

Carbohydrate Metabolism

Glycolysis

Also known as carbohydrate embden meyerhof pathway (EM Pathway)

Metabolic pathway that converts 6-C glucose into pyruvate (aerobic glycolysis) and lactate (anaerobic glycolysis) with the production of energy.

Glycolysis occurs in presence of the oxygen (aerobic) or in the absence of oxygen (anaerobic)

Glycolysis is a major pathway for ATP synthesis in tissues lacking mitochondria eg: RBC, cornea, ...

Site of glycolysis - Cytosol.

Steps of Glycolysis

- 1) Glucose is phosphorylated to Glu-6-phosphate with help of hexokinase / Glucokinase. ATP split into ADP and P_i .

Require Mg^{2+}

Irreversible step

Glu-6-phosphate is a central molecule for glycogenesis, gluconeogenesis and HMP shunt pathway.

- 2) Isomerization of Glu-6-P (an aldose sugar) to Fructose-6-P (a ketose sugar), catalyzed by phosphohexose isomerase

Reversible

3) Fructose-6-Phosphate is phosphorylated to Fructose-1,6-bisphosphate with the help of Phosphofructokinase (PFK)

* Irreversible step
Rate limiting step.

4) The 6C Fructose 1,6 Bisphosphate is split into two 3-C compounds, Glyceraldehyde-3-phosphate and dihydroxy acetone phosphate (DHAP).

Reversible
enzyme - Aldolase

5) Phosphotriose isomerase catalyze the reversible interconversion of DHAP and glyceraldehyde-3-P.

Two molecules of Glyceraldehyde - 3-P are obtained from one molecule of glucose.

6) Glyceraldehyde - 3-P. Dehydrogenase converts Glyceraldehyde - 3-P to 1,3-bisphosphoglycerate.

A high energy compound (1,3 Bisphosphoglycerate) and NADH are formed

In the aerobic condition, NADH enters in ETC and generates 5 ATP by oxidative phosphorylation

In the ~~ab~~ anaerobic condition this NADH is utilised by LDH

In the anaerobic ..

7) 1,3-bisphosphoglycerate kinase act on 1,3-Bisphosphoglycerate and convert it to 3-Phosphoglycerate with production of ATP.

- Reversible (only kinase reaction which is reversible in glycolysis)

Substrate level Phosphorylation.

Phosphorylation at the level of substrate or formation of a high energy compound (Phosphorylation) without entering to ETC, is coupled with conversion of substrate to product.

8) 3-Phosphoglycerate is converted to 2-Phosphoglycerate by mutase enzyme

The high energy compound phosphoenol pyruvate is formed from 2-Phosphoglycerate by enolase enzyme.

- Fluoride inhibit enolase action by removing Mg^{2+} ions.

9) Phosphoenol pyruvate $\xrightarrow[\text{enzyme}]{\text{Pyruvate Kinase}}$ pyruvate

