ENZYMES

Content Statements:

C1.1.11 Intracellular and extracellular enzyme-catalysed reactions

C1.1.12 Generation of heat energy by the reactions of metabolism

C1.1.13 Cyclical and linear pathways in metabolism

C1.1.14 Allosteric sites and non-competitive inhibition

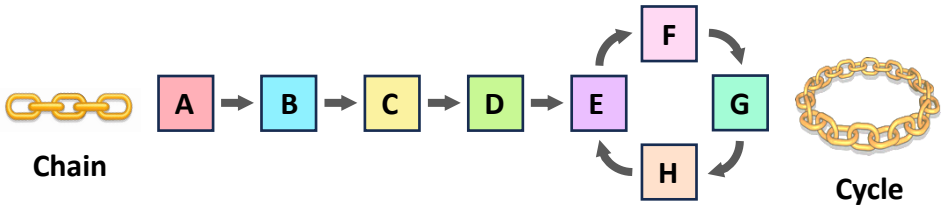
C1.1.15 Competitive inhibition as a consequence of an inhibitor binding reversibly to an active site

C1.1.16 Regulation of metabolic pathways by feedback inhibition

C1.1.17 Mechanism-based inhibition as a consequence of chemical changes to the active site caused by the irreversible binding of an inhibitor

METABOLIC PATHWAYS

Most chemical changes in a cell result from a series of reactions (metabolic pathways), with each individual step controlled by a specific enzyme. Metabolic pathways can be found within the cytoplasm (**intracellular**) or outside of the cell (**extracellular**). Examples of intracellular reactions include the stages of cell respiration (glycolysis and the Krebs cycle), while an example of an extracellular reaction is the breakdown of nutrients within the gut (chemical digestion). Metabolic pathways are typically organised into either **chains** or **cycles** of enzyme-catalysed reactions. Linear chains occur in processes such as glycolysis and blood clotting, while cyclical pathways are present in processes such as the Krebs cycle and the Calvin cycle. Metabolic pathways allow for a greater level of regulatory control, as a chemical change is controlled by multiple intermediates.



ENERGETICS

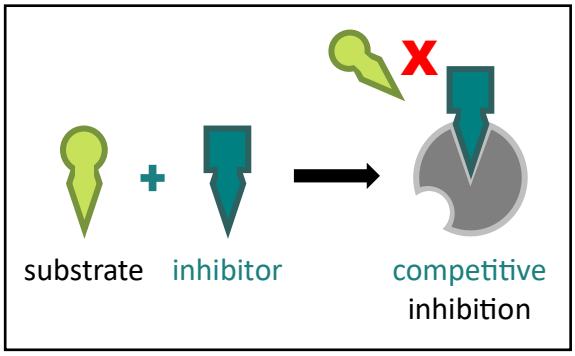
Metabolic reactions are not 100% efficient in their energy transfers – a proportion of energy is always lost as **heat**. Certain animals (such as mammals and birds) use this heat generation to maintain a constant body temperature (**endotherms**). The level of heat production by these animals can be regulated by controlling their level of metabolic activity. Some animals may even enter a state of torpor to reduce heat production.

INHIBITORS

An enzyme inhibitor is a molecule that binds to an enzyme and disrupts substrate interaction. Inhibitors can be produced by cells to regulate metabolic processes by preventing catalysis. Inhibitors are also introduced from the external environment to damage cells (e.g. **venoms**). Inhibitors can be categorised based on their mechanism of action (competitive vs non-competitive) or their consequence on cellular activity (feedback inhibition or mechanism-based inhibition). Inhibition can be **reversible** (by forming weak hydrogen bonds) or **irreversible** (by forming strong covalent bonds). Inhibitors can be used to treat some disease conditions.

