Subject : Biochemistry

Semester : II

Name of the Teacher : Dr. Ruma Das

Topic : Core Course 4

Regulation of Enzyme Activity

Regulation of Pyruvate dehydrogenase complex

Enzyme Regulation

Enzymes are biocatalyst. The most striking characteristics of enzyme are their catalytic power and specificity. Enzymes are highly specific both in their reaction, which they catalyze and the choice of reactants.
The activity of enzyme is regulated in various way so that they function at proper time and place.
The regulation may occur is different ways.
e.g. a) Allosteric control
b) Covalent modification
c) Proteolytic activation
d) Isozyme (different or multiple forms of enzyme)
e) Controlled amount of Enzyme production
f) Control of enzyme activity by various molecules e.g Ca^{2+} or hormones like insulin, glucagon etc.

Regulation of multienzyme Complex

What is multienzyme comple?
Multienzyme complexes are stable assembly

of more than one enzyme generally involved in sequential catalytic transformation.

Example of such enzymes are

i) pyruvate dehydrogenase complex,
ii) fatty acyl synthease complex
iii) glutamin synthase
iv) rubisco

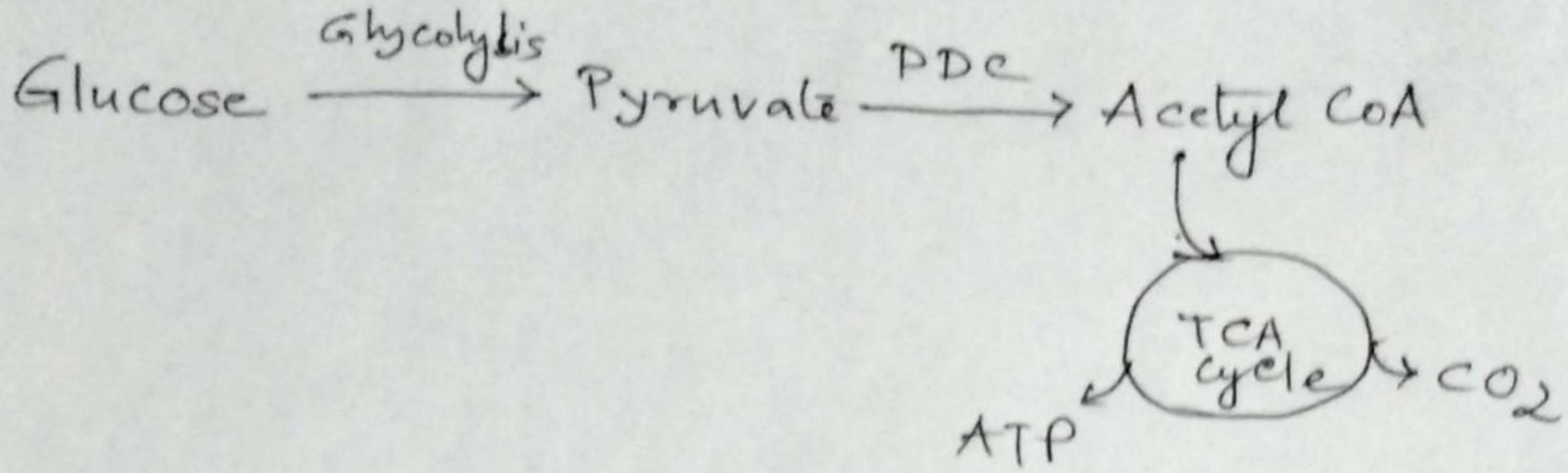
Pyruvate dehydrogenase Complex (PDC)

PDC is located in the mitochondrial matrix and pyruvate is transported from cytosol to mitochondrial matrix by an enz. pyruvate translocase. In mitochondrial matrix pyruvate is converted to acetyl CoA by the action of PDC.

PDC is a complex of 3 enzymes namely pyruvate dehydrogenase, dihydrolipoyl transacetylase dihydrolipoyl dehydrogenase.

