

Bio Factsheet



Number 31

Enzyme Control of Metabolic Pathways

It is essential that the various biochemical processes occurring within an organism are adaptable. This means that the rates of biochemical reactions need to vary in response to change. In humans, for instance, these reactions need to cope with a sudden abundance of glucose in cells after a carbohydrate-rich meal (e.g. lots of rice or potatoes). Another example is that muscles may rapidly require usable energy for sudden locomotion. There would be severe problems if the rates of chemical reactions breaking down glucose and supplying energy remained constant; there would be an over-supply of glucose or shortage of usable energy. Coping with over-supply and shortages are two main reasons why the rates of biochemical reactions are variable.

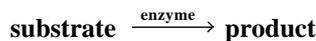
Usable Energy

Energy has to be in a particular form to cause the muscle to contract. Usable energy is stored in molecules called adenosine triphosphate (ATP). More ATP molecules means more energy.

Biochemical systems therefore need to be flexible to achieve adaptability. This flexibility can be achieved by varying the rates at which enzymes work.

Enzymes

Enzymes are protein molecules which change the rate of a chemical reaction without themselves being permanently changed by the reaction. Enzymes help change a substrate (the molecule on which they are acting) into a product.



How is the rate of enzyme activity changed?

Four major factors influence the rate at which enzymes work:

1. Enzyme concentration
2. pH
3. Temperature
4. Substrate concentration

Enzyme concentration

Influencing the rate of a biochemical reaction by changing the enzyme complex is expensive in terms of energy. The cell has to make complex enzyme molecules from simpler molecules; this process involves the consumption of energy and also takes time and may therefore be unsatisfactory for urgent responses.

pH and temperature variation

It is important to think about which external (outside the enzyme) conditions are likely to be most influential within the body or cell of an organism. The wide range of pH and temperature variation in a laboratory test tube may have little relevance to an organism in which body temperature and pH are closely controlled e.g. human blood is usually maintained within a pH range of 7.35 - 7.45 and a temperature range of 37- 38°C. Even reptiles are capable of maintaining their body temperature within quite narrow limits. However, in practice, the body rarely attempts to control the rate of metabolic pathways by deliberately altering pH or temperature.

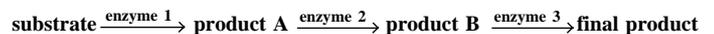
Metabolic Pathways

There are two types of metabolic reactions:

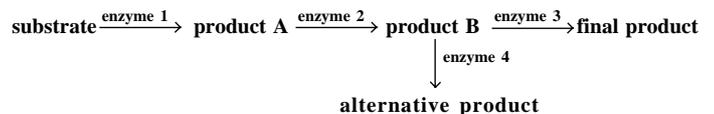
Anabolic - in which larger molecules are made from smaller ones e.g. proteins from amino acids.

Catabolic - in which larger molecules are broken down into smaller ones e.g. proteins into amino acids during digestion.

Often several reactions are linked together in a linear chain, with several different types of molecules, known as metabolites, being formed between substrate and final product. Each stage is often controlled by a different enzyme:



This is known as a **metabolic pathway**. **Metabolism** is the general term for all the chemical reactions in the body. Metabolic pathways can be branched so that it is possible to switch into another route should an accumulation of products occur at the end of one route (gridlock).



The end products of one reaction very often become the starting substrate for a second reaction or pathway. The consumption of the end products may stimulate the first reaction. In this way an equilibrium situation is avoided and metabolic pathways are continuously restimulated. Each step of a metabolic pathway is catalysed by a different enzyme, and since each enzyme effectively represents a control point, the cell retains close control over the overall rate of reaction. The different enzymes involved in a complex metabolic cycle or pathway (e.g. glycolysis) may require different biochemical conditions and hence may occur in different parts of a cell. Such compartmentalisation allows optimum conditions to be maintained. In turn, this helps to maximise the rate of reactions.

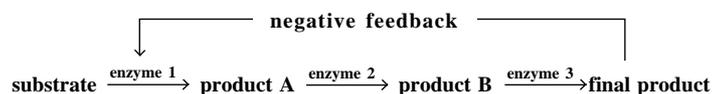
Substrate and product concentration

A high substrate concentration may increase the rate of enzyme action to ensure its rapid breakdown.

A high product concentration may also inhibit enzyme action so that less product is formed. This is an example of **negative feedback**.

Metabolic pathways and regulatory enzymes

Many metabolic reactions occur in a series of steps (e.g. glycolysis) and the rate at which a substrate is used, or a product formed, can be controlled by altering the rate at which enzymes work. Some enzymes in the pathway are more important than others in the regulation of the rate of reaction along the pathway. These may be compared to variable speed controls along a motorway. The targeted enzymes are called **regulatory enzymes**. They often occur at the first step in a metabolic pathway.



