Methods and Principles in Medicinal Chemistry

Edited by
Gerhard F. Ecker and Peter Chiba

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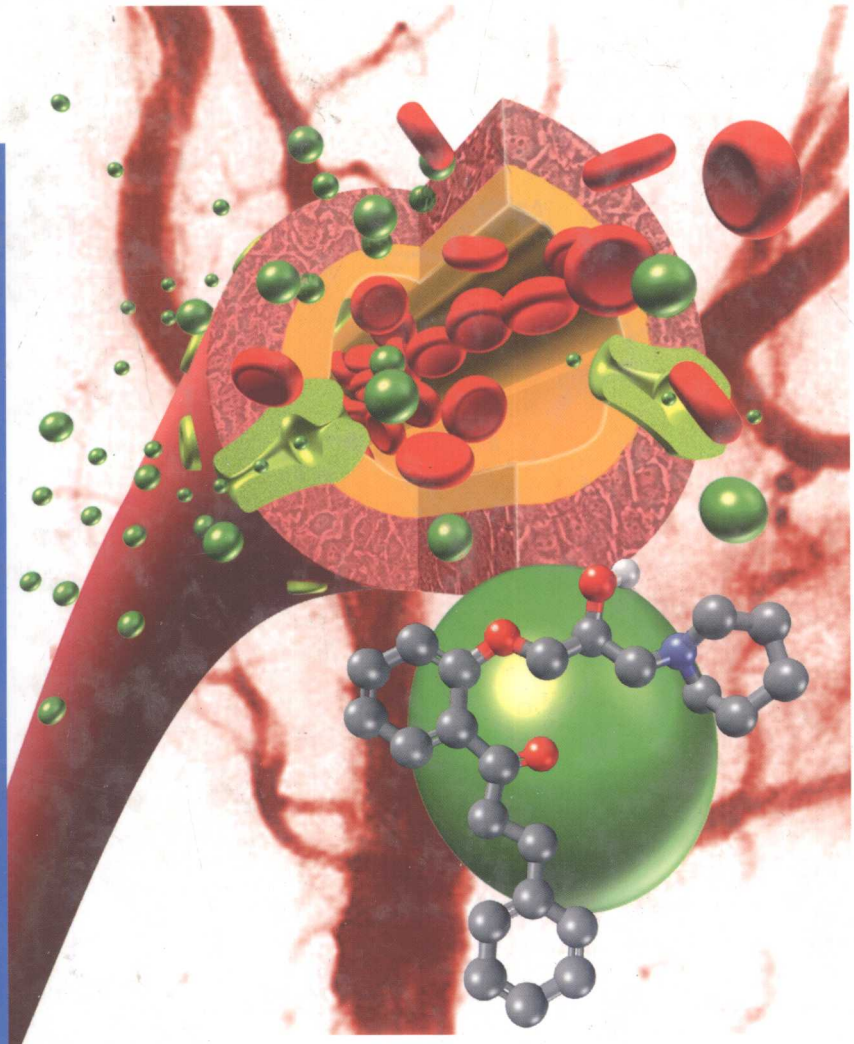
Transporters as Drug Carriers

Structure, Function, Substrates



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Preface

Although the phenomenon of multidrug resistance of bacteria was observed more than fifty years ago, it took 20 years until the first drug transporter, P-glycoprotein, was discovered as the responsible cellular factor for the outward transport of xenobiotics of different chemical structure. Another ten years later, experimental results on different tumor cell lines indicated that P-glycoprotein also occurs in advanced cancers and plays a major role in contributing to the non-response to chemotherapy.

The broad role of transporters in drug absorption, distribution and elimination, as well as in drug-drug interactions and (multi)drug resistance has only been recognized in recent decades. For almost a century it seemed clear that lipophilicity governs drug absorption and distribution. It was well accepted that drugs that mimic endogenous substrates, like amino acid, sugar and nucleoside analogs, use transporters to cross cell membranes but it was considered to be limited to such compound classes. However, in recent years more and more transporters were discovered and with this increasing number also more and more cases of active drug transport were observed. This fact even generated the speculation that in drug absorption active transport is rather the rule than the exception, another extreme hypothesis. A definite answer to this open question cannot be given at the very moment but it is interesting to watch the engaged discussion on the pros and cons.

In addition to their role in drug absorption, distribution and elimination, transporters are also responsible for certain drug-drug interactions. Drugs like verapamil, propafenone and quinidine are P-glycoprotein inhibitors; co-medication of these drugs with other active agents, normally eliminated by P-glycoprotein, may generate serious side effects. Non-sedating H_1 antihistaminics cross the blood-brain barrier like the classical, sedating antihistaminics but active efflux avoids their interaction with central histamine receptors. The opiate loperamide is a selective antidiarrhoic agent; however, if P-glycoprotein is inhibited by quinidine, loperamide exerts the typical central effects of all other opiates. Some drugs and even "harmless" agents, such as St. Johns Wort or grapefruit juice, induce the expression of drug-metabolizing cytochromes and of drug transporters, leading to other drug-drug interactions.