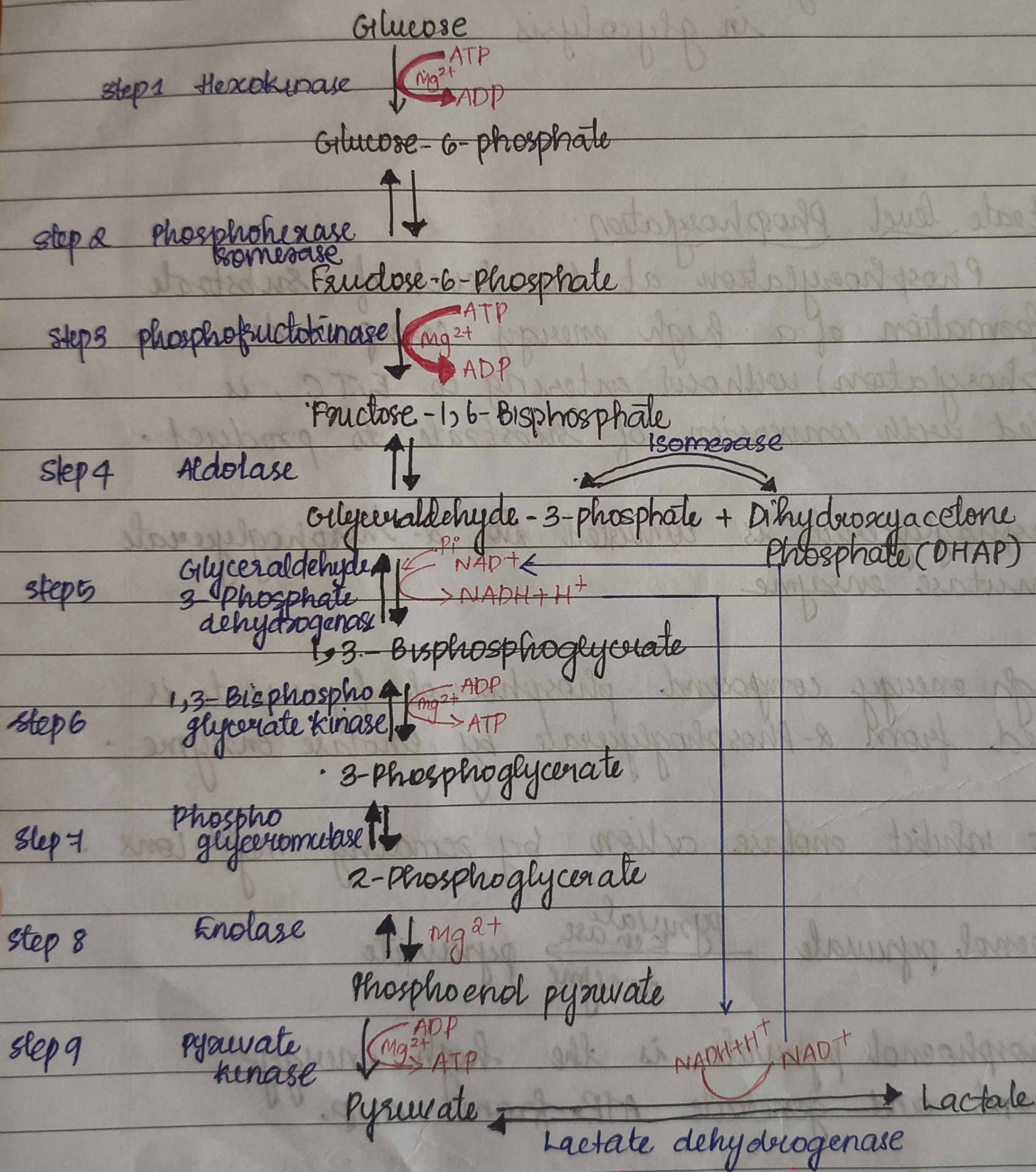
Phosphoenol pyruvate is the high energy compound and generate ATP from ADP.

This is another example for substrate level Phosphorylation.

2 molecules of ATP are released in this step

10) In the Anaerobic condition, pyruvate converts to Lactate in presence of Lactate dehydrogenase.

This enzyme utilizes NADH generated in glyceraldehyde-3-phosphate dehydrogenase step.



