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PRODRUGS: AN APPROACH TOWARDS BETTER TARGETTING

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ABSTRACT

Prodrugs, the pharmacologically inactive derivatives of active drugs, are designed to maximize the amount of active drug that reaches its site of action, through manipulation of the physicochemical, biopharmaceutical or pharmacokinetic properties of the drug. But new developments are increasingly taking the concept beyond issues of availability to include targeting. The development of prodrugs promises to be very effective method for treatment of diseases in future. This approach has several advantages over conventional drug administration. In this mini review, prodrugs are discussed with a focus on the viability of the prodrug approach as a means of attaining targeted drug delivery. Next, several examples of where the prodrug approach has been used to achieve targeted delivery will be discussed.

Key words: prodrugs, targeting, targeted drug delivery.

INTRODUCTION

A drug can be defined as a chemical used for treating, curing or preventing disease in human beings or in animals. In the process of treatment, drugs are also used for medical diagnosis and for restoring, correcting, or modifying physiological functions. Conventional drugs suffer from many drawbacks in their performance like site specificity, permeability and resistance. Almost all drugs possess some undesirable physicochemical and biological properties. Their therapeutic efficacy can be improved by minimizing or eliminating the undesirable properties while retaining the

desirable ones ¹. This can be achieved through following means.

- The biological approach is to alter the route of administration which may or may not be acceptable to patient.
- The physical approach is to modify the design of dosage form such as controlled drug delivery of drug.
- The third and best approach in enhancing drug selectivity while minimizing toxicity is the chemical approach for design of prodrugs ².

The Prodrug Concept

Albert and his coworkers were the first ones to suggest the concept of prodrug approach for increasing the efficiency of drugs in 1950. They described prodrugs as pharmacologically inactive chemical

derivatives that could be used to alter the physicochemical properties of drugs, in a temporary manner, to increase their usefulness and/or to decrease associated toxicity². Subsequently such drug-derivatives have also been called 'latentiated drugs', 'bioreversible derivatives', and 'congeners', but 'prodrug' is now the most commonly accepted term. Thus, prodrug can be defined as a drug derivative that undergoes biotransformation enzymatically or nonenzymatically, inside the body before exhibiting its therapeutic effect. According to IUPAC (International Union of pure and applied chemistry): Prodrug is defined as any compound that undergoes biotransformation before exhibiting its pharmacological effects³.

Characteristics of a Prodrug

In recent years numerous prodrugs have been designed and developed to overcome barriers to drug utilization such as⁴:

- Low oral absorption properties
- Lack of site specificity
- Chemical instability
- Toxicity
- Bad taste
- Bad odour
- Pain at application site^{4,5}

Ideal properties of prodrug

It should have intrinsic pharmacological activity that means it should not change receptor configuration that is necessary for pharmacological response. It should rapidly transform into the active form where desired and metabolic fragment, apart from the active drug should be nontoxic⁶.

Limitation of prodrug⁷

The problem associated with prodrug design is its toxicity which is due to

- Formation of unexpected metabolite from the total drug conjugates.
- Toxicity may be due to inert carrier generated by cleavage of moiety and drug conjugate which is converted into toxic metabolite.
- The prodrug might consume a vital cell constituent such as glutathione during its activation stage which causes depletion of prodrug⁸.

Classification of Prodrugs

A) Carrier linked prodrug

Contain a group that can be easily removed enzymatically (such as ester) to reveal the true drug as shown in fig.1. Ideally the group removed is pharmacologically inactive and nontoxic while the connecting bond must be labile for efficient activation in vivo. Prodrugs are the ones where the active drug is covalently linked to an inert carrier transport moiety. They are generally esters or amides. Such prodrugs have greatly modified lipophilicity due to the attached carrier and the active drug is released by hydrolytic cleavage, either chemically or enzymically⁹. It can be further subdivided into-

Bipartate- Composed of one carrier (group) attached to the drugs.

Tripartate- Carrier group is attached via linker to drug.

Mutual Prodrugs- Two drugs linked together.

B) Bio precursors

Metabolized into a new compound that may itself be active or further metabolized to an active metabolite as shown in fig.2 (e.g. amine to aldehyde to carboxylic acid)¹⁰.