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The book by Gerhard Ecker and Peter Chiba collects and evaluates the available evidence for further research in this hot area. For this purpose, the editors assembled a team of experienced scientists to discuss the important role of drug transporters in detail. We are very grateful to all authors for their excellent contributions, as well as to Frank Weinreich and Waltraud Wüst for their ongoing engagement for our series Methods and Principles in Medicinal Chemistry, in which this book will be another highlight.

April 2009

Raimund Mannhold, Düsseldorf
Hugo Kubinyi, Weisenheim am Sand
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A Personal Foreword

An Introduction to the Medicinal Chemistry of Drug Transport

Membrane transporters are encoded by numerous gene families, comprising in total 883 genes encoding a broad variety of transporters. This so-called transportome performs important functions for the cell, such as providing nutrients, protecting the cell from xenotoxins, and establishing electrochemical gradients across membranes. Numerous disorders caused by mutations in transporter and channel genes underscore the physiological relevance of transport proteins. These include the Dubin–Johnson syndrome (ABCC2), sitosterolemia (ABCG5/G8), and Tangier disease (ABCA1), to mention a few. Membrane transporters also play a key role in ADME, affecting absorption, distribution, and elimination of drugs. Recently, this has also been recognized by regulatory authorities and the FDA published guidance for how to deal with transport processes. In addition, some ABC (ATP-binding cassette) transporters such as the multiple drug resistance transporter ABCB1 (P-glycoprotein) mediate energy-dependent efflux of drugs and thereby significantly contribute to the development of drug resistance. With respect to the latter, one should also note that numerous transporters have been identified in bacteria, fungi, and plasmodia and are responsible for resistance against chemotherapeutic agents in these organisms.

Given the large number of transport proteins and potential substrates, only a very small percentage of the possible pharmacological interactions among them have been studied so far. Those interactions may be particularly important in the chemotherapy of cancer, for drug–drug and drug–nutrient interactions, and for the bioavailability and brain permeation of drug candidates. Classical examples include the interaction of cyclosporin A with several statins and also the well-known multifactorial interaction of grape fruit juice: naringine is blocking OATP1A2, hesperidin is blocking ABCB1, and bergamottin is interacting with CYP3A4. This leads to a reduction in the plasma concentration of, for example, fexofenadine, talinolol, and celiprolol. However, drug–drug interactions at transport proteins might also be used in a beneficial way. During the Second World War, the so-called wartime tactic was applied by coadministering penicillin with probenecid. Blocking of hOAT

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transporters in the kidney by probenecid enabled a significant reduction in the penicillin dosing and thus treatment of a higher number of patients. An identical approach has recently been proposed for tamiflu.

Nonetheless, a systematic study of the transportome's role in ADE (absorption, distribution, and elimination), chemosensitivity, and chemoresistance is still lacking. Furthermore, from a systems point of view, the situation is even more complex. Nuclear receptors, cytochromes, and transporters form a protein network responsible for elimination and toxification/detoxification of most of the drugs currently used. This network is subject to multifactorial influences, such as induction of the expression of P-glycoprotein by St. John's wort. Last but not the least, there is increasing evidence of considerable species-specific differences. Thus, using quantitative proteomics could demonstrate that in humans the amount of ABCG2 at the blood–brain barrier is twofold the amount of ABCB1, whereas in rodents the ratio is almost 1: 1. Another example is the CNS toxicity of ivermectin in collie dogs, which lack functional P-glycoprotein at the blood–brain barrier due to an MDR1-1delta mutation.

This volume of *Methods and Principles in Medicinal Chemistry* features different classes of membrane transport proteins and highlights their importance in the field of medicinal chemistry. Part One highlights the importance of several human transporter families as drug carriers. Special focus is given on the structure and function of P-glycoprotein, the paradigm protein in the field. The recently published X-ray structure of mouse P-gp now also paves the way for structure-guided modeling studies. The chapter on CNS transporters has been kept short as these will be covered in an upcoming volume of this series. Part Two focuses on drug transporters in bacteria and fungi, which are relevant for medicinal chemists. Part Three gives an overview on rational drug design approaches pursued for prediction of interaction of transporters with their ligands. Part Four is devoted to the role of drug transporters at physiological barriers as well as the interplay of transporters and metabolic enzymes. Finally, an overview on systems biology approaches and the role of drug transporters under pathophysiological conditions is given.

We were in the favorite position to win a number of high-profile research scientists to contribute to this effort and share their views and opinions. We would like to thank all authors for their excellent contributions and also for their patience during the editing process. We would also like to express our sincere appreciation to Frank Weinreich, Waltraud Wüst, and the helpful hands at Wiley-VCH for their excellent support in the production of this book. Finally, we also thank Raimund Mannhold, Hugo Kubinyi, and Gerd Folkers for their enthusiasm and continuous efforts to provide the medicinal chemistry community with this outstanding Methods and Principles series of books.

Enjoy reading!

Vienna, Summer 2009 *Peter Chiba* and *Gerhard Ecker*

Contents

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