Enzymology- An overview-4

Regulation of enzyme activity

Several ways to regulate enzyme activity:

1. Modulation of enzyme activity:

    A- Covalent modification.

    B- Allosteric modulation.

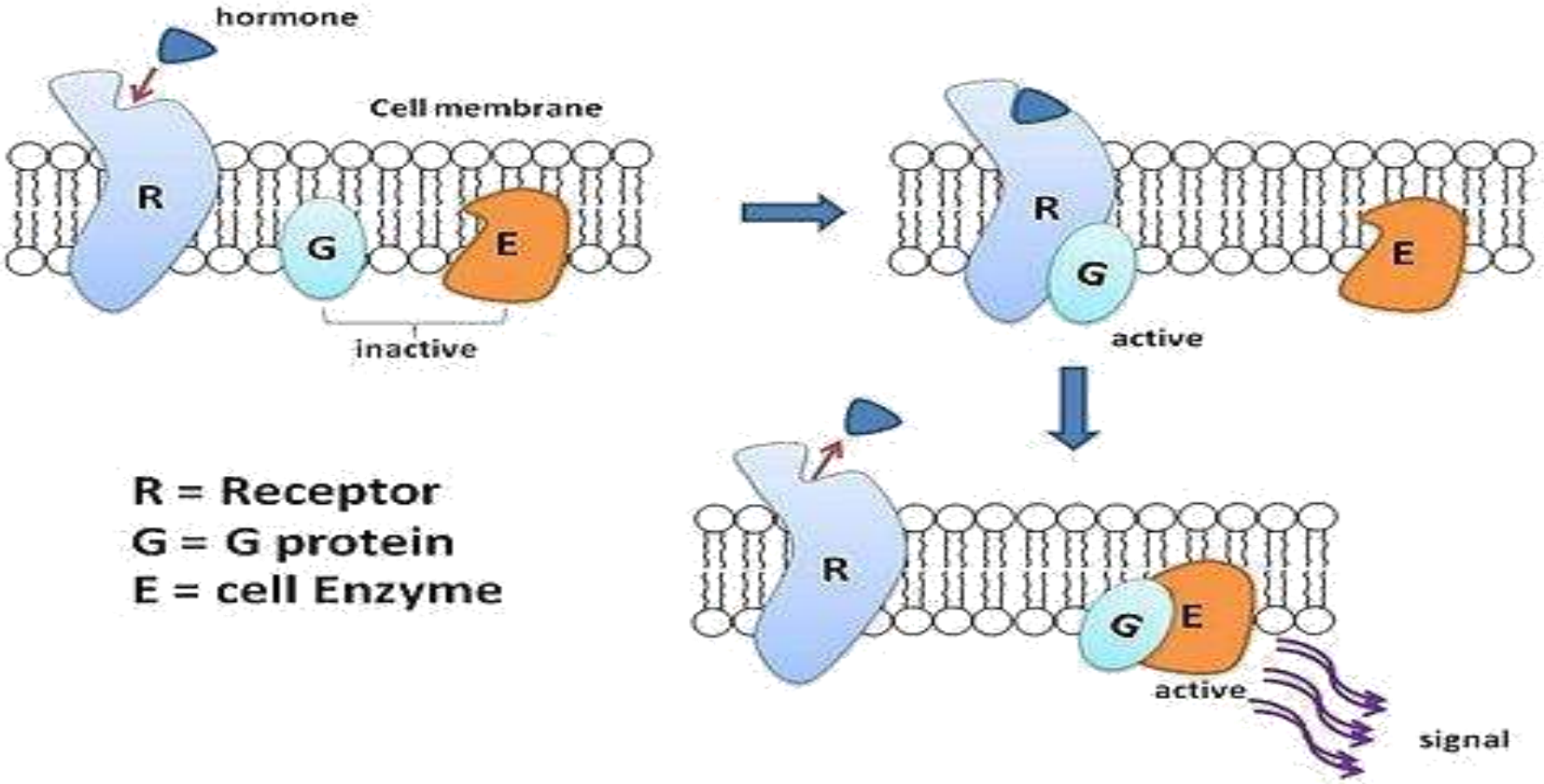
2. Proteolytic cleavage of proenzymes.

