

Institute of Experimental and Clinical Pharmacology and Toxicology

Chair of Clinical Pharmacology and Clinical Toxicology

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Research Focus

- Molecular characterization of drug transporters
- Expression and function of uptake transporters in the gastrointestinal tract
- Pharmacogenomics
- Molecular and clinical characterization of therapeutic targets in the L-arginine-NO-nitrate pathway
- Safety in drug therapy

Structure of the Department

The Chair of Clinical Pharmacology and Clinical Toxicology constitutes together with the Chair of Pharmacology and Toxicology and the Dorenkamp-Professorship of Innovations in Animal and Consumer Protection the Institute of Experimental and Clinical Pharmacology and Toxicology. The position of the executive director of the Institute rotates between the Chair of Pharmacology and Toxicology (Prof. A. Ludwig) and the Chair of Clinical Pharmacology and Clinical Toxicology (Prof. M. Fromm) on a two-year basis.

32 persons are working at the Chair with 13 of them being funded by extramural sources. In July 2008 a Professor of Clinical Pharmacology (W2) was appointed. Research is conducted by eight scientists, three of them being specialists in clinical pharmacology, ten MD or PhD students and eight technicians.

The groups at the Chair of Clinical Pharmacology and Clinical Toxicology investigate mechanisms underlying interindividual differences in drug effects using molecular and cellular biology as well as clinical studies. The Chair has excellent opportunities for drug analytics and a clinical trial unit. In addition, a drug information service is available for the physicians of the

Universitätsklinikum Erlangen and for external physicians.

The following topics, which are funded e.g. by the German Research Council (DFG), the German Cancer Aid, the German Federal Ministry of Health (BMG) and the German Federal Ministry of Education and Research (BMBF), are in the focus of our studies: uptake and efflux transporters for drugs, genetic determinants of drug effects (pharmacogenomics), drug metabolism, drug uptake in tumors, cardiovascular pharmacology and risk factors, alterations of the L-arginine-NO-metabolism, safety in drug therapy.

Research

Molecular characterization of drug transporters

Project managers: J. König, M.F. Fromm
Transport proteins located in distinct plasma membrane domains are important for the uptake, the distribution and the final excretion of drugs and drug metabolites. Therefore, modulation of transport function may result in adverse drug reactions (ADR). Two molecular mechanisms can account for such modulations of transport function. On the one hand, variations in transporter genes (polymorphisms) may result in mutated transport proteins with altered transport kinetics. Secondly, one drug can influence the transport kinetics of a second coadministered drug if both are substrates for one transport protein (transporter-dependent drug-drug interactions). The molecular characterizations of both processes together with expression studies are in the focus of our studies, which are funded by the DFG and the German Cancer Aid.

In cooperation with the Clinic of Gynecology and Obstetrics and the Institute of Pathology of the Universitätsklinikum Erlangen we analyzed the expression and localization of uptake transporters of the OATP family (organic anion transporting polypeptides) in normal breast tissue and breast cancer tissue. In normal breast tissue, OATP3A1 and OATP5A1 localized to the plasma membrane of epithelial cells of the lactiferous ducts whereas in breast cancer tissue these transporters are highly expressed in the plasma membrane as well as intracellularly. Since hormones and hormone metabolites are substrates of OATPs and since it has been shown that hormones may promote tumor growth, these findings may be relevant for studies on tumor progression as well as for can-

cer treatment using anticancer agents which are substrates for these uptake transporters.

The functional consequences of genetic variations have been studied in cooperation with the University of Paris. It was shown that the variant OATP1B1*5 shows reduced transport of metabolites of the immunosuppressant mycophenolic acid and that mycophenolic acid tolerance is influenced in renal transplant recipients by this polymorphism.