Regulation of Glycolysis

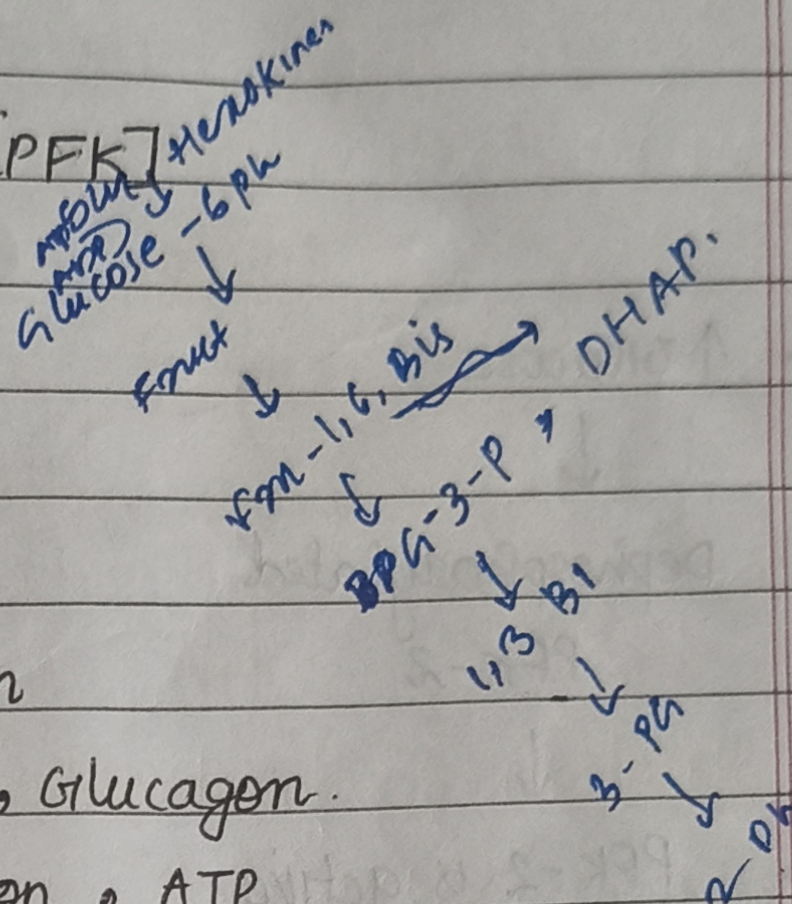
Irreversible steps in Glycolysis
Catalysed by

Hexokinase or Glucokinase

Phosphofructokinase [PFK]

Phosphofructokinase [PFK]

Pyruvate kinase



Regulatory enzymes of glycolysis

Enzyme - Activation

Inhibition

HK

Insulin

G-6-P, Glucagon.

PFK

Insulin, AMP.

Glucagon, ATP

F-6-P, PFK-2,

citrate, low PH,

F-2,6-BP

cyclic AMP.

PK

Insulin, F-1,6-BP

Glucagon, ATP, PK.

cyclic AMP.