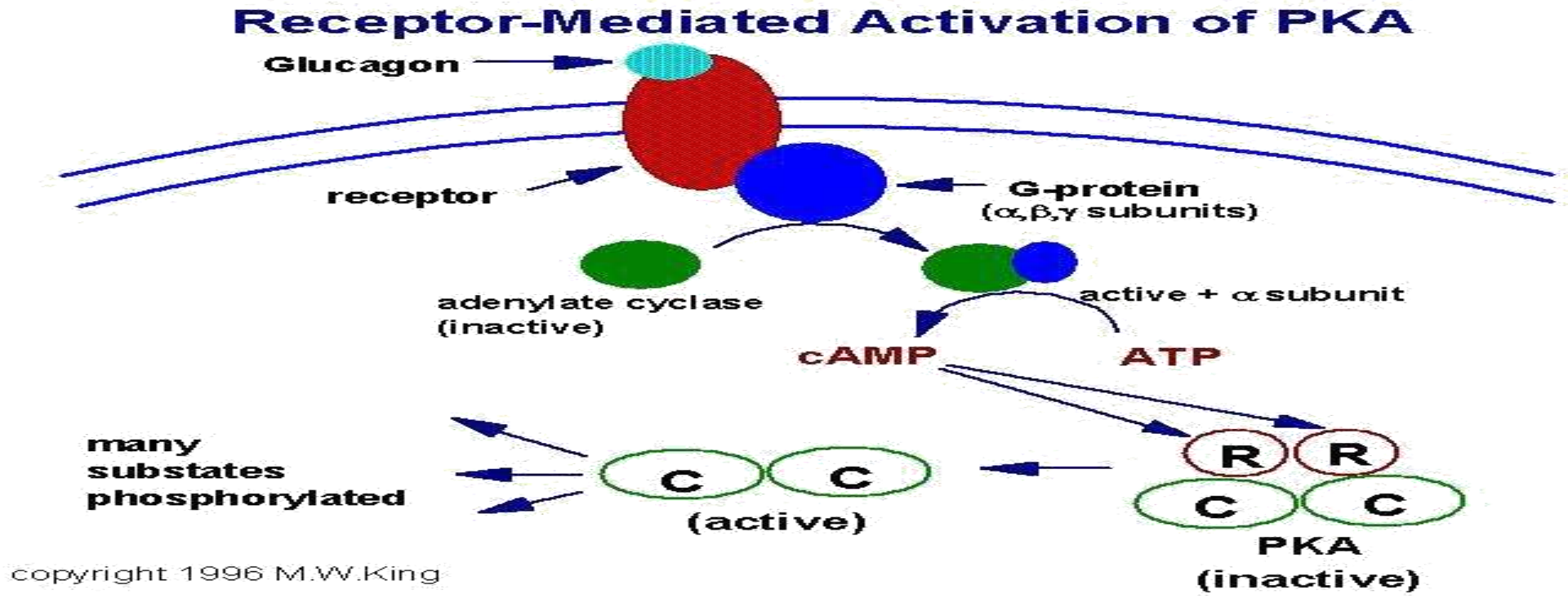
3. Compartmentation.

