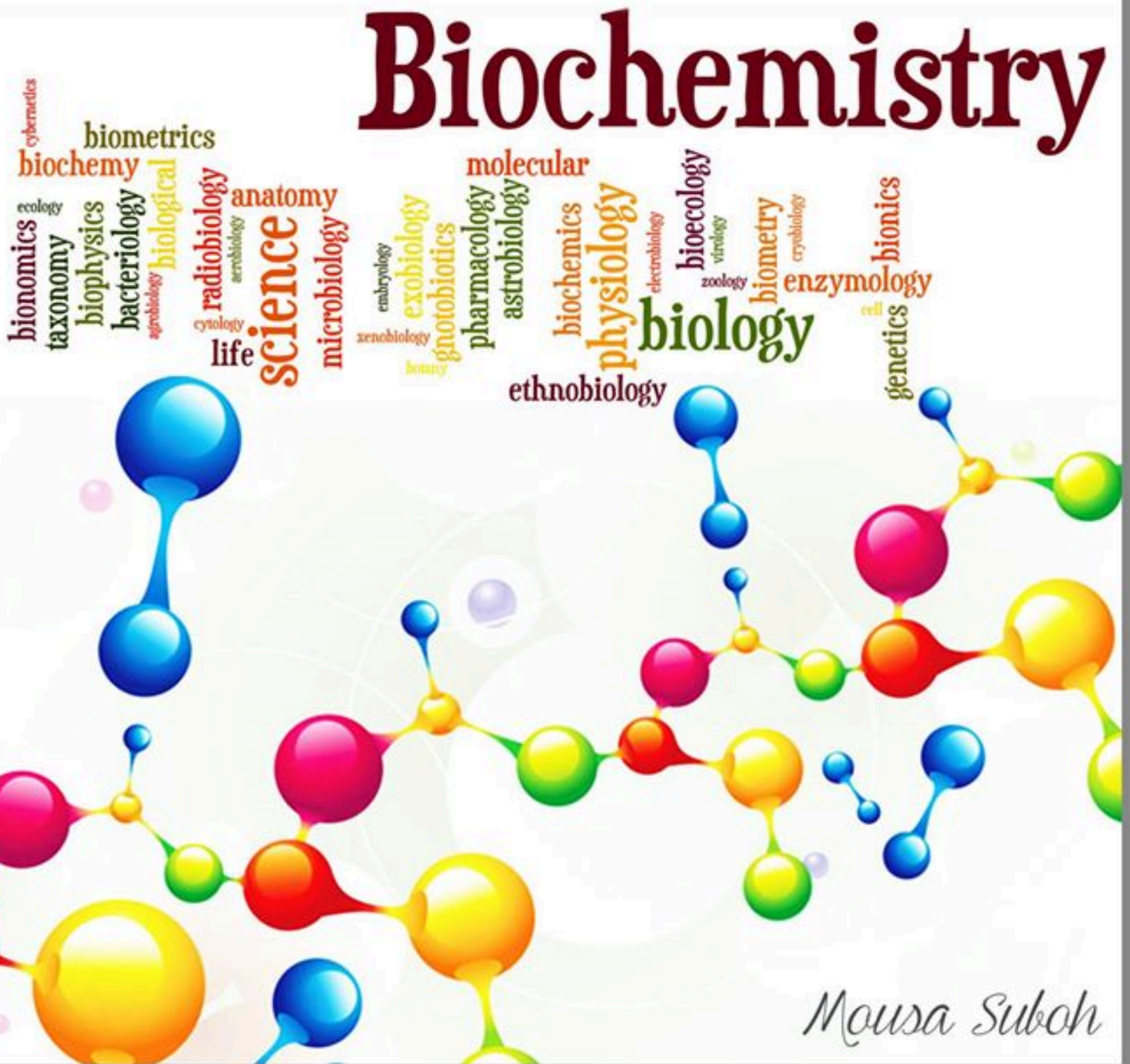
Slide :..Enzymes 6.....

Dr. Name :..Dr.Nayef Kradsheh

Sections : ...4,5,6.....