2nd messenger

enz
HX F-6-P
PFK P-1,6-BP

in
F-2,6-BP
PFK-2

9-ATP
GI-AMP
cyclic
AMP

Tandem / bifunctional enzyme

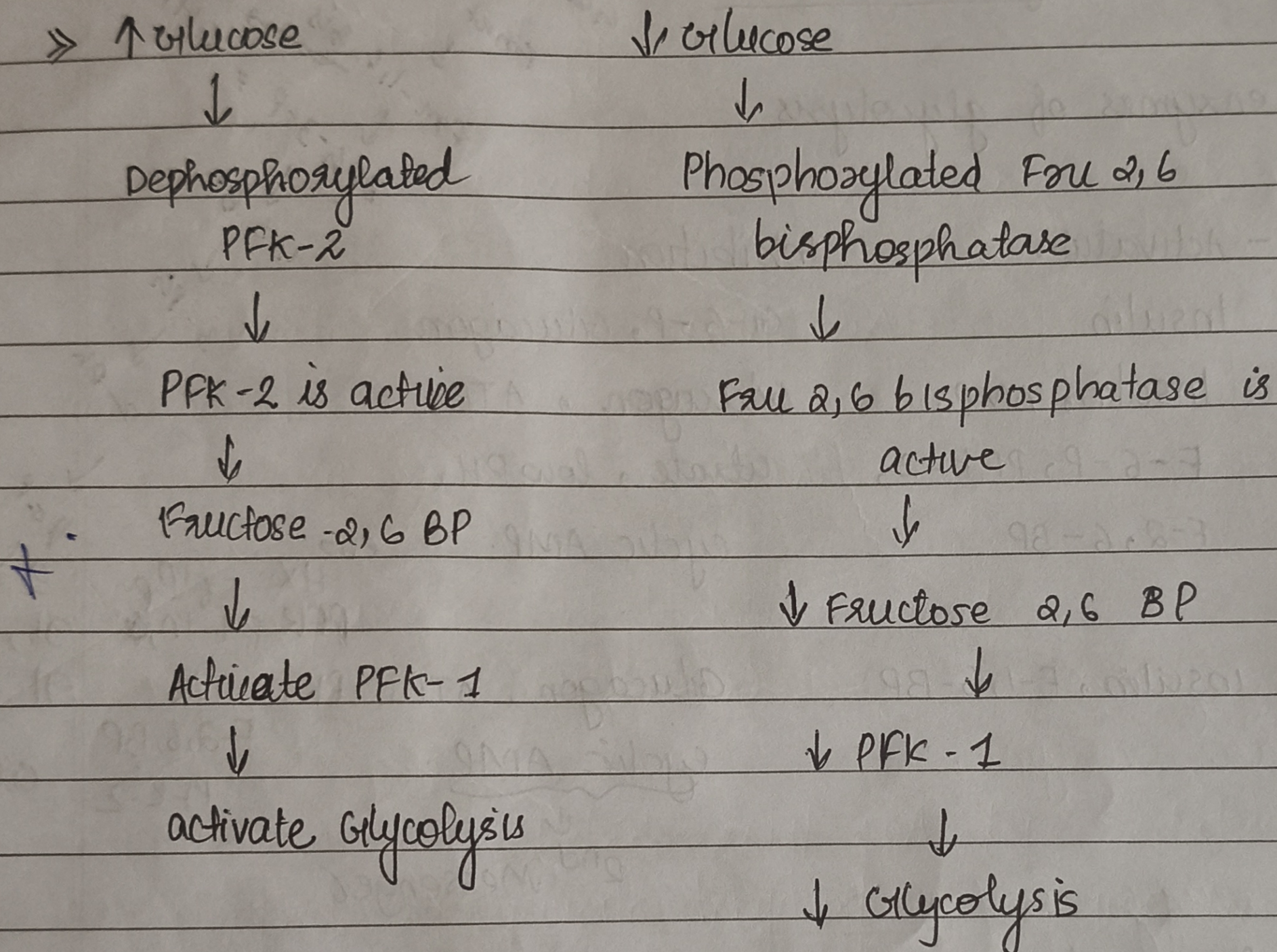
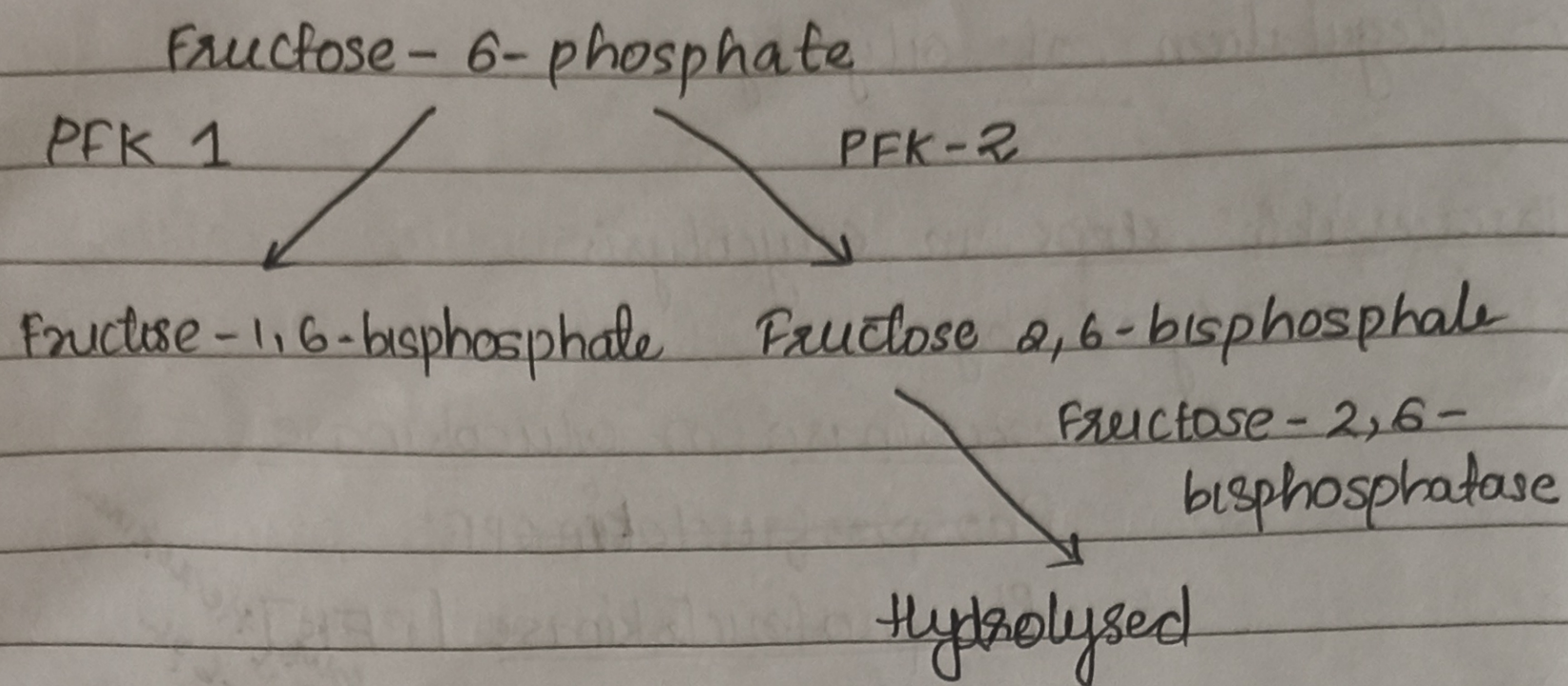
Phosphofructokinase - 2 (PFK-2)