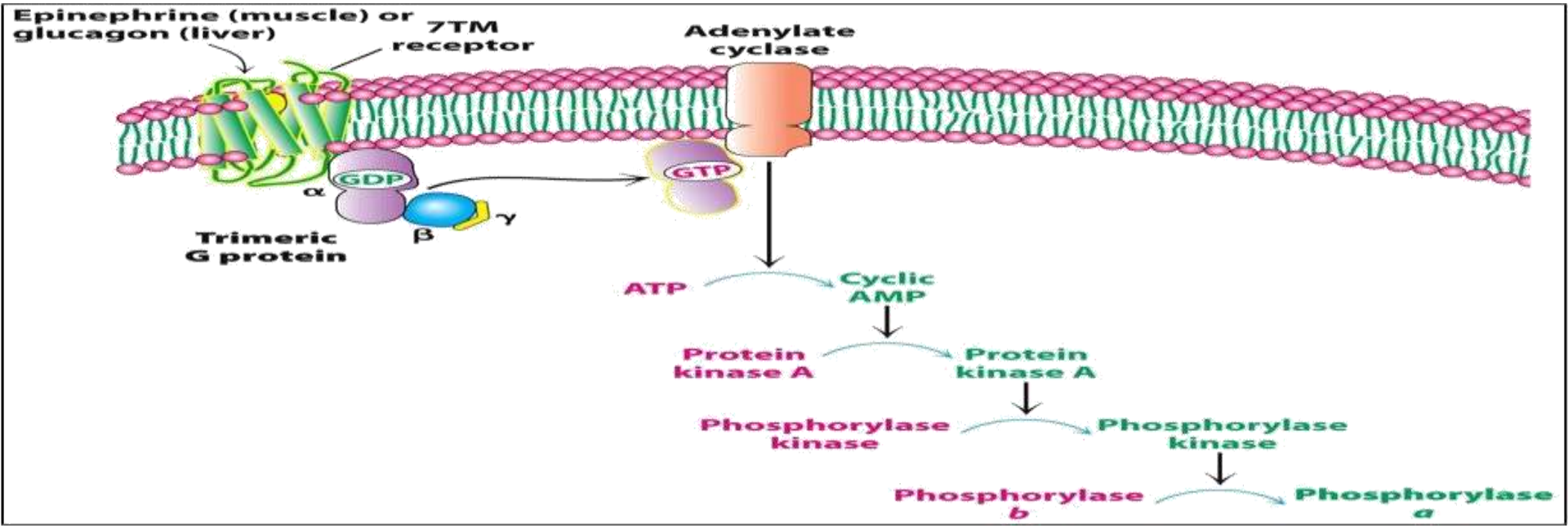
4. Enzyme production.

5. Feedback inhibition

- Usually by the addition of or lysis of phosphate (PO4) groups to and from enzymes.
- Some enzymes are active when phosphorylated, while, others are inactive when phosphorylated.



