2 Enzymes in Medicine: Advantages and Disadvantages

2.1 Native Enzymes in Therapy and Clinical Analysis

Before discussing particular problems connected with the use of enzymes in medicine, let us make some general statements. It is well known that enzymes are highly specific catalysts, facilitating appropriate reactions in subcellular compartments, cells, tissues and the organism as a whole.

It is quite natural that deviations from the normal functioning of one or several enzymes, which can result from some "errors" in their biosynthesis or the biosynthesis of their direct or indirect regulators, usually lead to disturbances in the normal homeostasis and the appearance of different diseases. Two questions arise: the first—how to influence the biosynthesis of a specific enzyme or its inhibitor in order to increase or to decrease its concentration in the affected tissue or in the whole organism; the second—is it possible to use exogenous enzymes or inhibitors in order to increase the concentration of the corresponding physiologically active compound in the organism. The current method now is the normalization of pathological shifts by the administration of exogenous enzymes or inhibitors.

Studies devoted to the use of enzymes as drugs are quite advanced and several books are already available in this field [1–3]. It is important to mention that during the last years, many new diseases have been described (usually inherited) connected with the deficiency of some lysosomal enzymes (so-called storage diseases) which can be treated only by the administration of exogenous enzymes [4–6]. Already, several approaches to enzyme therapy exist which can be divided (at least, conditionally) into several groups: (1) enzymes for replacement therapy, (usually digestive enzymes) which are used after surgery of the digestive tract, when the enzyme activity of the organism itself is not sufficient for effective food utilization; (2) the use of antitumor enzymes, usually possessing the specific ability to destroy some aminoacids, which are required for tumor growth; (3) enzymes for the treatment of inherited storage diseases (4) thrombolytic enzymes, which can act either directly—by lyzing thrombi, or indirectly—by activation of the fibrinolytic system of the blood; (5) enzymes active in some bacterial and viral infections; and (6) hydrolytic and antiinflammatory enzymes, for their action on pathologic or necrotic tissues.
The most evident and technologically simple is the use of digestive enzymes mixtures for replacement therapy. In this case, the drug is usually administered orally [1, 7], using capsules or tablets containing mammalian enzymes (mainly, proteases and lipases) mixed with stabilizers and fillers. In the stomach or in the intestine, enzymes release from tablets and can function long enough to provide complete digestion of a single food portion. Numerous preparations of the described type which are available now on the international pharmaceutical market, can be probably further improved by varying the ratio of the active components. This group also includes lactase, widely used in the treatment of lactose intolerance.

Antitumor enzymes are increasingly acquiring application in therapy. As it was already mentioned, their therapeutic action is based on their ability to decrease (via enzymatic break-down) the blood levels of nutrient essential for tumor growth. As a rule, these compounds are aminoacids. The principal requirements for these antitumor enzymes are formulated in [3]: (1) these enzymes should have low $K_M$ value towards the appropriate substrate; (2) they should express maximal activity at physiological pH values; (3) and be sufficiently stable in the blood and other biological fluids; (4) their life-time in the circulation should be reasonably long; (5) they should not be inhibited by the reaction product even at high concentrations of the latter; (6) they should not require a cofactor or an easily dissociating prostetic group for their activity; (7) their preparations should contain minimal impurities such as endotoxins.

Among the antitumor enzymes, asparaginase is one of the most frequently used [8]. Asparaginase belongs to a group of wide-spread enzymes produced by both pro- and eucariotes. This enzyme hydrolyzes asparagine via desamination of the amino acid with the formation of aspartic acid:

$$\text{H}_2\text{NOC--CH}_2\text{CH--COOH} \xrightarrow{\text{asparaginase}} \text{HOOC--CH}_2\text{CH--COOH}$$

The therapeutic action of asparaginase is based on the high requirement of some tumor cells for asparagine. For the first time, this effect was discovered in experiments with the administration of guinea-pig serum to animals with lymphoma. It turned out that only serum with sufficient asparaginase content suppressed tumor growth.

Later, asparaginase was used in the experimental treatment of different malignant diseases. The enzyme is active against acute lymphoblastic leukemia, but is ineffective against myeloid leukemia and other tumors. At the same time, the use of asparaginase in combination with other antitumor drugs sometimes potentiates the activity of the latter.

Asparaginase preparations used now in clinical practice are mainly of microbial origin. The enzyme sometimes is the only successful drug when no other antitumor agents can be used. At the same time, in some cases, the enzyme is