Metabolism of ketone bodies :-

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Aceto acetate ($CH_3COCH_2-\overset{O}{\overset{\|}{C}}-OH$)
β-hydroxy butyrate ($CH_3-\overset{OH}{\underset{}{CH}}-CH_2-\overset{O}{\overset{\|}{C}}-OH$)
Acetone ($CH_3-CO-CH_3$)

} Collectively known as Ketone bodies

These are water soluble energy producing substances. Acetone is volatile & excreted from body through breathing.

Ketogenesis :-

Generation of ketone bodies from acetyl-CoA is called ketogenesis.

Liver cell is the only place for ketogenesis

Location : Mitrochondrial Matrix of liver cells.

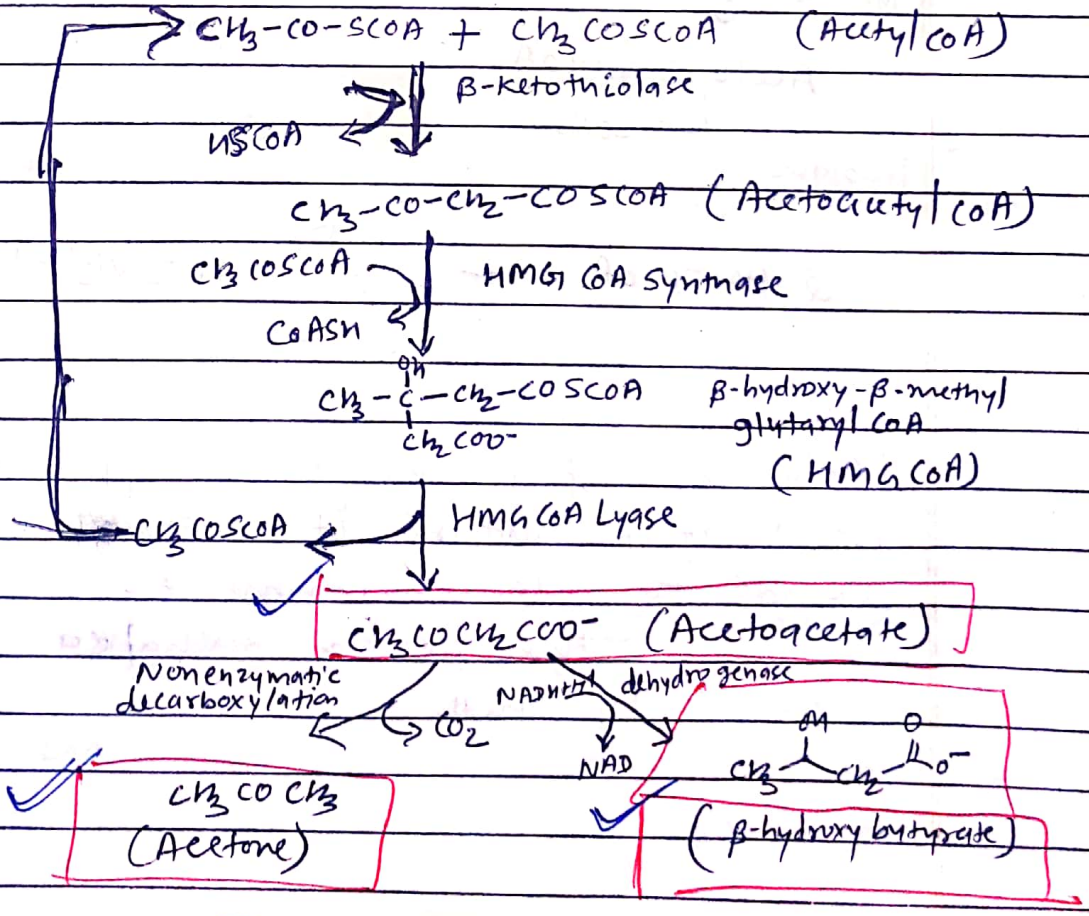

Fig :- Ketogenesis

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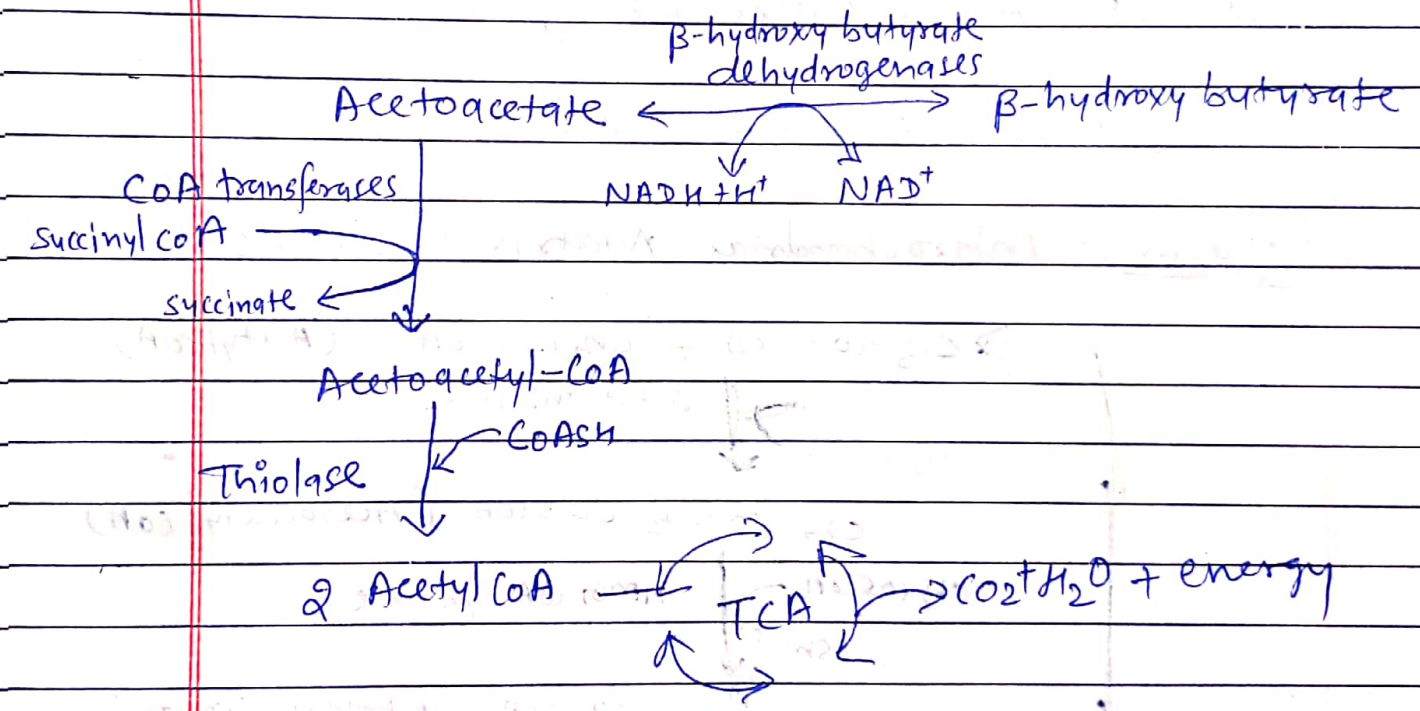
Utilization of ketone bodies :-

Though ketone bodies formed in liver cell but hepatic cell can't utilize these ketone bodies.

Because liver cell don't have the enzyme CoA-transferases, so they cannot utilize it. so these ketone bodies transfered from the liver cell to extrahepatic tissue or cells through blood supply.



Metabolism of acetone is not happened due to it's volatile nature, it is exhaled by the lungs to outer environment.

The person exhaled acetone smell like fruity smell.

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Significance of Ketogenesis :-

⇒ It allows liver to metabolise excess quantity of acetylCoA

⇒ During low supply of carbohydrate (starvation or in diabetes mellitus) — these ketone bodies serve as alternative energy source.

⇒ In long starvation, brain receive maximum supply by ketone bodies.

