

Enzymes in Thrombolytic Therapy

Anthony Cichoke, MA, DC, DACBN

As in the inflammation reaction, the clotting of blood is an example of a defense mechanism which can overreact and require therapeutic intervention. It is now known that in normal tissues, there is a constant dynamic equilibrium between blood coagulation (clotting) and fibrinolysis (the process of dissolving the clotted blood). The maintenance of proper balance in this equilibrium is extremely important. If fibrinolysis is increased by a pathological cause, a predisposal to excessive bleeding results. On the other hand, if fibrinolysis is weakened so that clot formation is favored, conditions occur that are called thromboses (clots formed in and remaining in blood vessels) and embolisms (sudden blockages of blood vessels caused by circulating fragments of clots). These can be life threatening. In chronic cases, cholesterol and other fatty materials may aggregate around clotted deposits in blood vessels. When this pathological condition is well established, it is called atherosclerosis -- hardening of the arteries.

Although there are chemical anti-coagulants (such as heparin) available as well as corrective surgical techniques, acute thromboses and embolisms (which are lumped together as acute thromboembolic vascular diseases) are still the largest single cause of death and disease in the middle-aged and elderly populations of the Western World.

The mechanism used by the body for controlling the equilibrium between clot formation and dissolution is a complex one involving a series of enzymes, proenzymes, activators, and proactivators. A brief outline of the highlights of the process will be helpful in understanding the therapeutic method. In forming a clot, the plasma protein, fibrinogen, is converted to insoluble fibrin by the enzyme thrombin. Fibrin forms the clot. The enzyme plasmin, which dissolves the clot, exists in the blood as the pro-enzyme plasminogen. Activators convert plasminogen to plasmin for dissolving the clot.

Just as nature uses enzymes in maintaining this crucial balance, so is man learning how to use enzymes to restore the balance once it is lost. Clinical studies have shown that the best approach to therapeutic thrombolysis (dissolution of clots) is an intravenous injection of an enzyme capable of converting plasminogen to plasmin -- the enzyme which dissolves the clot. This type of therapy is known as thrombolytic (thrombus or clot-splitting) or fibrinolytic (fibrin-splitting) therapy. The enzymes most frequently used for this are streptokinase (from bacteria) and urokinase (from human urine). Three "new" thrombolytic enzymes which have seen some therapeutic use in the last 20 years are arvin (from a Malayan pit viper), reptilase (from a South American snake), and brinase (from the mold *Aspergillus oryzae*).

Fibrinolytic therapy has been used successfully in the treatment of occlusions (blockages) of veins and arteries. It can be a lifesaving treatment in cases involving pulmonary embolisms and myocardial infarctions (blockages of vessels in lungs and heart, respectively). A pulmonary embolism is usually composed of a recently formed clot. Its first effects produce strain on the right side of the heart -- the side which pumps blood to the lungs.

Several groups of physicians have reported successful lysis of pulmonary embolisms by use of enzymes. These agents are most effective in massive pulmonary embolisms involving large blood

vessels, since clots in these vessels are more accessible to circulating enzymes than are those in smaller arteries of the lungs. Surgical removal of a pulmonary embolism is a dangerous procedure, so it seems likely that the use of thrombolytic therapy will increase in patients afflicted with this condition.

A group of clinicians from various hospitals, reporting together as the "European Working Party," in 1971, described a controlled experiment which confirmed the superiority of streptokinase over heparin (a chemical anticoagulant) in reducing deaths due to acute myocardial infarction. Both the total number of deaths, and the number of deaths within 24 hours of being stricken, were significantly lower in the enzyme-treated patients. There was also a significant decrease in the number of infarcts reformed and in the number of deaths due to heart failure in the enzyme-treated group when compared with the heparin-treated patients.

A danger in fibrinolytic therapy is the possibility of a clot re-forming. After a clot is dissolved, the tissue in that area remains damaged and the likelihood of new formation at that spot is high. Therefore, fibrinolytic therapy is followed up with anticoagulants, such as heparin. Major problems associated with streptokinase therapy are fever, a tendency of bleeding, antigenicity (as in any foreign protein), and the difficulty of determining the proper dose. Bleeding seems to be the most serious of these; it is also a problem when anticoagulants are used alone.

Urokinase (formed in the kidneys and obtained from human urine) seems to be safer than streptokinase, but, because of the difficulty and expense in producing it, clinical exploitation has been limited. (2,300 liters of urine yield 29 milligrams of highly purified urokinase. A milligram is one-thousandth of a gram).

Arvin and reptilase have been used less frequently but are possible successors to heparin as anticoagulants. Controlled studies of these enzymes and of brinase are needed before they are widely accepted for therapeutic uses.

References

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AUGUST 1990