Denovo synthesis of fatty acids

fatty acids are synthesis by adding 2C units (acetyl CoA)

Sites
Liver
adipose tissue
mammary gland
Adrenal gland.

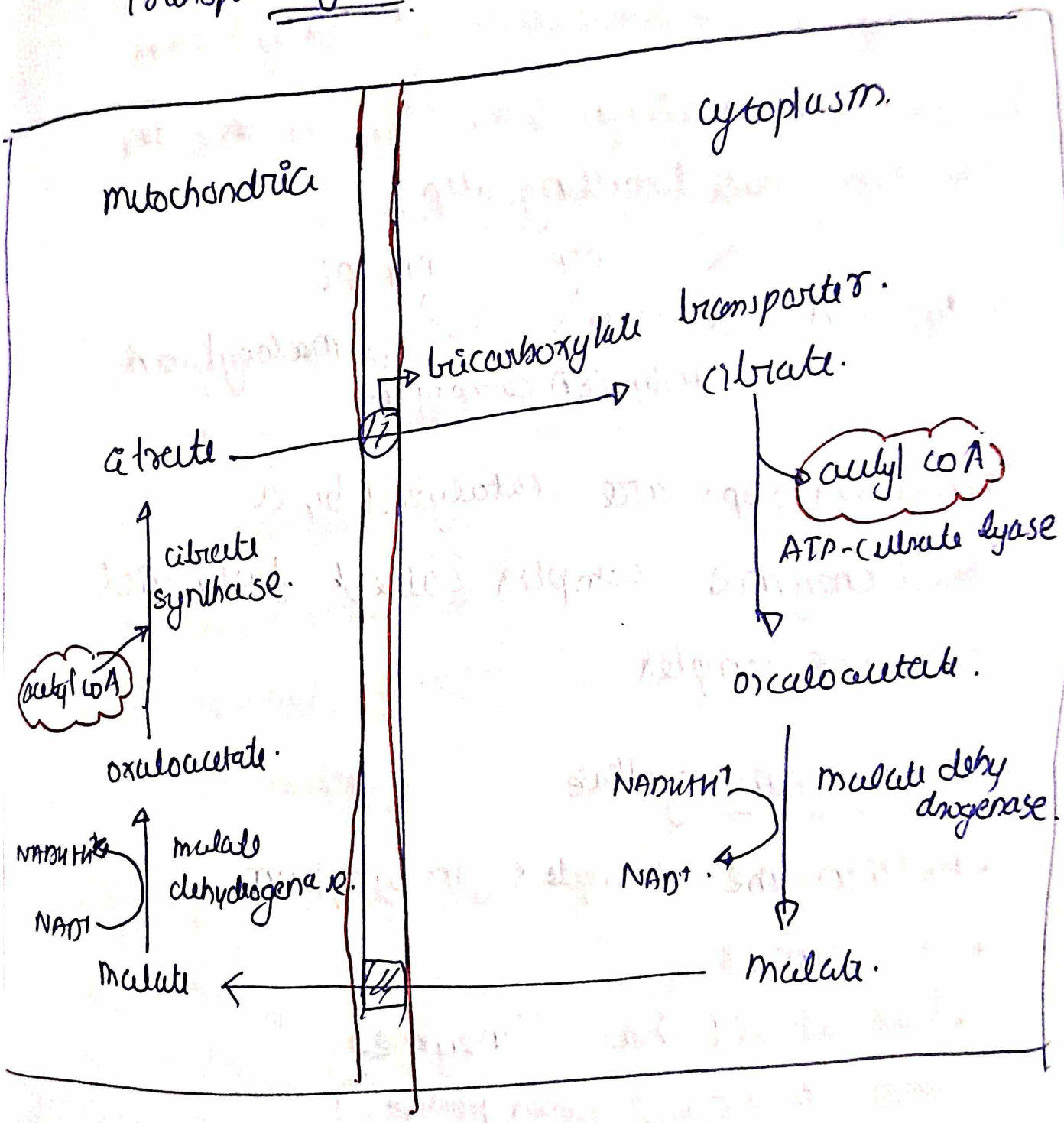
Organelle.
occurs in cytoplasm.
acetyl CoA is usually produced in mitochondria.

