Pharmaceutical Biotechnology • Volume 12

Membrane Transporters as Drug Targets

Edited by
Gordon L. Amidon and
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Kluwer Academic / Plenum Publishers
New York, Boston, Dordrecht, London, Moscow

Library of Congress Cataloging-in-Publication Data

Membrane transporters as drug targets / edited by Gordon L. Amidon and Wolfgang Sadee.
p. cm. -- (Pharmaceutical biotechnology ; v. 12)
Includes bibliographical references and index.
ISBN 0-306-46094-7
1. Drug targeting. 2. Drugs--Physiological transport. 3. Carrier proteins. 4. Drug carriers (Pharmacy) I. Amidon, Gordon L. II. Series.
[DNLM: 1. Membrane Proteins--physiology. 2. Biological Transport--physiology. 3. Carrier Proteins--physiology. 4. Drug Carriers. 5. Receptors, Drug. W1 PH151N v.12 1999]
RM301.65.M45 1999
615'.7--dc21
DNLM/DLC
for Library of Congress 99-37278
CIP

ISBN: 0-306-46094-7

233 Spring Street, New York, N.Y. 10013

10 9 8 7 6 5 4 3 2 1

A C.I.P. record for this book is available from the Library of Congress

Printed in the United States of America

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Preface to the Series

A major challenge confronting pharmaceutical scientists in the future will be to design successful dosage forms for the next generation of drugs. Many of these drugs will be complex polymers of amino acids (e.g., peptides, proteins), nucleosides (e.g., antisense molecules), carbohydrates (e.g., polysaccharides), or complex lipids.

Through rational drug design, synthetic medicinal chemists are preparing very potent and very specific peptides and antisense drug candidates. These molecules are being developed with molecular characteristics that permit optimal interaction with the specific macromolecules (e.g., receptors, enzymes, RNA, DNA) that mediate their therapeutic effects. Rational drug design does not necessarily mean rational drug delivery, however, which strives to incorporate into a molecule the molecular properties necessary for optimal transfer between the point of administration and the pharmacological target site in the body.

Like rational drug design, molecular biology is having a significant impact on the pharmaceutical industry. For the first time, it is possible to produce large quantities of highly pure proteins, polysaccharides, and lipids for possible pharmaceutical applications. Like peptides and antisense molecules, the design of successful dosage forms for these complex biotechnology products represents a major challenge to pharmaceutical scientists.

Development of an acceptable drug dosage form is a complex process requiring strong interactions between scientists from many different divisions in a pharmaceutical company, including discovery, development, and manufacturing. The series editor, the editors of the individual volumes, and the publisher hope that this new series will be particularly helpful to scientists in the development areas of a pharmaceutical company, (e.g., drug metabolism, toxicology, pharmacokinetics and pharmacodynamics, drug delivery, preformulation, formulation, and physical and analytical chemistry). In addition, we hope this series will help to

build bridges between the development scientists and scientists in discovery (e.g., medicinal chemistry, pharmacology, immunology, cell biology, molecular biology) and in manufacturing (e.g., process chemistry, engineering). The design of successful dosage forms for the next generation of drugs will require not only a high level of expertise by individual scientists, but also a high degree of interaction between scientists in these different divisions of a pharmaceutical company.

Finally, everyone involved with this series hopes that these volumes will also be useful to the educators who are training the next generation of pharmaceutical scientists. In addition to having a high level of expertise in their respective disciplines, these young scientists will need to have the scientific skills necessary to communicate with their peers in other scientific disciplines.

RONALD T. BORCHARDT
Series Editor

Preface

This monograph appears at a propitious time. Researchers from molecular biology, human genetics, bioinformatics, and drug development are converging on an integrated approach to studying membrane transporters. With the recent cloning of numerous transporter genes, substrate translocation across membranes is coming into focus at the molecular level. Moreover, with the complete sequencing of entire genomes, we have a first glimpse at not just a few transporter families, but all transporters in a living organism. This wealth of information is bound to change research directions by broadening our general understanding of the physiological role of transporters, their diversity and redundancy within an organism, and differences among various species. Soon, the entire human genome will be sequenced, and we will then deal with a large, but finite number of transporter genes. One might estimate that there are 2000–4000 human transporter/ion exchanger genes. Methodology to deal with such large gene numbers is now available, and a genomics-driven approach to transporter mechanisms and functions will likely transform this field in the near future. The chapters in this book already presage this transition, by including not just single transporters, but entire transporter gene families. Yet, only a fraction of all human transporters has been cloned, and much more work needs to be done.

While this book focuses on the interaction of drugs with transporters, scientists from various disciplines have contributed chapters providing in-depth analyses of the physiology, molecular biology, and regulation of select transporter families. Moreover, scientists traditionally involved with drug development have increasingly incorporated molecular biology into their work, a crucial step in understanding the complexities of drug absorption, distribution, and targeting in the body. This book demonstrates that these diverse disciplines are no longer separate entities, and that the boundaries among them have blurred. A physiologist needs to be concerned with the relevance of a transport function to drug targeting, where-

as a scientist in drug development must delve into the molecular biology of the many transporters that could determine efficacy and, hence, clinical success of a new drug entity. Juxtaposing these various views of transporters in this book provides insight into the current state of development of this field, providing a reliable beacon for future developments. We therefore think that this monograph will remain topical for some time to come.

The book is divided into three main portions, the first dealing with background information, including drug transport methodologies and transporter classification, the second providing an integral pharmaceutical view of drug transport in several organs of the body, and the third focusing on individual transporter families. This last portion is not meant to be all-inclusive, but rather to provide examples of well-studied transporter families, presented by prominent scientists in different disciplines. In the future we intend to revisit this topic, and include additional large transporter families, some of which double as drug receptors *per se,* rather than drug targeting devices, e.g., the neurotransmitter transporters. Moreover, the ion exchangers, structurally related to transporters, interact with many drugs, and these are also not included here.

Given the number and complexity of human transporter families, and the importance they have in drug action, we can anticipate rapid expansion of this field and of the number of investigators involved in it. This will also lead to increasing focus on pharmacogenetics, i.e., the study of interindividual differences at the genetic level. Already a central theme in drug metabolism, particularly with focus on genetic polymorphism of the cytochrome P450 enzymes, virtually nothing is known about genetic polymorphism of drug transporters. For example, the intestinal H^+/dipeptide transporter appears to play a role in the oral absorption of cephalosporins, but we have not yet even tested whether some patients carry mutations that abrogate cephalosporin transport. This is certainly likely, the main question being what fraction of the population would have such genetic defects. We think that the information provided in this book will form the basis of addressing the pharmacogenetics of transporters in general. Seen from a genomics perspective, with an all-inclusive approach for all possible transporters, this might rather be called the pharmacogenomics of drug transporters. Much can be gained by understanding the entirety of human transported genes, their relevance to any chosen drug, and the genetic variations distributed throughout the patient population. This book advances the current state of the transporter field toward these goals.

Gordon L. Amidon
Wolfgang Sadée

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