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
- Transporter-mediated drug-drug interactions
- Personalized drug therapy
- Molecular and clinical characterization of therapeutic targets in the L-arginine-NO-nitrate pathway
- Analysis of drugs and endogenous substances
- Safety in drug therapy

Structure of the Institute

The Chair of Clinical Pharmacology and Clinical Toxicology constitutes together with the Chair of Pharmacology and Toxicology and the Doerenkamp-Chair for Innovations in Animal and Consumer Protection (which expired on 30.06.2013) 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. Dr. A. Ludwig) and the Chair of Clinical Pharmacology and Clinical Toxicology (Prof. Dr. M.F. Fromm) on a biennial basis. 29 persons are working at the Chair of Clinical Pharmacology and Clinical Toxicology with six of them being funded by extramural sources. Research is conducted by six scientists, two of them being specialists in clinical pharmacology, twelve MD or Ph.D. students, and five technicians. The working 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 UK Erlangen and for external physicians. The following topics, funded e.g. by the DFG, the German Cancer Aid, the German Federal Ministry of Health (BMG), and the BMBF, are in the focus of our studies: Uptake and efflux transporters for drugs, mechanismsm underlying drug-drug interactions, genetic determinants of drug effects (pharmacogenomics), transporter expression and regulation in tumors, cardiovascular pharmacology and risk factors, alterations of the L-arginine-NO-metabolism, and safety in drug therapy.

Research

Molecular characterization of drug transporters

Project managers: Prof. Dr. J. König, Prof. Dr. M.F. Fromm

Transport proteins located in distinct membrane domains are important for the uptake, distribution, and excretion of drugs and drug metabolites. Therefore, the molecular characterization of drug transporters is in the focus of our research.

We could demonstrate that the transport of HMG-CoA-reductase inhibitors (statins) can be allosterically modified by non-steroidal anti-inflammatory (NSAIDs) or oral antidiabetic drugs in addition to the competitive transport inhibition by these drugs. Structure-function relationship studies currently investigate which amino acids or protein regions within the drug uptake transporters OATP1B1 and OATP1B3 are responsible for substrate recognition and allosteric transport modulation. Furthermore, the expression and epigenetic regulation of drug transporters in human head and neck squamous cell carcinoma samples was investigated in a cooperation with the Department of Otorhinolaryngology – Head and Neck Surgery. For the investigation of transcellular transport processes and for the analysis of transporter-metabolism interplay, several multiple-transfected cell lines were established recombinantly overexpressing transport proteins or transporters together with metabolizing enzymes. In cooperation with Prof. Dr. A. Birkenfeld (University Hospital Carl Gustav Carus, Dresden), we characterized the human sodium-coupled citrate transporter NaCT which is now under further investigation regarding its possible role as target for drug therapy.

Transporter-mediated drug-drug interactions

Project managers: Prof. Dr. J. König, Prof. Dr. M.F. Fromm

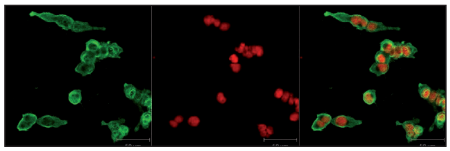
Simultaneously administered drugs or food constituents can inhibit transporter-mediated uptake or elimination of victim drugs. This leads to altered plasma concentrations of the victim drug and to altered drug effects or an increased risk of adverse drug reactions. In collaboration with colleagues from Fukushima Medical University (Japan), we could show by in vitro studies and a clinical study in healthy volunteers that green tea markedly reduces the plasma concentrations of the ß-blocker nadolol and that this is likely due to inhibition of transporter (OATP2A1)-mediated uptake of nadolol by ingredients of green tea (catechins) in the small intestine. We presently investigate the influence of catechins on hepatic uptake transport mediated by OATP1B1 and OATP1B3. Using MDCKII cells stably overexpressing the human renal cation transporters OCT2, MATE1, and MATE2-K, we could clarify the molecular mechanisms underlying the renal secretion of the antiviral drug lamivudine as well as renal drug-drug interactions. In further in vitro investigations as well as in clinical studies in humans, we investigated the impact of the antibiotic trimethoprim on pharmacokinetics and effects of the frequently used oral antidiabetic drug metformin and characterized the endogenous metabolite N^1-methylnicotinamide as potential biomarker for renal drug-drug interactions mediated by cation transporters.

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

Project manager: Prof. Dr. 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 the methylarginines 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. In an intramural IZKF-project as well as in cooperation with researchers from the University Hospital in Dresden, the research group investigates alternative pathways for the metabolism of methylarginines. In collaborations with other groups from the Chair of Clinical Pharmacology and Clinical Toxicology, we investigate transporter-mediated translocation of methylarginines. In a DFG-funded collaboration project conducted together with the Institute and Outpatient Clinic of Occupational, Social, and Environmental Medicine as well as

the Framingham Heart Study (USA), we could present first data for elevated plasma nitrate as a risk marker for mortality in the general population.