eg: pyruvate $\xrightarrow[PDH]{}$ acetyl CoA

Fatty acids $\xrightarrow[\beta \text{ oxidation.}]{}$ acetyl CoA

It has to be transported to cytoplasm

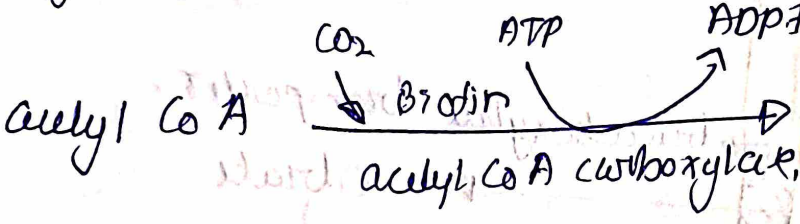
Transport of acetyl CoA to ytoplasm.



Citrate → tricarboxylate.

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 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.

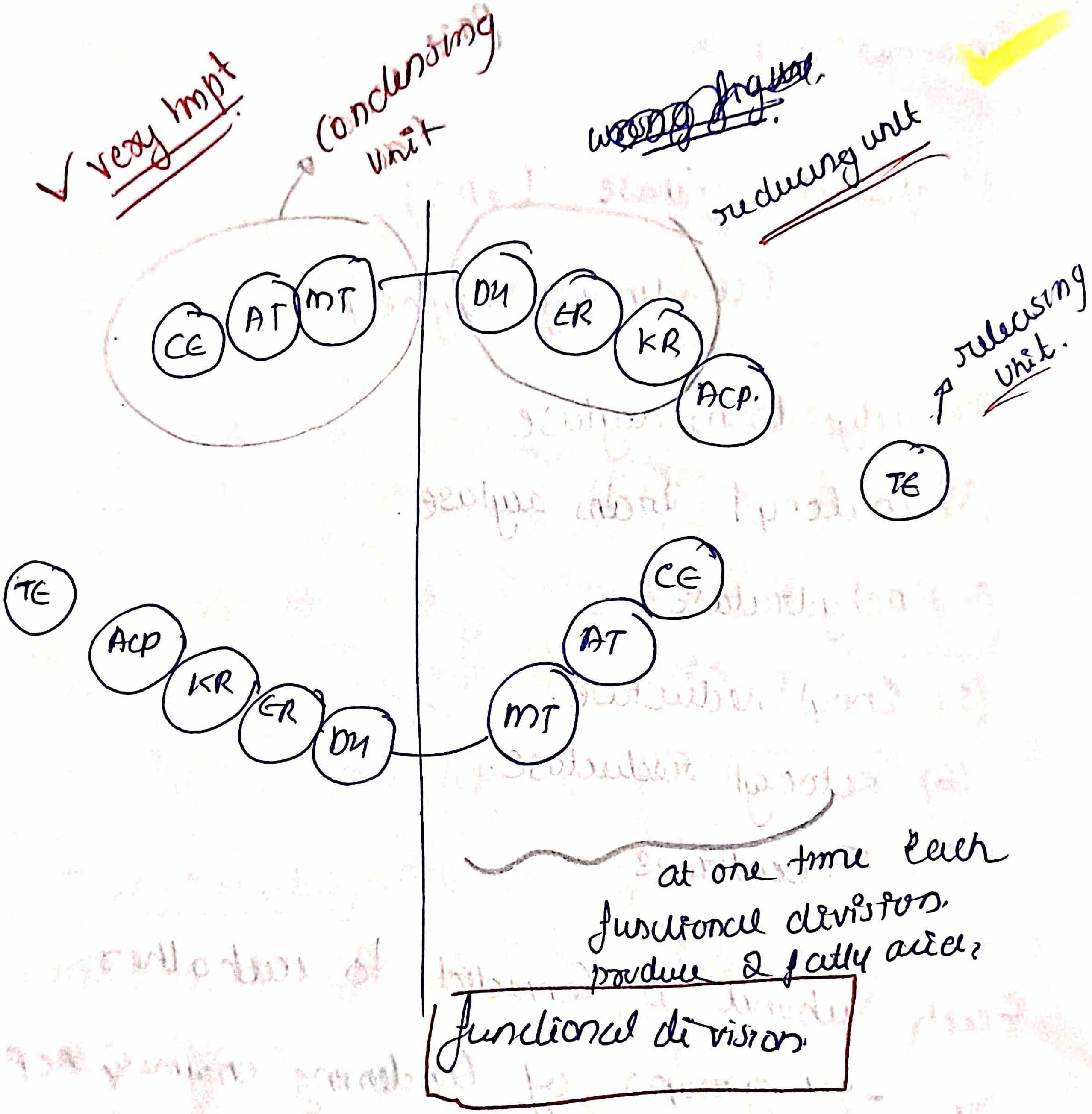
(4) Dehydratase.