Regulation of ketogenesis :

Triglycerides

lipolysis ↓

Glucagon — stimulate lipolysis

Insulin → Inhibit lipolysis

Free fatty acid

β-oxidation ↓

↑ level of CAT-I → ↑ β-oxidation

Starvation ↑ β-oxidation

Acetyl-CoA

Low oxaloacetate → favors ketogenesis

Ketogenesis → Ketone bodies

High oxaloacetate favors TCA cycle path

TCA Cycle → Energy

Low oxaloacetate concentration may be due to prolong starvation, improper carbohydrate metabolism or diabetes mellitus

Disorders of ketone body metabolism

(1) Ketosis :⇒

Normal conc. of ketone body in ver less in blood is (0.2 mmol/L)

Hepatic cell ⟶ responsible for ketogenesis

Non Hepatic cell ⟶ responsible for utilization of ketone bodies

So when rate of formation of ketone bodies exceeds their utilization by periferal tissues. There is increase of ketone bodies in blood

rise in ketone body in blood ⟶ ketonemia

rise in ketone body in urine ⟶ ketonuria

ketonuria + ketonemia = ketosis

(2) Ketoacidosis :⇒

Acetoacetate & β-hydroxybutyrate are behave as moderate acids.

So if their conc. increase in blood, the bicarbonate ions (alkali) compensate with this. so bicarbonate conc. ↓ & deplete the body alkali reserve. This leads to ketoacidosis. (Blood pH decreases)

This condition is mainly found in type-I diabetes patient.

In type-II diabetes – relatively rare.

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De-novo synthesis of fatty acids (Lipogenesis)

New synthesis of fatty acid from acetyl CoA is called De novo lipogenesis.

⇒ Mainly occurs in liver & lactating mammary glands.

⇒ In minute amount – adipose tissue, kidney & brain cell.

3 Steps involved for lipogenesis.

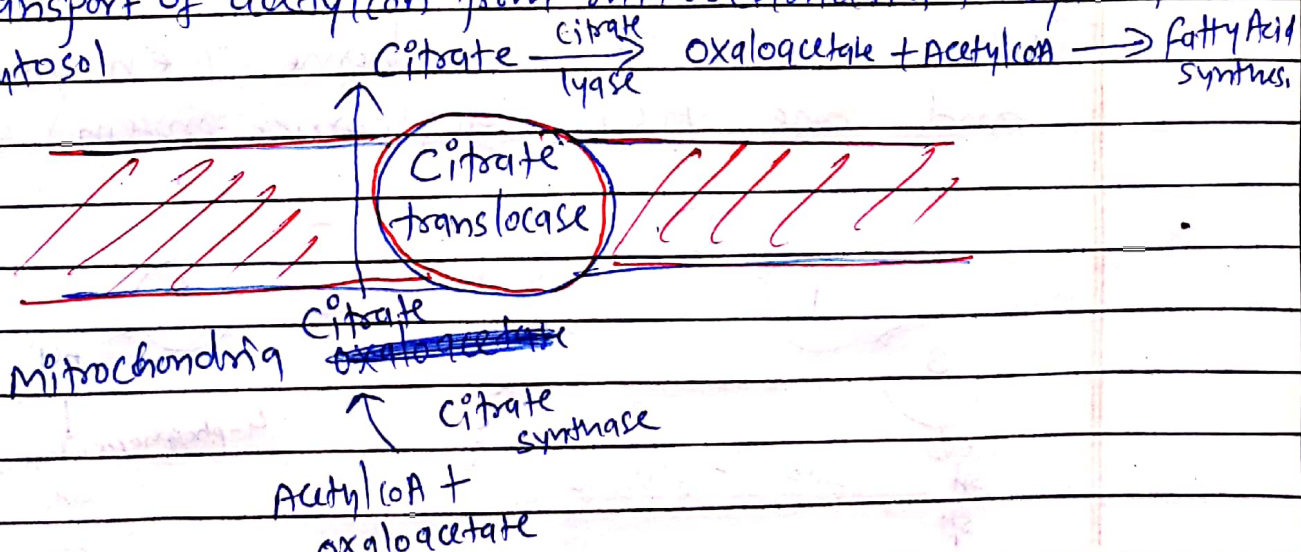
(C16 Palmitic Acid synthesis)