Characterization of a cell line stably overexpressing human CAT2A (cationic amino acid transporter 2A) using confocal laserscanning microscopy (green: CAT2A, red: nuclei).
With kind permission from Springer Science+Business Media: J. Strobel, F. Müller, O. Zolk, B. Endreß, J. König, M.F. Fromm, R. Maas. Amino Acids, Transport of asymmetric dimethylarginine (ADMA) by cationic amino acid transporter 2 (CAT2), organic cation transporter 2 (OCT2) and multidrug and toxin extrusion protein 1 (MATE1), 45, 2013, 989-1002. Middle section of figure 1d.

Analysis of drugs and endogenous substances

Project manager: Dr. M. Mieth

The drug analysis unit uses samples from both, cell culture experiments and clinical trials. Analytical methods are developed, optimized, and validated in our laboratory. The spectrum of the analytes ranges from various drugs, such as pravastatin, etoposide, metformin, clopidogrel, trimethoprim and β-lactam antibiotics, to endogenous substances, such as derivatives of arginine, N^1-methylnicotinamide and β-aminoisobutyric acid. Challenges are very low concentrations, small sample volumes, and the determination of an analyte in different matrices (e.g. lysate, plasma, urine).

Safety in drug therapy

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

An important research focus is safety in drug therapy. As partners in a project which is part of the "Action Plan for Drug Therapy Safety" (funded by the Federal Ministry of Health, BMG), we implemented and evaluated measures to improve therapeutic safety on an emergency ward. Prerequisite for this was the creation of an infrastructure that permits identification and recording of adverse drug events. This infrastructure is still available and used in new projects. As a partner in the BMBF funded cluster Medical Valley EMN – therapeutic systems project, we currently work on new software and chemoinformatic databases to improve drug safety in psychiatry. As a result of interest to a broader audience, we identified and published critical inconsistencies in officially approved prescribing information. In addition, problems of safety of drug therapy in elderly patients are in the focus of collaborative projects.

Teaching

The Chair of Clinical Pharmacology and Clinical Toxicology 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. In a coopertion project with the Technical University of Munich, we developed an online teaching module for drug therapy of common diseases. Students of pharmacy and medicine are welcome to work with us during their final year (clinical rotation).

Selected Publications

König, J, Müller F, Fromm MF. Transporters and drug-drug interactions: important determinants of drug disposition and effects. Pharmacol Rev 2013, 65(3): 944-66

Zolk O, Schnepf R, Muschler M, Fromm MF, Wendler O, Traxdorf M, Iro H, Zenk J. Transporter gene expression in human head and neck squamous cell carcinoma and associated epigenetic regulatory mechanisms. Am J Pathol 2013, 182: 234-243

Misaka S, Yatabe J, Müller F, Takano K, Kawabe K, Gläser H, Yatabe MS, Onoue S, Werba JP, Watanabe H, Yamada S, Fromm MF, Kimura J. Green tea ingestion greatly reduces plasma concentrations of nadolol in healthy subjects. Clin Pharmacol Ther 2014, 95: 432-438

Kittel A, Müller F, König J, Mieth M, Sticht H, Zolk O, Kralj A, Heinrich MR, Fromm MF, Maas R. Alanine-glyoxylate aminotransferase 2 (AGXT2) polymorphisms have considerable impact on methylarginine and -aminoisobutyrate metabolism in healthy volunteers. PLoS ONE 2014, 9: e88544

Schächtele S, Tümena T, Gaßmann K-G, Fromm MF, Maas R. Implementation of warnings from dear doctor letters (Rote-Hand-Briefe): an analysis of medication data from a large cohort of elderly patients. Dtsch Arztebl Int 2014, 111: 255-263

Pfistermeister B, Saß A, Criegee-Rieck M, Bürkle T, Fromm MF, Maas R. Inconsistencies and misleading information in officially approved prescribing information from three major drug markets. Clin Pharmacol Ther 2014, 96: 616-624

International Cooperations

Prof. J. Backman, Prof. M. Niemi, Department of Clinical Pharmacology, University of Helsinki, Helsinki: Finland

Prof. S. Misaka, Department of Pharmacology, School of Medicine, Fukushima Medical University, Fukushima: Japan

Prof. S.R. Vasan, MD, Boston University School of Medicine, Boston: USA

Prof. C. Zoccali, CNR-IBIM and Nephrology-Transplant Unit, Ospedali Riuniti, Reggio Calabria: Italy

Research Equipment

Applied Biosystems, API 4000 MS/MS System Package

Zeiss, Konfokales Laserscanning-Mikroskop LSM 5 Pascal