and

Fructose - 2,6-Bisphosphatase

These 2 enzymes are components of a single polypeptide, so called bifunctional enzymes

The activities of both enzymes are reciprocally regulated.



Energy yield from glycolysis

i) ATP utilisation

2 molecules are utilised per molecule of glucose

(ii) ATP production (under Aerobic condition)

A) substrate level Phosphorylation

1. 1,3-bisphosphoglycerate kinase reaction 2ATP

2. Pyruvate kinase reaction 2ATP

4 ATP

net yield $4+5=9$ minus $2=7$

Obic condition)

ation

ate kinase reaction - 2ATP

tion = 2ATP

al $\rightarrow$ 4ATP Net yield = $4-2$

= 2ATP

in RBC.

rocytes

olysis is passed on this

ted

phoglycerate instead of directly -
phosphoglycerate is converted into

3 Bisphosphoglycerate (2,3-BPG)

G mutase.

converted to 3-phosphoglycerate by

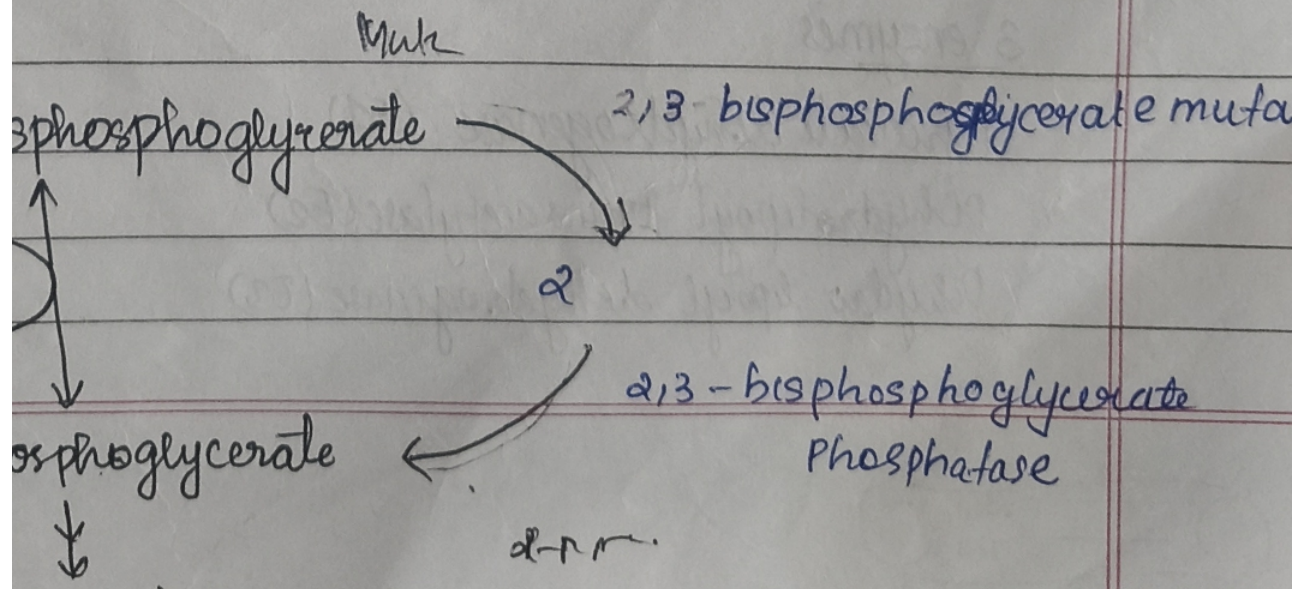
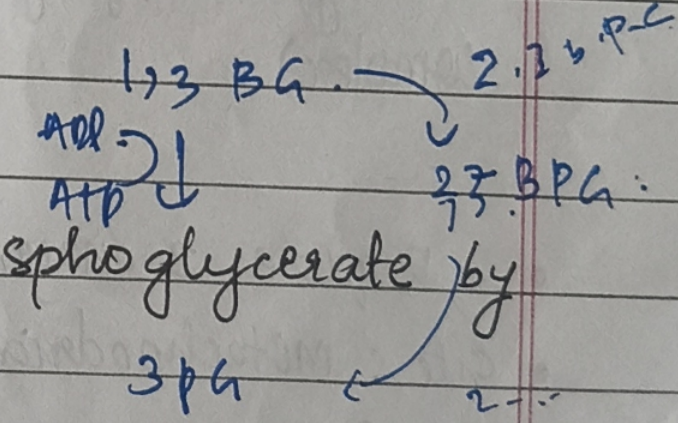
se

