Institute of Experimental and Clinical Pharmacology and Toxicology

Doerenkamp-Chair for Innovations in Animal and Consumer Protection (until July 2013)

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Research Focus
- Analgesics (Consumer Protection)
- Non-invasive functional imaging (Animal Protection)

Structure of the Division

The endowed Doerenkamp-Chair constituted together with the Chair of Clinical Pharmacology and Clinical Toxicology and the Chair of Pharmacology and Toxicology the Institute of Experimental and Clinical Pharmacology and Toxicology. The funding of the Doerenkamp-Chair has ended in 2013.

There was a close collaboration of this Chair with researchers of the other two chairs. The research goals of the endowed Doerenkamp-Chair are pursued in close collaboration with Prof. Dr. B. Hinz (formerly senior scientist at the Institute of Experimental and Clinical Pharmacology and Toxicology, presently chairman of the Department of Toxicology and Pharmacology at the University of Rostock) and PD Dr. A. Hess (member of the Chair of Pharmacology and Toxicology at the Institute of Experimental and Clinical Pharmacology and Toxicology). In collaboration with these senior co-workers, the following results were achieved.

Research

Analgesics (Consumer Protection)

Cyclooxygenase (COX) inhibitors (analgesics, anti-rheumatics) are the most widely used drugs. They are effective, but also prone to cause unwanted drug effects. Together with Prof. Dr. B. Hinz, we analyzed PK/PD (pharmacokinetic/pharmacodynamic) of the most common drugs, including acetaminophen, aspirin, diclofenac, etoricoxib, ibuprofen, lumiracoxib, etc., by applying an ex vivo technique in volunteers. We could show that acetaminophen is a selective (preferential) inhibitor of COX-2, associated with unrelated serious hepatotoxicity. The data accrued are presently used as argument to eliminate acetaminophen from the OTC (over-the-counter)-market.

We found that most new and old COX inhibitors are chronically overdosed in most patients. With the aid of our ex vivo PK/PD analyzing concept for tissue, toxicity sparing doses were developed.

The analysis of older drugs, including – aside of acetaminophen – metamizol (dipyrone), showed that dipyrone is overdosed under clinical conditions.

Recently, COX-inhibitors were shown to cause cardiac infarctions and accelerated artherosclerosis in certain patients. Using NT-proBNP, a new biomarker (N-terminal pro-Brain natriuretic peptide), we could show that determining the NT-proBNP level is helpful in singling out patients at risk.

Finally, it is helpful to connect individual data of patients in the clinic of internal medicine with information about the drugs applied in order to detect unwanted drug effects in time.

Searching for undiscovered risks of COX-inhibitors, we observed that amateur and professional athletes abuse these drugs in dangerous proportions. Several publications in German print media led to a first boost of awareness. These investigations will be continued.

Non-invasive functional imaging (Animal Protection)

One of the central aims of the endowed Doerenkamp-Chair was to establish non-invasive imaging techniques in experimental pain research. This approach turned out to be extremely successful. Together with Prof. Dr. H.U. Zeilhofer (Zurich), we could identify the role of glycinergic receptors in the spinal cord for pain control. Together with Dr. J.M. Penninger (Vienna) and Dr. C.J. Woolf (Boston), we could employ this technology to identify pain controlling genes which had been identified in a drosophila assay system. One gene turned out to be of major importance not only for pain perception, but also for synesthetic experiences encountered by about 4 % of the human population. Moreover, employing genetically modified mice (e.g. overexpressing TNFα), we could show that anti-TNFα-treatment in mice (overexpressing TNFα) and men (rheumatoid arthritis patients) instantaneously relieved pain in experimental animals and men.

The successful implementation of functional MR-imaging has proven to be a successful tool for non-invasive, non-demanding animal experimentation in pain research. The activity of the group will continue under the leadership of Prof. Dr. M. Uder who has taken over the administrational control of the unit devoted to employ imaging techniques in experimental research involving animals. There is hope that this division will continue to flourish.

