Therapeutic Enzymes

Using the Body's Helpers as Healers

Chris D. Meletis, N.D., and Jason E. Barker, N.D.

Enzyme therapies are becoming more prevalent in medicine today, with many manufacturers targeting their advantages in disease treatment. In the last 100 years, enzymes have been increasingly used to treat various diseases.

Early observations of *Bacillus pyocyaneus* revealed that its secretions could destroy anthrax bacilli and protect mice from inoculation with this deadly bacterium. Scientists deduced that the secretions were able to destroy anthrax by chewing apart its nucleic acids, via enzymatic degradation. This early observation paved the way for the use of enzymes in medicine. Today, enzymes are used as oncolytics, anticoagulants, thrombolytics, anti-inflammatories, fibrinolytics, mucolytics, antimicrobials, and digestive aids.

Enzymes are found throughout the natural world; the number of uses for them in various fields of industry in addition to medicine is staggering. Enzymes are found in animal and plant sources. Enzymes can be thought of as protein molecules with a specific mission—to initiate and regulate countless biologic reactions in living organisms.

Enzymes are used for metabolic and digestive processes. Metabolic enzymes greatly increase the speed at which chemical processes take place within the body; without enzymes, cells could not perform their multiple functions. Every aspect of life depends on the energetic stimulus that enzymes provide.

Perhaps therapeutic enzymes are used most often for enhancing digestive function. Enzymes help food break down into its smallest components. Enzymes secreted by humans include pepsin and protease for breakdown of proteins, lipase for fats, and amylase for carbohydrates. Cellulase, which helps with digestion of plant cells, is not produced by humans but is extracted from plant tissues as they are mechanically broken down. Plant-based foods are often cooked but heat destroys enzymes; a plant food in its raw, fresh state produces considerably more enzyme activity than one that has been cooked.

Mechanisms of Action

Enzymes, like their application in medicine, exert their effects in a multitude of ways. One primary focus of enzymatic action is on the protein fibrin. Fibrin is an insoluble protein involved in blood clotting. In the many steps of the clotting cascade, fibrin is the final product. It is derived from its soluble protein precursor, fibrinogen. Fibrin is laid down inside blood vessels that have been compromised by disease or injury. Fibrin forms minuscule strands that eventually dry and harden, which captures the blood vessel components effectively.

Certainly, fibrin occupies a vital role in health and healing; however, fibrin may also be responsible for an overzealous propensity to form inappropriate clots in the body. Inappropriate clotting, of course, is a major risk factor for myocardial infarctions and strokes.[1]

When correctly balanced, deposition and removal of fibrin maintains an avoidance of blood loss and adverse viscosity in the vascular system. A balance tipped in favor of fibrin overproduction leads to dangerous clotting.

Nattokinase: Prevention and Treatment of Heart Conditions

In the interest of preventive medicine, proteolytic enzymes can be used as interventional medicines that serve to inhibit overactivity of fibrin. One particular enzyme, known as nattokinase, has demonstrable fibrinolytic activity.[2] Nattokinase is derived from a Japanese food known as natto, a preparation of soybeans that has undergone fermentation with a bacterium known as *Bacillus subtilis natto*.[3] Hiroyuki Sumi, M.D., University of Chicago, Illinois, is credited with the discovery of nattokinase. Thought to be produced specifically from this process of fermentation, nattokinase is not derived directly from other soy-based foods. Nattokinase causes mild enhancement of fibrinolysis in plasma, as evidenced by its effect on fibrinolytic parameters and production of tissue plasminogen activator, a potent thrombolytic agent that causes fibrinolysis at the site of a blood clot.[4]

Nattokinase is thought to work by stopping plasminogen activator inhibitor 1 (PAI–1).[5] That is, nattokinase works by preventing the blockage of the formation of plasminogen activator, thereby allowing for the degradation of the clotting process.

