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Research Work

Non-endocrine regulation

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Introduction :

Metabolic regulation in the body is acheived through several interconnected control systems that work together to maintain internal balance. While the endocrine system plays a major role through hormone secretion , many metabolic processes are also regulated by non-endocrine mechanisms. These mechanisms act locally,rapidly, and often independently of hormonal control. Understanding non-endocrine regulation and in underlying mechanisms is essential for explaining how cells and tissues adjust their metabolic activity in response to changing physiological conditions.

Definition :

Non-endocrine regulation is the control of cellular and physiological processes without the direct involvement hormones . It relies on local chemical factors and allosteric regulation of enzymes , allowing cells and tissues to respond rapidly and directly to internal or external changes.

Mechanisms of non-endocrine regulation :

1-Intracellular regulation:

This mechanisms happen inside the cell:

1-1-Allosteric regulation:

Allosteric enzymes are composed of an even number of subunits arranged around an axis of symmetry. Allosteric enzyme has two sites: a catalytic site for substrate binding and an allosteric site where effectors binds.

Allosteric regulation can be controlled and modified by negative and positive effectors /metabolites through non covalent interaction.

•Positive effectors/allosteric activators: binding of the effectors to the enzyme increases its activity.

Example: ADP is allosteric activator for phosphofructokinase enzyme.

•Negative effectors/allosteric inhibitors: binding of the effectors to the enzyme causes decreases in its activity.

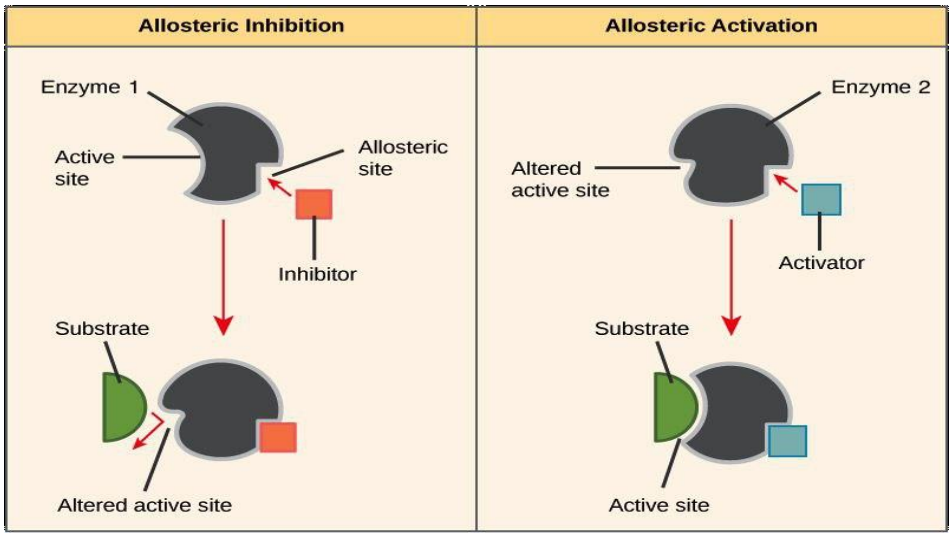

Figure 1:conformational changes in allosteric regulation

Example:

•ATP and citrate are allosteric inhibitors for phosphofructokinase enzyme in glycolysis.

•Glucose 6 phosphate is allosteric inhibitor for hexokinase.

Binding of the allosteric effector to the regulatory site causes conformational changes in the catalytic site , which becomes more fit for substrate binding in allosteric activator, and becomes unfit for substrate binding in allosteric inhibitor.

1-2-Feedback regulation:

Feedback regulation of an enzyme occurs when a product of the reaction binds to an allosteric site on the enzyme and effects its catalytic activity. Through feedback inhibition, the cell responds to the amount of reaction product in order to regulate its further production. The higher concentration of the final product, the more likely that the product will bind to the allosteric site of the enzyme. Shutting down that pathway.