(1) Transport of acetyl CoA from mitrochondria to cytosol

(2) Carboxylation of acetyl CoA to from malonyl CoA

(3) Reaction of fatty acid synthesis using fatty acid synthase Complex

(1) Transport of acetyl CoA from mitrochondria to cytosol



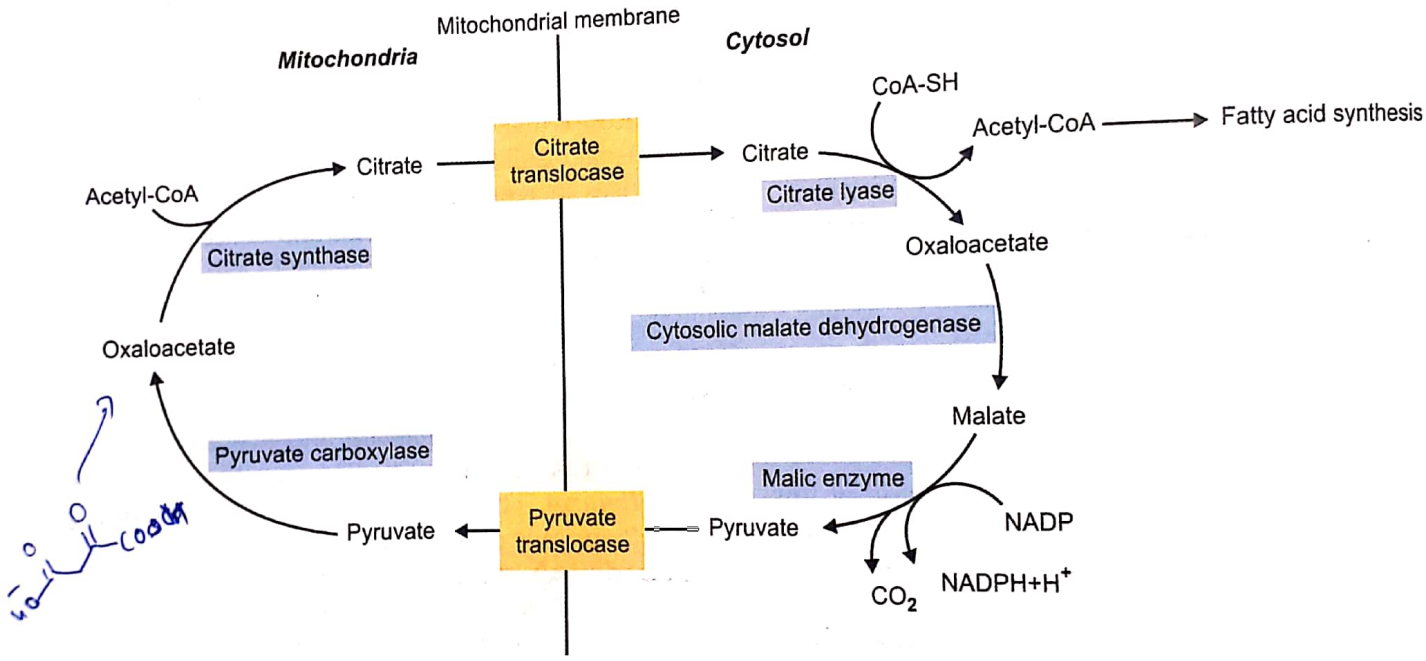


Figure 13.16: Transfer of acetyl-CoA from mitochondria to the cytosol

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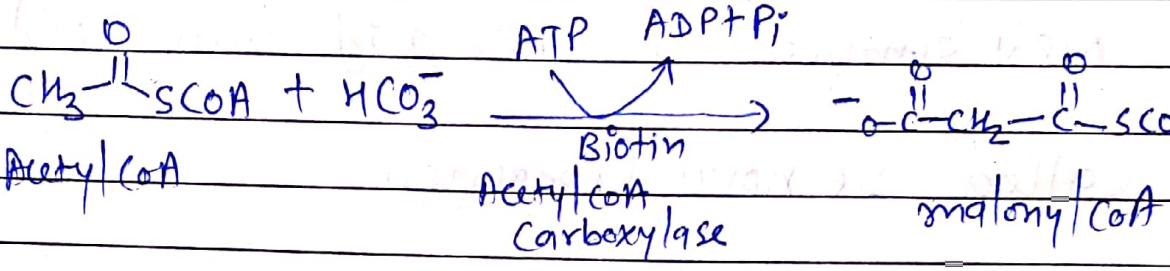
(2) Carboxylation of acetyl CoA to malonyl-CoA