The fibrinolytic activity of nattokinase is fourfold that of plasmin, a main fibrinolytic enzyme found in the body.[6] In animal studies, nattokinase can reduce markedly the thickening of blood vessel walls that normally occurs following an injury to the endothelium. In addition, nattokinase leads to dissolution of clots that build inside vessel walls as responses to injuries.[7] These actions suggest that nattokinase can be used to treat and prevent atherosclerosis because of its fibrinolytic activity at the blood-vessel wall.

When taken orally in humans, nattokinase retains its activity (thereby escaping degradation during the digestive process) and has been shown to raise the level of fibrinolytic activity significantly for several hours after dosing.[4] Other applications of nattokinase include treating cardiovascular diseases, such as stroke, angina, deep-vein thrombosis, atherosclerosis, venous stasis, peripheral vascular disease, and claudication.

Arteriosclerosis, excessive clotting, and inflammation are routine in developing arterial plaques. Enzyme therapy digests the fibrin and reverses the inflammation, which decreases the size of the artery-obstructing plaques.

We have noted that symptoms of angina, impaired blood flow to the brain, and poor circulation to the legs often disappear with enzymatic treatment for cardiovascular conditions. The gentle, yet effective use of nattokinase for preventing cardiovascular diseases makes this an optimal choice from preventive and treatment perspectives.

Combination with other anticoagulative therapies or drugs should be approached with great caution, however. Nattokinase is widely available today; one particular version of this enzyme is marketed as a preventive treatment for deep-vein thrombosis on long flights.[8]

Other Conditions Treated by Proteolytic Enzymes

Use of enzymes in controlling fibrin can be applied in several other disease models. One interesting aspect of fibrin control is the use of fibrinolytic enzymes in multiple sclerosis (MS). Researchers at the University of California, San Diego, School of Medicine found that, when fibrin was removed from the body (in animal models of MS), tissue damage resulting from MS was decreased and the lifespans of animals were lengthened. These animals had decreased inflammatory measures and expression of major histocompatibility complex class I antigens, and reduced demyelination.[9] Fibrin is known better for its role in blood clotting. However, in a study that examined the roles of fibronectin, fibrin, fibrinogen, and albumin in MS, fibrin was shown to accumulate in the affected nerves of patients with MS, leading to further breakdown of their myelin sheaths.[10]

Fibrinolysis via proteolytic enzymes may also affect some conditions that have historically been resistant to treatment. Conditions, such as Peyronie's disease, Dupuytren's contracture, and Ledderhose's disease, are all marked by loss of elasticity and possible tearing of tissue, leading to bleeding and clot formation. This formation of localized clots is marked by fibrin deposition as well. Over time, continuous treatment with fibrinolytic enzymes may lead to resolution of scar tissue that has formed at sites of repeated trauma and bleeding.

Several disease processes in humans are marked by their inflammatory components and scarring; one classic example of this is asthma. Over time, the continual inflammatory state of asthma can lead to scarring of the alveoli. Prophylactic therapy with enzymes is a therapeutic option for treating such conditions.

Well-known for their role in the digestive process, enzymes can be used effectively in maintaining health by breaking up circulating immune complexes and controlling the amount of fibrin deposited in wounds, fractures, and joints. Enzymes digest necrotic debris and excess fibrin in the bloodstream as well.

Neoplastic (cancerous) cells are often found surrounded by a coating of fibrin.[11] This has been speculated to be a protective element devised by cancer cells, allowing them to escape destruction by the cells of the immune system. Appropriate dosing with proteolytic enzymes has been utilized as an adjunctive cancer treatment.