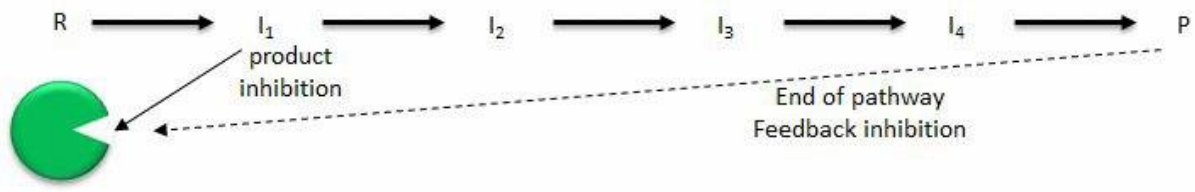

Figure 2:Product and end product of an inhibition enzyme

•Negative feedback results in the inhibition of an enzyme in a biochemical pathway, reducing the activity of earlier enzyme, and stopping the pathway.

•Positive feedback results in the activation of more enzymes, thus increasing its production of the product.

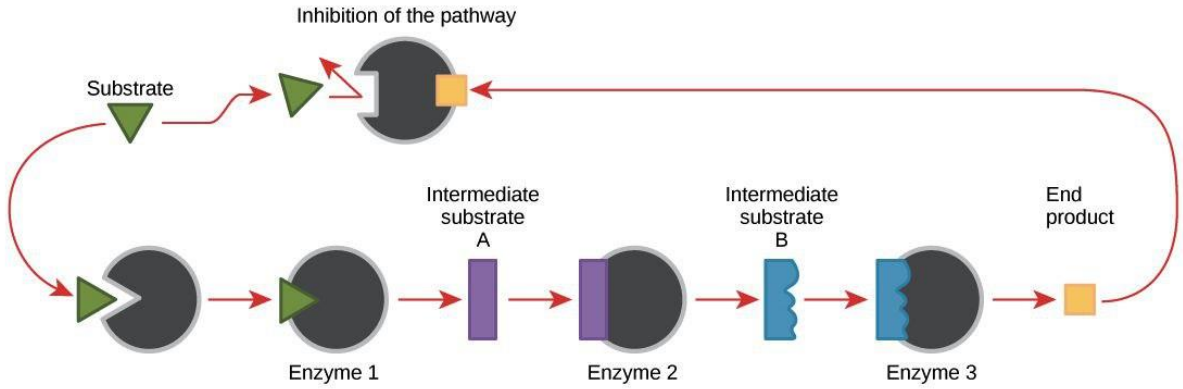

Figure 3:Product and end product of an inhibition enzyme

1-3-Covalent modification:

Covalent modification is the modification of enzyme activity through formation of covalent bonds. Common modifying group include: phosphoryl, methyl, adenyl, hydroxyl.

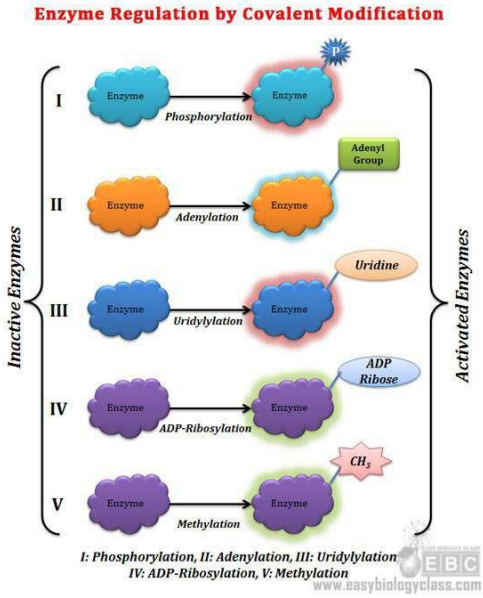

Figure 4:Enzyme regulation by covalent modification

Examples:

•Phosphorylation occurs by addition of phosphate group to the hydroxyl group of the serine, threonine or tyrosine by protein kinase enzyme.

•Dephosphorylation occurs by removal of phosphate group from the hydroxyl group of the serine, threonine or tyrosine by phosphatase enzyme.