COMPETITIVE INHIBITION

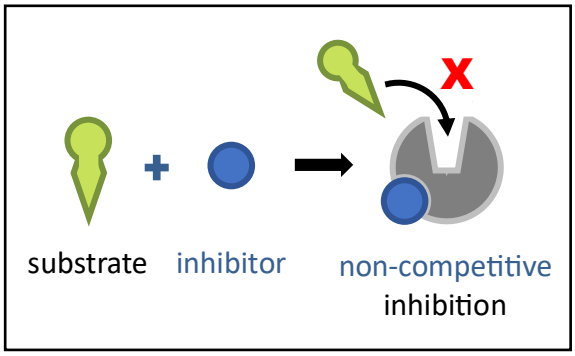
Competitive inhibition involves a molecule, other than the substrate, binding reversibly to an enzyme's active site. The molecule (inhibitor) is structurally and chemically similar to the substrate. The competitive inhibitor functions to **block the active site** and thus prevents substrate binding. As the inhibitor is in competition with the substrate, its effects can be reduced by increasing the concentration of the substrate.



Statins are common cholesterol lowering drugs that function as competitive inhibitors. Statins bind to the active site of the enzyme **HMG-CoA reductase** which forms a part of the metabolic chain responsible for cholesterol synthesis. By blocking this metabolic chain, cholesterol production is reduced, minimising the health consequences associated with high cholesterol levels (such as symptoms of coronary heart disease).

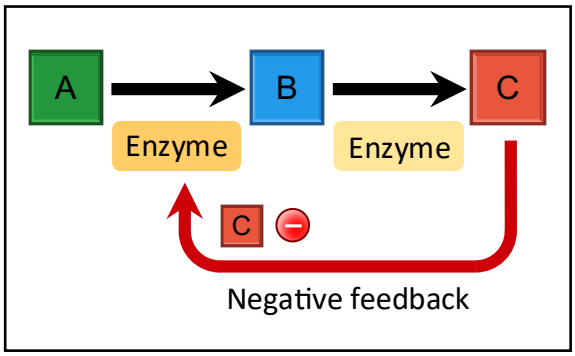
NON-COMPETITIVE INHIBITION

Non-competitive inhibition involves a molecule binding to a site other than the active site (**allosteric site**). The binding of an inhibitor to the allosteric site causes a conformational change to the enzyme's active site. As a result of the change, the active site and substrate will no longer share specificity, meaning the substrate cannot bind. Increasing the substrate levels cannot mitigate inhibitor's effect (not in competition).



FEEDBACK INHIBITION

Feedback inhibition is a form of negative feedback by which metabolic pathways can be regulated. In feedback inhibition, the **final product** in a series of reactions inhibits an enzyme from an earlier step in the sequence. The product will bind to an allosteric site and temporarily inactivates the enzyme. As an enzyme can no longer function, the reaction sequence is halted and the product formation rate will be decreased.



An example of feedback inhibition is the regulatory control of **isoleucine production** in bacteria. Isoleucine may be synthesised from **threonine** in a multi-step pathway. Isoleucine can bind to an allosteric site on the first enzyme in this pathway and function as a non-competitive inhibitor. As excess production of isoleucine inhibits further synthesis, it ensures stocks of threonine are not cannibalised in a cell (feedback inhibition).

MECHANISM-BASED INHIBITION

Mechanism-based inhibition involves molecules other than a substrate binding to an active site and being chemically altered. Covalent bonds form between the enzyme and **substrate analogue**, causing *irreversible* inhibition. An example of a mechanism-based inhibitor is penicillin, which inhibits specific transpeptidases from synthesising the bacterial cell wall. This prevents the bacteria from regulating the hydrostatic pressure within the cell, causing it to lyse. Penicillin is therefore a commonly used **antibiotic**, as it targets a feature unique to prokaryotic cells (peptidoglycan cell wall). However, certain strains of bacteria have mutations to their transpeptidase gene, resulting in low affinity for penicillin. These strains are resistant to treatments of penicillin and can potentially transfer this resistance to other strains via a process of **bacterial conjugation**.