Teaching

The engagement of Prof. Dr. Dr. h.c. K. Brune as speaker at international conferences and his membership in several administrative bodies and advisory structures has led to many additional invitations to comment on current problems of drug therapy in man. In addition, Prof. Dr. Dr. h.c. K. Brune is engaged in the production of many national and international guidelines, textbooks, etc. A sample of publications related to these activities can be found on the homepage of the Institute. Prof. Dr. Dr. h.c. K. Brune was a member of the Executive Committee of IUPHAR (International Union of Basic and Clinical Pharmacology) until 2015. Kay Brune has been elected full member of the 'Arzneimittelkommission der deutschen Ärzteschaft' (AkdÄ; Drug Commission of the German Medical Association), 2014-2018.

Selected Publications

Kuster M, Renner B, Oppel P, Niederweis U, Brune K. Consumption of analgesics before a marathon and the incidence of cardiovascular, gastrointestinal and renal problems: a cohort study. BMJ Open 2013 Apr 19;3(4): pii: e002090

Neubert A, Dormann H, Prokosch HU, Bürkle T, Rascher W, Sojer R, Brune K, Criegee-Rieck M. E-pharmacovigilance: development and implementation of a computable knowledge base to identify adverse drug reactions. British journal of clinical pharmacology 2013, 76: 69-77

Stammschulte T, Brune K, Brack A, Augenstein H, Arends G, Gundert-Remy U. Unexpected hemorrhage complications in association with celecoxib. Spontaneously reported case series after perioperative pain treatment in gynecological operations. Der Anaesthesist 2014, 63: 958-60

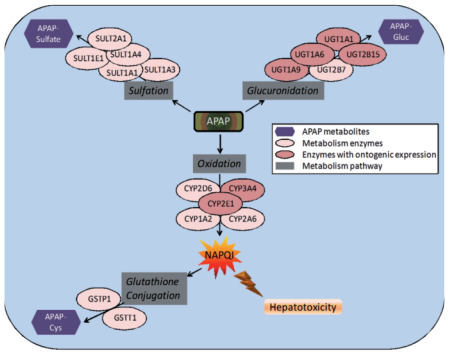
Tiegs G, Karimi K, Brune K, Arck P. New problems arising from old drugs: second-generation effects of acetaminophen. Expert review of clinical pharmacology 2014, 7: 655-62

Brune K. Diclofenac: increase of myocardial infarctions at low doses? Pharmacoepidemiology and drug safety 2014, 23: 326-8

Brune K, Renner B, Tiegs G. Acetaminophen/paracetamol: A history of errors, failures and false decisions. Eur J Pain 2014 Nov 27. doi: 10.1002/ejp.621

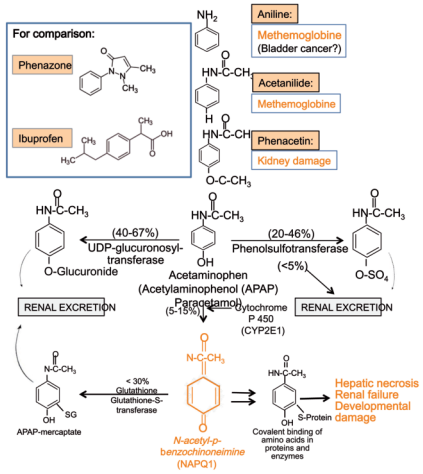
Research Equipment

Bruker, BioSpec 70/30 (Kleintier-MRT 7.0. Tesla)



Enzymes and metabolic steps that are involved in the chemical conversion of paracetamol within the human body.
(Modified and transferred from: 'Pharmacogenomics of acetaminophen in pediatric populations: a moving target', Krasniak et al., Front Genet. 2014; with permission of the publisher. From K. Brune: 'Paracetamol: gefährlicher, als man denkt!': ChiuZ, 2015, in print).
Abbreviations:

SUL	*Sulfatation*
UG	*Glucuronidation*
CYP	*Oxydation*
GS	*Glutathione S-transferase*



From aniline to paracetamol: The complex metabolization and elimination causes many risks.
(Modified and transferred from: 'Acetaminophen/paracetamol: A history of errors, failures and false decisions': Eur J Pain, 2014; with permission of the publisher).