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Multifunctionality of Drug's Pharmacophores within an Organism

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Abstract

By definition of term, it is thought that drug's pharmacophores function only to have biological or pharmacological interaction with an active site of target molecules within an organism. However, in fact pharmacophores also possess pharmacokinetic aspects such as absorption, distribution, metabolism, excretion, and toxicity (ADMET). Thus, it is important to include pharmacokinetically advantageous elements in drug design. Both chemical knowledge and biological knowledge are needed for such drug design. In this short review, multifunctionality of drug's pharmacophores is described with three examples (pravastatin, penicillin, and enalapril).

Introduction

Total syntheses of natural products such as (-)-strychnine [1] are regarded as art works due to their coherent manners. However, in synthetic research study of drugs for seed or lead compounds, researchers, especially synthetic chemists or medicinal chemists, are demanded to have not only organic synthetic knowledge but also biological knowledge. Drug design cannot be accomplished only with synthetic capability because there is not any idea about what to synthesize. Thus, biological aspects are needed for compound designs and research theme decisions. In this short review, I introduce the subject of multifunctionality of pharmacophores to show importance of possession of chemical and biological knowledge in drug design.

Discussion

Statins such as pravastatin (Figure 1) are HMG-CoA reductase inhibitors and reduce the production of cholesterol. The 3,5-dihydroxyheptanoic acid side chain of pravastatin pharmacodynamically functions as a pharmacophore. Interestingly, statins are absorbed from blood to liver, which is a target organ, by OATP1B1 (organic anion transporting polypeptide 1B1) [2] and then after eliciting the activity are excreted from liver to bile acid by MRP2 (multidrug resistance-associated protein 2) [3]. OATP1B1 and MRP2 are anion transporters. In the process, the anionic pharmacophore side chain is recognized by these transporter proteins. Moreover, this side chain renders the molecule water-soluble. Thus, the pharmacophore exhibits pharmacokinetic aspects in addition to pharmacodynamic aspects.

Second, the β-lactam unit of penicillin (Figure 1) forms the main skeleton as a scaffold. The steric constitution of L-Cys-D-Val partial structure of penicillin containing β-lactam is very similar to that of D-Ala-D-Ala residues of peptides linking to the polysaccharide chains (glycans) of bacterial cell walls. Thus, the β-lactam of penicillin inhibits the transpeptidase to elicit antibacterial activity as a pharmacophore [4]. From the point of pharmacokinetic view, penicillins are absorbed in small intestine by PEPT1 (peptide transporter 1) [5]. In the process, L-Cys-D-Val partial structure of penicillin containing β-lactam plays a role of a transporter recognition unit. Drug-resistant strain of bacteria opens β-lactam by acquired penicillinase or β-lactamase. Ironically, the pharmacophore acts as substrates of metabolic enzyme. In the case of penicillin, the pharmacophore has pharmacodynamic and pharmacokinetic functions.

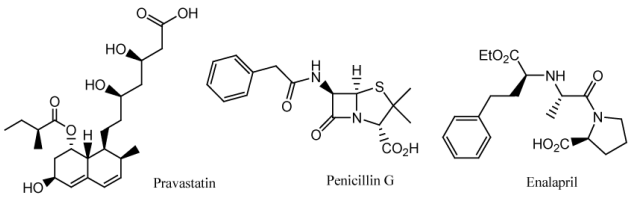

Figure 1. Examples of drugs with a suggestive pharmacophore

Third, enalapril is a prodrug of enalaprilat and elicits antihypertensive activity. The tripetide mimic dicarboxylate unit of enalapril functions as a pharmacophore to inhibit angiotensin converting enzyme (ACE). The tripetide mimic interacts with the active site of ACE and a hydrolyzed carboxylate is chelated to the zinc of ACE [6]. As for absorption and distribution, the tripetide mimic of enalapril is recognized by PEPT1 [7] and then absorbed in small intestine because PEPT1 is a peptide transporter. In addition, such peptide mimic structure prevents the enalapril molecular from penetrating the blood brain barrier (BBB). Generally, membrane permeation of peptides is based on active transport rather than passive transport. As just described, the pharmacophore of enalapril acts pharmacodynamically and pharmacokinetically.

Conclusions

In view of the examples of three famous drugs, the pharmacophores have both pharmacokinetic aspects and pharmacodynamic aspects. To make a pharmacophore have multifunctionality such as pharmacodynamic activity and pharmacokinetic transporter recognition unit is ultimate drug design. There are many kinds of

transporters containing uptake and efflux transporters within an organism. Thus, most drugs may interact with transporter proteins more or less somewhere in vivo. In addition, metabolically instable compounds cannot be drugs. In drug design, these designs should be avoided in consideration of hydrolysis or metabolism of enzymes or CYPs (cytochrome P450).

Accordingly, a verity of functional elements must be packed in a limited molecular structure. Those who are able to design drugs are researchers with chemical and biological knowledge. Without both chemical and biological capabilities, drug design cannot be conducted well. Nevertheless, all the origins of three drugs which I introduce in this review are natural products. Nature has the incredible capability of molecular design. However, human being has wisdom.

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