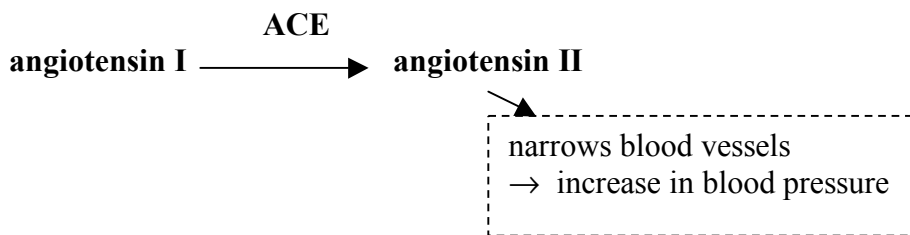


## Enzyme Inhibitors are ACE!

Cardiovascular disease is one of the most prevalent causes of disease in humans today. A major risk factor in many heart attacks is hypertension (high blood pressure).

How does blood pressure change? There are many factors, but one protein, angiotensin II, is known to be a major contributor. Angiotensin II is a very potent chemical that causes the muscles surrounding blood vessels to contract, thereby narrowing the blood vessels, leading to high blood pressure. An enzyme, angiotensin-converting enzyme (ACE) is responsible for the production of angiotensin II in the blood.



Many people with high blood pressure and at risk of heart attack are now prescribed medications classified as ACE inhibitors. Controlled studies have shown that patients with high blood pressure and heart failure, and also those who have had heart attacks, who were treated with an ACE inhibitor lived statistically longer than patients who did not take this type of medication.

## Enzyme Inhibitors

ACE inhibitors belong to an important class of molecules known as **enzyme inhibitors**. We know that enzymes regulate all metabolic reactions in the body. Knowledge of specific enzymes, and their roles in maintaining healthy cells, or in actually causing disease, has led to the ever growing field of rational drug design of enzyme inhibitor molecules, with the aim to inhibit the activity of a specific enzyme to treat a specific human condition or disease.

### Questions

1. ACE inhibitor drugs impeded the activity of the angiotensin-converting enzyme. Explain how inhibiting the activity of the ACE enzyme may lead to a decrease in blood pressure and thus a reduction in the risk of heart attack.

## Mode of action of enzyme inhibitors

Enzyme inhibitors may work in one of two main ways to inhibit the activity of an enzyme:

1. by binding to the enzyme's active site, thus blocking the substrate's ability to form an enzyme-substrate complex; or
2. binding to a part of the enzyme, not in the active site, that then changes the shape of the enzyme's active site.

Some enzyme inhibitors are reversible in their action; others are not. Irreversible inhibitors usually react with the enzyme itself, changing it chemically and thus reducing or stopping its action.

### Questions

2. Draw diagrams to illustrate the two main mechanisms of enzyme inhibition.
3. One of these mechanisms could be described as competitive. Which one? Explain your answer.

### Rational drug design of enzyme inhibitors

Scientists are now using rational drug design techniques to develop drug molecules that will interact and inhibit specific enzyme molecules. Some of these may be naturally occurring molecules such as the antibiotic penicillin, which inhibits the enzymes that produce and then cross link the strands of peptidoglycan in the cell wall of certain bacteria. Other inhibitors can be synthesized to chemically interact with the enzyme.

Rational drug design uses the 3-dimensional structure of an enzyme's active site to predict which molecules might be inhibitors of that enzyme. These molecules are then tested to identify which actually do inhibit enzyme activity. Further modification of the molecule may occur to improve its ability to bind specifically with the enzyme before it is then used in laboratory trials on cultured cells, and later on, in patients.

### Questions

4. *Nelsonase is a hypothetical enzyme that enhances concentration of year 12 students during Biology lessons. Nelsonase is thought to stimulate production of the neurotransmitter Nelsonotin. However, excessive levels of Nelsonotin can lead to a debilitating condition that causes the student to write down balanced chemical equations for photosynthesis and respiration uncontrollably. A pharmaceutical company has identified two possible molecules that may be inhibitors of Nelsonase. Design a controlled experiment, to be conducted using cell cultures in a laboratory, that tests the effectiveness of each of the two molecules in inhibiting the action of Nelsonase.*

### Specific and potent

Medical enzyme inhibitors are judged by their specificity and potency.