■ Slide □ Sheet

Medical Committee
The University of Jordan



B Covalent Modification :-

1- Phosphorylation is a highly effective mean of switching the activity of ~~target~~ Proteins :-

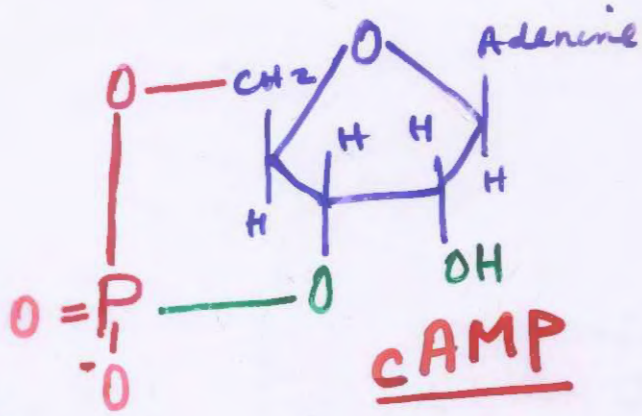
- Dedicated protein kinases - bind single protein
- Multifunctional protein kinases - phosphorylate many proteins
  - phosphorylation of Ser & thr
    : : tyr. by tyr kinase
  -
- Protein phosphatases :- reverse phosphorylation

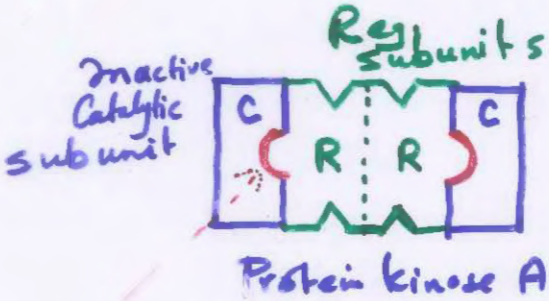
Phosphorylation is a very effective process for controlling

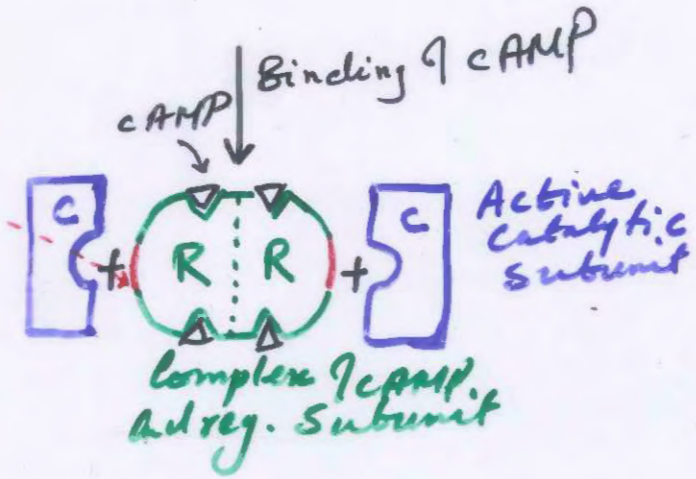
- phosphoryl gr. add two -ve charges
- phosphoryl gr. can form three hydrogen bonds
- Free-energy of phosphorylation is large
  ~ - 12 Kcal/mole
- phosphorylation-dephosphorylation can occur in less than a sec —— Min
- High amplification effect

