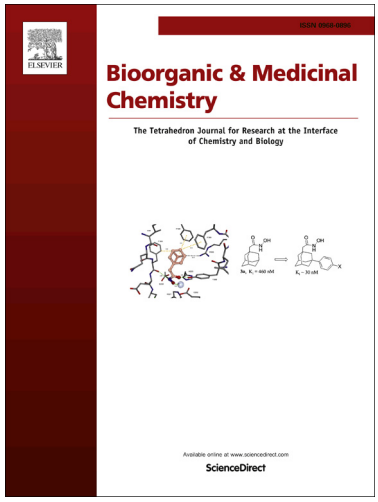
Accepted Manuscript



Review

Intriguing possibilities and beneficial aspects of transporter-conscious drug design

Toshihiko Tashima

PII: S0968-0896(15)00516-7
DOI: http://dx.doi.org/10.1016/j.bmc.2015.06.022
Reference: BMC 12378

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 30 March 2015
Revised Date: 2 June 2015
Accepted Date: 10 June 2015

Please cite this article as: Tashima, T., Intriguing possibilities and beneficial aspects of transporter-conscious drug design, *Bioorganic & Medicinal Chemistry* (2015), doi: http://dx.doi.org/10.1016/j.bmc.2015.06.022

Bioorganic & Medicinal Chemistry
journal homepage: www.elsevier.com

Intriguing possibilities and beneficial aspects of transporter-conscious drug design

Toshihiko Tashima*

Nippon Pharmaceutical Chemicals Co., Ltd, 2-8-18 Chodo, Higashi-Osaka, Osaka 577-0056, Japan

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Transporter-conscious drug design
Drug design
Transporter
Drug delivery
BBB
ADMET

ABSTRACT

It has been revealed that many types of drugs interact with transporter proteins within an organism. Transporter proteins absorb or excrete materials, including drugs and nutrients, across the cell membrane. Some hydrophobic drugs are excreted from the cell as xenobiotics by ATP-binding cassette (ABC) transporters. However, solute carrier (SLC) transporters are tissue-specifically expressed and have substrate specificities. Thus, transporter-conscious drug design is an excellent method of delivering drugs to pharmaceutical target organs and provides advantages in absorption, distribution, excretion, and toxicity of drugs (ADMET) due to transport systems. In fact, based on this strategy, the bioavailability of prodrugs designed as peptide transporter 1 (PEPT1) substrates was better than that of the corresponding parent compounds due to the transport system in the small intestine. Furthermore, in central nervous system (CNS) drug developing, drug delivery into brain across the blood-brain barrier (BBB) is a serious problem. However, this problem can be also solved by the use of the transport systems at the BBB. Therefore, transporter-consciously designed drugs not only may effectively elicit activity but also may control adverse side effects caused by off-targets and drug-drug interactions and, consequently, may show good performance in clinical trials. In this review, I introduce possibilities and advantages of transporter-conscious drug designs.

1. Introduction

The transportation of drugs across the cell membrane is a serious problem in drug development. However, the use of transport systems within an organism can be an effective solution. Transporters [1] are proteins that take in or excrete materials such as nutrients and metabolites across the cell membrane and are involved in the absorption, distribution, excretion, and toxicity of drugs (ADMET). They are tissue-specifically expressed in the apical or basolateral membranes and totally function in a coordinated manner to maintain homeostasis *in vivo*. It is well known that many types of drugs interact with transporter proteins [2-4]. Thus, when designing biologically active compounds, a transporter-conscious design [5] method can be beneficial when used in addition to designs based on structure-activity relationships (SAR), computational chemistry using the active site 3D-structure of a target protein, and physical properties such as clogP and molecular weight according to Lipinski's rule of five [6].

In general, in the research of pharmaceutical agents, particularly in the early stage, optimization of activities and compound ~~structures~~ is established by the results of structure-activity relationships *in vitro*. However, such compounds do not always show the same activity in *in vivo* assays as they do in *in vitro* assays. The cell membrane is composed of a lipid bilayer so that hydrophobic compounds can enter the cells easily by passive diffusion from the outside and elicit activity there. In contrast, there are many obstacles and barriers in the living body that drugs must overcome to reach the pharmaceutical target molecules. Thus, comprehensively, the concept of bioavailability has become very important. Accordingly, transporter-conscious design is essential for drug design. In this review, I will introduce possibilities and advantages of transporter-conscious drug designs.

2. Discussion

2.1. Characterization of transporters

Transporters are tissue-specifically expressed under epigenetic regulations such as DNA methylation [7, 8] and are categorized into two families: the ATP-binding cassette (ABC) transporter superfamily and the solute carrier (SLC) transporter superfamily

* Corresponding author. Tel.: +81 06 6781 0346; fax: +81 06 6787 0771.
E-mail address: t-tashima@nichiri.co.jp (T. Tashima).