PDC converts pyruvate to Acetyl CoA and AcetylCoA is then used in TCA cycle. Hence PDC links glycolysis to TCA cycle.

$$\text{Pyruvate} + \text{CoA} + NAD^+ \longrightarrow \text{Acetyl CoA} + CO_2 + NADH + H^+$$



Structural Component of PDC in Prokaryotes & Eukaryotes

Enzyme	Cofactors	Subunits Prok	Subunits Euk	Reaction Catalyzed
Pyruvate dehydrogenase (E1)	TPP	24	30	Oxidative decarboxylation of Pyruvate
Dihydrolipoyl transacetylase (E2)	Lipoate CoA	24	60	Transfer of acetyl group to CoA
Dihydrolipoyl dehydrogenase (E3)	FAD NAD^+	12	12	Regeneration of the oxidized form of Lipoate

Regulation : Glucose is converted to Pyruvate by the process Glycolysis and pyruvate can be converted to glucose by Gluconeogenesis. But the formation of Acetyl CoA from pyruvate is an irreversible step and thus pyruvate is unable to convert acetyl CoA back into glucose

Since PDC is a critical enzyme, so its activity is controlled stringently.

Reaction:

$$\text{Pyruvate} + \text{COA} + \text{NAD}^+ \xrightarrow{\text{PDC}} \text{Acetyl CoA} + CO_2 + \text{NADH} + H^+$$

- High conc. of reaction product inhibit the reaction.
  i) Acetyl CoA inhibits the transacetylase (E2) component of PDC by direct binding
  ii) NADH inhibits the dihydrolipoyl dehydrogenase (E3) component of PDC.

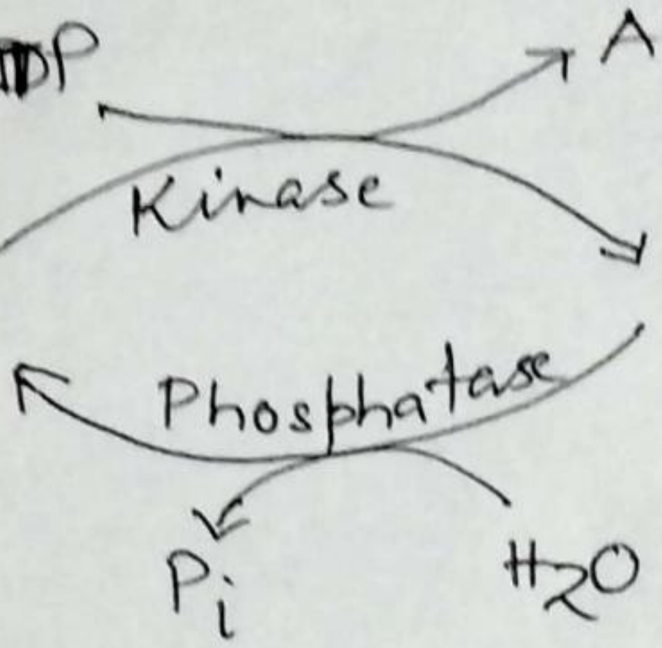
  So, from the reaction it can be concluded, if the system has high conc. of Acetyl CoA or NADH, PDC is not functional and therefore formation of Acetyl CoA is stopped.

- The key regulation of PDC in eukaryotes is by covalent modification.

  Phosphorylation of the pyruvate dehydrogenase component (E1) by pyruvate dehydrogenase Kinase I (PDK) switches off the activity of the complex. Deactivation of PDC is reversed by the pyruvate dehydrogenase phosphatase.

  At rest, muscle does not require energy production, hence PDC is deactivated.

In otherwords, high conc. of acetyl CoA, NADH, ATP inhibit PDC's activity.



Regulation of PDC

During exercise, glycolysis occur. and ADP conc. and pyruvate is increased. ~~Increase conc. of ADP and pyruvate~~.

PDC is then activated by inhibiting kinase and phosphatase is stimulated by Ca^{2+}. A rise in cytoplasmic Ca^{2+} level elevates mitochondrial Ca^{2+} level. The rise in mitochondrial Ca^{2+} activates phosphatase and enhances PDC activity.

In some tissue, phosphatase is also regulated by hormone e.g insulin. In liver and adipose, insulin activates phosphatase and thus PDC gets activated. PDC in turn convert pyruvate into acetyl CoA. This acetyl CoA if not used in TCA cycle is again converted to fatty acid.

Hence, in these tissue PDC is activated to convert glucose to pyruvate and finally to Acetyl CoA. Acetyl CoA ultimately converted to fatty acids

So, this multienzyme complex PDC is regulated in so many ways. e.g end product inhibition, covalent modification (by the action of kinase and phosphatase).