Allosteric interaction

The rate at which regulatory enzymes work is often altered by molecules binding at sites other than the active site.

Active site

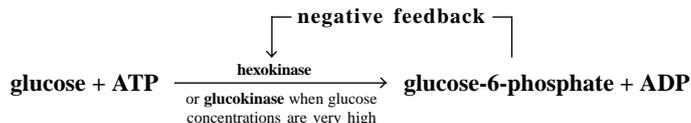
Only a small part of an enzyme, acts upon the substrate which attaches to it. This region usually consists of between 3 and 12 amino acids and it is called the 'active site'. It is thought that the **conformation** (shape and structure) of the enzyme is changed slightly when the substrate binds to it. This model for the attachment of the substrate is known as 'induced fit'.

Such regulatory enzymes are called **allosteric enzymes**. The alternative binding site is called an **allosteric site**. Molecules which influence regulatory enzymes by binding to allosteric sites are called **allosteric effectors**. Allosteric effectors change the conformation of the enzyme they regulate, in particular the **tertiary structure** i.e. the way a polypeptide chain coils and folds.

Product regulation

The phosphorylation of glucose is catalysed and regulated by two enzymes, **hexokinase** and **glucokinase**, which are therefore important in controlling the metabolic pathway of glycolysis.

When glucose enters the cells of respiring tissues it is first modified to glucose-6-phosphate. This is the first reaction in the glycolysis pathway. High concentrations of glucose-6-phosphate then inhibits hexokinase which prevents too much product accumulating. Glucose-6-phosphate is therefore an example of a product which regulates a reaction. This is called **end product inhibition**.



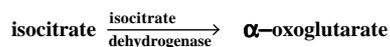
This reaction is important because:

- The addition of a phosphate group (phosphorylation) makes the glucose molecule more reactive.
- The phosphorylation of the glucose molecule makes it more difficult for it to escape out of the cell.
- It is the main regulatory step in the glycolysis pathway.

Hexokinase is inhibited by the product glucose-6-phosphate (an example of negative feedback - see Factsheet #28). However, when blood glucose levels become too high, some of it needs to be converted to glycogen and this can only happen if it is first converted to glucose-6-phosphate. The problem is solved by glucokinase which is less inhibited by glucose-6-phosphate and is activated by higher glucose concentrations.

ATP regulation

A key regulatory enzyme in the Krebs' cycle is **isocitrate dehydrogenase**; a simplified version of the reaction it controls is:

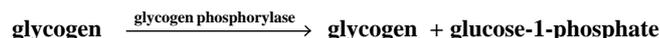


ATP inhibits isocitrate dehydrogenase and ADP activates it. When the ATP attaches to isocitrate dehydrogenase, the conformation of the enzyme's active site is altered which reduces its ability to attach to its substrate. When there is higher concentration of ADP than ATP, the ADP displaces the ATP attached to the allosteric site and the enzyme is able to catalyse the reaction.

Reversible covalent modification

The rate of enzyme action can also be adjusted by reversible covalent modification. This involves modifying the enzyme structure by making or breaking covalent bonds.

A well known example of reversible covalent modification involves the regulatory enzyme **glycogen phosphorylase**. This is involved in glycogen breakdown and releases small glucose units, as glucose-1-phosphate, from the ends of the glycogen molecule. Glycogen phosphorylase exists in two different forms, an active 'a' form and an inactive 'b' form. The activity of glycogen phosphorylase is regulated by adding a phosphate group, producing the 'a' form, or removing it and producing the 'b' form.

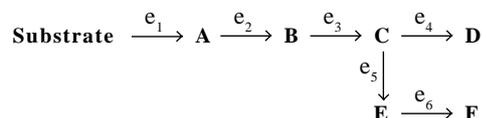


Summary

- The various biochemical reactions occurring in cells need to respond to change by varying the rates of reaction.
- This is achieved by controlling the rate at which enzymes operate.
- Enzymes can either be activated or inhibited.
- Metabolic pathways are not usually equally controlled at each individual step; there are often specific enzymes, called regulatory enzymes, which dominate the control system.
- Substrate activation and feedback inhibition control the rate at which regulatory enzymes operate.

Practice Questions

The figure below shows a branched metabolic pathway in which a substrate is processed into a series of products A, B, C, D, E and F. Enzymes e_1 , e_2 , e_3 , e_4 , e_5 , and e_6 are involved in the pathway.



- Suggest how over-production of D could favour lower production of F. (5 marks)
- Suggest two possible reasons why it may be advantageous for the cell to produce a final product in several steps rather than one step. (2 marks)

Answers

Semicolons indicate marking points.

- High concentration of D; inhibits; enzymes e_1 and /or e_2 , e_3 , e_5 , e_6 ; by negative feedback; reduces rates of reaction;
- Production of useful intermediate molecules/metabolites; slow rather than rapid and potentially destructive release of energy;

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