Molecular and Physiologic Mechanisms of Systemic Enzyme Therapy: A Review for Clinicians

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For reasons that are both political and clinical, naturopathic physicians need to have a complete, and preferably molecular or genomic, understanding of the interventions they use, whether dietary, nutritional, botanical or manual/manipulative. This is important politically because we have a need to explain the mechanisms of our treatments to our patients, as well as to policymakers, researchers and other clinicians. Failure to explicate and articulate the mechanisms of their treatments makes otherwise effective and brilliant clinicians appear ignorant and unprofessional.

Clinically, mechanistic and molecular understandings of our interventions help us to fine-tune and synergize our treatments for the best possible clinical outcomes by guiding which patients will be treated and which additional therapeutics will be co-administered. Given that the oral administration of pancreatic/proteolytic enzymes for systemic benefits ("systemic enzyme therapy") is one of the most common nutritional/botanical treatments used by naturopathic doctors, this article will provide a review of this treatment's clinical benefits and molecular mechanisms, with emphasis on the latter. In this discussion, systemic enzyme therapy or the use of "oral enzymes" will be specified to mean the oral, between-meal administration of supplements containing pancreatin, bromelain, papain, amylase, lipase, trypsin and alpha-chymotrypsin; according to the research literature as well as clinical experience, polyenzyme preparations are more effective than the use of single enzymes.

Past and Current Use

Systemic enzyme therapy has been clinically used for more than a century, beginning with the early publications of Beard and Cutfield who both showed the anti-cancer effects of orally administered enzymes in animals and patients, respectively. Although these and other early reports showed impressive efficacy and lack of toxicity in the treatment of cancer, they were generally ignored due to enthusiasm surrounding interventional radiation, since "X-rays" had been discovered by Roentgen just a few years earlier and radiation's cancer-causing effects were then unknown.

Current clinical uses of pancreatic/proteolytic enzymes are varied, ranging from improved digestion (when taken with meals) to systemic benefits (when taken between meals). Briefly, systemic enzyme therapy commonly is used in the treatment of cellulitis, diabetic ulcers, sinusitis, bronchitis, injury-related disorders including contusions, sprains, lacerations, and muscle injuries and osteoarthritis (OA). Use of systemic enzyme therapy in the treatment of cancer is well-supported by experimental and clinical studies.

Physiologic Effects

Physiologic mechanisms of systemic enzyme therapy have been discussed in several of my recent reviews and will briefly be listed here before advancing to the more detailed molecular mechanisms. Briefly, proteolytic enzymes are well-absorbed from the gastrointestinal tract into the systemic circulation to exert anti-tumor, anti-inflammatory, anti-edematous and immunostimulatory actions which are the result of different and synergistic effects including: 1) dose-dependent stimulation of reactive oxygen species production and anti-cancer cytotoxicity in human neutrophils; 2) a pro-differentiative effect; 3) reduction in PG-E2 production; 4) reduction in substance P production; 5) modulation of adhesion molecules; 6) fibrinolytic effects; and 7) an anti-thrombotic effect mediated at least in part by a reduction in 2-series thromboxanes.

Molecular Mechanisms - New Data

Patients with degenerative and inflammatory arthropathies (e.g., osteoarthritis and rheumatoid arthritis (RA)) have increased synovial concentrations of tissue-destroying proteases such as the matrix
metalloproteinases (MMP) and cathepsin B. Normally these proteolytic enzymes are inhibited by endogenous proteinase inhibitors such as alpha-1-antitrypsin and alpha-2-macroglobulin. Oral administration of pancreatic/proteolytic enzymes such as trypsin and chymotrypsin has been shown to increase serum levels of alpha-1-antitrypsin and alpha-2-macroglobulin. In this way, oral administration of therapeutic proteases/proteinases stimulates the body's production of endogenous proteinase inhibitors, which then inhibit endogenous joint-destroying proteinases. Stated more simply, systemic enzyme therapy stimulates internal defenses to protect against joint destruction. Systemic enzyme therapy also modulates cytokine levels and thereby shifts "immune balance" away from the autoreactive cell-mediated Th-1 response and more toward a Th-2 response. Significant reductions in tumor necrosis factor-alpha, interleukin-1b, and autoreactive T-cells have been reported following the administration of oral enzymes in experimental and/or clinical settings.

Importantly, systemic enzyme therapy can result in reductions in circulating immune complexes in patients with RA that are directly related to the degree of clinical improvement. The greater the enzyme-induced reduction in immune complexes, the greater the clinical response; this clearly suggests a mechanistic cause-and-effect benefit from systemic enzyme therapy in immune-complex mediated disease. However, we also know that RA is a prototype of dysbiosis-induced systemic inflammation, and thus the recent article by Biziulevicius proposing that the immunostimulatory action of oral enzymes may be derived from direct and indirect intra-intestinal bactericidal and antimicrobial actions, raises an alternate hypothesis that the anti-rheumatic and immune-complex-lowering benefits of systemic enzyme therapy may result, not only from intravascular proteolysis of preformed immune complexes, but primarily from a reduction in de novo immune complex formation due to antimicrobial and thus anti-dysbiotic effects. These effects of systemic enzyme therapy are summarized in Table 1.

**Conclusions**

The molecular and physiologic mechanisms of action by which systemic enzyme therapy exerts its numerous safe and significant benefits are numerous and are increasingly well-defined. Armed with this understanding, clinicians can more effectively treat their patients and more convincingly explain the mechanisms and merits of their treatments to policymakers, researchers and other clinicians. Clinicians are wise to avail themselves of the benefits of proteolytic/pancreatic enzymes, which deserve - based on impressive safety and diverse clinical applications - to be a routine component of patient care.

**References**


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