(5) Enoyl reductase.

(6) Ketoacyl reductase.

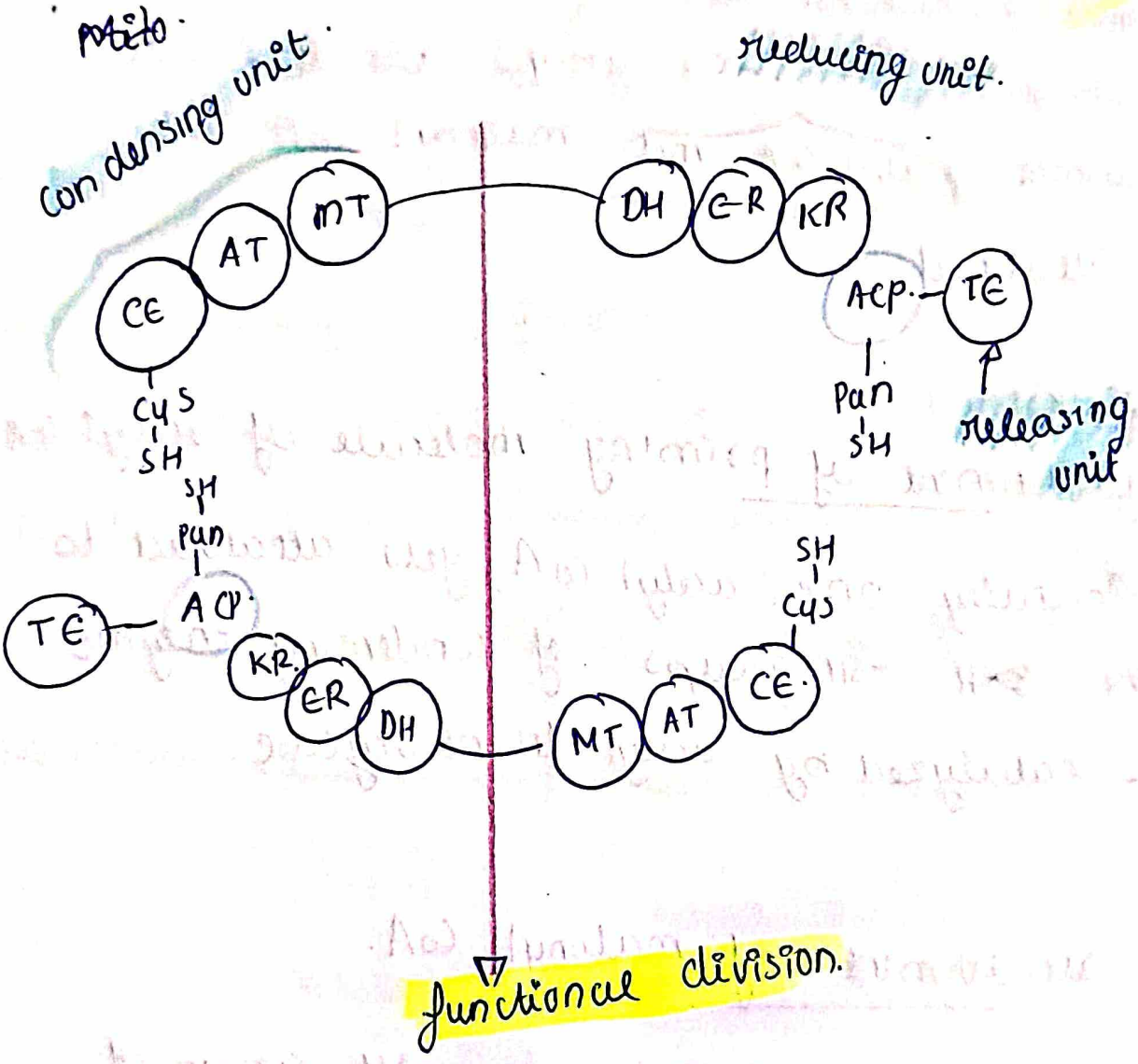
(7) Thioesterase.

