Regulatory Enzyme Unit-4

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- A regulatory enzyme is an enzyme in a biochemical pathway which, through its responses to the presence of certain other bio-molecules, regulates the pathway's activity.
- This is usually done for pathways whose products may be needed in different amounts at different times, such as hormone production.
- Regulatory enzymes are usually the enzymes that are the rate-limiting or committed step, in a pathway, meaning that after this step a particular reaction pathway will go to completion.
- Frequently, regulatory enzymes are at or near the initial steps in a pathway, or part of a branch point or cross-over point between pathways (where a metabolite can be potentially converted into several products in different pathways). In general, a cell needs to conserve energy - therefore costly (in metabolic terms) biosynthetic reaction pathways will not be operational unless a particular metabolite is required at a given time.
- Regulatory enzymes control the overall quantities of enzyme or concentration of substrates present or lead to alteration of the catalytic efficiency of the enzyme
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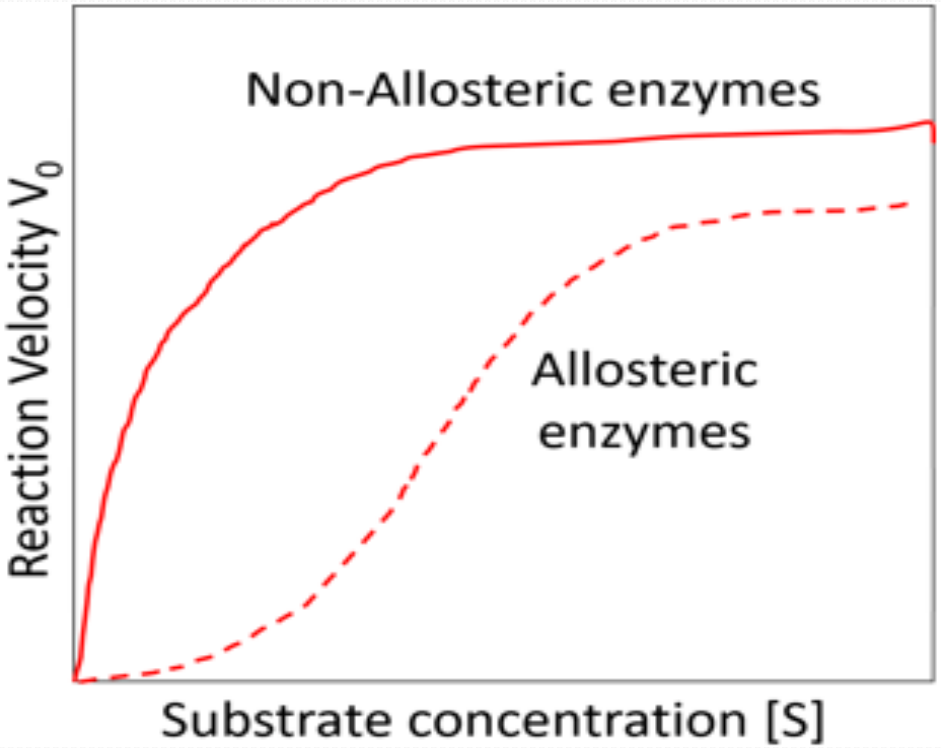
Non-Allosteric enzymes
Allosteric
enzymes
Reaction Velocity V_0
Substrate concentration [S]

Types of Regulatory Enzymes

Regulatory enzymes are of two types

1.Allosteric enzymes

2.Covalently modulated enzymes.

Allosteric enzymes:

Allosteric means an additional space/site to active site where modulator (effector) molecule interacts with enzyme.