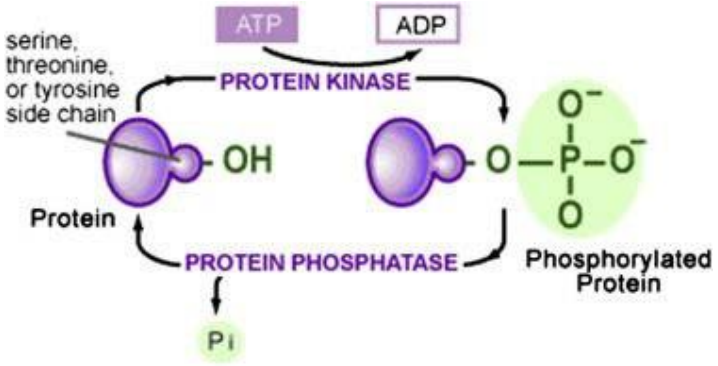

Figure 5:Phosphorylation and dephosphorylation of an enzyme

1-4-Protein-proteininteraction :

An Enzyme which have many protein subunits, the enzyme may be present in an inactive form through interaction between its protein subunit.
The whole enzyme, formed of regulatory and catalytic subunits, is inactive.

Activation of the enzyme occurs by separation of the catalytic subunits from the regulatory subunits, for example Protein kinase A enzyme is an example for regulation of enzyme activity through protein interaction.
The PKA having 2 regulatory and 2 catalytic domain and it is an inactive form. cAMP (cyclic adenosine monophosphate) activates the enzyme by binding to the 2 regulatory (2R) subunits releasing the 2 catalytic (2C) subunits and hence activating the enzyme.

1-5-Metabolite availibility:

Metabolites availibility means that the presence, absence, intermediates, cofactors, or energy molecules directly controls the rate of a metabolic pathway.
The pathway speeds up when its substrates are available and slowdown when substrates are missing or products accumulate.

Example:

•High amount of ATP inhibits PFK1 means slowdown of glycolysis.

•Low amount of ATP and high AMP activates PFK1, speed up of glycolysis.

•Low NAD+ causes slow down in isocitrate dehydrogenase enzyme, and amount speed up isocitrate dehydrogenase activity. Availibility of NAD+ regulate the citric acid cycle.

2-Extracellular regulation:

2-1 -Autocrine Signaling :

A cell sends a signal to itself to control its own actions.

Example:

Muscle cell can produce IGF1, which acts on the same cell through autocrine signaling. This causing indirectly more GLUT 4 to move to the cell membrane, which stimulate glucose uptake.

2-2P-aracrine signaling:

Cells release signals that affect nearby cells. These signals don't last long and act locally.

Example:

Pancreatic islet cells regulate each other through local signals: α-cells boost β-cell insulin release with glucagon, δ-cells suppress both insulin and glucagon with somatostatin, most of these hormones stay inside the islet rather than circulating in bloodstream.

2-3- Synaptic Signaling :

Nerve cells send signals (called neurotransmitters) across tiny gaps (synapses) to other nerve or muscle cells. This happens very quickly.

Example:

When a motor neuron releases acetylcholine, it binds to nicotinic receptors on the muscle cell, triggering muscle contraction. This increases intracellular calcium and activates AMPK(AMP-activated protein kinase), which causes GLUT4 transporters to move to the cell membrane. As a result, glucose uptake and glycolysis are stimulated in the muscle independently of insulin.

Conclusion :

Non-endocrine regulation plays a central role in maintaining metabolic homeostasis by providing rapid, local, and highly specific control of cellular activity. Unlike endocrine signals that act systemically, non-endocrine mechanisms both intracellular and extracellular allow cells and neighboring tissues to adjust metabolism instantly in response to changes in energy demand, nutrient availability, and environmental conditions. Through this fast and localized control, non-endocrine regulation ensures metabolic flexibility, prevents unnecessary hormone use, and supports coordinated function within tissues.

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