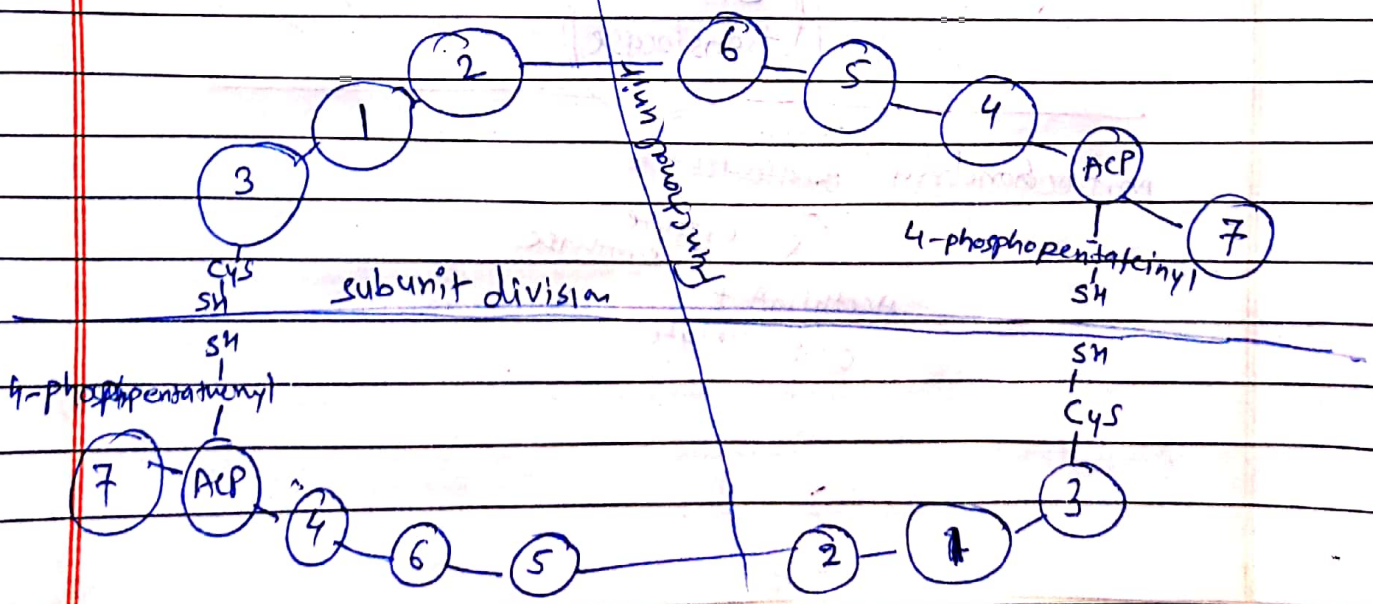
The Carboxylation of acetyl CoA is the rate limiting step in fatty acid synthesis

(3) Reactions of fatty acid synthase complex

Fatty acid synthase complex is a multi enzyme complex which have different catalytic reaction ~~place~~ site on it.

The active complex is dimeric and arrange in head to tail fashion.

This synthase Complex have 7 enzyme site and one ACP (acyl carrier protein) site.