Expression and function of uptake transporters in the gastrointestinal tract

Project manager: H. Gläser

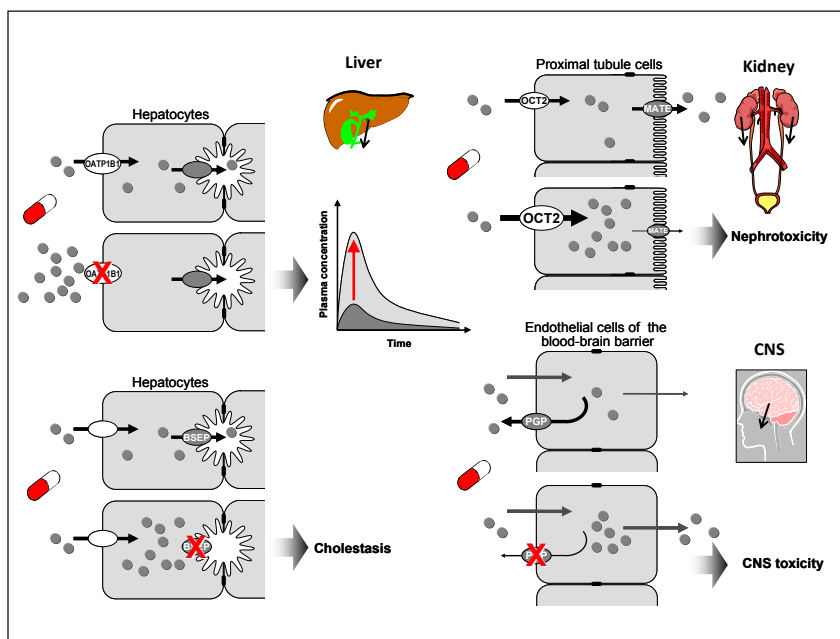
The knowledge about the clinical relevance of OATP uptake transporters for drug absorption, physiology and pathophysiology in the human gastrointestinal tract is still limited. With the performed studies, which are funded by the DFG, it was shown that the prostaglandin transporter OATP2A1 is localized in parietal cells of human gastric mucosa. Interestingly, the function of OATP2A1, which specifically transports prostaglandins, can be modified by NSAIDs. Some of these drugs are able to inhibit the function of OATP2A1, whereas others lead to a stimulation of OATP2A1 transport activity. Such functional modifications may contribute to NSAID-induced side effects such as ulceration or bleeding in the human gastric mucosa. Currently, we are investigating the influence of OATP2A1 on the local prostaglandin effects in human gastric mucosa.

In further *in vitro* studies a possible relevance of the drug uptake transporters OATP1A2 and OATP2B1, which are expressed in human intestine, for drug-drug interactions was investigated. It was demonstrated that the OATP1A2- and OATP2B1-mediated cellular uptake of fexofenadine (antihistaminic drug) and atorvastatin (HMG-CoA reductase inhibitor) is inhibited by naturally occurring flavonoids such as apigenin, kaempferol and quercetin. Considering the broad abundance of flavonoids in herbal drugs and food, inhibition of OATP1A2 and OATP2B1 may be a relevant mechanism for drug-drug and/or food-drug interactions.

Pharmacogenomics

Project managers: O. Zolk, M.F. Fromm

Frequently marked differences in treatment effects between individual patients are observed leading to treatment failure or enhanced toxicity. In this project variations in genes involved in drug transport or metabolism that give rise to differing response to drugs are investigated. A collaborative project with the Heart Cen-



Schematic illustration of major mechanisms underlying adverse drug reactions due to alterations of drug transport. Grey circles: drug molecules, ovals: drug transporters

ter Bad Krozingen focuses on the association of polymorphisms in drug metabolizing enzymes (CYP2C19) with the inhibitory effect of the frequently used drug clopidogrel on platelet aggregation. Moreover, the impact of polymorphisms in drug transporter genes for the pharmacokinetics of the oral antidiabetic drug metformin was investigated. Another clinical study focused on the impact of gender and differences in genes involved in transport and metabolism of drugs on the pharmacokinetics of the diuretic torasemide.

Molecular and clinical characterization of therapeutic targets in the L-arginine-NO-nitrate pathway

Project manager: R. Maas

A major focus of the group is the experimental and clinical characterization of new cardiovascular risk factors as potential targets for therapeutic intervention. Presently we study the regulation of the L-arginine-NO-nitrate pathway by endogenously formed compounds such as ADMA and SDMA and the metabolic fate and transport of these compounds. For *in vitro* and *in vivo* investigations new isotope and mass spectrometry-based methods are developed. Collaborating with the Medizinische Klinik 4 in an intramural IZKF-project we currently investigate alternative pathways for the metabolism of methylarginines. In a DFG-funded collaboration project with the local Institute and Outpatient Clinic of Occupational, Social, and Environmental Medicine and the Framingham Heart Study in the USA we currently examine the human nitrate metabolism. Complementary studies are conducted in cooperation with the partners at the Institute of Bio-Medicine of

the National Research Council in Italy and at the Ohio State University, USA.

