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Biochemistry, Proteins Enzymes

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Introduction

Every day, trillions upon trillions of chemical reactions occur in our body to make essential metabolic processes occur. Enzymes are proteins that act upon substrate molecules and decrease the activation energy necessary for a chemical reaction to occur by stabilizing the transition state. This stabilization speeds up reaction rates and makes them happen at physiologically significant rates. Enzymes bind substrates at key locations in their structure called active sites. They are typically highly specific and only bind certain substrates for certain reactions. Without enzymes, most metabolic reactions would take much longer and would not be fast enough to sustain life.

Fundamentals

There are six main categories of enzymes: oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases. Each category carries out a general type of reaction but catalyzes many different specific reactions within their own category. Some enzymes, called apoenzymes, are inactive until they are bound to a cofactor, which activates the enzyme. A cofactor can be either metal ions (e.g., Zn) or organic compounds that attach, either covalently or noncovalently, to the enzyme. The cofactor and apoenzyme complex is called a holoenzyme. Enzymes are proteins comprised of amino acids linked together in one or more polypeptide chains. This sequence of amino acids in a polypeptide chain is called the primary structure. This, in turn, determines the three-dimensional structure of the enzyme, including the shape of the active site. The secondary structure of a protein describes the localized polypeptide chain structures, e.g., α-helices or β-sheets.

The complete three-dimensional fold of a polypeptide chain into a protein subunit is known as its tertiary structure. A protein can be composed of one (a monomer) or more subunits (e.g., a dimer). The three-dimensional arrangement of subunits is known as its quaternary structure. Subunit structure is determined by the sequence and characteristics of amino acids in the polypeptide chain. The active site is a groove or crevice on an enzyme in which a substrate binds to facilitate the catalyzed chemical reaction. Enzymes are typically specific because the conformation of amino acids in the active site stabilizes the specific binding of the substrate. The active site generally takes up a relatively small part of the entire enzyme and is usually filled with free water when it is not binding a substrate.[1][2]

Molecular Level

There are two different models of substrate binding to the active site of an enzyme. The first model called the lock and key model, proposes that the shape and chemistry of the substrate are complementary to the shape and chemistry of the active site on the enzyme. This means when the substrate enters the active site, it fits perfectly, and the two binds together, forming the enzyme-substrate complex. The other model is called the induced fit model, and it hypothesizes that the enzyme and the substrate don't initially have the precise complementary shape/chemistry or alignment, but rather, this alignment becomes induced at the active site by substrate binding. Substrate binding to an enzyme is

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generally stabilized by local molecular interactions with the amino acid residues on the polypeptide chain. There are four common mechanisms by which most of these interactions are formed and alter the active site to create the enzyme-substrate complex: covalent catalysis, general acid-base catalysis, catalysis by approximation, and metal ion catalysis.

1. Covalent catalysis occurs when one or multiple amino acids in the active site transiently form a covalent bond with the substrate. This reaction usually takes the form of an intermediate through a nucleophilic attack of the catalytic residues, which helps stabilize later transition states.
2. General acid-base catalysis takes place when a molecule other than water acts as a proton donor or acceptor. Water can be one of the proton donors or acceptors in the reaction, but it cannot be the only one. This characteristic can sometimes help make catalytic residues better nucleophiles, so they will more easily attack substrate amino acids.
3. Catalysis by approximation happens when two different substrates work together in the active site to form the enzyme-substrate complex. A common example of this involves water entering the active site to donate or receive a proton after a substrate has already bound to form better nucleophiles that can form and break bonds easier.
4. Metal ion catalysis involves the participation of a metal ion at the active site of the enzyme, which can help make the attacking residue a better nucleophile and stabilize any negative charge in the active site.

Enzymes can be either be a single subunit or comprised of multiple subunits. The subunits in a multisubunit enzyme can sometimes work together in a mechanism called “cooperativity,” in which one subunit influences another for either positive, activity boosting effects or negative, inhibiting effects. Through cooperativity between subunits, an enzyme can either take on a T-state or an R-state. The T-state, or “tense” state, results in less affinity for binding substrate than regular state enzyme would. The R-state, or “relaxed” state, results in higher affinity and increased substrate binding for the enzyme as a whole. There are also two different models for the relationship between these two states of a multisubunit enzyme. The concerted model states that when an enzyme is in the T-state, if one subunit changes to the R-state, then all of the other subunits will change to the R-state at the same time, resulting in increased binding and affinity for other effectors. This model is also reversible, for if all subunits are in the R-state and an effector dissociates, then they will all go towards the T-state. On the other hand, the sequential model states that once one effector binds to one of the subunits, the rest of the subunit’s affinity for the effector increases, but they all do not necessarily change from one state to the other. They are merely more likely to change as well.[3][4][5][6]

Function

$E+S \leftrightarrow ES \leftrightarrow E+P$

The initial step occurs when an enzyme binds to a substrate to form an enzyme-substrate [ES] complex (reaction 1). Increasing the concentration of a substrate [S] will, in turn, increase the rate of reaction until it reaches maximum velocity. After forming the ES, a product forms that dissociates from the enzyme, and the enzyme is then ready to repeat the catalysis steps.

Enzymes do not alter or shift the equilibrium of a given reaction but instead affect the free energy required to initiate a conversion, which affects the reaction rate. The energy hump that must be surmounted for a reaction to progress is called the activation energy; this is the highest energy on a reaction diagram. It is the most unstable conformation of the substrate in the reaction. Enzymes generally do not add energy to the reaction but instead lower the transition state energy to require less activation energy.

Inhibitors are regulators that bind to an enzyme and inhibit its functionality. There are three types of models in which an inhibitor can bind to an enzyme: competitive, non-competitive, and uncompetitive inhibition.

1. Competitive inhibition occurs when the inhibitor binds to the active site of an enzyme where the substrate would usually bind, thereby preventing the substrate from binding. For enzymes obeying Michaelis-Menten kinetics, this results in the reaction having the same max velocity but less affinity for the binding substrate.
2. Non-competitive inhibition occurs when the inhibitor binds to a site on the enzyme other than the active site but results in a decreased ability of the substrate to bind to the active site. The substrate is still able to bind in this model, but the active site functions less effectively. The max velocity under non-competitive inhibition decreases, but the affinity for substrate stays the same.
3. Uncompetitive inhibition (also called anti-competitive inhibition) occurs when an inhibitor binds only to the enzyme-substrate (ES in reaction 1). This reaction usually occurs when there are two or more substrates or products in a reaction. In uncompetitive inhibition, the max velocity and binding affinity both decrease.

Another kind of inhibition occurs with allosteric enzymes. These can bind a molecule called an allosteric effector, which will affect either the Vmax of the catalytic reaction or the substrate binding affinity.[7][8][9]

Clinical Significance

Knowledge about enzymes is essential in medicine for diagnosing many diseases. In clinical studies, enzymes can act as markers that identify disease states within the body. Doctors can often determine what kind of disease is affecting a patient and which organ is damaged by characterizing the enzymes released into circulation. Enzymes can also be a component in a tissue biopsy and provide detailed diagnostic information.[10]

Review Questions

- Access free multiple choice questions on this topic.
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