Enzyme therapy for musculoskeletal trauma is an excellent first-line therapy. Proteolysis can block the production of pain-inducing chemicals from inflamed tissue. In patients with osteoarthritis (OA), treatment with a combination enzyme product (Phlogenzym,™ MUCOS Pharma GmbH & Co., Geretsreid, Germany) produced similar results for relieving pain and improving knee function compared to a popular OA drug, diclofenac.[12] Early and aggressive use of enzymes following musculoskeletal trauma can promote inflammation control and enhanced recovery. In a study examining the use of enzymes in wound healing, topical application of enzymes helped to clean the wound area of necrotic tissue and sped the tissue recovery process.[13]

Serrapeptase for Inflammation

Also known as serratiopeptidase, serrapeptase is used in Japanese medicine. Serrapeptase is isolated from the microorganism *Serratia* E15, which dwells in the intestine of the silkworm. The true purpose of this organism is to help silkworms dissolve their own cocoons. Serrapeptase is adept at dissolving necrotic tissue, blood clots, arterial plaques, and inflammatory factors.

Used clinically in Europe and Asia for nearly a quarter century, serrapeptase is utilized for its anti-inflammatory actions to treat conditions, such as chronic sinusitis, thinning of bronchopulmonary secretions, sprains and strains, edema, and even postoperative inflammatory states. New research on this novel enzyme demonstrates its efficacy for treating several disease states. Studies on serrapeptase have focused on its use for treating chronic lung disease; ear, nose, and throat disorders; carpal tunnel syndrome; and edema following injury and surgery.

In patients with chronic airway disease (in which mucus production and removal are problematic), treatment with 30 mg per day of serrapeptase for 4 weeks resulted in changes in sputum. Weight, viscosity, elasticity, and neutrophil content were all decreased. Coughing and expectoration frequency were significantly decreased.[14] Using serrapeptase for treating chronic lung conditions in which sputum production is a problem (for example, cystic fibrosis) leads to improved lifestyle parameters.

Other Applications for Serrapeptase

- *Carpal tunnel syndrome*—10 mg of serrapeptase, twice daily for 6 weeks, led to significant clinical improvement in 65 percent of patients treated. Improvements were confirmed using electrophysiologic measurements (nerve-conduction studies), and no side-effects were noted during or following the treatment period.[a]
- *Breast engorgement*—70 patients with breast engorgement were treated with an unspecified dose of serrapeptase, resulting in an 85 percent reduction in symptoms. Serrapeptase in this study was superior to placebo for resolving symptoms of breast pain, breast swelling, and induration. As in previous studies, no side-effects were noted in the study period.[b]
- *Inflammatory venous disease*—A comparison study between two different forms of serrapeptase was conducted on patients with venous inflammatory disease. Efficacy of the two forms of enzyme therapy was determined to be 65 percent and 85 percent, with only 1 case of adverse reaction (diarrhea). This side-effect was halted by a temporary reduction in dosage. Patients in this study were shown to benefit from serrapeptase enzyme therapy.[c]

[a]Malshe PC. A preliminary trial of serratiopeptidase in patients with carpal tunnel syndrome. J Assoc Physicians India 1999;47:1170–1172; [b]Kee WH, Tan SL, Lee V, Salmon YM. The treatment of breast engorgement with serrapeptase (Danzen): A randomised double-blind controlled trial. Singapore Med J 1989;30:48–54; [c]Bracale G, Selvetella L. Clinical study of the efficacy of and tolerance to seaprose S in inflammatory venous disease. Controlled study versus serratio-peptidase. Minerva Cardioangiol 1996;44:515–524.

In a separate investigation, serrapeptase was studied in conjunction with chronic sinusitis in adults. Again, a dose of 30 mg a day, for 4 weeks, led to significant decreases in viscosity but not elasticity of nasal mucus in this study, providing a better quality of life for these patients.[15] Researchers did not speculate about the contribution that enzyme therapy could make in cases of chronic sinusitis in which mucus removal is enhanced, thereby leading to quicker resolution of the condition.

