Lock and Key Vs Induced fit

A case study of how a scientific model is modified over time

In 1894, Emil Fischer wrote: "To use a picture, I would like to say that enzyme and glucoside have to fit to each other like a lock and key in order to exert a chemical effect on each other." At that time, the prevailing view was that enzymes were carbohydrates and nothing was known about the active site.

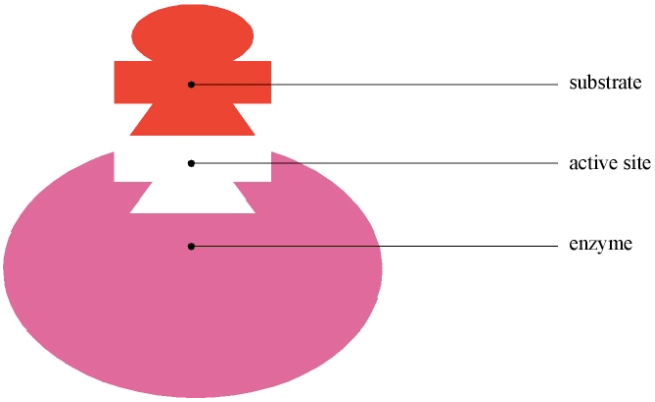

Figure 1 The 'lock and key' model of enzyme action

Fischer's powerful model explained the experimental observations produced by researchers at the time and remained the accepted theory for 60 years. As new experimental techniques allowed researchers to probe enzyme action more closely, a number of experimental observations emerged that did not fit with the 'lock and key' model.

Further work in the 1930s, by J.B.S. Haldane, developed the idea that enzyme catalysis was confined to a small region called the active site. He suggested that the bulk of the enzyme had no purpose other than to hold the active site groups in the correct position. It was also around this time that scientists discovered that all enzymes were proteins and that they were responsible for all chemical reactions within cells.

In the late 1950s, a biochemist, called Daniel Koshland, started to think that the 'lock and key' model required some modifications. He realised that the observation of non-competitive inhibition did not fit with the existing theory. How could a molecule that binds to a location away from the active site interfere with substrate binding?

Koshland proposed a new theory – the 'induced fit' model. His model predicted that enzyme action requires the precise orientation of catalytic groups in the active site. When the substrate binds, it causes a noticeable change in the three-dimensional position of the amino acids at the active site. This brings the catalytic groups into the required position for catalysis to take place. A non-substrate molecule, even if it could bind, would not bring about the required change in the enzyme shape.

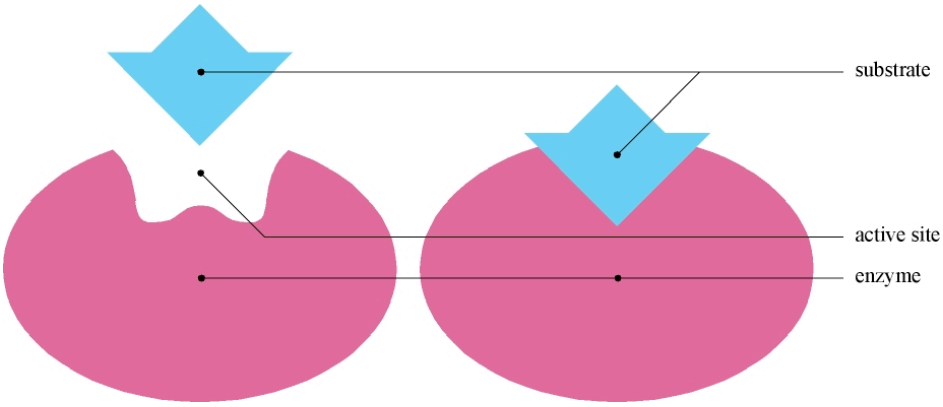

Figure 2 The 'induced fit' model of enzyme action

Initially, Koshland experienced difficulty getting his ideas published in scientific journals. Later, with further evidence from his laboratory, other scientists gradually saw the explanatory power of the theory and supporting observations came from their experiments. The evidence was initially indirect; for example, certain chemicals, known not to bind to the active site, altered the binding and catalysis of the substrate. Direct evidence for the flexibility of enzymes had to wait for the refinement of a new experimental technique – X-ray protein crystallography. In 1957, Kendrew used X-ray crystallography to produce the first low-resolution model of a protein, myoglobin. As this new technology improved, it allowed scientists to measure the very small movements of chemical groups in the active site. With research becoming more technical, involving specialist knowledge from once separate branches of science, the collaboration of chemists, biologists, mathematicians, physicists and engineers was essential.

The 'induced fit' theory did not disregard the 60-year-old 'lock and key' model as obsolete; it just required it to flex a little. The idea of enzyme and substrate fitting together in a complementary way remained, but now enzymes were thought to be flexible. Koshland likened it to a hand in glove.

As technology, such as computer modelling, allows increasingly detailed analysis, some researchers (papers published 1993–2002) think that the theories of Haldane and Koshland require further modification. They propose a theory called the 'shifting specificity model' for enzyme catalysis. The current view is that enzyme action depends on even greater disorder and flexibility. Search the internet if you would like to explore this area in more depth.

Over recent decades, advances in computing power and software design supported progress in our understanding of enzyme structure and action. With the amino acid sequences of proteins, computers can predict three-dimensional

enzyme structures. Scientists can design molecules that interact with enzymes and affect their catalytic action.

Questions

1. How does the 'induced fit' model help to explain non-competitive inhibition?
2. Why do you think that, initially, Koshland experienced difficulty in getting his papers published and his ideas accepted?
3. Explain your thoughts on whether you think the title of this activity, 'lock and key' versus 'induced fit', is appropriate.
4. Why do you think the 'lock and key' model is still a powerful way to explain enzyme action?
5. What factors affect the speed at which new evidence for a theory emerges?
6. What do you think is meant by a multidisciplinary approach to research?
7. Why are enzymes important targets for drugs?