PRODRUG MEDIATED TARGETED DELIVERY

Targeting viruses

The topic of targeted delivery of antiviral agents has been recently reviewed¹¹. One of the best and simplest examples of targeted drug delivery via a prodrug approach is the antiviral agent. Acyclovir (9-(2-hydroxyethoxymethyl) - guanine). As shown in Fig. 3, its targeting is achieved primarily by site-selective activation. The herpes virus encoded enzyme, pyrimidine deoxynucleoside (thymidine) kinase, is responsible for converting acyclovir to its phosphate monoester. Subsequently, cellular enzymes catalyse the conversion of the monoester to the di- then triphosphorylated species. This latter species is the pharmacologically active one, and the enzymatic conversion to triester occurs to a significantly greater extent in the herpes-infected cells. Because of its site-specific activation, acyclovir displays a high therapeutic activity against herpes virus, essentially no activity against adenovirus, minimal metabolic degradation following systemic administration, and very low toxicity against uninfected host cells^{12, 13}.

Targeting the colon

A fundamentally simple example of targeting which exploits both site-specific transport and activation is the colon-specific delivery of drugs illustrated in Fig. 4. With this approach, prodrugs are formed by coupling the drug to a hydrophilizing moiety that is susceptible to cleavage by enzymes secreted by the bacterial microflora associated with the lower gastrointestinal tract¹⁴. Following oral administration of the prodrug, drug absorption in the stomach and small intestines is decreased due to the polar nature of the moiety; therefore, greater levels of the drug, in the form of the prodrug, can reach the colon. Within the colon, the bacterially derived enzymes catalyze the conversion of the prodrug to the

more lipophilic drug which is now available for absorption through the colonic membrane. This targeting concept has been recently reviewed. Glycosidic and glucuronidic prodrugs, of agents such as dexamethasone, naloxone, and menthol, that exploit bacterial glycosidases and glucuronidases have been studied for their colon-targeting potential¹⁵.

Targeting the kidney

Site-selective prodrug activation, by exploiting the relatively high response site activity of an enzyme, has also been achieved with targeted delivery to the kidney. For example, dopamine was found to selectively accumulate in the kidney following the intraperitoneal administration of the double prodrug, γ -glutamyl-L-dopa, to mice¹⁶. As shown in Fig. 5, the prodrug is activated by the sequential catalytic actions of two enzymes that possess high activity in the kidney. First, γ -glutamyl transpeptidase catalyzes the cleavage of the γ -glutamyl linkage: the L-dopa which is formed is then decarboxylated to dopamine by L-amino acid decarboxylase. The end result is that dopamine is more readily available to exert its therapeutic effect (i.e., renal vasodilation) at the response site while causing less effects at non-response sites (as was demonstrated by an unchanged systemic blood pressure).

Targeting the liver

To achieve targeted drug delivery to the liver, researchers have attempted to exploit site-selective transport pathways. One such pathway is the bile acid transport system associated with the sinusoidal membrane of hepatocytes¹⁷. The bile acid prodrugs of several compounds, such as chlorambucil, thyroid hormone (L-T), and HMG-CoA reductase inhibitors¹⁸ have demonstrated some degree of hepatic targeting.

Targeting the brain

To preferentially deliver amine-containing drugs to the brain¹⁹ have developed a prodrug delivery system which exploits the oxidative conversion of a dihydropyridine promoiety to its corresponding pyridinium salt (Fig. 6). With this approach, an amine-containing drug is coupled to a lipophilic dihydropyridine promoiety that facilitates the penetration of the drug, in the form of the prodrug, through the blood-brain barrier (BBB). Oxidation of the dihydropyridine functionality in the peripheral compartments results in the formation of the corresponding polar pyridinium salt which can be readily excreted from the body, whereas formation of the pyridinium salt in the CNS results in site retention because of the poor permeation characteristics of the charged species and the permeability characteristics of the BBB. Subsequent cleavage of the pyridinium salt promoiety releases the drug which is now present at elevated levels within the brain. The proof-of concept has been demonstrated for a wide variety of amine-containing drugs.