Cyclic AMP activates Protein kinase A by unleashing its Catalytic subunits

- PK-A
- c-AMP



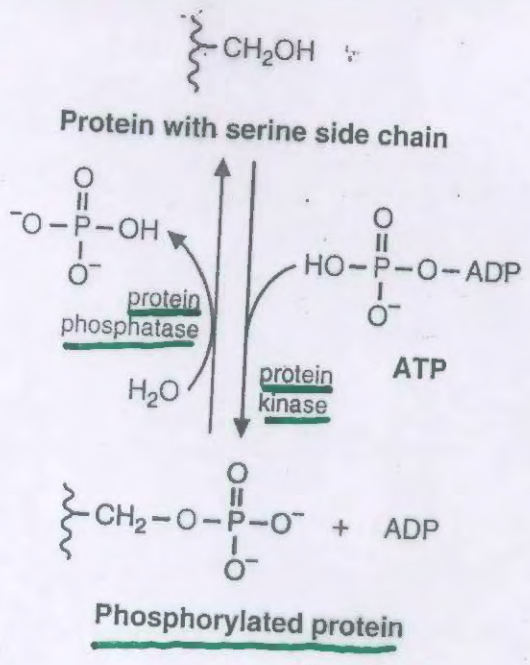




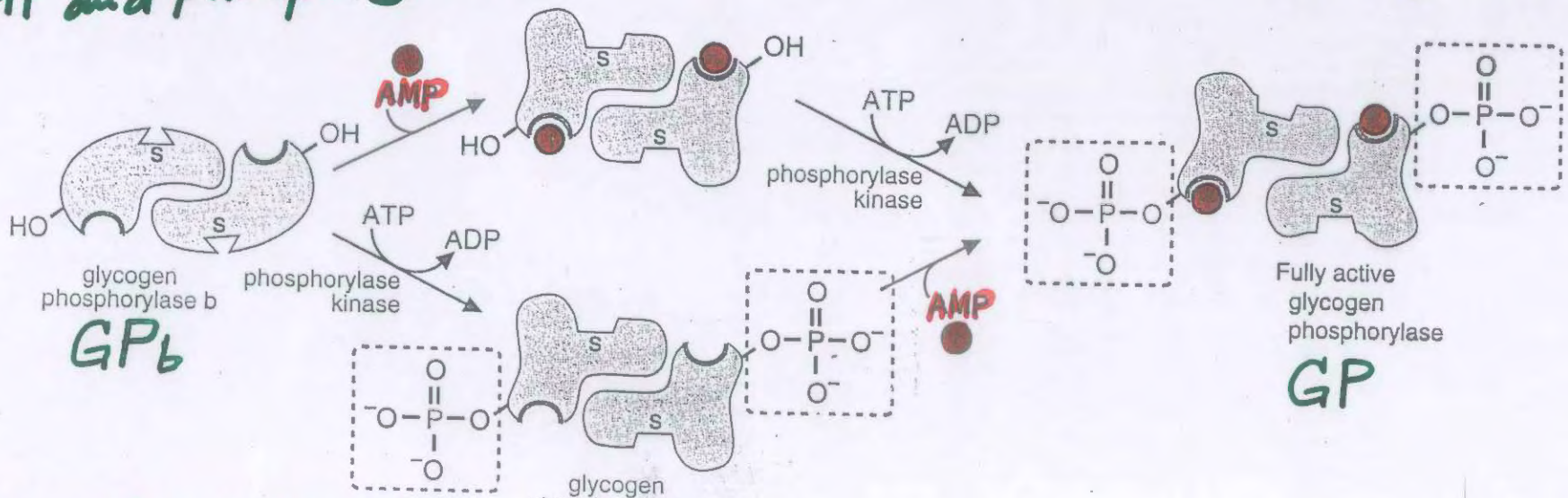
- Protein phosphatases

COVALENT MODIFICATION

(1) - phosphorylation — dephosphorylation of proteins

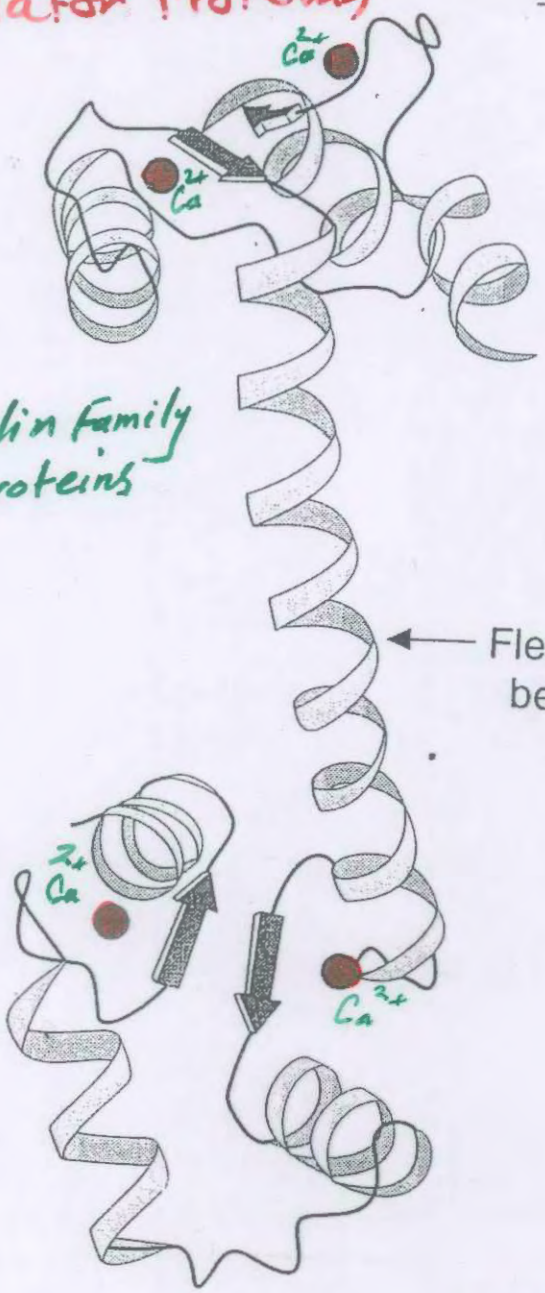


(2) - Activation of GP by AMP and phosphorylation



