Enzyme Regulation

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Enzyme regulation helps to maintain body equilibrium, and homeostasis. It also helps in regulation of metabolic pathways.

There are two regulatory mechanisms for enzyme activity:

1) Control of Enzyme Quantity: Enzyme quantity control is influenced by:

i) Altering the rate of enzyme synthesis and degradation,

ii) Induction, and

iii) Repression.

2) Altering the Catalytic Efficiency of the Enzyme: Alteration in the catalytic efficiency of enzyme is done by:

i) Allosteric regulation,

ii) Feedback inhibition,

iii) Proenzyme (zymogen),

iv) Covalent modification, and

v) Protein-protein interaction

i) Altering the rate of enzyme synthesis and degradation

Enzymes are protein molecules, synthesised from amino acids under gene control, in a cell and and are degraded into amino acids after doing its work. Accelerated syntnesis, reduced degradation or both might be the cause of greater enzyme quantity. Reduced enzyme quantity may be due to the reduced synthesis, accelerated degradation or both.

For example, protein-rich food accelerates the synthesis of liver arginase enzyme which increases its quantity.

ii) Enzyme Induction

Enzyme induction is defined as the increase in the rate of enzyme synthesis by substances called inducers. On the basis of response produced by the inducer enzymes are of two types:

1) Constitutive Enzymes: The concentration of these enzymes is independent of added inducer.

2)Inducible Enzymes: The concentration of these enzymes depends on the added inducer.

For example, induction of lactase enzyme in bacteria grows on glucose media.

iii) Enzyme Repression

Enzyme Repression refers to the prevention of enzyme synthesis at gene expression level by repressor. Repressors are low weight molecules that reduce the rate of enzyme synthesis at the level of gene expression.

Generaly, repressors are end products of biosynthetic reaction therefore sometimes repression is also known as feedback regulation.

For example, dietary cholesterol reduces the rate of synthesis of HMG CoA reductase (P-hydroxy P-methyl glutaryl CoA reductase), which is a crucial enzyme of cholesterol biosynthesis.

i) Allosteric regulation

The enzymes that change their conformation on binding with the effector are termed as allosteric enzymes.

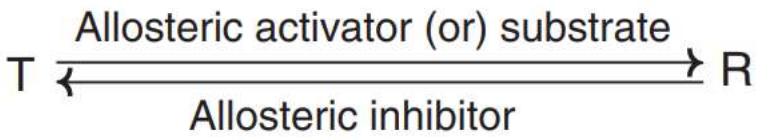
Classes of allosteric enzymes:

K-class of allosteric enzymes, the effector changes the Km and not the Vmax. Double reciprocal plots, similar to competitive inhibition are obtained e.g. phosphofructokinase.

V-class of allosteric enzymes, the effector alters the Vmax and not the Km. Double reciprocal plots resemble that of non-competitive inhibition e.g. acetyl CoA carboxylase.

Conformational changes in allosteric enzymes: Most of the allosteric enzymes are oligomeric in nature. The subunits may be identical or different. The non-covalent reversible binding of the effector molecule at the allosteric site brings about a conformational change in the active site of the enzyme, leading to the inhibition or activation of the catalytic activity.

Allosteric enzymes exist in two conformational states – the T (tense or taut) and the R (relaxed). The T and R states are in equilibrium.



i) Allosteric regulation

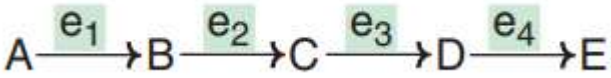
Allosteric inhibitors favour T state whereas activators and substrates favour R state. The substrate can bind only with the R form of the enzyme.

The term homotropic effect is used if the substrate influences the substrate binding through allosteric mechanism, their effect is always positive.

Heterotropic effect is used when an allosteric modulator effects the binding of substrate to the enzyme. Heterotropic interactions are either positive or negative.

ii) Feedback inhibition

The process of inhibiting the first step by the final product, in a series of enzyme catalysed reactions of a metabolic pathway is referred to as feedback regulation.