ose

3-phosphoglycerate

phosphoglycerate

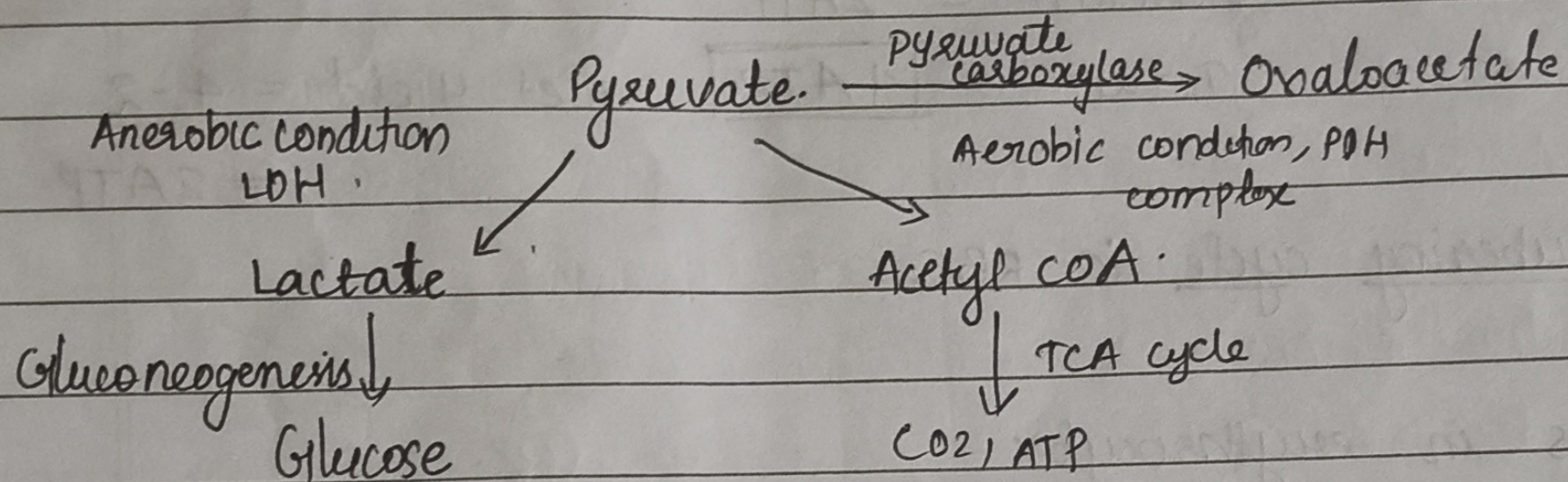
phosphate



significance of 2,3-BPG

- 2,3-BPG combines with Hb and reduces its affinity towards O₂. This helps oxy Hb to unload O₂ to tissues
- 2,3 BPG level increase during hypoxia, anemia conditions and life at high altitudes

Fate of pyruvate



8 Mark Pyruvate dehydrogenase complex (PDH complex)

- Pyruvate is converted to acetyl CoA by oxidative decarboxylation
- Catalysed by pyruvate dehydrogenase enzyme (multi enzyme complex)
- Require 3 enzymes and 5 coenzymes
- Site: mitochondria (Pyruvate is transported to MC from cytoplasm by a pyruvate transporter)

3 enzymes

Pyruvate dehydrogenase (E1)

Dihydrolipoyl transacetylase (E2)

Dihydrolipoyl dehydrogenase (E3)

5 co factor/co enzymes.