**Specificity** refers to how it binds to other, non-target proteins. The more specific it is, the fewer side effects there may be.

**Potency** refers to how much of the inhibitor is needed to be effective medically. The more potent the molecule, the less of the drug will need to be administered.

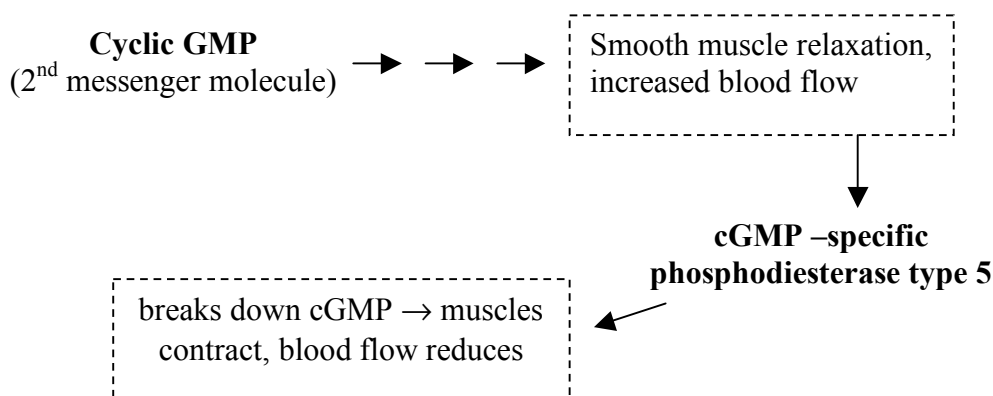
High specificity and potency ensures that a drug will have fewer side effects, and thus lower toxicity to the patient.

## Enzyme inhibitors in action

ACE inhibitors are just one class of enzyme inhibitors that have been widely used in medicine in the last 30 years. There are many others:

Sildenafil, better known as Viagra, is one drug that made headlines in the 1990's –. Sildenafil was initially designed as a drug to treat hypertension and angina pectoris (a form of cardiovascular disease). However, phase I clinical trials indicated that it had little effect on angina, but that it may be more useful to treat male erectile dysfunction (impotence). It was patented for this use in 1996, and was first approved for treatment generally in the US in 1998. Since then sales of sildenafil have totalled billions of dollars.

Sildenafil is an inhibitor of the enzyme that degrades cyclic GMP (cyclic guanosine monophosphate) – a molecule that acts as a second messenger in the responses of cells to some hormone. One of these responses leads to smooth muscle relaxation and enhanced blood flow in the corpus cavernosum of the penis, which causes an erection. Since sildenafil decreases the activity of cGMP –degrading enzyme (known as cGMP-specific phosphodiesterase type 5), its main effect is to make this signaling for muscle relaxation and blood flow last longer.



### Questions

- Use a flow diagram, similar to the one above, to explain how sildenafil can be used to treat impotence.

Another enzyme inhibitor that is commonly used in cancer chemotherapy is **methotrexate**. Methotrexate is structurally very similar to folic acid. Folic acid is an oxidized form of the substrate of the enzyme dihydrofolate reductase. This enzyme is critical for thymidine biosynthesis. Thymidine is made up of a pentose sugar and the nitrogen base thymine, and forms part of one type of nucleotide. Thus, by blocking thymidine synthesis, methotrexate is toxic for rapidly growing cells (such as those in a tumour), but not to non-dividing cells.

### Questions.

6. *Is methotrexate a competitive or non-competitive inhibitor of the enzyme dihydrofolate reductase? Explain your answer.*
7. *Methotrexate disrupts nucleic acid synthesis – Is this DNA or RNA synthesis? Explain your answer.*
8. *Explain how methotrexate is specific to cancerous cells?*
9. *Reproductive tissues (that give rise to sperm or eggs) may also be affected by methotrexate – infertility or reduced fertility is a possible side effect. Explain why.*