- Other Covalent modifications
Acetyl-, ADP-ribose, lipid

C-Protein-Protein Interaction
(Modulator Proteins)



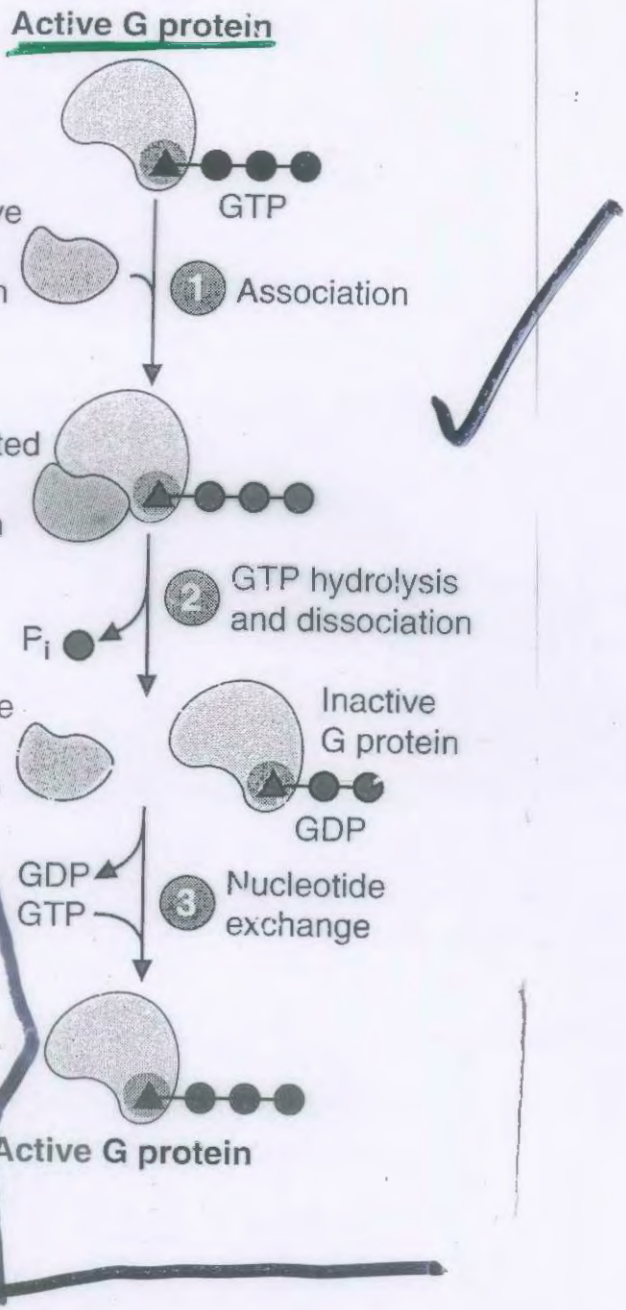
(1)
Ca-Calmodulin family
of modulator proteins

GP Kinase ↑ by cAMP
also
GP Kinase ↑ by Ca-Calmodulin

- Tropinin C binds Ca^{2+}
  - regulatory subunit of tropinin - a regulator of muscle contration
  - member of Ca^{2+} - Calmodulin superfamily