Serrapeptase has also been used to treat several chronic conditions with ear, nose, and throat pathology in which inflammatory processes are a component.[16] This study on chronic conditions was performed at several treatment centers and 193 subjects were involved. Treatment lasted for 7–8 days and was compared to a placebo. The serrapeptase-treated group experienced significant reduction of symptoms beginning after 3 days of treatment. The researchers noted a more rapid response to serrapeptase compared to placebo. The treatment group tolerated the enzyme therapy well. The investigators concluded that serrapeptase produced anti-inflammatory, antiedemic, and fibrinolytic activity and produced more rapid action than placebo.

Similarly, serrapeptase was used to treat swelling of the buccal membrane following a specified surgical procedure (Caldwell-Luc antrotomy) for chronic empyema in that area.[17] A total of 174 patients underwent the procedure, 80 of whom received treatment with the enzyme. The dose of serrapeptase was 30 mg per day, in divided doses, on the day before the procedure, the day it was performed, and 5 days postprocedure.

Patients treated with serrapeptase had significantly less buccal membrane swelling compared to patients who received a placebo at each point of observation following the operation. The point of maximal swelling in these patients never approached that of the patients treated with placebo. Subjects receiving treatment reported no side-effects from the enzyme therapy.

In another surgical study using serrapeptase, the amount of postoperative swelling in ankle joints was studied.[18] This study examined swelling intensity following surgery for acute rupture of lateral ankle ligaments. Patients who received serrapeptase after surgery experienced a 50 percent decrease in swelling by the third day following surgery. Patients treated with conventional postsurgical measures (leg elevation, bed rest, ice) had no reductions in swelling. Degrees of pain abatement also correlated well with reductions in swelling. The investigators concluded that serrapeptase is a viable treatment for postsurgical swelling; the enzyme produced results far better than those of standard conservative measures.

For additional applications of serrapeptase, see the box entitled Other Applications for Serrapeptase.

Dosage Recommendations for 2 Enzymes*

- Nattokinase—72–200 mg (higher doses as clinically indicated)
- Serrapeptase—10–30 mg (higher doses as clinically indicated)

**WARNING*: Tell patients not to use these products if they have blood coagulation disorders. Close professional supervision and laboratory monitoring should occur before patients take these products if patients are taking any drugs that affect blood coagulation, such as prescription vitamin K, heparin, or warfarin (coumadin), or if patients are pregnant or breastfeeding. In addition, these products should be used with caution if active gastrointestinal irritation or ulceration is present.

Conclusions

Natural medicines, such as enzymes, provide a safe, nontoxic therapy for addressing several conditions. One is reminded of the incredible bounty that nature provides when we are able to use a secretion produced by a microorganism found dwelling in the innards of another creature!

Enzymes are not only useful in promoting chemical reactions within the body to ensure its smooth function. These versatile chemicals can also be used to help prevent and treat a number of conditions. It is important, however, that patients be told not to take enzymes on their own as they can have side-effects involving blood coagulation as well as having negative effects on patients who are pregnant or breastfeeding. Used with proper laboratory testing prior to treatment and with close clinical supervision, however, enzymes can be helpful for patients with heart conditions and various types of inflammation. □

References

1. Nesheim M. Myocardial infarction and the balance between fibrin deposition and removal. Ital Heart J 2001;2:641–645.
2. Fujita M, Nomura K, Hong K, Ito Y, Asada A, Nishimuro S. Purification and characterization of a strong fibrinolytic enzyme (nattokinase) in the vegetable cheese natto, a popular soybean fermented food in Japan. Biochem Biophys Res Commun 1993;197:1340–1347.
3. Sumi H, Hamada H, Tsushima H, et al. A novel fibrinolytic enzyme (nattokinase) in the vegetable cheese natto; a typical and popular soybean food in the Japanese diet. Experientia 1987;43:1110–1111.