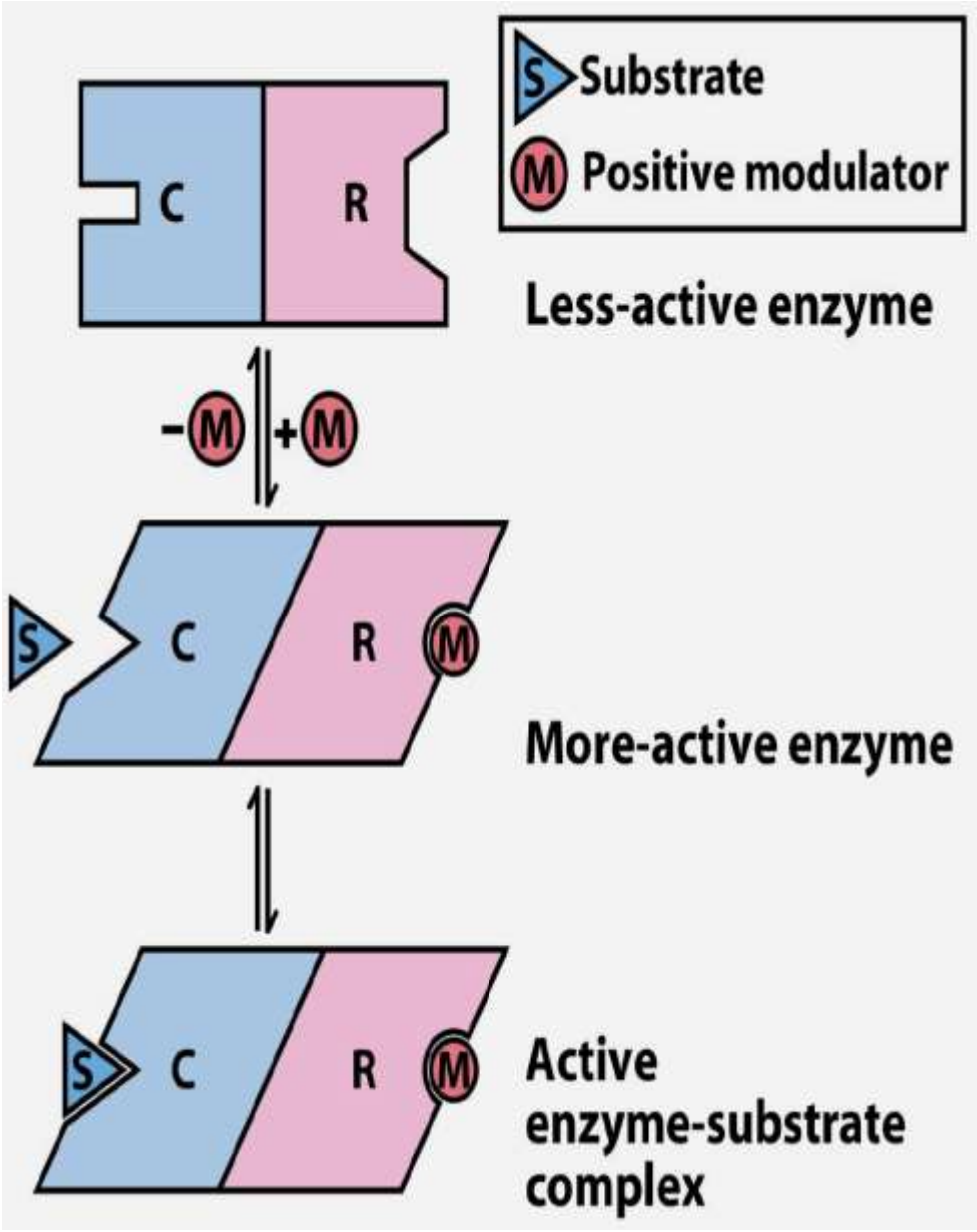

Receptor-Mediated Activation of PKA
Glucagon
receptor
G-protein
(α,β,γ subunits)
adenylate cyclase
(inactive)
active + α subunit
cAMP
ATP
many
substates
phosphorylated
C
C
(active)
R
R
C
C
PKA
(inactive)
copyright 1996 M.W.King

