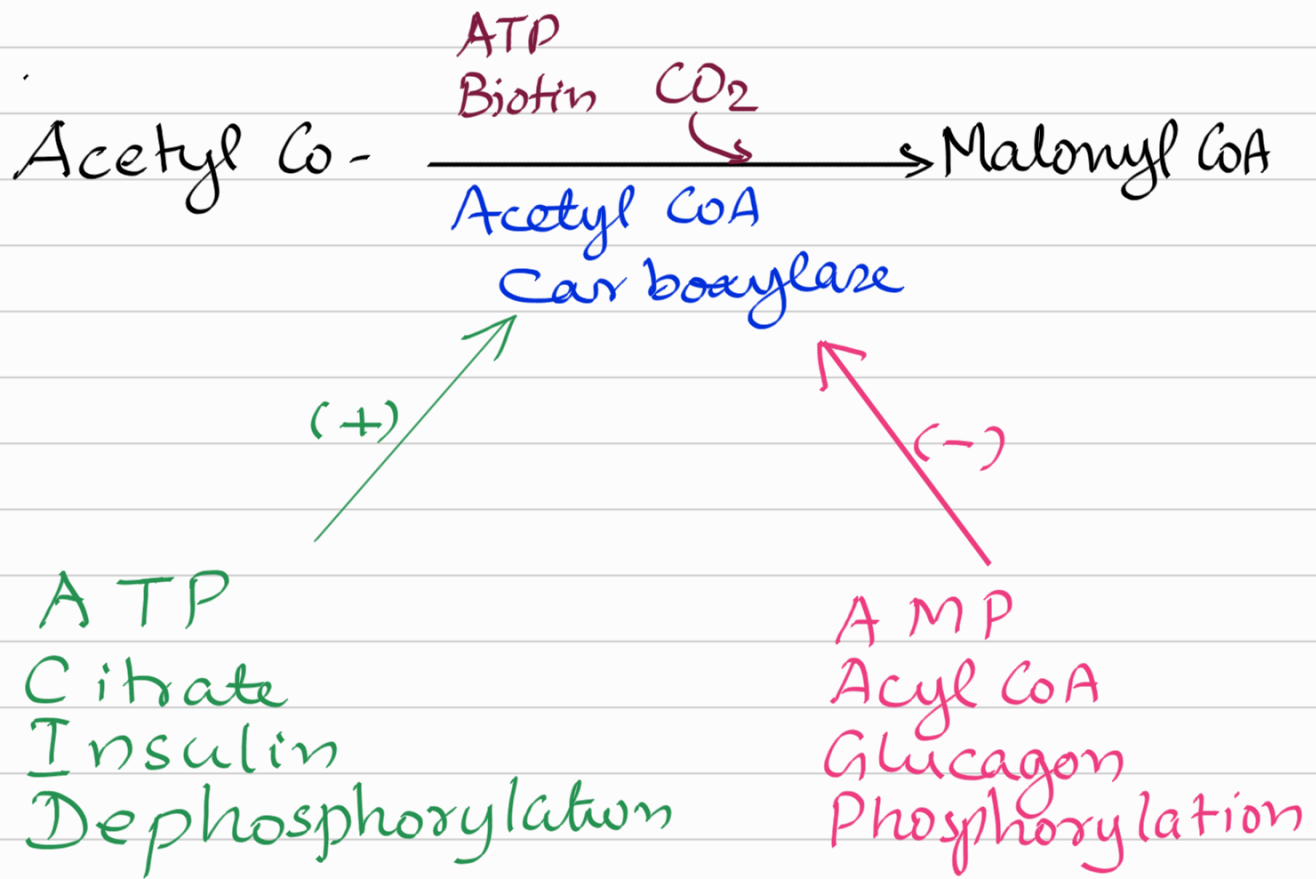
→ Desaturation

In lactating mammary gland a β -thioesterase acts at C8, 10 or 12 length

Regulation

Key enzyme

- Acetyl CoA carboxylase



① Nutritional state

① ATP and citrate (More in well fed state) - activates acetyl CoA carboxylase

② AMP and Acyl CoA (Starvation and lipolysis) inhibit the enzyme

② Hormonal regulation

① Insulin activates and Glucagon inhibits acetyl CoA carboxylase through covalent modification

② Insulin ↓ lipolysis → ↓ acyl CoA
→ activates acetyl CoA carboxylase

Glucagon ↑ lipolysis → ↑ acyl CoA
→ Inhibit acetyl CoA carboxylase

③ Covalent modification

Acetyl CoA carboxylase is active in dephosphorylated state.

Insulin causes dephosphorylation
Glucagon causes phosphorylation