- So allosteric enzymes have additional site to active site where modulator interacts.
- The rates of enzyme-catalyzed reactions in biological systems are altered by activators and inhibitors, collectively known as effect or molecules or modulators.
- Interaction of modulator with enzyme is reversible and non-covalent.
- Allosteric enzymes generally have two or more polypeptides and are more complex than non regulatory enzymes.
- In allosteric enzymes, the binding of a substrate molecule to one active site affects the binding of other molecules of substrate to other active sites in the enzyme. Thus different active sites behave cooperatively. Allosteric enzymes are multi-subunit proteins, with one or more active sites on each subunit. The binding of substrate at one active site induces a conformational change in the protein that is conveyed to other active sites, altering their affinity for substrate molecules.
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Types of Regulation

- • Homotrophic (or: homotropic) responses: This refers to allosteric modulation of enzyme activity by substrate molecules. This necessarily must occur in multisubunit enzymes.
- • Heterotrophic (or heterotropic) responses: This refers to regulation by non-substrate molecules or combinations of non-substrate and substrate molecules. • Allosteric regulation can be positive or negative.
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- A plot of V_o against (S) for allosteric enzyme gives a sigmoidal curve rather than the hyperbolic plots predicted by the Michaelis-Menten equation for non-regulatory enzymes. The sigmoidicity is thought to result from the cooperativity of structural changes between enzyme subunits (again similar to oxygen binding to hemoglobin). NOTE: A true Km cannot be determined for allosteric enzymes, so a comparative constant like $S_{0.5}$ or $K_{0.5}$ is used.
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- The curve has a steep section in the middle of the substrate concentration. So there is a rapid increase in the enzyme velocity which occurs over a narrow range of substrate concentration. This property makes the allosteric enzymes more sensitive towards substrate concentration.
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- Cooperativity - in relation to multiple subunit enzymes, changes in the conformation of one subunit leads to conformational changes in adjacent subunits. These changes occur at the tertiary and quaternary levels of protein organization and can be caused by an allosteric regulator.
- Homotropic regulation - when binding of one molecule to a multi-subunit enzyme causes a conformational shift that affects the binding of the same molecule to another subunit of the enzyme.
- Heterotropic regulation - when binding of one molecule to a multi-subunit enzyme affects the binding of a different molecule to this enzyme (Note: These terms are similar to those used for oxygen binding to hemoglobin)
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- **Feedback Inhibitions**
- In metabolic pathway the end products often inhibits the committed step earlier in the same pathway to prevent the buildup of intermediates and unnecessary use of metabolites and energy and the process is known as feedback inhibition.
- End product inhibition is negative feedback used to regulate the production of a given molecule.
- **Reversible covalent modification**
- It involves making or breaking of covalent bond between nonprotein group and an enzyme molecule.
- A range of nonprotein groups may be reversibly attached to enzymes which effect their activity. The most common modification is the addition and removal of a phosphate group called as phosphorylation or dephosphorylation respectively.
- Phosporylation is catalysed by protein kinases, often using ATP as the phosphate donar, and deposphorylation is catalysed by protein phosphatases. The addtion and deletion of phosphate group causes changes in the tertiary structure of the enzyme that alter its catalytic activity.
- A phosphorylated enzyme may be either more or less active than its dephosphorylated form. Thus phosphorylation and dephosphorylation may be used as a rapid, reversible switch to turn a metabolic pathway on or off according to the needs of cell.

- **Isozymes:**
- An enzyme which has multiple molecular forms in the same organism catalyzing the same reaction is known as isozyme. Example is Lactate dehydrogenase (LDH)
- LDH occur in five possible forms in organs of most vertebrates, as observed by electrophoretic separation.
- Basically two different types of LDH occur. One type, which predominates in the Heart, is called heart LDH (H_4). The second types are characteristic of Muscles (M_4).
- The Heart LDH consists of four identical monomers which are called H subunits. The muscle enzyme consists of four identical M subunits. The two types of subunits H and M, have same molecular weight (35000) but different amino acid composition.
- There is genetic evidence that two subunits are produced by two separate genes.
- Combination of H and M subunits will produce three additional types of hybrid enzymes. These possible combinations are M_4, M_3H, M_2H_2, MH_3, H_4.
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Feed-Back Inhibition

- Feed-back inhibition is a common feature of complex biosynthetic pathways.
- It prevents the accumulation of unwanted intermediates and allows regulation of the level of important metabolites.
- • Because the substrate and final product of the pathway are generally chemically different, this demands that the final product bind at a different site relative to the substrate of the allosteric enzyme.
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Thanks