Targeting with antibodies

Selective activation of a prodrug of an anticancer agent at tumor sites is severely limited by the commonality of enzymes associated with normal and neoplastic tissues. Therefore, two approaches utilizing monoclonal antibodies²⁰ have been studied as a way of selectively activating a prodrug at the tumor site. These approaches, which have received considerable attention over the last decade, are Antibody- Drug Conjugates and Antibody-Directed Enzyme Prodrug Therapy (ADEPT). Antibody-drug conjugates (immune conjugates) are macromolecular prodrugs that are formed by covalently linking cytotoxic agents to monoclonal

antibodies reactive with tumor associated antigens. A number of chemical coupling methods have been utilized to produce the drug-antibody conjugates, and several tumor-associated antigens have been identified, and the respective monoclonal antibodies have been produced. In order for targeting to be achieved, the drug must be cleaved from the antibody after the immune conjugate binds to a tumor cell; this usually occurs intracellularly (e.g. lysosomal degradation) after internalization of the conjugate Fig. 7a shows a simplified depiction of this process²¹.

Antibody-directed enzyme prodrug therapy (ADEPT)

A simplified scheme of the ADEPT approach to targeted drug delivery is shown in Fig. 7b. Ideally, administration of an enzyme, which is covalently linked to a monoclonal antibody, binds selectively to the respective tumor-associated antigen. After the antibody-enzyme conjugate (Ab-E) has localized within the tumor and has been cleared from non-target sites, a prodrug, that is a substrate for the enzyme, is administered. Upon contact with the targeted enzyme, the prodrug is converted to the drug at the tumor site. This targeting approach has been well reviewed. An important dosing consideration with the ADEPT approach is optimizing the time interval between administration of the Ab-E and the prodrug. To attain adequate tumor uptake, high plasma and extracellular fluid levels of the Ab-E should typically be maintained for several hours^{22, 23}. Once adequate tumor levels are achieved (and prior to prodrug administration), sufficient time should be allowed for significant plasma clearance or inactivation of the non-tumor-associated Ab-E to minimize prodrug activation at non tumor sites (a potential source of toxicity).

CONCLUSION

The area of prodrug-mediated targeted drug delivery has made many strides within the last decade; however, there is still a great need for additional work to further improve existing approaches and to develop newer ones. At present prodrug are not prevalent in clinical use, in future there will be prodrugs for every known drug to make them effective in treatment. Drug discovery and prodrug development appear to be complementary for the generation of target specific medicines of future. The sole use of a prodrug to achieve targeted drug delivery is limited unless the target site possesses a

unique enzyme system for activating the prodrug (as in the case of acyclovir). Hence, the combination of a prodrug approach with an additional approach which facilitates the targeting, as exemplified by the ADEPT. At present the research in this area is at a nascent stage due to lack of information, regarding all enzymes or receptors, most suitable for targeting purposes. As the unrevealing of the microbiological details of affected targets become clear, prodrug development will surely decrease side/toxic effect of drugs and also trigger development of more potent primary drugs.



Fig.1. Carrier linked prodrugs.



Fig.2. Bio precursor.

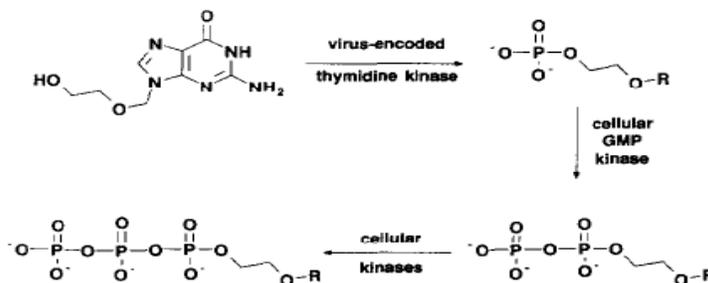


Fig.3. Bioconversion of the antiviral agent acyclovir, to the pharmacologically active triphosphate ester⁷ the site –selective activation arises from the catalytic involvement of herpes virus – encodes thymidine kinase.

