BOTANY

Regulation of Enzyme Action

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(Enzymology)

&

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Paper - I

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Regulation of enzyme activity

Methods of regulation of enzyme activity

- Allosteric control
- Reversible covalent modification
- Isozymes (isoenzymes)
- Proteolytic activation

Allosteric Enzymes

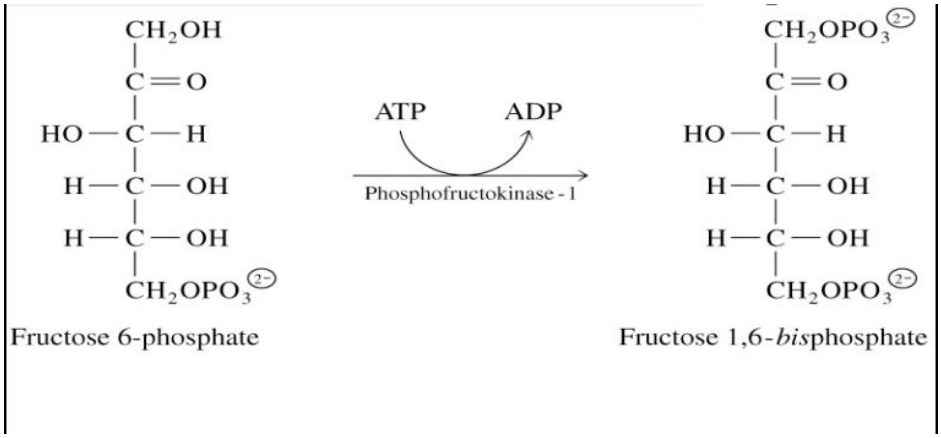
Allosteric enzymes have a second regulatory site (allosteric site) distinct from the active site.Allosteric enzymes contain more than one polypeptide chain (have quaternary structure).
Allosteric modulators bind noncovalently to allosteric site and regulate enzyme activity via conformational changes.

2 types of modulators (inhibitors or activators)

• Negative modulator (inhibitor)
–binds to the allosteric site and inhibits the action of the enzyme
–usually it is the end product of a biosynthetic pathway - end-product (feedback) inhibition
• Positive modulator (activator)
–binds to the allosteric site and stimulates activity
–usually it is the substrate of the reaction.

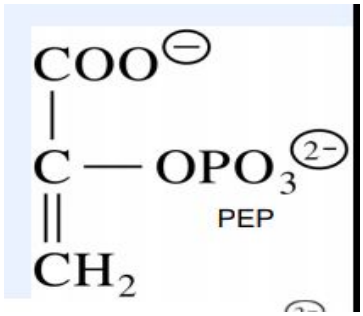
Example of allosteric enzyme - phosphofructokinase-1 (PFK-1)

PFK-1 catalyzes an early step in glycolysis
• Phosphoenol pyruvate (PEP), an intermediate near the end of the pathway is an allosteric inhibitor of PFK-1.



Fructose 6-phosphate

Fructose 1,6-*bis*phosphate



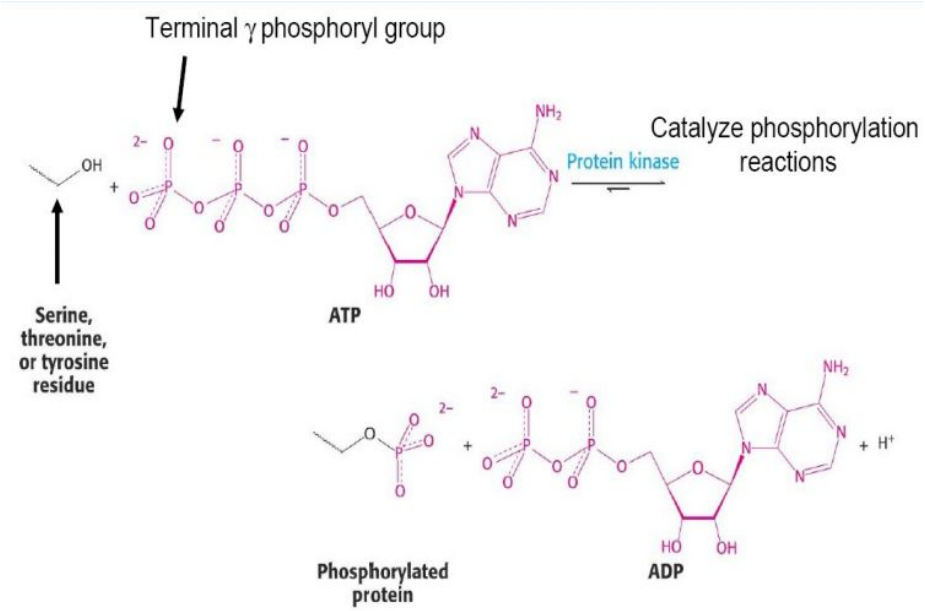
Regulation of enzyme activity by covalent modification

