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 gastrointestinal tract
- Pharmacogenetics of cardiovascular drugs
- Molecular and clinical characterisation of therapeutic targets in the L-arginine-NO-nitrate pathway

Structure of the Institution

The Chair of Clinical Pharmacology and Clinical Toxicology forms together with the Chair of Pharmacology and Toxicology and the Doerenkamp-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.
35 persons are working at the Chair with 10 of them being funded by extramural sources. In July 2008 a Professor of Clinical Pharmacology (W2) was appointed. Research is conducted by 6 scientists with 4 of them being specialists in clinical pharmacology, 10 MD or PhD students and 10 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 University Hospital and for external physicians.

The following topics, which are funded e.g. by the German Research Council (DFG) and the German Cancer Aid, are in the focus of our studies: uptake and efflux transporters for drugs, genetic determinants of drug effects (pharmacogenomics), drug metabolism (cytochrome P450 enzymes), drug uptake in tumors, cardiovascular pharmacology and risk factors, alterations of the L-arginine-NO-metabolism.

Research

Molecular characterization of drug transporters

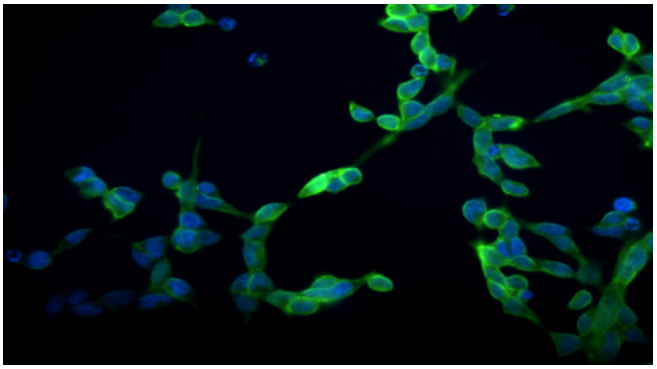
Project manager: J. Koenig, M. F. Fromm
Transporter proteins located in distinct plasma membrane domains are important for uptake, distribution and excretion of drugs and drug metabolites. Therefore, modulation of transport function may result in adverse drug reactions (ADR). Two molecular mechanisms can account for such modulations of transport function. First, variations in transporter genes (polymorphisms) may result in mutated transporter proteins with altered transport kinetics. Second, 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 are in the focus of our studies.
Organic Anion Transporting Polypeptide 1B1 (OATP1B1) is an important uptake transporter located in the basolateral hepatocyte membrane mediating the uptake of several endogenous compounds and drugs from the portal venous blood into the liver. In a cooperation with the University of Greifswald we could demonstrate that the cholesterol-lowering drug ezetimibe inhibited OATP1B1-mediated uptake and that the metabolite ezetimibe-glucuronide is a substrate of this transporter. Furthermore, we have demonstrated that a frequent polymorphism of the OATP1B1 protein (variant OATP1B1*5) is associated with reduced uptake rates for ezetimibe-glucuronide compared to the wild type protein. These results are in agreement with results from a clinical study conducted in parallel.
OATP1B1, together with the OATP family members OATP1B3 and OATP2B1 that are also expressed in human hepatocytes were in the focus of studies investigating transporter-mediated drug-drug interactions. First, we could demonstrate that macrolides inhibit OATP1B1- and OATP1B3-mediated pravastatin uptake. *In vivo*, this reduced hepatic uptake may lead to elevated pravastatin plasma concentrations with an increased risk of adverse drug reactions. A second study showed that frequently prescribed oral antidiabetic drugs inhibit OATP-mediated pravastatin uptake.

Expression and function of uptake transporters in gastrointestinal tract

Project manager: H. Glaeser, M. F. Fromm
The knowledge on the importance of OATP uptake transporters for drug transport, physiology and pathophysiology in the human gastrointestinal tract is still limited. Therefore, studies regarding the expression and function of OATPs in human stomach and intestine were performed. In collaboration with the University of Kentucky, (Lexington, KN, USA), the University of Western Ontario (London, Ontario, Canada) and the Vanderbilt University (Nashville, TN, USA; Prof. W. Lee und Prof. R. B. Kim) the expression of the OATP1B3 in multiple colon carcinoma samples was detected. Moreover, OATP1B3 mediated apoptosis resistance in several colon carcinoma cell lines after treatment with the antineoplastic agents oxaliplatin and camptothecin.
A further member of the human OATP-family is the prostaglandin transporter OATP2A1. The transport of prostaglandins from the extracellular space to the cytosol by OATP2A1 contributes to the termination of prostaglandin effects. In collaboration with the Institute of Pathology (Prof. K. U. Amann, Dr. T. Rau) it was possible to show the localization of OAT2A1 in parietal cells and deep glands of corpus and antrum of human stomach, respectively. Furthermore, using OATP2A1-overexpressing cell lines we were able to demonstrate that NSAIDs (non steroidal anti-inflammatory drugs) can stimulate or inhibit the function of OATP2A1. Such functional modifications may contribute to NSAID-induced side effects such as ulcerations or bleeding in the human gastric mucosa.