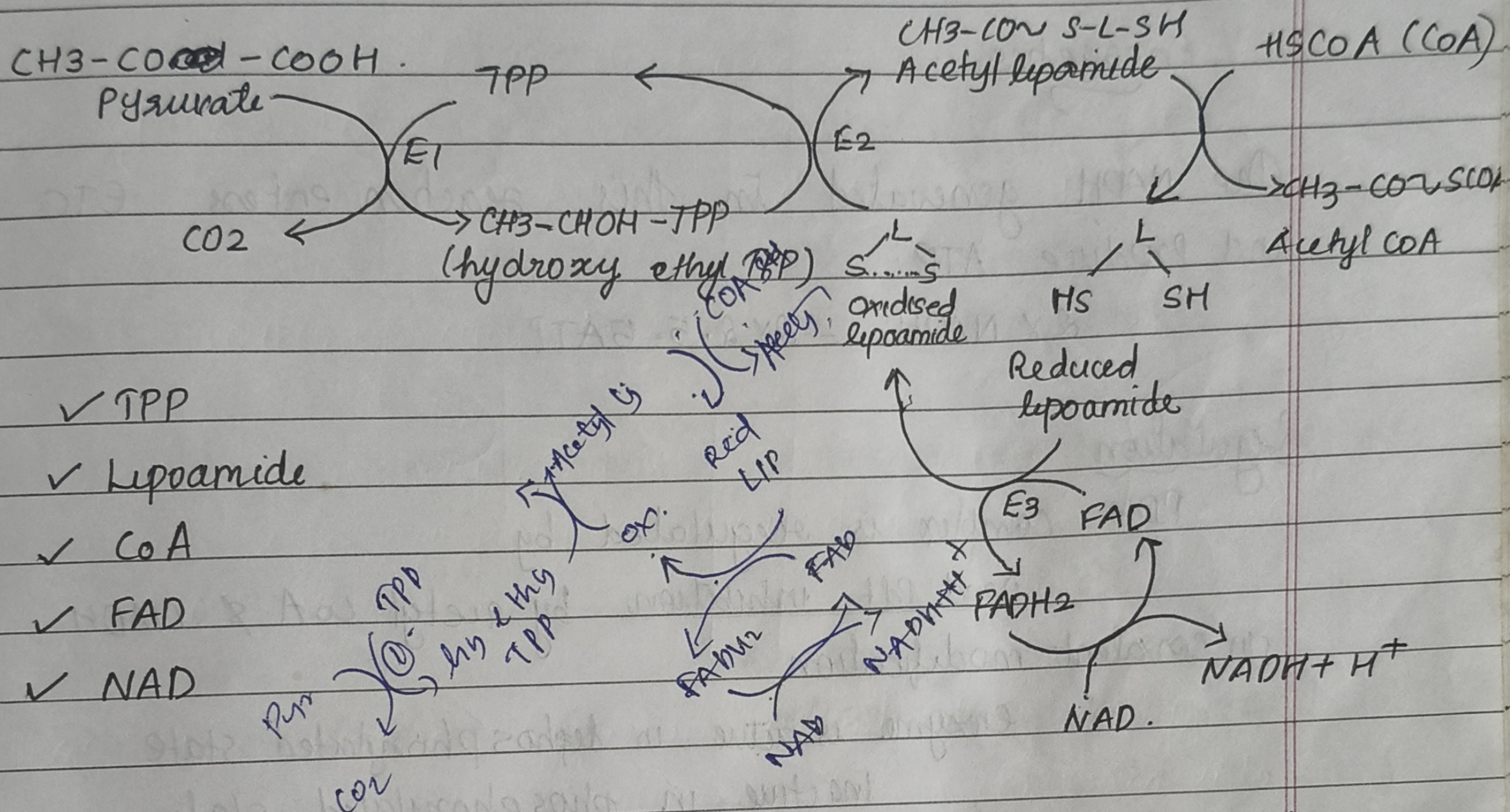
Thiamine pyrophosphate (TPP)

lipoamide

CoA

FAD

NAD.



Pyruvate dehydrogenase : catalyse oxidative decarboxylation, result in the formation of hydroxy ethyl TPP.

Coenzyme for this reaction : TPP [coenzyme form of Vet B1 (Thiamine)]

Dihydrolipoyl transacetylase : hydroxyl group is oxidised to acetyl group and is transferred from TPP to lipoamide to form Acetyl lipoamide

Dihydrolipoyl dehydrogenase : oxidation of lipoamide.

Regeneration of TPP, lipoamide and FAD.

Importance of PDH.

completely irreversible process

Pyruvate $\rightarrow$ acetyl CoA $\rightarrow$ Fatty acid

No net synthesis of glucose from fat, as it is reversible.

Energetics

The NADH generated in this reaction enters ETC and produce ATP.

$$2 \times \text{NADH} = 2 \times 2.5 = 5 \text{ATP}$$

Regulation

PDH complex is regulated by

Reversible inhibition by acetyl CoA & NADH

(1) Covalent modification

Enzyme is active in dephosphorylated state

Inactive in phosphorylated state

Clinical Aspects.

Thiamine deficiency

- PDH activity decreased

- Pyruvate is converted to lactate

- Lactate acidosis