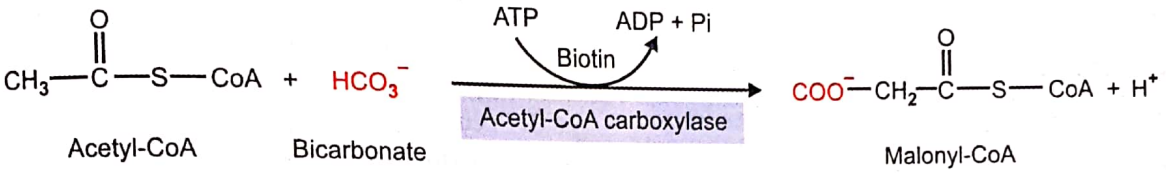


Figure 13.17: Biosynthesis of malonyl-CoA

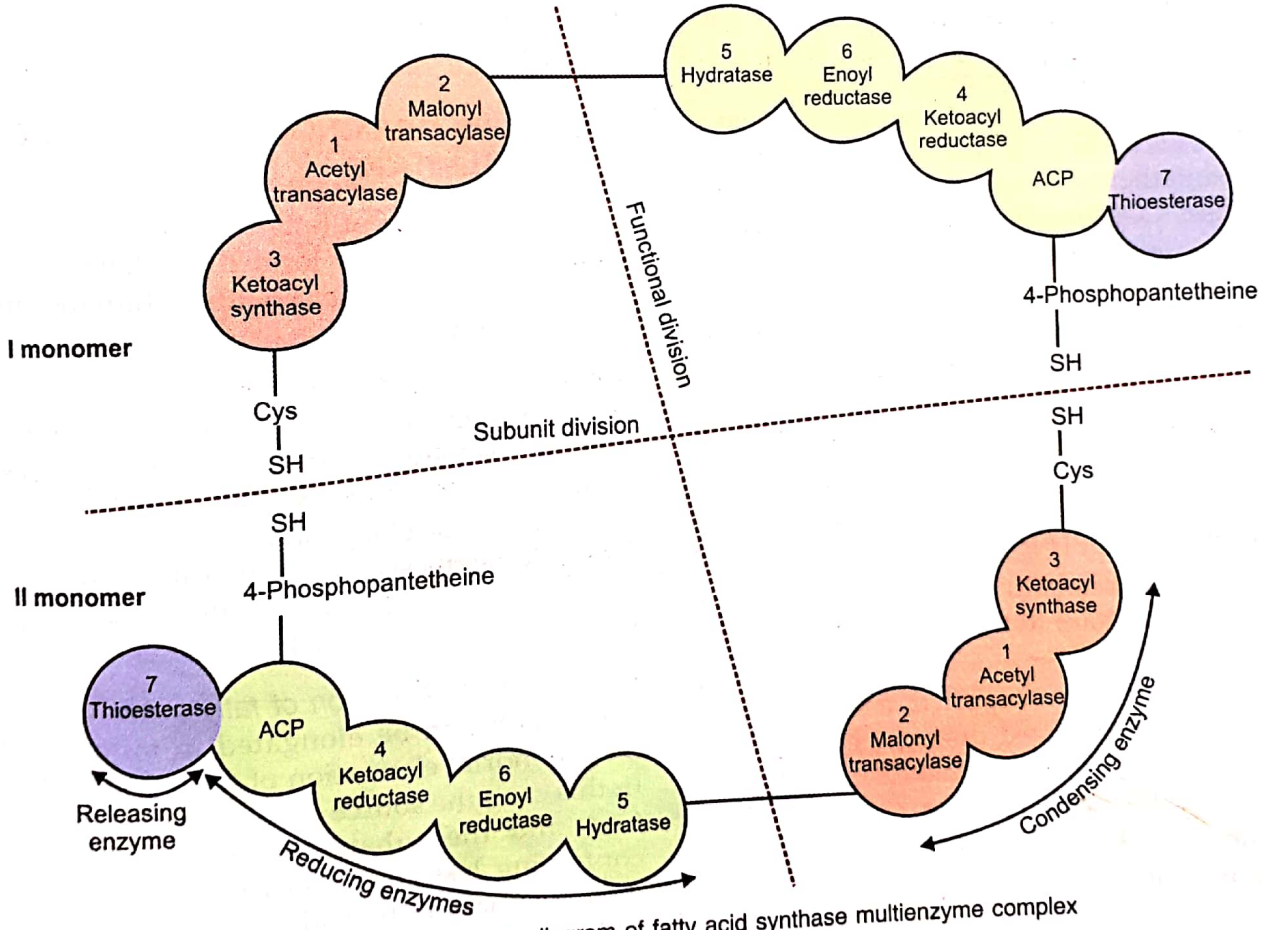
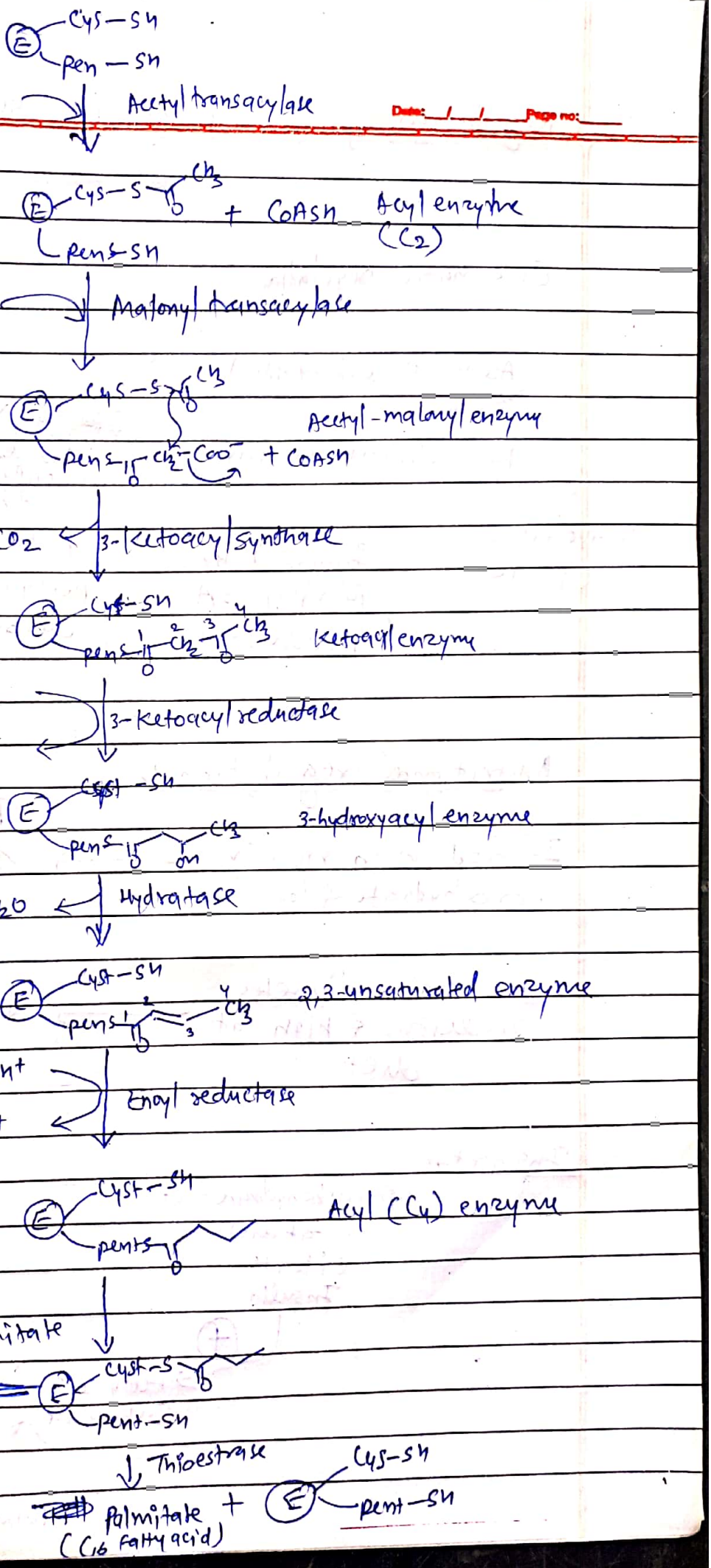