Safety in drug therapy

Project managers: R. Maas, M.F. Fromm

An important research focus is safety in drug therapy. Here we are partners in a project funded by the German Ministry of Health (BMG) to implement and evaluate measures to improve therapeutic safety in an emergency ward. As a partner in the German Federal Ministry of Education and Research (BMBF) funded cluster "Medical Valley Europäische Metropolregion Nürnberg" therapeutic systems project we currently work on new software and chemoinformatic databases to improve drug safety.

Teaching

The Chair coordinates the interdisciplinary lecture series and seminar Clinical Pharmacology / Pharmacotherapy for medical students applying problem-based learning. In addition, we teach students of dental medicine, molecular medicine, pharmacy and medical process management in Clinical Pharmacology by lectures, seminars and practical exercises. Students of pharmacy are welcome to work with us during their final year.

Selected Publications

Birkenfeld AL, Jordan J, Hofmann U, Busjahn A, Franke G, Krüger N, Igel S, Mürdter T, Drescher S, Shi S, Engeli S, Schwab M, Eichelbaum M, Luft FC, Fromm MF (2009) Genetic influences on the pharmacokinetics of orally and intravenously administered digoxin as exhibited by monozygotic twins. *Clin Pharmacol Ther*, 86: 605-8

Maas R, Xanthakis V, Polak JF, Schwedhelm E, Sullivan LM, Benndorf R, Schulze F, Vasan RS, Wolf PA, Böger RH, Seshadri S (2009) Association of the endogenous nitric oxide synthase inhibitor ADMA with carotid artery intimal media thickness in the Framingham Heart Study offspring cohort. *Stroke*, 40: 2715-9

Franke RM, Kosloske AM, Lancaster CS, Filipiński KK, Hu C, Zolk O, Mathijssen RH, Sparreboom A (2010) Influence of Oct1/Oct2-deficiency on cisplatin-induced changes in urinary N-acetyl-beta-D-glucosaminidase. *Clin Cancer Res*, 16: 4198-206

Hochholzer W, Trenk D, Fromm MF, Valina CM, Stratz C, Bestehorn HP, Büttner HJ, Neumann FJ (2010) Impact of cytochrome P450 2C19 loss-of-function polymorphism and of major demographic characteristics on residual platelet function after loading and maintenance treatment with clopidogrel in patients undergoing elective coronary stent placement. *J Am Coll Cardiol*, 55: 2427-34

Mandery K, Bujok K, Schmidt I, Wex T, Treiber G, Malfertheiner P, Rau TT, Amann KU, Brune K, Fromm MF, Glaeser H (2010) Influence of cyclooxygenase inhibitors on the function of the prostaglandin transporter organic anion-transporting polypeptide 2A1 expressed in human gastroduodenal mucosa. *J Pharmacol Exp Ther*, 332: 345-51

König J, Zolk O, Singer K, Hoffmann C, Fromm M (2011) Double-transfected MDCK cells expressing human OCT1/MATE1 or OCT2/MATE1: determinants of uptake and transcellular translocation of organic cations. *Br J Pharmacol*, 163: 546-55

International Cooperation

Prof. Mikko Niemi, Department of Clinical Pharmacology, University of Helsinki, Helsinki, Finland

Prof. Laurent Becquemont, Service de Pharmacologie, Hôpital Bicêtre, Le Kremlin Bicêtre Cedex, France

Prof. Ramachandran Vasan, Framingham Heart Study, Framingham, MA, USA

Prof. Arturo Cardounel, Ohio State University, Internal Medicine and Pharmacology, Columbus, OH, USA

Research Equipment

Applied Biosystems API 4000 MS/MS System Package

Zeiss Confocal Laser Scanning Microscope LSM 5 Pascal