Chapter 3
Therapeutic Enzymes Used for the Treatment of Non-Deficiency Diseases

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ABSTRACT

Therapeutic enzymes have a broad variety of specific uses and clinical applications, particularly as antineoplasic agents, wound debridement therapeutics, and anti-inflammatory drugs, etc. These enzymes can elicit immune response, contributing allergic reactions. Newer drugs with improved stability and less antigenicity have been developed. Covalent modification of enzymes is used to circumvent this immunogenicity. Advancements in drug delivery have revolutionized enzyme therapy. Microencapsulation and artificial liposomal entrapment are some of the techniques used to increment the stability and half-life of enzyme drugs. Several enzymes are now used as prodrug that metabolizes inactive substances into active metabolites through bioactivation process. This approach comprises a suit of techniques that allow activation of drugs locally and at the site of action. This chapter gives an outline of clinical uses of therapeutic enzymes used in non-deficiency diseases. Developments of these enzymes are reviewed with a particular focus on bioengineering applied to the native proteins.

1.INTRODUCTION

Enzyme therapies are becoming more prevalent in clinical medicine, with many producers targeting their advantages in disease treatment. In the last 100 years, enzymes have been increasingly used to treat various diseases. With the progression of enzymology, therapeutic applications of newly discovered enzymes were explored. They as therapeutics hold some advantages over non-enzymatic drugs with their amazing specificity towards targets as well as multiple substrate conversion. Enzymes are not only used for the treatment of topical disorders, but also for the therapy of systemic diseases. Today, therapeutic enzymes have a broad variety of specific uses and find clinical applications, particularly as antineoplasic agents, wound debridement therapeutics, and anti-inflammatory drugs, etc (Table 1). Additionally, there is a growing group of miscellaneous enzymes of diverse function obtained from micro-organisms. Some

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enzyme preparations are isolated from animal and plant organisms. These enzyme preparations introduced upon intravenous infusion are generally considered as foreign substances by the body. This could elicit immune response, contributing severe allergic reactions and life-threatening conditions. Newer drugs with improved stability and less antigenicity have been developed. Advances in the knowledge of therapeutic uses of enzymes have heightened interest in the manufacture and processing of these macromolecules. Indeed, covalent modification of enzymes by molecules such as polyethylene glycol is used to circumvent the immunogenicity.

Advancements in drug development and delivery over the past few decades have revolutionized enzyme therapy. Microencapsulation and artificial liposomal entrapment are some of the techniques used to increment the stability and half-life of enzyme drugs. Some commercial enzymes are currently available in oral form. A number of chemical modifications have been employed and include binding to inert surfaces and encapsulation to increase the resistance of these intrinsically labile macromolecules to decomposition.

The development of efficacious and safe enzyme-based therapies has occurred hand in hand with some remarkable advances in the preparation of the often specifically designed recombinant enzymes. Approved recombinant enzymes are now used as therapy for chronic gout (Pegloticase), tumor lysis syndrome (TLS) (Rasburicase), leukemia (Pegasparaginase), detoxification of drugs (Glucarpidase), etc.

Other enzymes like Collagenase, Trypsin, Chymotrypsin, and Chondroitinase ABC are frequently constituents of products marketed as wound-debriding agents and anti-inflammatory agents. Enzymes like Hyaluronidase have been widely employed as a "spreading factor" for anesthesia and have a history of safe and effective usage.

Several enzymes are now used as prodrug, a drug that is administered in an inactive or significantly less active form, but once administered it is metabolized in vivo into an active metabolite through bioactivation process. This approach is called enzyme prodrug therapies (EPT), which comprise a suit of techniques that allow synthesizing the drugs locally and at the site of action.

This chapter gives an outline of clinical uses of therapeutic enzymes used in non-deficiency diseases. Developments of these therapeutic enzymes are reviewed with a particular focus on bioengineering and modifications applied to the native proteins. Additional modifications for functional improvements of proteins including post-translational modifications such as Pegylation are discussed. Together with information on the involved mechanisms, safety findings recorded so far on the various adverse events and problems of immunogenicity of these enzymes are presented. For better understanding, these enzymes were organized into different subcategories according to their clinical use.

2.ENZYMES USED FOR CANCER THERAPY

Cancer therapy involves inhibition of cancer cell proliferation without damaging the normal cells. Amino acid deprivation is the main methodology used in cancer enzyme based therapy and it consists in the induction of starvation of amino acids in tumor cells, which are auxotrophic to particular amino acids. This method often reduces tumor proliferation. Indeed, some tumor cells may require unusual or specific nutrients derived from the bloodstream, or may require a nutrient in higher concentration than normal cells. In this area, microbial derived L-Asparaginase has been approved for the treatment of some forms of leukemia, and glutaminase is also under study for treatment of neoplastic diseases. Furthermore, enzyme therapy for cancer treatment can be made by the use of EPT.