Enzyme Regulation, 2018

Basic Principles of Metabolic Regulation

Passive: Substrate Availability and Compartmentation

Active: Regulation of Rate Limiting Enzyme

Substrate availability and Compartmentation

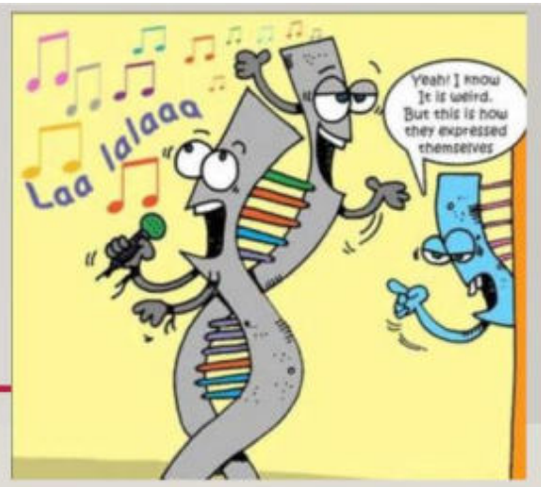
- **Passive mechanism**
- **Limited capacity**
- **Anabolic and Catabolic pathways separated**

E.g. Fatty acid synthesis & Fatty acid oxidation

- **Specialized subcellular compartments** (Hydrolases in Lysosomes)

Controlling Rate Limiting Enzyme

Regulation of Enzyme quantity	• Regulation of Enzyme synthesis
Regulation of Enzyme catalytic activity	• Allosteric Regulation • Covalent Modification



Regulation of enzyme synthesis

- **Gene Transcription induction and Repression**
- **HMG-CoA reductase by cholesterol**
- **PEP carboxykinase by insulin and glucagon**
- **Cytochrome P450 by various drugs**
- **Slow Process**
- **Long Term Effect**

Regulation of enzyme catalytic activity
Allosteric Regulation

- Within seconds
- **Allosteric Enzymes**: Catalysis at active site modulated

by presence of effector at allosteric site

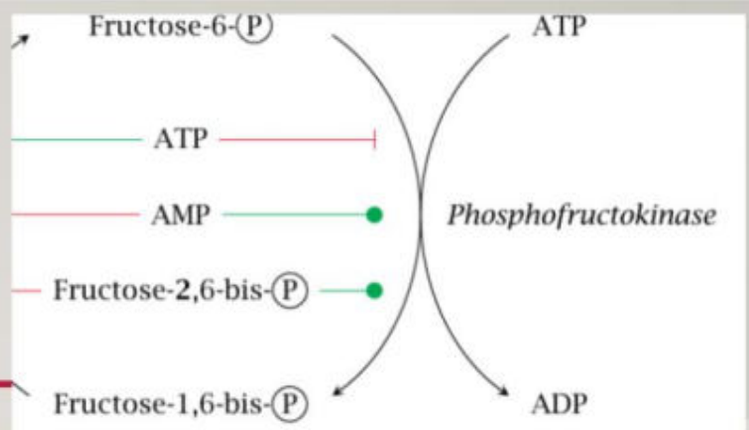
- **Positive or negative effectors**
- May affect affinity (**K series**) or
- Catalytic activity (**V series**)

Homotropic or Heterotropic effectors

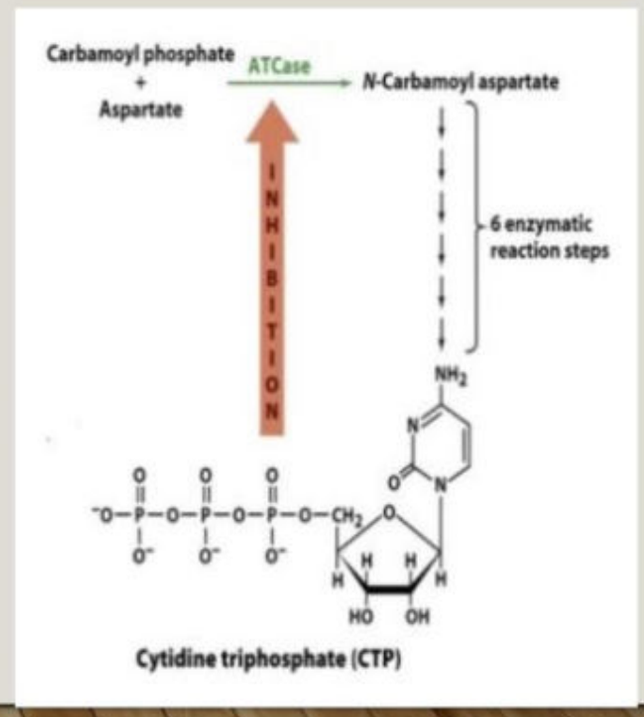
- **Homotropic:**
- **Substrate itself an effector**
- **Mostly, Positive effector**
- **Exhibit cooperativity**
- **Hyperbolic curve**
- **Hills equation define characteristics**

- **Heterotropic**
- **Effector different from substrate**
- **Feedback inhibition**

Examples of allosteric regulation



- **Most of the rate limiting steps in metabolic pathways**
- **Feedback inhibitions**
- **Phosphofructokinase**
- **Aspartate transcarbamoylase**



- **Which of the following describes a characteristic of most allosteric enzymes?**

- **(A) They are composed of single subunits.**
- **(B) They show cooperativity in substrate binding.**
- **(C) They have allosteric activators that bind in the catalytic site.**
- **(D) They have irreversible allosteric inhibitors that bind at allosteric sites.**

