“Drugs need to be designed with delivery in mind” is what the late Professor Takeru Higuchi said to Professor V. J. Stella in the mid-1970s. This paradigm is very important in terms of drug discovery, and it should be borne in mind at all stages of drug development. DMPK research has helped to develop drugs with suitable pharmacokinetic properties. Novel formulation approaches also help overcome basic delivery limitations caused by problematic physicochemical or biochemical properties. Furthermore, prodrug design is an integral approach of drug discovery.

The development of prodrugs – chemically modified versions of the pharmacologically active agent that must undergo transformation in vivo to form the active drug – is now well established as a strategy to improve the physicochemical, biopharmaceutical or pharmacokinetic properties of parent active agents. For example, prodrugs provide possibilities for overcoming inherent limitations of the parent active drug, such as limited solubility, poor absorption/permeability, instability, pharmacutical formulation difficulties, side effects or toxicity. In addition, the development of prodrugs with improved properties can also result in patent line extension for a certain drug.

Currently, 5–7% of the drugs approved worldwide can be classified as prodrugs, and interest in prodrugs has grown over the past 10 years. From 2000 to 2008, 236 new drugs were approved worldwide. Of these 191, or 81%, were low-molecular-weight drugs; the other 19% were either new biological entities or high-molecular-weight drugs, mostly polypeptides. Of the 191 new chemical entities, 12.6% were clearly identified as prodrugs, while another 5.2% may be considered prodrugs. The latter group consists mainly of antivirals or anticancer drugs that must be metabolized to their phosphate or polyglutamate forms to become active. Furthermore, two soft drugs were approved during same period. In contrast to prodrugs, soft drugs are active drugs that are designed to undergo a predictable and controllable deactivation or metabolism in vivo after achieving their therapeutic effect. The two soft drugs, clevidipine and landiolol, are short-acting drugs with half-lives of a few minutes.

The prodrug approach to drug design is a versatile, powerful method that can be applied to a wide range of drug administration routes. However, the majority of prodrugs are clinically used with the aim of enhancing drug permeability by increasing lipophilicity. Some of best examples of prodrugs in this category include ACE inhibitors and antibiotic prodrugs. Oseltamivir is an oral prodrug of oseltamivir carboxylate, a selective inhibitor of neuraminidase glycoprotein in influenza A and B. A more recent example of a prodrug is ximelagatran, a prodrug of melagatran, which is the first example of an orally administered direct thrombin inhibitor. The very low 3% oral bioavailability of melagatran is increased to 20% by the double prodrug ximelagatran, which contains an ethyl ester group at the carboxylic acid end and an N-hydroxyamidine group at the amidine end. Therefore, the formation of melagatran requires two metabolic reactions: reduction by P450 and hydrolysis by carboxylesterase.

In most cases, prodrugs are simple chemical derivatives that require only one or two chemical or enzymatic transformation steps to yield the active parent drug. In addition, esters are the most common prodrugs used due to their enhanced lipophilicity. It is estimated that approximately 49% of all marketed prodrugs are activated by hydrolyses, including carboxylesterase (CES), butyrycholinesterase (BChE) and paraoxonases (PON). CES and BChE are members of the serine esterase family; CES is ubiquitously expressed in mammalian tissues and BChE is present in the plasma. Also, PON is present in the plasma as a component of HDL. Although some functions of these hydrolases are being studied, we need more information including that on species differences. There are many kinds of hydrolases in the body, and they are possibly responsible for the biotransformation of prodrugs to parent active drugs. However, their function and pharmacokinetic properties are mostly obscure. The limited information on hydrolases is therefore a bottleneck in the prodrug approach.

In contrast, transporter studies have significantly contributed to the development of prodrugs targeted toward specific membrane transporters. Peptide transporters appear to be attractive targets for prodrug design because they are widely distributed throughout the small intestine and show sufficiently high transport capacity and broad substrate specificity. Good examples of prodrugs that exploit peptide transporters are valacyclovir, valganciclovir and midodrine. Another example is XP13512, which is a carbamate prodrug of gabapentin. This prodrug takes advantage of both a monocarboxylate transporter type 1 (MCT1) and a sodium-
dependent multivitamin transporter (SMVT). The oral bioavailability of gabapentin was increase from 25% to 84% by use of XP13512 in monkeys.

The prodrug approach is an integral part of the drug design process, as illustrated by the number of approved prodrugs. Furthermore, a combination of the prodrug approach and the pharmaceutical formulation approach should result in successful prodrugs. A long-acting anti-influenza prodrug was approved in 2010. This prodrug is the octanoyl ester of laninamivir, a neuraminidase inhibitor, and, after intratracheal administration, it is retained over long periods in the lung and trachea, the primary site of influenza virus infection. The long retention might be achieved by the combination of adequate hydrophobicity by substitution of the octanoyl group and bioconversion by site-specific hydrolase, thereby enabling this prodrug to be developed for delivery by inhalation.

I believe that prodrug design will be increasingly applied. The rational prodrug approach at early stages of the drug discovery process will lead to the development of compounds with better drug-like properties. A better understanding of the mechanisms of enzymes and transporters that exist in certain tissues will certainly provide more insight in the design of prodrugs.

References


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