- **Covalent attachment of a molecule to an amino acid side chain of a protein can modify activity of enzyme**

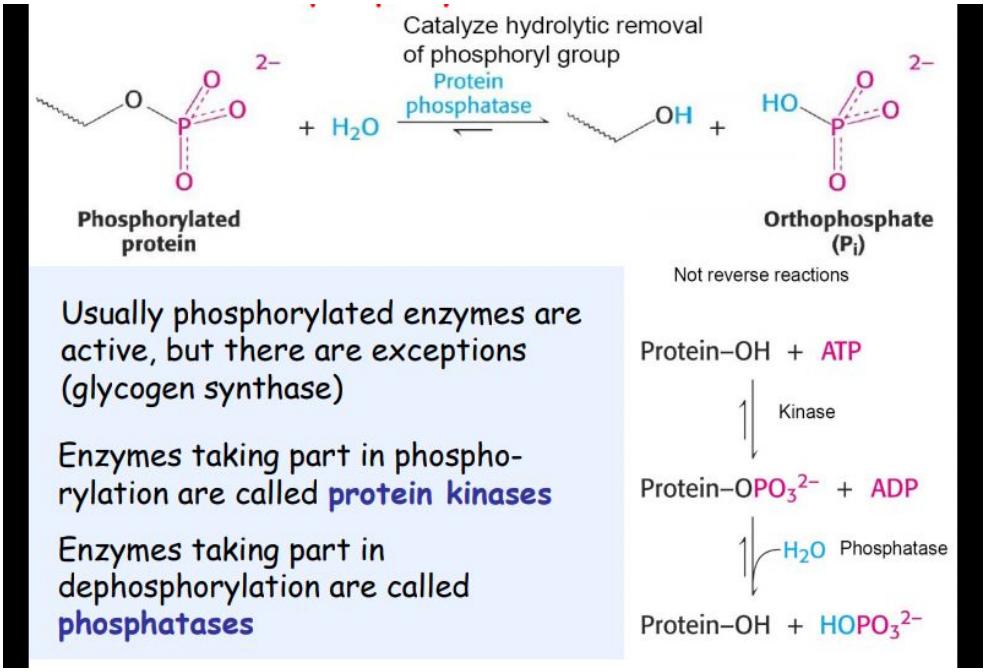
Common covalent modifications of protein activity

Modification	Donor molecule	Example of modified protein	Protein function
Phosphorylation	ATP	Glycogen phosphorylase	Glucose homeostasis; energy transduction
Acetylation	Acetyl CoA	Histones	DNA packing; transcription
Myristoylation	Myristoyl CoA	Src	Signal transduction
ADP-ribosylation	NAD	RNA polymerase	Transcription
Farnesylation	Farnesyl pyrophosphate	Ras	Signal transduction
γ-Carboxylation	HCO_3^-	Thrombin	Blood clotting
Sulfation	3′-Phosphoadenosine-5′-phosphosulfate	Fibrinogen	Blood-clot formation
Ubiquitination	Ubiquitin	Cyclin	Control of cell cycle

Phosphorylation reaction



Dephosphorylation reaction



Isoenzymes (isozymes)

Some metabolic processes are regulated by enzymes that exist in different molecular forms - isoenzymes

Isoenzymes - multiple forms of an enzyme which differ in amino acid sequence but catalyze the same reaction Isoenzymes can differ in: kinetics, regulatory properties, the form of coenzyme they prefer and distribution in cell and tissues Isoenzymes are coded by different genes.