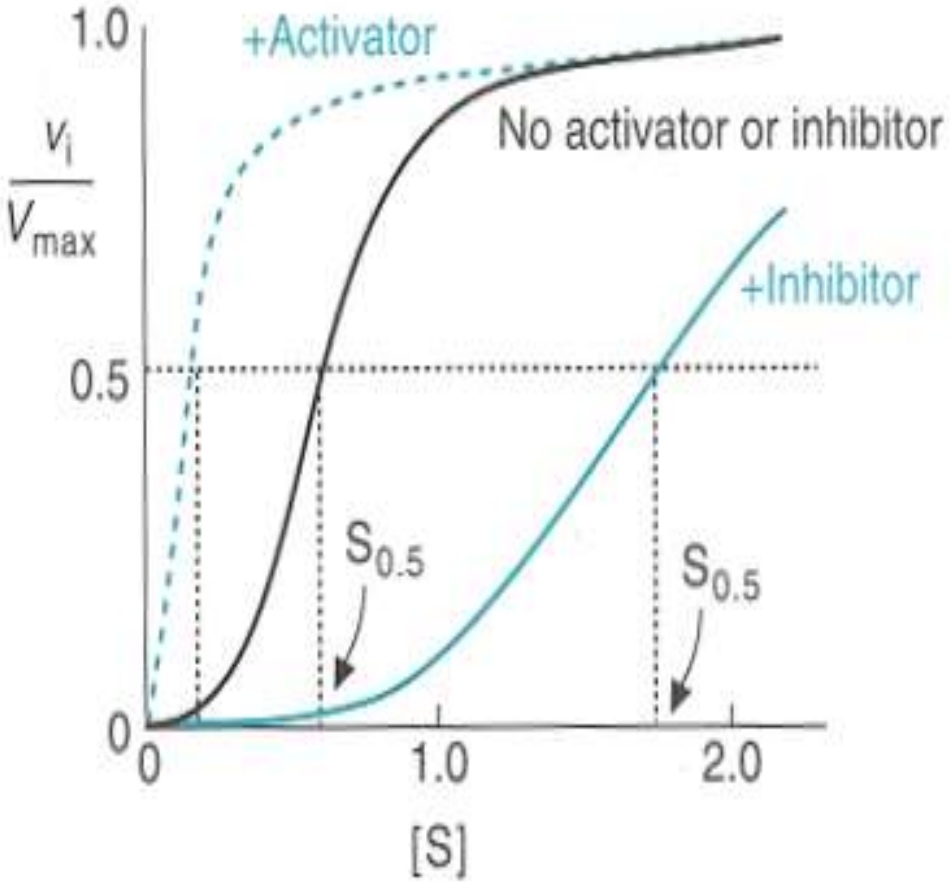

Epinephrine (muscle) or
glucagon (liver)
7TM
receptor
Adenylate
cyclase
GDP
GTP
α
β
γ
Trimeric
G protein
ATP
Cyclic
AMP
Protein
kinase A
Protein
kinase A
Phosphorylase
kinase
Phosphorylase
kinase
Phosphorylase
b
Phosphorylase
a

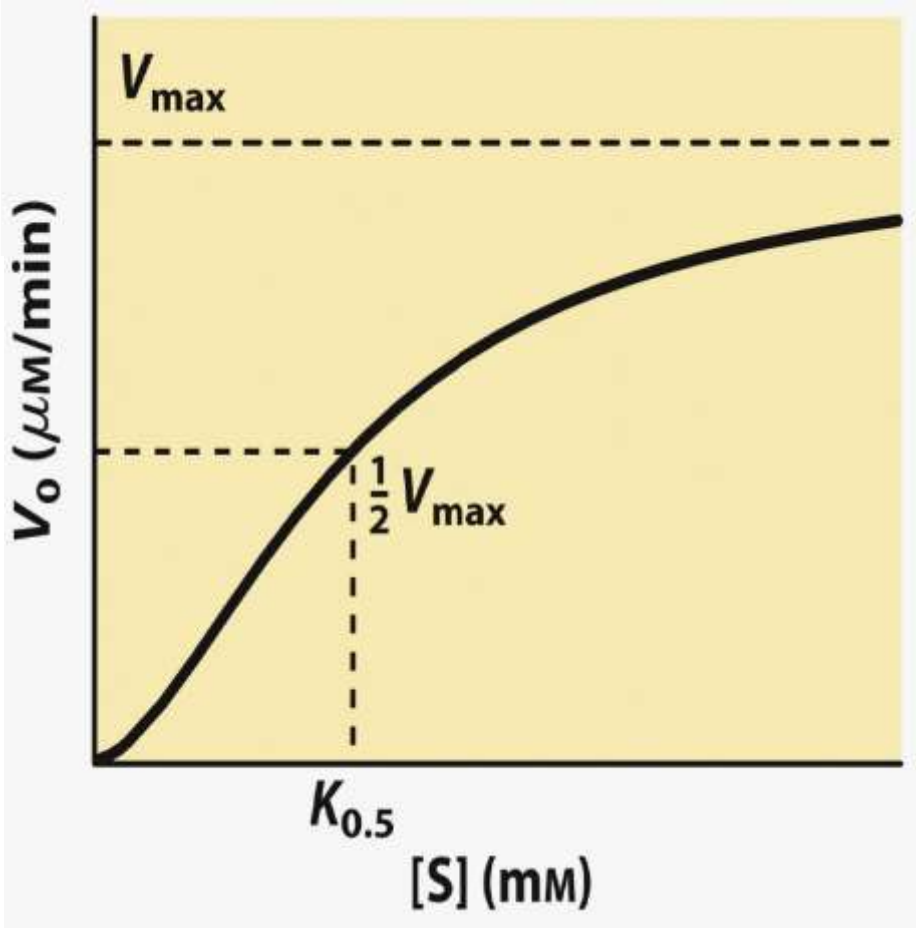
B- Allosteric regulation:

