8.1 ENZYMES

- Enzymes are globular protein molecules composed of living cells
- They can be defined as *biological catalysts* (i.e they speed up reactions) without being used up
- Their presence does not alter the nature or properties of the end product of the reaction
- A very small amount of catalyst effects the change of a large amount of substrate
- Their activity varies with pH, temperature, pressure and substrate and enzyme concentrations
- A single enzyme generally will catalyze a single reaction

Metabolic pathways consist of chains and cycles of enzyme catalyzed reactions.

Metabolic reactions:

- Anabolic (involved in synthesis)
- Catabolic (involved in breakdown)

Pathways:

- Two or more reaction chains (eg respiration which involves glycolysis, Krebs Cycle and oxidative phosphorylation)

Active Site

A small portion of the enzyme (3 – 12 amino acids), which comes into direct contact with the substrate in the enzyme/substrate complex.

Substrate + enzyme → enzyme / substrate complex → enzyme / products

"Key" + "Lock"

The induced fit model

The induced fit hypothesis states that when a substrate combines with an enzyme, it causes changes in the enzyme structure. The amino acids, which constitute the active site, are taking a precise formation, which enables the enzyme to perform its catalytic function more effectively.

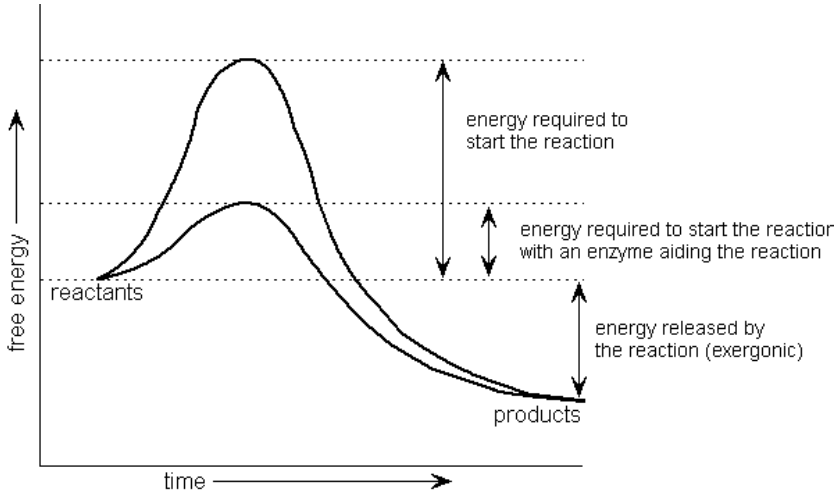
What the induced fit model describes, is that if the shape of an active site alters when substrates bind, several but similar substrates could easily bind successfully to it.

ACTIVATION ENERGY (E_a)

→ The energy required to make substrate react

The greater the amount of activation energy required, the slower will be the rate of reaction at a given temperature. Enzymes, by functioning as catalysts, serve to reduce the activation energy required for a chemical reaction to take place.

During a reaction, energy is given out as new bonds are made. In ***exergonic*** reactions (catabolic reactions) this amount of energy is greater than the activation energy. In ***endergonic*** (anabolic reactions) reactions it is less.



Activation Energy Profile of a Reaction Aided by an Enzyme

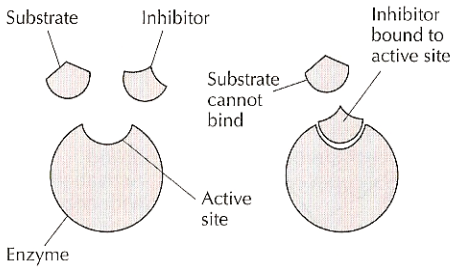
DIFFERENCES BETWEEN COMPETITIVE & NON-COMPETITIVE INHIBITION

Some chemical substances reduce the activity of enzymes or prevent it completely. These substances are called inhibitors.

COMPETITIVE INHIBITION

A compound, *structurally similar* to that of the usual substrate, associates with the enzyme's active site, but it is unable to react with it.

While it remains there it prevents access of any other molecules of true substrate. As the genuine substrate and the inhibitor **compete** for position in the active site, this is called *Competitive Inhibition*.



<u>Effect of Inhibitor Concentration</u>

When the inhibitor concentration is low, any increase in the substrate concentration will gradually reduce the effect of the inhibitor.

As substrate molecules increase, they will win the competition and will bind to the active site. Therefore, maximum enzyme activity is reached as when there was no inhibitor.

<u>Example:</u>

Succinate ---------- > Fumarate

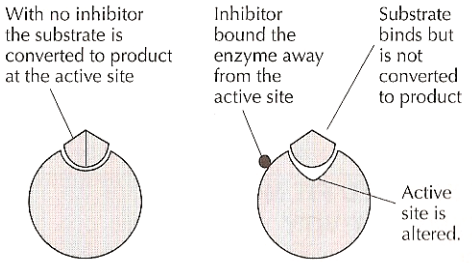
Succinate dehydrogenase

Succinate dehydrogenase is inhibited by **malonate**

NON-COMPETITVE INHIBITION

This type of inhibitor does not have a real structural similarity to the substrate. The inhibitor binds to the enzyme at a point on the enzyme other than the active site.

This causes the alteration of the shape of the enzyme so although the substrate may still be able to bind, but the active site will not catalyze the reaction.



Effect of Inhibitor Concentration

When the inhibitor concentration is low, any increase of substrate concentration will increase enzyme activity. This is because the substrate has more chances, since it is found in greater concentrations to occupy the active site.

However, the substrate can not prevent the binding of the inhibitor, since they are not competing for the same site. However, enzyme activity rate will be lower than when there is no inhibitor.

<u>Example:</u>

Arginine ---------- > nitric oxide and citrulline

Nitric oxide synthase

Nitric oxide synthase can be inhibited by **morphine**

The role of ALLOSTERY in the control of metabolic pathways by end-product inhibition

Allostery is a form of non-competitive inhibition

In many metabolic pathways, the product of the last reaction in the pathway inhibits the enzyme that catalyses the first reaction. This is called *end-product inhibition.* This inhibition causes the *decrease* of the enzyme's activity

The enzyme that is inhibited by the end products is an example of an *allosteric enzyme.*

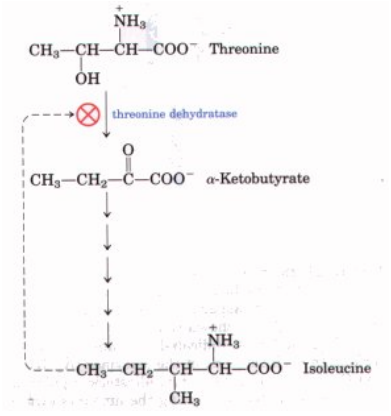
Allosteric enzymes have two binding sites and one of them is the active site, while the other is the allosteric site.

The allosteric site is the binding site for the end-product. When it binds, it is less likely for the substrate to bind to the active site. Hence, the end-product acts as an inhibitor.

If the inhibitor detaches, the enzyme returns to its original shape and a substrate can bind to the active site again.

Example:

Regulation of metabolism: When the end-products are found in excess the whole metabolic pathway is switched off and no intermediate products build up. See below the inhibition of threonine dehydratase by isoleucine:



Finding new anti-malarial drugs

- *Plasmodium* (malarial parasite) is resistant to most drugs.
- There are 5,655 chemicals that might act as enzyme inhibitors in *Plasmodium*
- Nine *Plasmodium* enzymes and their metabolic pathways are currently tested
- Inhibitors were found for six of them and these are now being researched as they can potentially act as anti-malarial drugs!