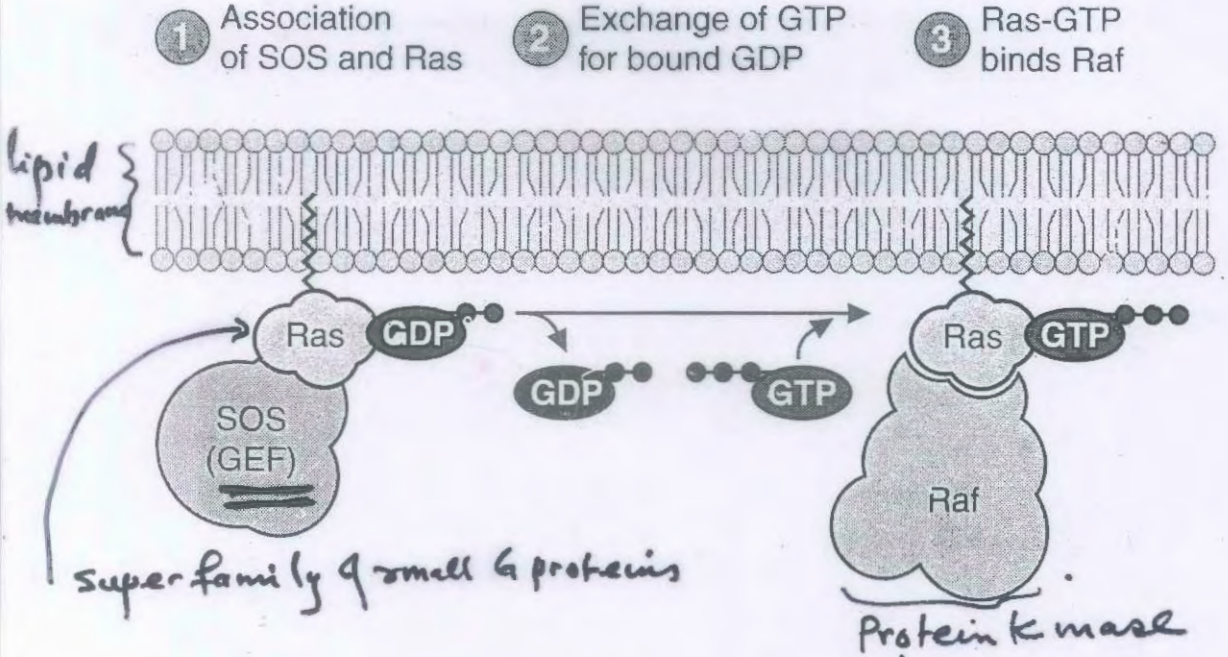
(2) Regulation by G proteins

- G proteins are the master of regulation through reversible protein association



Reg. of G-proteins

- GAP – GTPase activating Proteins
- GEF – guanine nucleotide exchange factor
- GDI – GDP dissociation inhibitor



superfamily of small G proteins

Protein kinase

↓

Activation of transcription of certain genes

D- PROTEOLYTIC CLEAVAGE

- Many Enzymes are Regulated by Specific Proteolytic Cleavage

  Digestive enzyme

  Blood clotting factors

  Pro enzyme or zymogen

- Isozymes Provide a Means of Regulation specific to Distinct tissues and Developomental stages