Pharmacogenetics of cardiovascular drugs

Project manager: O. Zolk, M.F. Fromm
Cardiovascular diseases are the most common, and cardiovascular drugs belong to the most frequently prescribed drugs. Their use contributes to reduced mortality from cardiovascular events, for example dual antiplatelet inhibition with ASS and clopidogrel significantly reduces the risk of fatal coronary stent thrombosis after PCI. However, there are marked differences in



Expression of the human uptake transporter OCT2 (green) in HEK293 cells

the treatment effects between individual patients with treatment failure or enhanced toxicity occurring in some patients. In this project genetic variations in genes involved in drug transport or metabolism that cause interindividual differences in response to cardiovascular drugs are investigated. In a collaborative project with the Heart Centre Bad Krozingen the association of polymorphisms in drug transporters and cytochrome P450 enzymes with the inhibitory effect of clopidogrel on platelet aggregation was investigated.

Another study focused on the impact of gender and genetic differences in genes involved in transport and metabolism of drugs on the pharmacokinetics of the diuretic torasemide. Moreover, in a collaborative project with the Department of Medicine 4 – Nephrology and Hypertensiology (University Hospital Erlangen) we investigate a potential association of polymorphisms in catecholamine transporter genes with the diagnosis of essential hypertension.

Molecular and clinical characterisation 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 interventions. Presently we study the regulation of the L-arginine-NO-nitrate pathway by endogenously formed compounds such as ADMA and L-NMMA and the metabolic fate of these compounds. For *in vitro* and *in vivo* investigations new isotope- and mass spectrometry-based methods are developed. In a DFG funded project and in cooperation with colleagues at the Department of Medicine 4 – Nephrology and Hypertensiology (University Hospital Erlangen) we investigate the biologic effects of disturbed methylarginine metabolism on vascular function in animal models and experimental studies. The experimental investigations are complemented by clinical and population-based studies performed in cooperation with the Department of Medicine 2 – Cardiology and Angiology and international partners at the Framingham Heart Study (USA) and at the Institute of Bio-Medicine of the National Research Council (Italy). With these partners we presently investigate causes and long term clinical effects of elevated plasma concentrations of ADMA and related substances.

In further projects we study genetic and biochemical/pharmacological causes of treatment failure in cardiovascular medicine, with a special focus on the prevention of thromboembolic events. Related health services research projects are directed at real life problems in translating knowledge and implementing guidelines into clinical practice.

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

Zolk O, Jacobi J, Pahl A, Fromm MF, Schmieder RE (2007) MDR1 genotype-dependent regulation of the aldosterone system in humans. Pharmacogenet Genomics, 17: 137-44

Bachmakov I, Glaeser H, Fromm MF, Koenig J (2008) Interaction of oral antidiabetic drugs with hepatic uptake transporters: focus on organic anion transporting polypeptides and organic cation transporter 1. Diabetes, 57: 1463-9

Gradhand U, Lang T, Schaeffeler E, Glaeser H, Tegude H, Klein K, Fritz P, Jedlitschky G, Kroemer HK, Bachmakov I, Anwald B, Kerb R, Zanger UM, Eichelbaum M, Schwab M, Fromm MF (2008) Variability in human hepatic MRP4 expression: influence of cholestasis and genotype. Pharmacogenomics J, 8: 42-52

Lee W, Belkhiri A, Lockhart AC, Merchant N, Glaeser H, Harris EI, Washington MK, Brunt EM, Zaika A, Kim RB, El-Rifai W (2008) Overexpression of OATP1B3 confers apoptotic resistance in colon cancer. Cancer Res, 68: 10315-23

Trenk D, Hochholzer W, Fromm MF, Chialda LE, Pahl A, Valina CM, Stratz C, Schmiebusch P, Bestehorn HP, Buettner HJ, Neumann FJ (2008) Cytochrome P450 2C19 681G>A polymorphism and high on-clopidogrel platelet reactivity associated with adverse 1-year clinical outcome of elective percutaneous coronary intervention with drug-eluting or bare-metal stents. J Am Coll Cardiol, 51: 1925-34

Lieb W, Benndorf RA, Benjamin EJ, Sullivan LM, Maas R, Xanthakis V, Schwedhelm E, Aragam J, Schulze F, Boeger RH, Vasan RS (2009) Plasma asymmetric dimethylarginine, L-arginine and left ventricular structure and function in a community-based sample. Atherosclerosis, 204: 282-7

International Cooperation

Prof. Carmine Zoccali, Renal Dialysis Transplantation and Hypertension Unit & Institute of Bio-Medicine of the National Research Council, Reggio Calabria, Italy

Prof. Ramachandran Vasan, Framingham Heart Study, USA

Prof. Jean-Luc Cracowski, INSERM Grenoble, France

Research Equipment

Applied Biosystems API 4000 MS/MS System Package

Zeiss LSM 5 Pascal