- Allosteric regulation is the term used to describe cases where an enzyme is functioning at one site, then, affected by binding of a regulatory molecule at another site.
- Allosteric regulation may either inhibit or stimulate an enzyme activity by changing the enzyme either to its active or inactive forms.
- The binding of an allosteric activator stabilizes its active form, while binding the allosteric inhibitor stabilizes the inactive form of the enzyme.
- End products are often inhibitors.
- Often allosteric modulators do not resemble the substrate or the product of the enzyme catalyzing the reaction.
- Allosteric modulators bind non-covalently to the enzyme at a site rather than the substrate binding site.

- Allosteric enzymes usually have quaternary structure
- Allosteric enzymes do not exhibit typical Michaelis- Menton kinetics.
- Instead, the curve is sigmoidal, which indicates that the binding of substrate to the enzyme changes (e.g. increases) the affinity of the enzyme for substrate.
- Some allosteric modulators alters the Km, the Vmax remains constant.
- The modulators are not altered by the enzyme.







Allosteric regulation gives sigmoidal curve

Effects of a positive (+) and a negative (-) modulator that alter the Km without altering the maximum velocity Vmax

2- **Proteolytic cleavage of proenzyme:**

- Zymogens activation: certain proteins are synthesized and secreted as inactive precursor proteins known as **proproteins**.

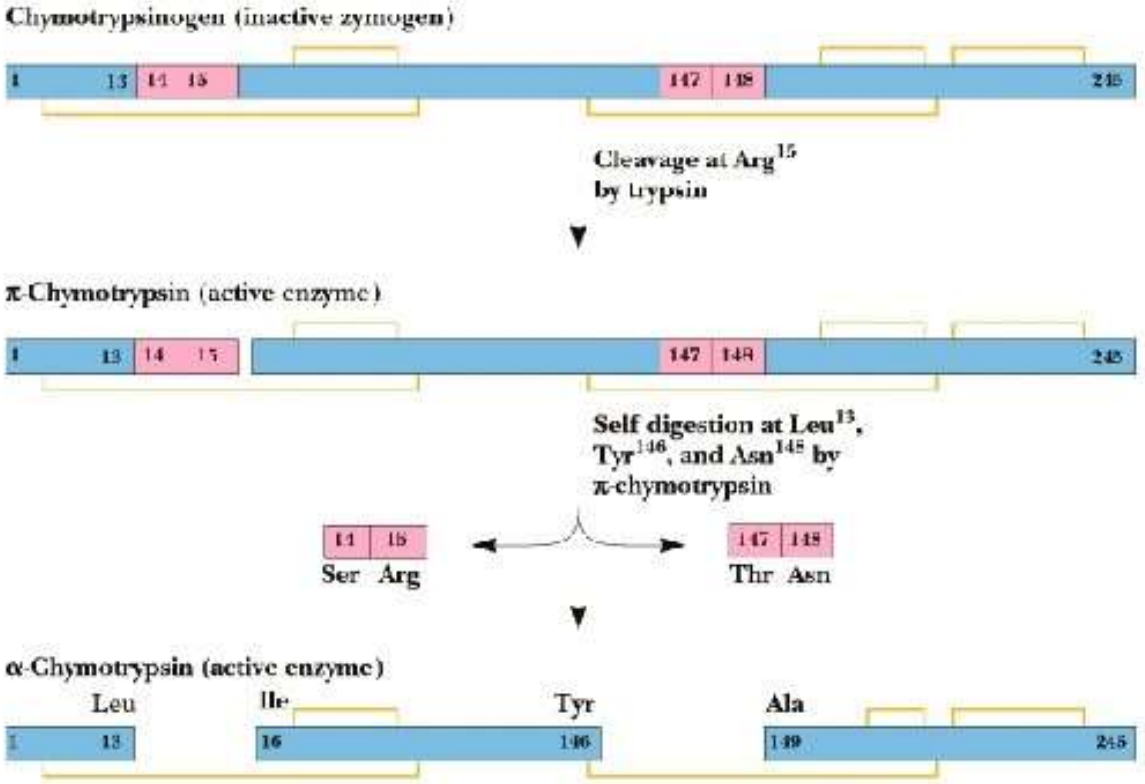
- The proproteins of enzymes are termed **proenzymes** or **zymogens**.