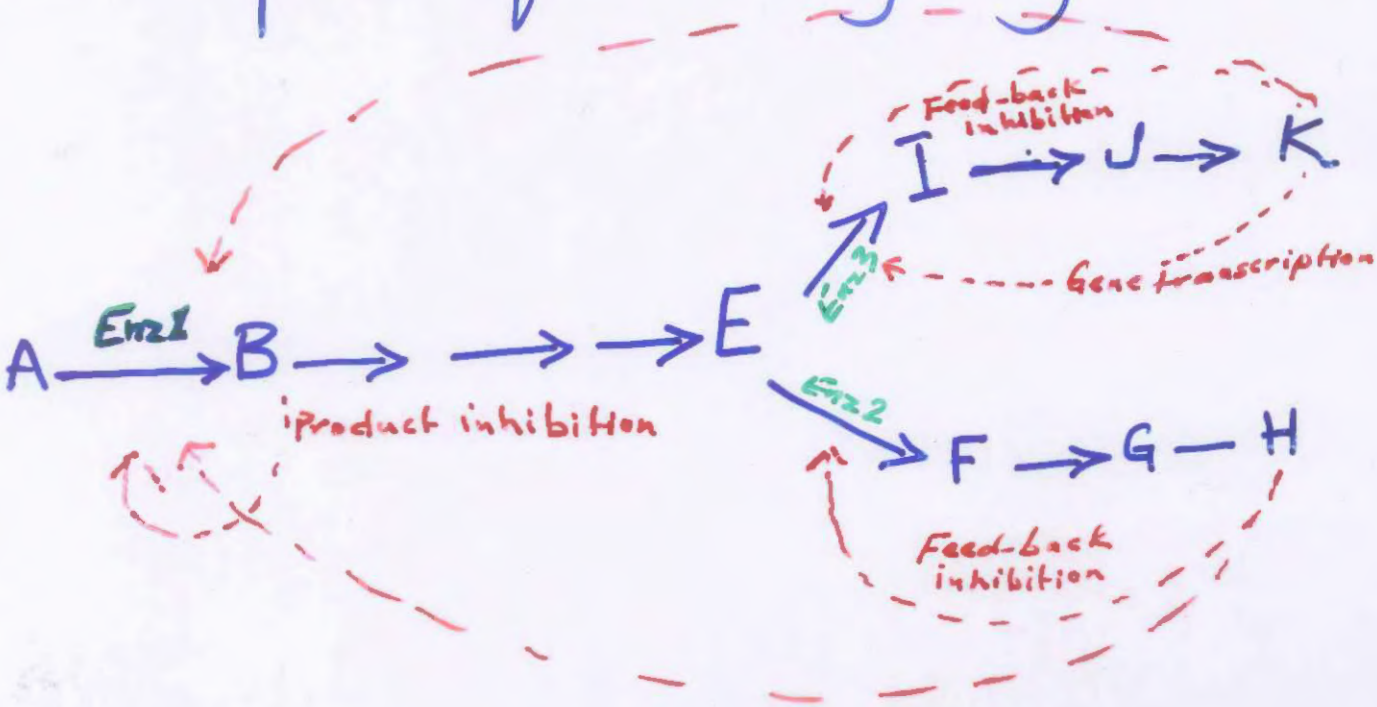
  e.g. LDH

LDH-1	LDH-2	LDH-3	LDH4	LDH-5
H_4	H_3M_1	H_2M_2	H_1M_3	M_4
Heart				Liver, Muscle

IV Regulation through Changes in Amount of Enzyme

- Enzyme synthesis
- Enzyme degradation

V Principles of Pathway Regulation



- Feedback regulation
- Feedforward regulation as in enzymes involved in toxic compounds disposal or
- Product inhibition
- Synergestic effect

- Compartmentation
- Multi Enzyme Complexes

Mechanisms for regulating enzyme activity

REGULATOR EVENT	TYPICAL EFFECTOR	RESULTS	TIME REQ. FOR CHANGE
• Substrate availability	substrate	change in velocity (v_o)	Immediate
• Product Inhibition	Reaction Product	changes in V_{max} and/or K_m	Immediate
• Allosteric Control	Pathway end-product	changes in V_{max} and/or $K_{0.5}$ ($S_{0.5}$)	Immediate
* Covalent modification	another enzyme	changes in V_{max} and/or K_m	Immediate to minutes
• Synthesis or Degradation of Enzyme	Hormone or metabolite	change in ammount of enzyme	Hours to days

Ribozymes (Catalytic RNAs)

Ribozymes are the RNA molecules that can act as catalysts. The catalytic efficiency of catalytic RNAs is less than that of protein enzymes. The catalytic efficiency of known RNA is greatly enhanced by association with protein subunits

Some Examples :-

- **Ribonuclease P (RNAase P)**
  Catalyzes the maturation of tRNA by removing nucleotides from the 5'-end of the precursor mole.
- **Peptidyl transferase**
  the RNA component of the ribosome that carries out protein synthesis
- **snRNA**
  small nuclear RNA in association with proteins that catalyze splicing of exons to form final m-RNA