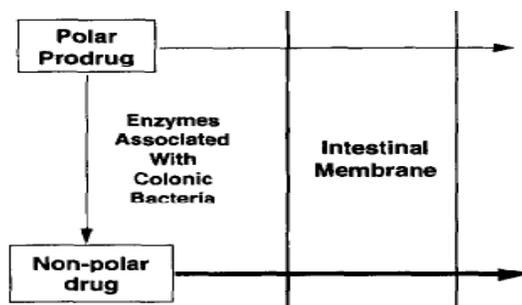


Fig.4. Scheme proposed by Friend and Chang ¹⁰ For prodrug- mediated targeted drug delivery to the colon by the use of glycosidic and glucuronic prodrugs.

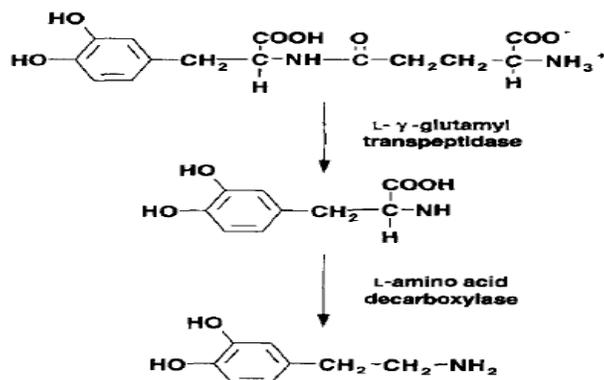


Fig.5. Kidney selective delivery of dopamine via the administration of $\text{L-}\gamma\text{-glutamyl-L-dopa}$.

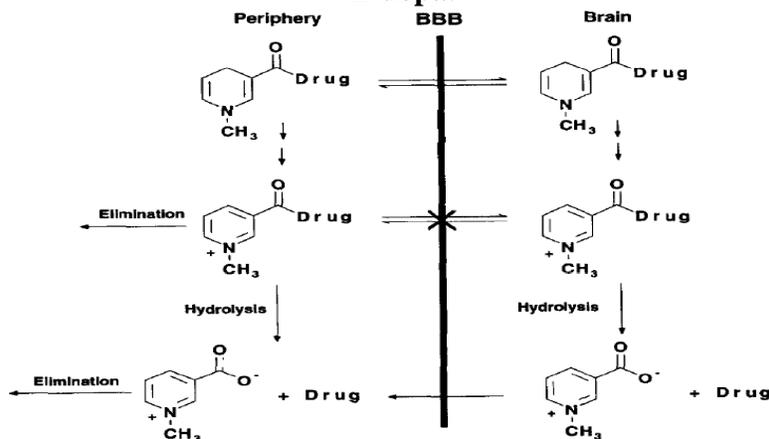


Fig.6. The redox based, prodrug- mediated, brain targeting system for amine containing drugs.

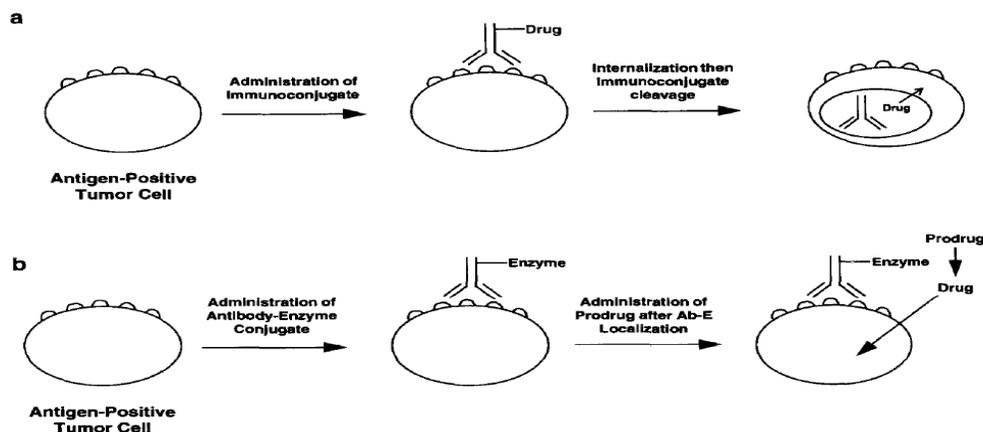


Fig.7. (a) simplified scheme of the site-selective delivery and activation of a monoclonal antibody-drug conjugate to a tumor cell. (b) Simplified scheme of the site-selective activation of a prodrug at a tumor cell using the ADEPT approach²³.

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