Each subunit is connected to each other by -SH groups of Condensing enzyme & ACP.



- for 1 fatty acid synthesis. both ~~subun~~ functional division are required.
- at same time 2 fatty acids can be synthesised from both functional division.

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 acyl CoA and malonyl CoA get attached.

STEPS.

① attachment of priming molecule of acyl CoA

Initially one acyl CoA gets attached to the -SH groups of condensing enzyme - catalyzed by acyl 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 - Keto acyl - Enzyme. This will remain attached to ACP.

CE

① – Cys – SH

② – Pan – SH

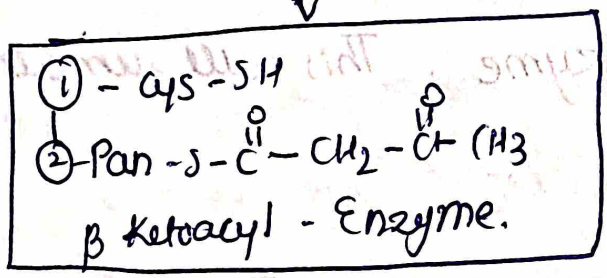
Acp

↓

① – cys · S ~ acetyl

② – Pan – S ~ malonyl

↓

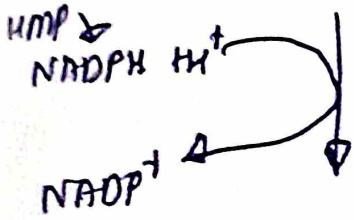


β Ketoacyl enzyme is reduced, dehydrated and reduced again to form 4C acyl - Enzyme.

① Cys – SH

② Pan – S·

β Ketoacyl - enzym

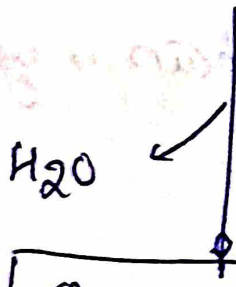


① – Cys – SH

② – Pan – S – C(=O) – CH_2 – CH(OH) – CH_3

α β

β hydroxyacyl Enzyme.



① – Cys – SH

② – Pan – S – C(=O) – CH = CH – CH_3

α β

α-β unsaturated acyl Enzyme.

HMP → NADPH + H⁺ → NADP⁺ ↓ enoyl reductase

① — Cys - SH
② — Pan - S ~ C(=O) — CH_2 — CH_2 — CH_3

acyl - Enzyme (4C)

another malonyl CoA gets attatched to ACP, displacing the acyl chain to condensing enzyme.

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

then it is released by
<u>Thioesterase</u> (De acylase)

Fate of palmitic acid.

activated to palmitoyl CoA.

→ Esterification to acyl glycerols

↘ formation of cholesteryl esters.