Covalent modification

Partial Proteolysis

Phosphorylation

Partial proteolysis

- Proteases synthesized as inactive precursor: Proproteins/Proenzymes/Zymogens
- Eg. Pepsin, Trypsin, Chymotrypsin, Clotting factors
- Irreversible modification
- Selective Proteolysis leads to conformation change and configures active site

Phosphorylation/Dephosphorylation

- Catalysed by Protein kinases and Phosphoprotein phosphatases
- Act on serine, threonine and tyrosine residues
- May increase or decrease activity

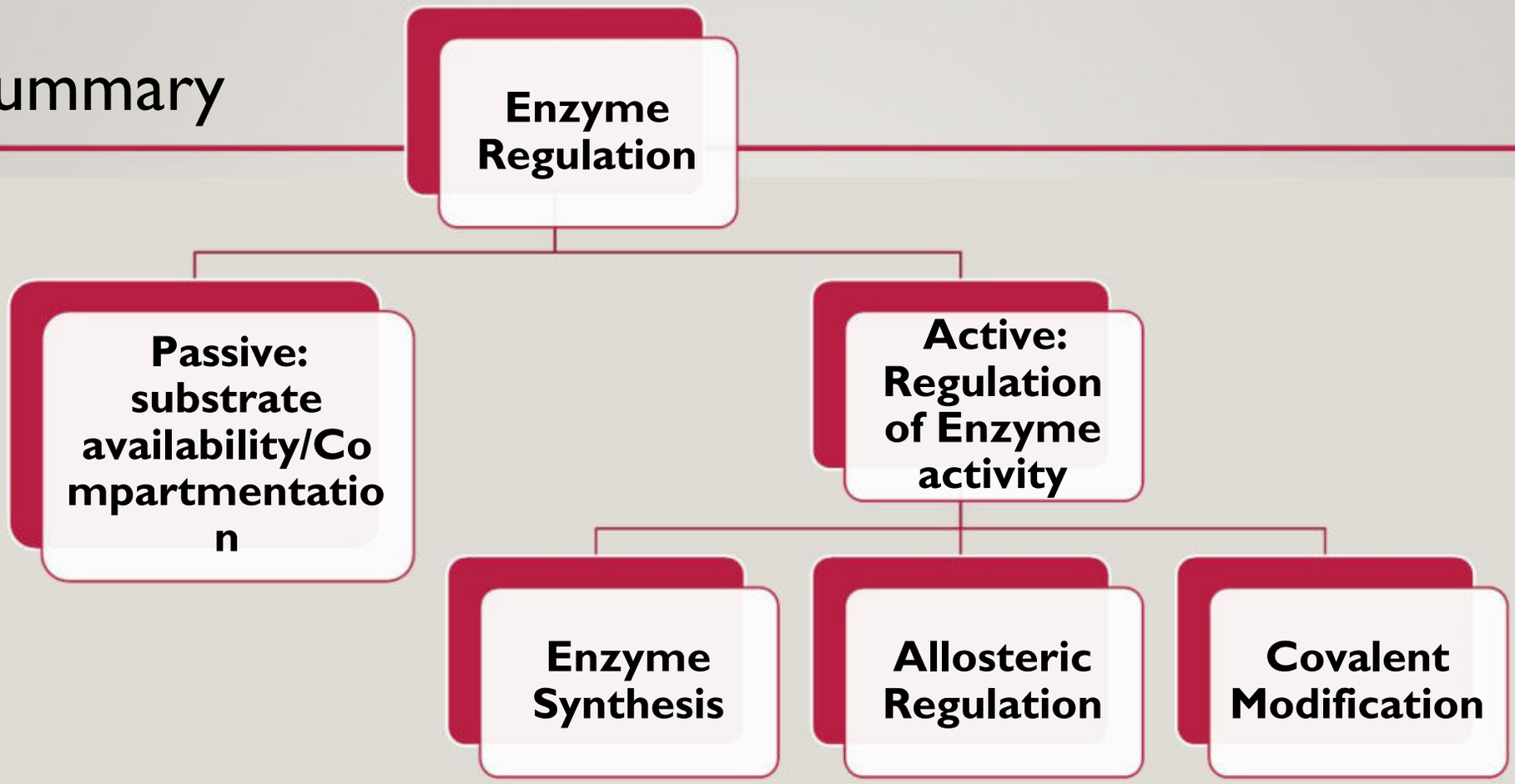
Example

- High Insulin/Glucagon Ratio decreases c AMP and Protein kinase A causing dephosphorylation of PFK-2 (Active)
- Active PFK2 increases Fructose 2,6-bisphosphate that increases PFK-1 activity causing increased glycolysis
- Reverse happens under the effect of glucagon that increases phosphorylation by in increasing c AMP

Phosphorylation/Dephosphorylation

- Most common mechanism employed for regulation
- Ease of interconversion
- Chemical nature of phosphoryl group helps in conformational changes of enzymes
  - H bond formation by O
  - Negative charge
- Insulin/ Glucagon hormones regulates enzymes

Summary



References

- Victor W. Rodwell, David A. Bender, Kathleen M. Botham, Peter J. Kennelly, P.Anthony Weil. Harper's Illustrated Biochemistry, 30th Edition
- Denise R. Ferrier; Lippincott Illustrated Reviews Biochemistry, 7th Edition

Thank You!