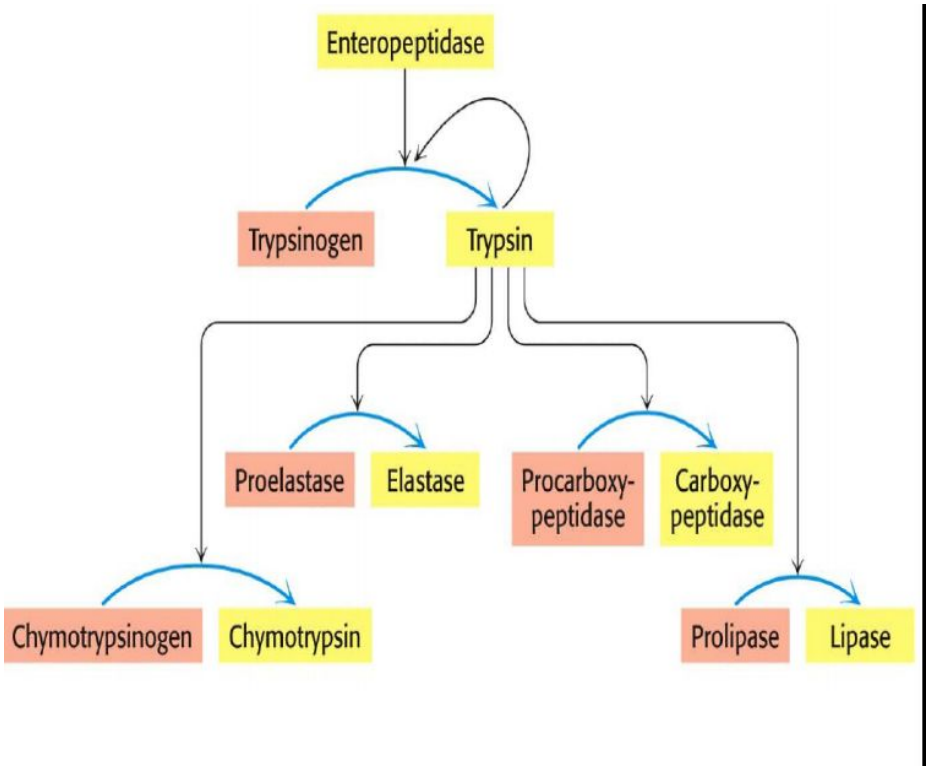
Example: lactate dehydrogenase (LDG)
Lactate + NAD+ pyruvate + NADH + H+

Lactate dehydrogenase – tetramer (four subunits)
composed of two types of polypeptide chains, M and H
There are 5 Isozymes of LDG:
H4 – heart
HM3
H2M2
H3M
M4 – liver, muscle

• H4
: highest affinity; best in aerobic environment
•M4
: lowest affinity; best in anaerobic environment
Isoenzymes are important for diagnosis of different diseases

Activation by proteolytic cleavage

• Many enzymes are synthesized as inactive precursors (zymogens) that are activated by proteolytic cleavage
• Proteolytic activation only occurs once in the life of an enzyme molecule
Examples of specific proteolysis
•Digestive enzymes
–Synthesized as zymogens in stomach and pancreas
•Blood clotting enzymes
–Cascade of proteolytic activations
•Protein hormones
–Proinsulin to insulin by removal of a peptide



Multienzyme Complexes and Multifunctional Enzymes

●Multienzyme complexes - different enzymes that catalyze sequential reactions in the same pathway are bound together
• Multifunctional enzymes - different activities may be found on a single, multifunctional polypeptide chain.

Metabolite channeling

• Metabolite channeling - “channeling” of reactants between active sites
• Occurs when the product of one reaction is transferred directly to the next active site without entering the bulk solvent
• Can greatly increase rate of a reactions
• Channeling is possible in multienzyme complexes and multifunctional enzymes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