Figure 13.18: Schematic diagram of fatty acid synthase multienzyme complex

Reactions


E
Cys–SH
Pen–SH
Acetyl CoA
Acetyl transacylase
Date: / / Page no:
Cys–S
CH3
O
+ CoASH
Acyl enzyme (C2)
Pen–SH
malonyl CoA
Malonyl transacylase
Acetyl-malonyl enzyme
CH2
COO⁻
+ CoASH
CO2
3-ketoacyl synthase
Ketoacyl enzyme
NADPH+H+
NADP+
3-ketoacyl reductase
3-hydroxyacyl enzyme
OH
H2O
Hydratase
2,3-unsaturated enzyme
Enoyl reductase
Acyl (C4) enzyme
Till C16 palmitate form
Thioesterase
Palmitate (C16 fatty acid)

Regulation of Denovo fatty acid synthesis

Enzymatic regulation

Hormonal regulation

Acetyl CoA Carboxylase

Rate limiting enzyme

Activated by Citrate

Inhibited by Palmitoyl CoA (Product)

Insulin

Activate Acetyl CoA Carboxylase

Glucagon epinephrine

Inactivate Acetyl CoA Carboxylase

Nutritional regulation :-

If food taken rich in Carbohydrate & low fat ⟶ ↑ synthesis & ↑ activity of Acetyl CoA Carboxylase

starvation, diabetes mellitus & High fat diet ⟶ ↓ synthesis of Acetyl CoA Carboxylase enzyme

In short :-

High Carbohydrate diet
low fat diet
Citrate
Insulin
(+)
→ Acetyl CoA Carboxylase ← (−)
Epinephrine, Glucagon
Palmitoyl-CoA, Starvation
High Fat diet