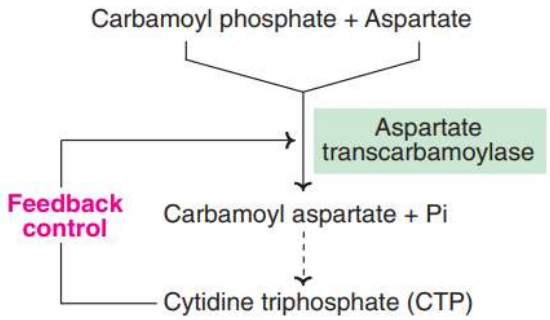


A is the initial substrate, B, C, and D are the intermediates and E is the end product, in a pathway catalysed by four different enzymes (e1, e2, e3, e4). The very first step is the most effective for regulating the pathway, by the final end product E. This type of control is often called negative feedback regulation since increased levels of end product will result in its (e1) decreased synthesis.

Feedback inhibition or end product inhibition is a specialised type of allosteric inhibition necessary to control metabolic pathways for efficient cellular function.

ii) Feedback inhibition

Aspartate transcarbamoylase is a good example of an allosteric enzyme inhibited by a feedback mechanism. Aspartate transcarbamoylase catalyses the very first reaction in pyrimidine biosynthesis.



Carbamoyl phosphate undergoes a sequence of reactions for synthesis of the end product, CTP. When CTP accumulates, it allosterically inhibits the enzyme aspartate transcarbamoylase by a feedback mechanism.

iii) Proenzyme (zymogen)

Zymogen or proenzyme is an inactive precursor due to the presence of a supplementary polypeptide chain which blocks the active site of the enzyme by masking. The removal of this polypeptide chain results in activation of zymogen.

Certain enzymes exist in the active and inactive forms which are interconvertible, depending on the needs of the body. The interconversion is brought about by the reversible covalent modifications, namely phosphorylation and dephosphorylation, and oxidation and reduction of disulfide bonds.

There are some enzymes which are active in dephosphorylated state and become inactive when phosphorylated e.g. glycogen synthase, acetyl CoA carboxylase, HMG CoA reductase.

A few enzymes are active only with sulfhydryl (SH) groups, e.g. succinate dehydrogenase, urease. Substances like glutathione bring about the stability of these enzymes.

iv) Covalent modifications

Altering the activity of enzyme over covalent bond formation is known as covalent modification. For example,

1) Methylation (addition of methyl group),
2) Hydroxylation (addition of hydroxyl group),
3) Adenylation (addition of adenylic acid), and
4) Phosphorylation (addition of phosphate group).

Utmost covalent modification for enzyme activity regulation is phosphorylation, in which phosphate group is added to the enzyme found in the amino acid (serine, threonine or tyrosine) hydroxyl group.

Examples of enzymes inactivated by phosphorylation, e.g.:

1) Glycogen synthetase, which catalyses biosynthesis of glycogen
2) Acetyl CoA carboxylase, which catalyses fatty acid biosynthesis.

Dephosphorylation is phosphate group removal of hydroxyl group from amino acids (serine, threonine or tyrosine) by phosphatase enzyme. Some enzymes have phosphorylated form as an active form whereas other enzymes have dephosphorylated form. Examples of enzymes of biosynthetic reaction activated by phosphorylation are:

1) Glycogen phosphorylase that breaks down glycogen into glucose
2) Citrate lyase that breaks down citrate

v) Protein-protein interaction

Enzymes formed of many protein sub-units may present in an inactive form that are formed through interaction between its protein sub-units. The whole enzyme is inactive and consists of regulatory and catalytic sub-units. The enzyme is activated by separating the catalytic sub-units from the regulatory sub-units.

A regulatory enzyme, protein kinase is formed of 2 regulatory (2R) and 2 catalytic (2C) sub-units. The whole enzyme is inactive and acts by interacting with proteins.

The cAMP (cyclic Adenosine Monophosphate) activates of the protein kinase is done by releasing the 2 Catalytic (2C) sub-units from 2 Regulatory (2R) sub-units.