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Review article

Strategies in the designing of prodrugs, taking into account the antiviral and anticancer compounds

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ABSTRACT

Prodrugs are a wide group of substances of low or no pharmacological activity. The search for prodrugs is aimed at obtaining drugs characterized by better pharmacokinetic properties, pharmaceutical availability and selective activity of the active substance. Prodrug strategies involve chemical modifications and syntheses of new structures as well as the establishment of systems that deliver active substances for therapeutic aims that is prodrug-based treatments. The paper describes decisive factors in prodrug designing, such as enzymes participating in their activation, concepts of chemical modifications in the group of antiviral drugs and new anticancer treatments based on prodrugs (ADEPT, GDEPT, LEAPT). Prodrugs are seen as a possibility to design medicines which are selective for their therapeutic aim, for example a tumorous cell or a microorganism. Such an approach is possible thanks to the knowledge on: pathogenesis of diseases at molecular level, metabolism of healthy and affected cells as well as metabolism of microorganisms (bacteria, fungi, protozoa, *etc.*). Many drugs which have been used for years are still studied in relation to their metabolism and their molecular mechanism of operation, providing new knowledge on active substances. Many of them meet the criteria of being a prodrug. The paper indicates methods of discovering new structures or modifications of known structures and their synthesis as well as new therapeutic strategies using prodrugs, which are expected to be successful and to broaden the knowledge on what is happening to the drug in the body, in addition to providing a molecular explanation of xenobiotics activity.

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1. Introduction

Prodrugs are substances of a low or non-existent biological activity. They become active by releasing active substances through chemical or enzymatic transformations occurring in the body [1–4]. The release of the active substance from the prodrug occurs before, during or after its absorption, sometimes even after it reaches the target [1,2]. The term "prodrug" was used for the first time by Adrien Albert in 1958 [5]. However, the idea of prodrugs was created a long time before that. Probably the first deliberately designed prodrug was methenamine, which was introduced to pharmacies in 1899 [6,7]. The first substance which complied with the criteria of being a prodrug was acetanilide. It has been used since 1867 as an anti-inflammatory drug. However, it was the discovery that its activity is caused by acetaminophen created as a result of aromatic ring hydroxylation that resulted in acetanilide being classified as a prodrug [8].

A constantly growing interest in obtaining and applying prodrugs has been observed since 1960s. It has been estimated that around 10% of the medicines worldwide available are prodrugs, while in 2008 they constituted 1/3 of all registered drugs with a small molecular mass [9].

The aim of designing prodrugs is to optimize the properties of compounds which have the required pharmacological effect, but cause problems in further development of the drug. There are three basic aims related to obtaining prodrugs, which frequently overlap each other:

- pharmaceutical – decreasing inconveniences in the form of the drug by improving its solubility, chemical stability, organoleptic properties (taste, smell) and decreasing the irritation and pain it causes after it is administered locally
- pharmacokinetic – improvement of ADME properties (absorption, distribution, metabolism, excretion) involving, among other things, better absorption (in case of oral use, but also other forms of administration), limitation of the drug metabolism until it reaches its target, increasing the selectiveness of carrying the drug to its effector site, modification of the method of crossing the blood-brain barrier and improving the drug life time
- pharmacodynamical – decreasing its toxicity, improving the therapeutic index, creating drugs with two active substances (the co-drugs strategy) [1,8,10].

The majority of the prodrugs currently used are the so-called carrier-linked prodrugs (Fig. 1a). These are compounds obtained as a result of a simple modification to the functional group of an active substance made by creating ester, amid, carbonate, carbamate, oxime, phosphate, *N*-Mannich base, imine or PEG (polyethylene glycol) conjugate [8,11]. In the body, the prodrug is subjected to transformation by removal of the carrier which realizes the active substance. It is necessary to choose an appropriate carrier, which will secure the active substance, last during drug storage and administration, and once it releases the active compound, the carrier should be subject to biodegradation, be decomposed into non-active metabolites and quickly excreted from the body. An ideal carrier should be non-expensive, easy to obtain and have no immunogenic properties [1,8,12,13].

Carriers linked prodrugs can be divided into bipartite ones, where the carrier is directly attached to the active substance, and tripartite drugs, where the carrier is linked to the drug via linker. In addition, there are also co-drugs (mutual drugs) created by the combination of two active substances, acting as carriers to one another [8,11]. The combination of L-DOPA and entacapone in a form of carbamate is an example of a co-drug. It increases the efficiency of delivering dopamine to the brain. Another example is the L-ascorbic and retinoic acid ester, thanks to which the skin absorption of both drugs is increased [14]. Another type of substances which require activation in the body is bio precursors (Fig. 1b). Those compounds do not include a carrier, and their structure is different than that of an active substance. Due to that, activation of bioprecursors is not based on a simple removal of the functional group, but rather on transformation into another compound, usually via oxidation or reduction. As a result of the reaction, a biologically active substance is created or it is further transformed into an active metabolite [8,11,15]. Bioprecursors include, among other things, dexpanthenol, sulindac and nabumetone [2,8,16].

The knowledge on the biotransformation processes has contributed to the discovery of new medicines. Many drugs are transformed into active metabolites inside the body. They frequently have a better safety profile than their parent substance and they can become drugs by themselves. The best example of such a case if acetaminophen, which is a metabolite of phenacetin. In comparison to the original substance, it shows better painkilling properties and it does not cause methaemoglobinaemia or haemolytic anaemia [15,17].

What is significant for the effectiveness of both prodrugs and their bio precursors is the speed of biotransformation into an active substance after the drug reaches the effector site (speed constant k_{bio}). It has to be quicker than the speed of elimination of the unchanged prodrug (speed constant k_{el1}) and the speed of elimination of the active substance (speed constant k_{el2}). Only then can the biologically active substance obtain a higher concentration than the threshold (Fig. 1).

An alternative method of obtaining prodrugs is the intramolecular chemical approach in which the designing is made on the basis of calculations with the use of molecular orbital (MO) methods, molecular mechanics (MM) and correlation between values obtained as a result of an experience and those obtained from calculations. In this method, no enzyme takes part in the conversion of the prodrug into the parent substance. Interconversion of the prodrug is controlled only at the stage of limiting the speed of intramolecular reaction [11].

2. Discussion

2.1. Enzymes activating prodrugs

In accordance with the definition, a prodrug is a non-active medicine. Because of that, its activation in the body is of a key important when obtaining a desired pharmacological effect. This

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