EKPO MFONISO GODWIN
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BTG 406: METABOLIC ENGINEERING

Mechanism of metabolic reaction

The metabolic pathways are complex and interdependent. With the changing environments the reactions of metabolism must be finely regulated to maintain a constant set of conditions within cells, a condition called homeostasis. Control of metabolic pathways also allows organisms to respond to signals and interact actively with their environments.

Concept of Regulation

Regulation of metabolic pathways includes regulation of an enzyme in a pathway by increasing or decreasing its response to signals.

Mechanisms of metabolic regulation.

1. Intrinsic regulation

For intrinsic regulation of metabolic pathways, the reactions self-regulate to respond to changes in the levels of substrates or products. For example, a decrease in the amount of product can increase the metabolic pathway. This is called a feedback mechanism.

2. Extrinsic control

Extrinsic control involves a cell in a multicellular organism changing its metabolism in response to signals from other cells.
The signals approach the pathways via soluble messengers such as hormones and growth factors. These act by being detected by specific receptors on the cell surface.

These signals are then transmitted inside the cell by second messenger systems that often involved the phosphorylation of proteins. For example, the hormone insulin from the beta cells of the pancreas is produced in response to rises in blood glucose levels. Binding of the hormone to insulin receptors on cells then activates a cascade of protein kinases that cause the cells to take up glucose and convert it into storage molecules such as fatty acids and glycogen.

3. Regulation of carbohydrate metabolism

Glucose homeostasis is a complicated interaction of metabolic pathways. It is vital for living organisms. These processes either increase or decrease the blood glucose concentration but they work together in order to maintain an optimal level.

Glucose is derived from carbohydrates taken in the diet. Carbohydrate is digested to the simple sugars: glucose, fructose and galactose. These sugars are absorbed in the intestine and transported to the liver via the portal vein. Thereafter the liver converts fructose and galactose into glucose. Rising levels of glucose in the blood stimulate the release of insulin from the b cells of the islets of Langerhans in the pancreas.

Insulin is the only hormone that reduces blood glucose levels, and it does this by activating the glucose transport mechanisms and glucose-utilizing metabolic pathways in different tissues of the body. Thus, insulin down-regulates glucose forming pathways.

Insulin stimulates:

uptake of glucose by muscle and adipose tissue glycolysis glycogenesis (formation of glycogen from free glucose) protein synthesis

Insulin inhibits:

gluconeogenesis (formation of glucose from amino acids, fatty acids etc.) lipolysis (breakdown of fatty acids) proteolysis (breakdown of proteins) ketogenesis (formation of ketone bodies)

Disturbed glucose homeostasis is vital in causation of diseases like diabetes.

4. Enzyme specific activity changing activity of the same amount of enzyme.

A major mechanism of enzyme regulation is regulating enzyme specific activity

There are two main types of mechanisms for regulation of enzyme specific activity:

- Allostery-Enzyme activity can be activated or inhibited through non-covalent interaction of the enzyme with small molecules called effectors, modulators, or allosteric regulators (AE). Effectors bind to the enzyme at a site other than the active site (allo means other). Reversible binding to enzyme- fast response time. Concentration dependent.

- Covalent modification- Covalent addition of a group to an enzyme changes the activity of the enzyme.

Mechanisms of Reciprocal Regulation:

To prevent complete futile cycling, regulation of enzyme activity by allosteric or covalent modification works reciprocally. That is, the specific activities of one or more enzymes of a

pathway are activated at the same time the specific activity of one or more enzymes of the opposing pathway is inhibited. Often the same mechanism is used (either the same modification system, or the same allosteric regulator). The same mechanism has opposite effects on enzymes of the opposing pathways.

Reciprocal regulation using allosteric- Binding of the same regulator to the enzymes of opposing reactions has the opposite effect (activation for one enzyme, inhibition for the other).

Reciprocal regulation using covalent modification- The modification system modifies enzymes catalyzing opposing reactions at the same time, the same type of modification has opposite effects on the two enzymes, activating one, while inhibiting the other that operates in the opposing pathway.