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Review article

Prodrug approach: An overview of recent cases

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ABSTRACT

In this review we highlight the most modern trends in the prodrug strategy. In drug research and development, the prodrug concept has found a number of useful applications. Selected examples of this approach are provided in this paper and they are classified according to the aim of their design.

Contents

1. Introduction

The concept of prodrug was first introduced in medicinal chemistry by Albert [1] in 1951: "A prodrug is a molecule which does not have any intrinsic biological activity but which is capable during the different phases of its metabolism to generate a biologically active drug". According to this definition and to that accepted by IUPAC [2], a prodrug is any compound that undergoes biotransformation before exhibiting its pharmacological effects. Prodrugs can thus be viewed as drugs that contain specialized non-toxic protective groups used in a transient manner to alter or to eliminate undesirable properties in the parent molecule.

Generally, the metabolic transformation necessary to convert the prodrug into the drug is catalyzed by specific enzymes, mainly hydrolases, and ideally this should selectively occur at the target tissue to prevent undesirable side effects.

In drug research and development, the prodrug concept has found a number of useful applications since it allows several, sometimes contradictory, biological and/or physicochemical objectives to be satisfied. Some examples are shown in Fig. 1, including cellular permeation, solubility, chemical or enzymatic

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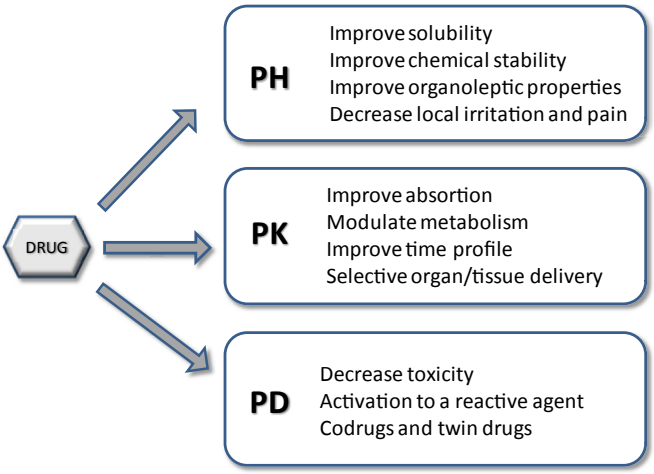

Fig. 1. A schematic classification of some objectives in prodrug research, classified by objectives related to pharmaceutical (PH), pharmacokinetic (PK) and pharmacodynamic (PD) phases.

stability, bioavailability, toxicity, or blood brain barrier penetration [3]. One has to bear in mind that many of these objectives are intertwined [4].

A potent suitable prodrug should overcome the crucial paradox: it has to be lipophilic enough to cross a membrane or metabolic barrier (Fig. 2) and simultaneously it should be hydrophilic enough to fulfill solubility, bioavailability and transport criteria [5,6].

Many therapeutically active agents have low bioavailability after oral administration due to poor absorption or susceptibility to first-pass metabolism, which leads to drug inactivation and/or the production of toxic metabolites. A possible approach to improve the oral absorption is a *formulation solution*, which improves oral bioavailability through the use of suitable excipients that increase intestinal membrane permeability. Such permeation enhancers can be surfactants, fatty acids, glycerides, steroidal detergents and amino acid derivatives amongst others. However, these excipients sometimes cause serious damage to the intestinal epithelium [7]. An attractive alternative is a *chemical solution* that involves a prodrug approach. The prodrug approach has also been widely used to improve delivery of drugs to their site of action by modulation of physico-chemical properties that affect absorption or by targeting specific enzymes or membrane transporters [8]. Thus, a prodrug design is a lead modification approach that is used to correct a flaw in a drug candidate and may be useful in circumventing problems associated with formulation and solubility, absorption and distribution, instability, site specificity of liberation, prolonged release and toxicity, amongst other effects [9].

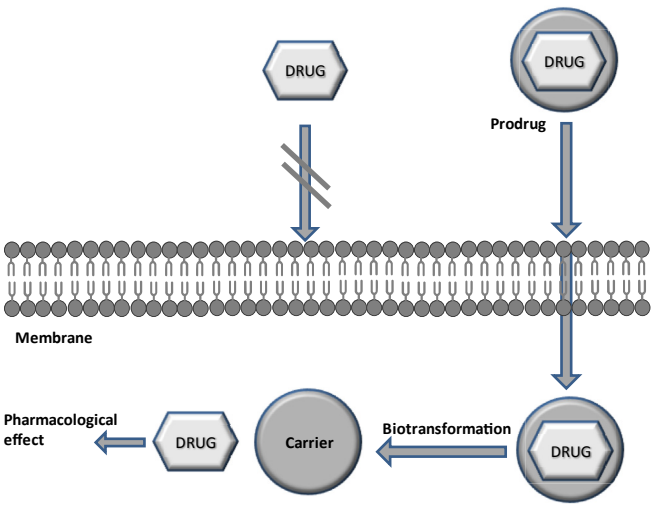

Fig. 2. Schematic representation of some prodrugs designed to by-pass a membrane (adapted from Ref. [6]).

2. Types of prodrugs

Prodrugs essentially fall into two classes, namely carrier-linked prodrugs and bioprecursor prodrugs. In carrier-linked prodrugs the drug is linked to a carrier moiety by a temporary covalent linkage. Cleavage of a carrier prodrug generates a molecular entity of increased bioactivity (drug) and at least one side product, the carrier, which may be biologically inert [for instance polyethylene glycol (PEG)] or may have targeting properties (for instance antibodies). The bioprecursors do not contain a carrier group and are activated by the metabolic modification of a functional group.

2.1. Carrier-linked prodrugs

According to IUPAC [2], a carrier-linked prodrug "is a prodrug that contains a temporary linkage of a given active substance with a transient carrier group that produces improved physicochemical or pharmacokinetic properties and that can be easily removed *in vivo*, usually by hydrolytic cleavage" (Fig. 3).

A well-designed carried-prodrug may satisfy the following criteria [10]:

- The linkage between the drug substance and the transport moiety is usually a covalent bond.
- As a rule, the prodrug is inactive or less active than the parent compound.
- The linkage between the drug substance and the transport moiety must be broken *in vivo*.
- The prodrug, as well as the *in vivo* released transport moiety, must be non-toxic.
- The generation of the active form must take place with rapid kinetics to ensure effective drug levels at the site of action and to minimize either alternative prodrug metabolism or gradual drug inactivation.

At least one functional group in the drug molecule is employed for attachment of the carrier moiety. Preferred functional groups are hydroxyl or amino groups, but carboxylic acids or carbonyl groups can also be found and, consequently, both the attachment chemistry and hydrolysis conditions can vary markedly between these functionalities. The carrier, which is generally lipophilic in nature, could be a small molecule, e.g., a fatty chain, a polymer or PEG, or a macromolecule, like albumin or an antibody. Carrier-linked prodrug activation may occur by enzymatic or non-enzymatic cleavage of the temporary bond between the carrier and the drug molecule, or by a sequential combination of both, i.e.,

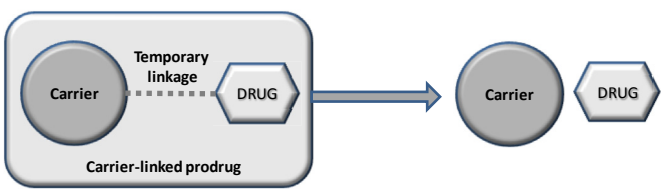

Fig. 3. Schematic representation of a carrier-linked prodrug.

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