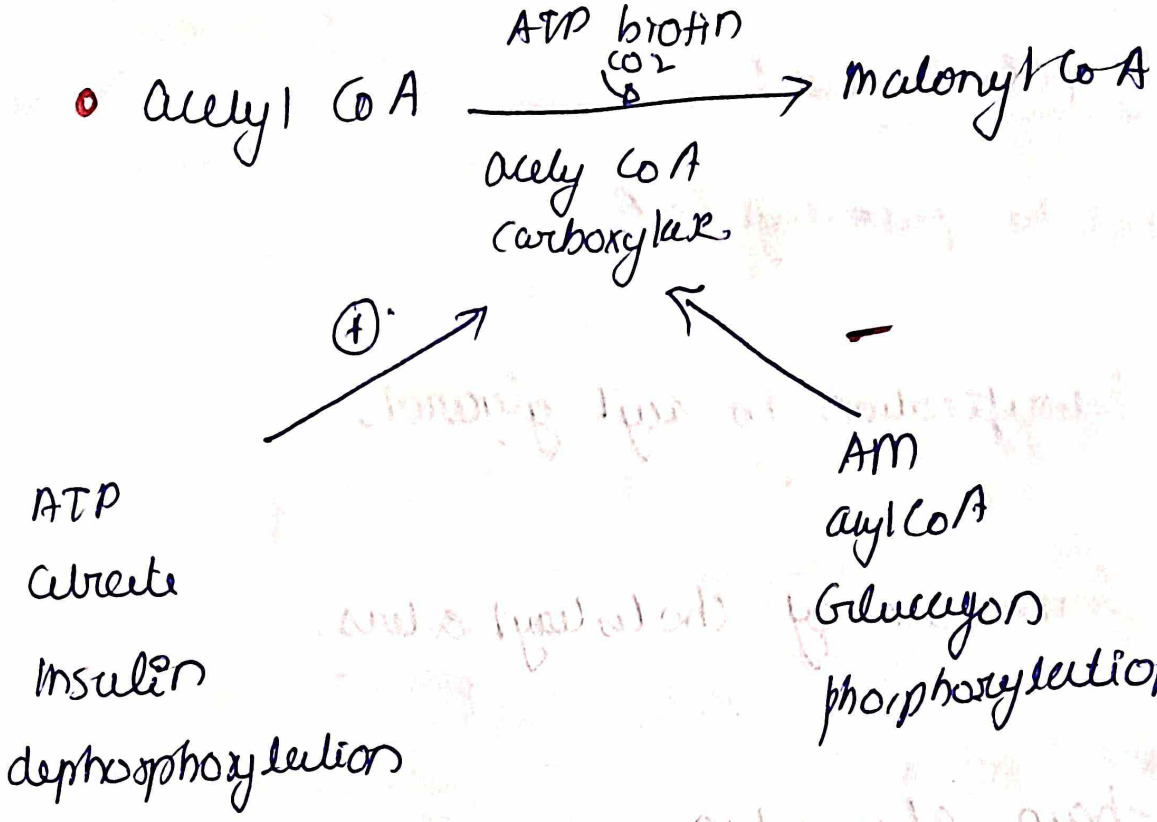
↘ chain elongation.

↘ Desaturation.

In lactating mammary gland a thioesterase acts at C_8 C_{10} C_{12} length.

Regulation

Key enzyme - acetyl CoA carboxylase.



① Nutritional state.

(A) ATP and citrate (more in well fed state)
- activates acetyl CoA carboxylase.
regulator of cellular starvation

(B) AMP & acyl CoA (starvation and lipolysis)
inhibit the enzyme.

---

② Hormonal regulation.

(a) Insulin activates and glucagon inhibits acetyl CoA carboxylase through covalent modification.

⑤ Insulin ↓ lipolysis → ↓ acyl CoA →
activate acetyl CoA carboxylase.

③ Covalent modification.

acetyl CoA carboxylase is active in dephosphorylated state.

Insulin causes dephosphorylation

Glucagon causes phosphorylation.

Regulation : must follow this order.

- Key enzyme
- steps including all co-enzyme
- activating & Inhibiting in same diagram.
- description.