4. Sumi H, Hamada H, Nakanishi K, Hiratani H. Enhancement of the fibrinolytic activity in plasma by oral administration of nattokinase. Acta Haematol 1990;84:139–143.
5. Suzuki Y, Kondo K, Matsumoto Y, et al. Dietary supplementation of fermented soybean, natto, suppresses intimal thickening and modulates the lysis of mural thrombi after endothelial injury in rat femoral artery. Life Sci 2003;73:1289–1298.
6. Fujita M, Hong K, Ito Y, et al. Thrombolytic effect of nattokinase on a chemically induced thrombosis model in rat. Biol Pharm Bull 1995; 18:1387–1391.
7. Suzuki Y, Kondo K, Ichise H, et al. Dietary supplementation with fermented soybeans suppresses intimal thickening. Nutrition 2003; 19:261–264.
8. Cesarone MR, Belcaro G, Nicolaides AN, et al. Prevention of venous thrombosis in long-haul flights with Flite Tabs: The LONFLIT-FLITE randomized, controlled trial. Angiology 2003;54:531–539.
9. Akassoglou K, Adams RA, Bauer J, Mercado P, Tseveleki V, Lassmann H, Probert L, Strickland S. Fibrin depletion decreases inflammation and delays the onset of demyelination in a tumor necrosis factor transgenic mouse model for multiple sclerosis. Proc Natl Acad Sci U S A 2004;101: 6698–6703; Epub 2004 April 19.
10. Sobel RA, Mitchell ME. Fibronectin in multiple sclerosis lesions. Am J Pathol 1989;135:161–168.
11. Bardos H, Molnar P, Csecsei G, Adany R. Fibrin deposition in primary and metastatic human brain tumours. Blood Coagul Fibrinolysis 1996;7:536–548.
12. Klein G, Kullich W. Short-term treatment of painful osteoarthritis of the knee with oral enzymes. Clin Drug Invest 2000;19:15–23.
13. Latha B, Ramakrishnan M, Jayaraman V, Babu M. Serum enzymatic changes modulated using trypsin: Chymotrypsin preparation during burn wounds in humans. Burns 1997;23:560–564.
14. Nakamura S, Hashimoto Y, Mikami M, Yamanaka E, Soma T, Hino M, Azuma A, Kudoh S. Effect of the proteolytic enzyme serrapeptase in patients with chronic airway disease. Respirology 2003;8:316–320.
15. Majima Y, Inagaki M, Hirata K, Takeuchi K, Morishita A, Sakakura Y. The effect of an orally administered proteolytic enzyme on the elasticity and viscosity of nasal mucus. Arch Otorhinolaryngol 1988;244:355–359.
16. Mazzone A, Catalani M, Costanzo M, Drusian A, Mandoli A, Russo S, Guarini E, Vesperini G. Evaluation of *Serratia* peptidase in acute or chronic inflammation of otorhinolaryngology pathology: A multicentre, double-blind, randomized trial versus placebo. J Int Med Res 1990;18:379–388.
17. Tachibana M, Mizukoshi O, Harada Y, Kawamoto K, Nakai Y. A multi-centre, double-blind study of serrapeptase versus placebo in post-antrotomy buccal swelling. Pharmatherapeutica 1984;3:526–530.
18. Esch PM, Gerngross H, Fabian A. Reduction of postoperative swelling: Objective measurement of swelling of the upper ankle joint in treatment with serrapeptase—a prospective study. Fortschr Med 1989;107:67–68, 71–72.

Chris D. Meletis, N.D., is a naturopathic doctor at Wellness Matters, an integrative medicine clinic in Portland, Oregon, and a senior science officer at the National College of Naturopathic Medicine, also in Portland. **Jason E. Barker, N.D.,** practices at Healthmax, an integrative sports medicine clinic in Portland, Oregon.

To order reprints of this article, write to or call: Karen Ballen, *ALTERNATIVE & COMPLEMENTARY THERAPIES*, Mary Ann Liebert, Inc., 2 Madison Avenue, Larchmont, NY 10538-1961, (914) 834-3100.