- Selective proteolysis converts a proprotein by one or more successive proteolytic "**clips**" to a form that exhibits the characteristic activity of the mature protein, such as , its enzymatic activity.

- The digestive enzymes pepsin, trypsin, and chymotrypsin (proproteins = pepsinogen, trypsinogen, and chymotrypsinogen, respectively), several factors of the blood clotting and blood clot dissolution cascades, are examples of Zymogen activation.

Proteolytic cleavage of proenzyme(zymogen)

Garrett & Grisham: Biochemistry, 2/e
Figure 15.4



Enzyme/substrate Compartmentation:

- Compartmentation **ensures metabolic efficiency** & **simplifies regulation**
- Segregation of metabolic processes into distinct subcellular locations like the cytosol or specialized organelles (nucleus, endoplasmic reticulum, Golgi apparatus, lysosomes, mitochondria, etc.) is another form of regulation

Plasma membrane	Amino acid transport systems, Na^+-K^+ ATPase
Cytosol	Glycolysis, glycogenesis and glycogenolysis, hexose monophosphate pathway, fatty acid synthesis, purine and pyrimidine catabolism, aminoacyl-tRNA synthetases
Mitochondria	Tricarboxylic acid cycle, electron transport and oxidative phosphorylation, fatty acid oxidation, urea synthesis
Nucleus	DNA and RNA synthesis
Endoplasmic reticulum (rough and smooth)	Protein synthesis, steroid synthesis, glycosylation, detoxification
Lysosomes	Hydrolases
Golgi apparatus	Glycosyl transferases, glucose-5-phosphatase, formation of plasma membrane and secretory vesicles
Peroxisomes	Catalase, D-amino acid oxidase, urate oxidase

4- <u>Enzyme production (hormonal regulation)</u>:

- Enzyme synthesis (transcription and translation of enzymes genes) can be induced or decreased by hormonal activity that controls the genes.
- This mechanism of enzyme regulation is slower than other mechanisms (**long-term regulation**), i.e. covalent and allosteric modulation of enzyme activity.
- Causes changes in the concentration of certain "inducible enzymes" (are adaptive, i.e. synthesized as needed by the cell). (Constitutive enzymes synthesis is at a constant rate).
- Induction occurs usually by the action of hormones, (e.g. steroid and thyroxine) and is exerted by changes in the expression of gene encoding the enzymes.
- More or less enzyme can be synthesized by hormonal activation or inhibition of the genes.

Example:

- Insulin induces increased synthesis of enzymes: glucokinase, glycogen synthase and PFK-1
- Insulin decreases the synthesis of several key gluconeogenic enzymes (amino acid ⟶ glucose).

5- <u>Feed back inhibition v/s feed back regulation</u>:

- It is the regulation of a metabolic pathway by using end product as an inhibitor within the pathway to keep cells from synthesizing more product than necessary.
- Dietary cholesterol decreases hepatic synthesis of cholesterol, (feedback regulation not feedback inhibition).
- HMG-CoA reductase, the rate-limiting enzyme of cholesterol synthesis, is affected, but cholesterol does not feedback-inhibit its activity.

- Regulation in response to dietary cholesterol involves the effect of cholesterol or a cholesterol metabolite on the expression of the gene that encodes HMG-CoA reductase (enzyme repression).