

Preface

In the past 15 years, there has been a dramatic increase in the extent of our knowledge regarding the importance of transporter proteins that govern drug disposition and response. For example, the human multidrug and toxin extrusion protein 1, which is important for the elimination of organic cations and drugs, was cloned and functionally characterized in 2005. Regarding their function, transporters can be classified as uptake or efflux transporters and mediate the uptake of endogenous compounds and drugs into or out of the cells, respectively. This book focuses on transporters of the solute carrier family (SLCs; e.g., organic anion transporting polypeptides, OATPs; organic anion transporters, OATs; organic cation transporters, OCTs; multidrug and toxin extrusion proteins, MATEs; apical sodium-dependent bile acid cotransporter, ASBT; sodium taurocholate transporting polypeptide, NTCP) and the ATP-binding cassette (ABC) transporters (e.g., bile salt export pump, BSEP; P-glycoprotein; multidrug resistance proteins, MRPs; breast cancer resistance protein, BCRP). Each tissue has a distinct pattern of expression for uptake and efflux transporters.

The main focus of this book is transporters expressed in the intestine, liver, and kidney of relevance to drug response and toxicity. Increasing intensity of research in this area has resulted in a much better understanding of the localization of transporters in cell membranes and their role for polarized drug transport. For example, drugs are delivered via the portal venous blood to the basolateral membrane of hepatocytes and taken up by distinct transporters localized in the basolateral membrane into hepatocytes with subsequent intracellular phase I and II metabolism and excretion of parent compounds or of metabolites via other transporters localized to the canalicular membrane into bile. Individual chapters in this book will also address the role of transporters located in tissues other than intestine, liver, and kidney to the local accumulation and effect of drugs at the site of action (e.g., CNS accumulation of HIV protease inhibitors and P-glycoprotein in the blood–brain barrier).

As highlighted in this book, transporters are also important to our understanding of (patho-)physiological processes as well as drug disposition and effects. For

example, the chapter on intestinal bile acid transporters highlights not only our current understanding of the absorption of bile acids from the intestinal lumen, but also shows how this knowledge is currently used for development of new hypocholesterolemic or hepatoprotective drugs.

Interindividual variability in drug response is a major problem for optimal drug therapy. The transporter field has contributed substantially to a better understanding of the determinants that account for intersubject differences in drug disposition and effects. Genetic polymorphisms in transporters can cause certain diseases, for example the Dubin-Johnson syndrome, in patients with certain mutations in the *ABCC2* gene encoding MRP2. Moreover, genetic polymorphisms in genes encoding uptake and efflux transporters have been identified as determinants of drug disposition. The knowledge summarized in this book on substrate specificity of individual transporters as well as the potential of drugs for inhibiting specific transporters has helped improve our understanding of mechanisms for drug–drug interactions. For example, increased plasma concentrations and toxicity of the cardiac glycoside digoxin with coadministration of multiple drugs (e.g., quinidine, verapamil) have been observed dating back to the 1970s, but the mechanism underlying these drug–drug interactions remained unclear for a long time. This changed when digoxin was identified as substrate of the efflux pump P-glycoprotein and when comedications such as quinidine and verapamil were identified as potent inhibitors of P-glycoprotein function.

For these reasons, regulatory agencies are increasingly asking pharmaceutical companies for detailed information on whether transporters are involved in disposition of a new drug entity and whether the new drug entity itself might cause undesired drug–drug interactions due to inhibition of specific drug transporters. This process is supported by the International Transporter Consortium, which recently published recommendations for investigations on Membrane Transporters in Drug Development (International Transporter Consortium 2010). However, it should be noted that our knowledge of the role of transporters in the disposition and effects of older, marketed drugs is far from complete and clearly requires further investigation.

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Reference

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