

Enzyme Regulation, 2018

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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

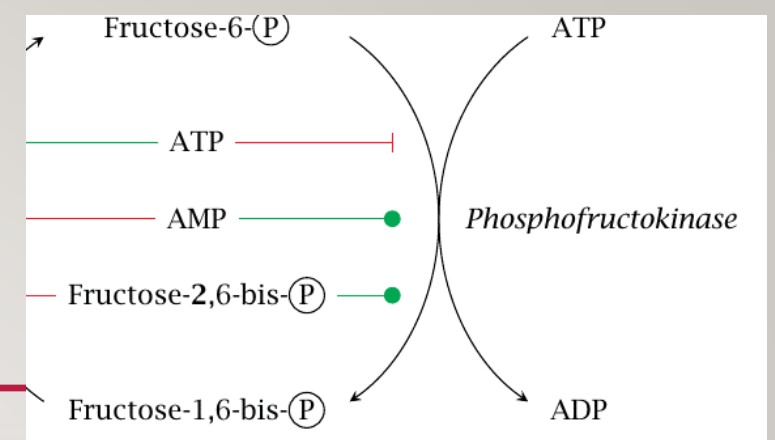
Allosteric Regulation

- 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**)

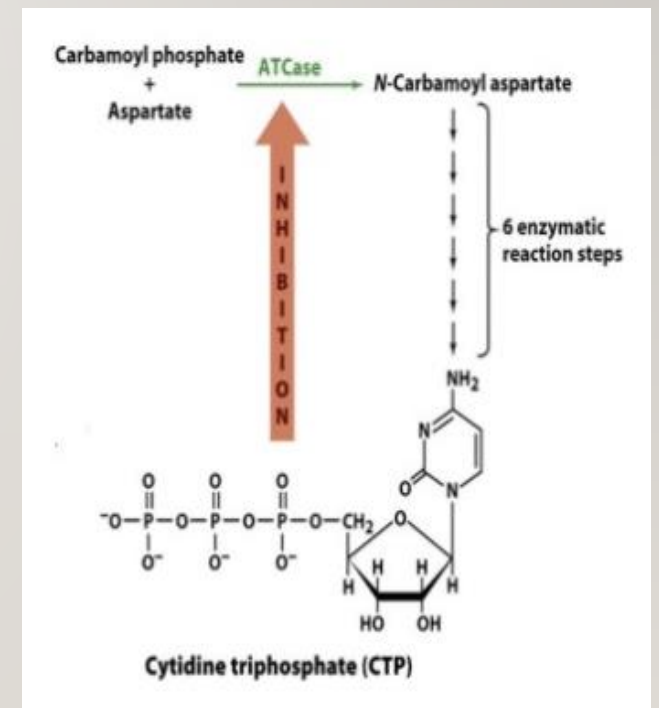
Homotropic or Heterotropic effectors

- **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**

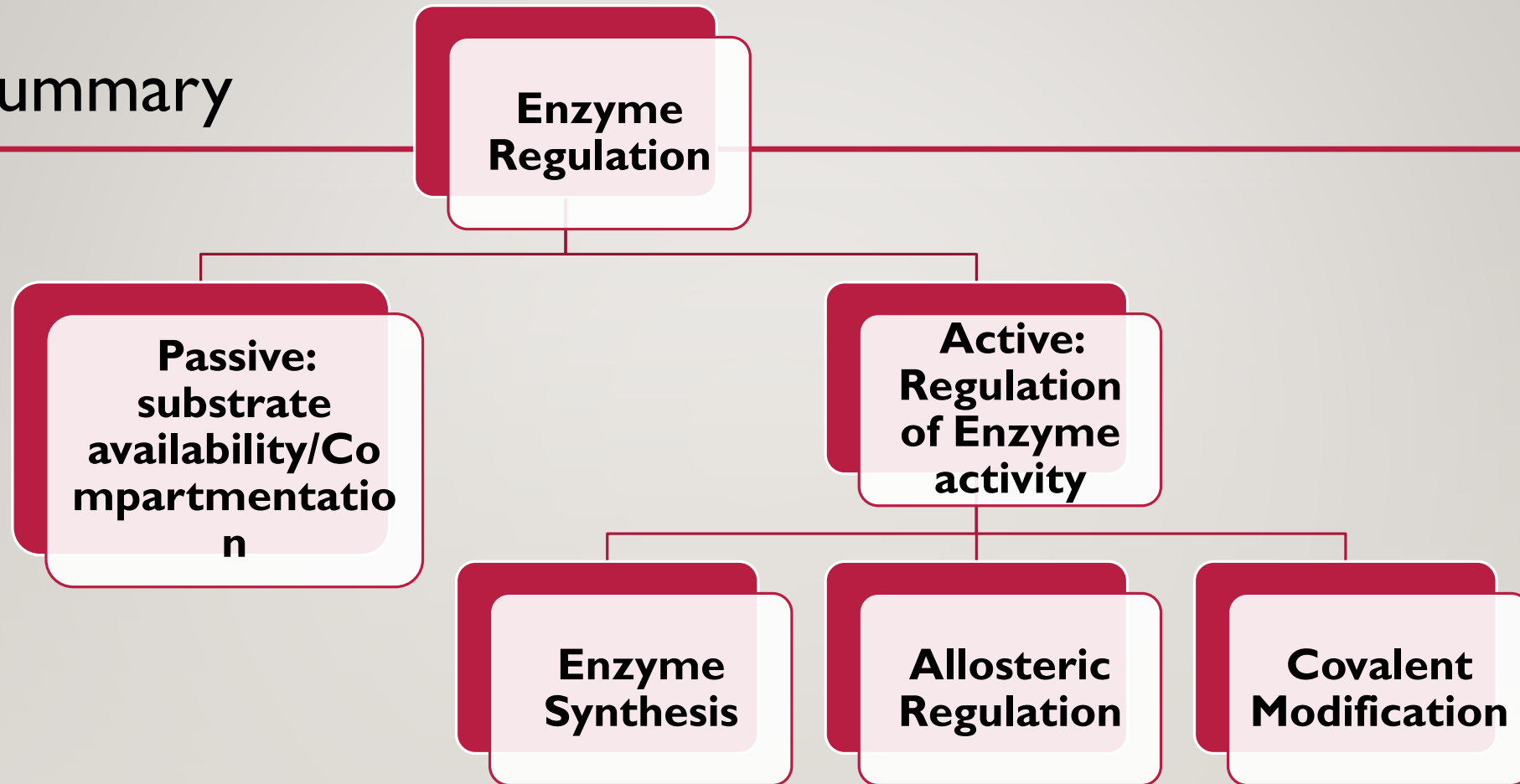
Example

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

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!

