

Enzymes and Clinical Medicine

How are enzymes used to promote human health? Enzymes are useful in modern medical practice for several reasons. Enzyme assays provide important information concerning the presence and severity of disease. In addition, enzymes often provide a means of monitoring a patient's response to therapy.

In the following discussion, the use of enzymes in the diagnosis of myocardial infarction and as therapeutic agents is described.

Diagnostic Enzymes

Myocardial infarction, the interruption of the heart's blood supply, leads to the death of cardiac muscle cells. The symptoms of myocardial infarction include pain in the left side of the chest that may radiate to the neck, left shoulder and arm, and irregular breathing. Several clinical tests for myocardial infarction are based on detection of enzymes and other proteins that leak from damaged tissue into the blood. Among the first enzymes used to detect heart damage was lactate dehydrogenase (LDH). Later, creatine kinase (CK) assays were developed. Both LDH and CK are produced by various cells in slightly different forms called **isozymes**. Isozymes can be distinguished from each other because they migrate differently during electrophoresis. LDH is a tetramer composed of two subunits: heart type (H) and muscle type (M). There are five different LDH isozymes. LDH 1 (H₄) and LDH 2 (H₃M) are found only in heart muscle and red blood cells. LDH 5 (M₄) occurs in both liver and skeletal muscle. LDH₃ and LDH₄ are found in other organs. The differences in the migration patterns of LDH isozymes of a normal individual and a myocardial infarction patient are illustrated in Figure 6A. CK,

which occurs as a dimer, has two types of subunit, muscle type (M) and brain type (B). Heart muscle contains CK₂ (MB) and CK₃ (MM). Only the MB isozyme is found exclusively in heart muscle. Its concentration in blood reaches a maximum within a day following the infarction. CK₃ (MM), which is also found in other tissues, peaks a day after CK₂ (Figure 6B). Of the two enzymes, CK is the first enzyme detected during a myocardial infarction. CK's serum concentration rises and falls so rapidly that it is of little clinical use after several days. LDH, whose serum concentration rises later, is used to monitor the later stages of heart damage.

In recent years the strategy of measuring LDH has been replaced with tests for the cardiac variant of troponin I (cTnI). (The troponin complex, composed of three different subunits, regulates striated muscle contraction.) Troponin I is highly specific for myocardial injury and can be detected earlier than CK-MB and its serum levels remain elevated longer than those of LDH.

Therapeutic Enzymes

The use of enzymes in medical therapy has been limited. When administered to patients, enzymes are often rapidly inactivated or degraded. The large amounts of enzyme that are often required to sustain a therapy may provoke allergic reactions. However, there have been several successful enzyme therapies, including the use of streptokinase and asparaginase. Streptokinase, a noncatalytic protein produced by *Streptococcus pyogenes*, is

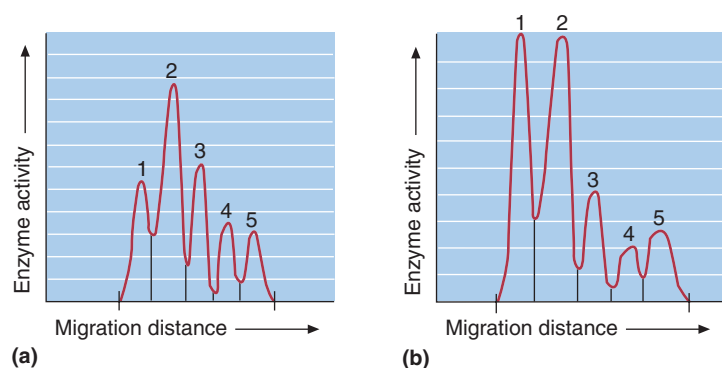


FIGURE 6A
Electrophoresis Pattern of Lactate Dehydrogenase Isozymes

(a) LDH isozymes from a normal individual. (b) LDH isozymes from a myocardial infarction patient. In recent years the use of LDH in the diagnosis of myocardial infarction has been replaced with test for cTnI.

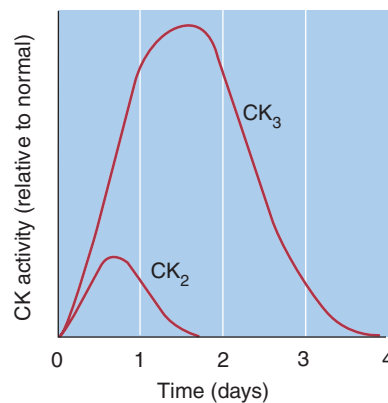


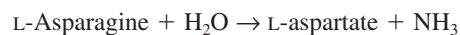
FIGURE 6B
Characteristic Pattern of Serum Creatine Kinase Concentrations Following a Myocardial Infarction



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used with great success in the treatment of myocardial infarction. Once injected into the bloodstream, streptokinase activates plasminogen, the inactive precursor of the proteolytic enzyme plasmin. Plasmin (a trypsinlike enzyme) digests fibrin, the primary component of blood clots. If administered soon after the beginning of a heart attack streptokinase can often prevent or significantly reduce further damage to the heart because it can dissolve blood clots that occlude the coronary arteries. Human tissue plasminogen activator (tPA), a product of recombinant DNA technology (Biochemistry in the Lab Nucleic Acid Methods I) that acts in a similar fashion, is also used to treat myocardial infarction.

The enzyme asparaginase is used to treat several types of cancer. It catalyzes the following reaction:



Asparaginase occurs in plants, vertebrates, and bacteria but not in human blood. Unlike most normal cells, the cells in tumors of certain kinds such as those in several forms of adult leukemia,

cannot synthesize asparagine. The infusion of asparaginase reduces the blood's concentration of asparagine and often causes tumor regression. Asparaginase therapy has several serious side effects, including allergic reactions and liver damage. Unfortunately, after several asparaginase treatments some patients develop *resistance*; that is, their tumor cells grow despite the presence of the drug that previously had caused tumor regression. Apparently, some tumor cells can induce the synthesis of asparagine synthetase, an enzyme that converts aspartate to asparagine.

In some diseases the body's capacity to produce certain digestive enzymes is compromised. In cystic fibrosis, for example, the absence of a functional chloride channel results in malabsorption of nutrients in the digestive tract. Inadequate chloride transport in the pancreas results in the failure to synthesize enzymes such as chymotrypsin and trypsin that digest food molecules. For this reason CF patients must consume digestive enzymes prepared by pharmaceutical companies during every meal.



SUMMARY: Specific enzymes are used in the diagnosis or treatment of a variety of human diseases.