Institute of Experimental and Clinical Pharmacology and Toxicology

Chair of Pharmacology and Toxicology

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Research Focus
- Molecular mechanisms of cardiac rhythmogenesis and arrhythmia
- HCN channels in the nervous system
- Renal function and sepsis
- Pharmacological imaging and image analysis

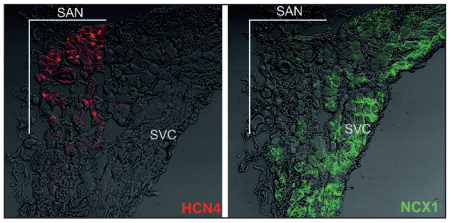
Structure of the Institute

The Chair of Pharmacology and Toxicology, the Chair of Clinical Pharmacology and Clinical Toxicology, and the Doerenkamp-Chair for Innovations in Animal and Consumer Protection (expired on 30.06.2013) form the Institute of Experimental and Clinical Pharmacology and Toxicology. The position of executive director 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 biennal basis. Research work is carried out by two professors, four Ph.D. graduates, seven postgraduate students, and five research technicians.
Main research areas are the function of various ion channels and exchangers in the heart with a focus on the generation of the cardiac rhythm. In addition, the role of HCN channels in the nervous system is studied. Other research areas are renal function and sepsis and small animal imaging and image analysis.
These areas are explored by combining methods from molecular biology, mouse genetics, whole-animal studies, electrophysiology, and functional MRI. Research is supported by the DFG and BMBF. Together with the Chair of Clinical Pharmacology and Clinical Toxicology, a drug information service is provided for clinicians of the UK Erlangen as well as for physicians in private practices.

Research

Molecular mechanisms of cardiac rhythmogenesis and arrhythmia

Project managers: PD Dr. J. Stieber, PD Dr. S. Herrmann, Prof. Dr. A. Ludwig
The mechanisms underlying the generation of the spontaneous cardiac rhythm in the sinoatrial node were studied by using various conditional mouse models. Mice with a selective deletion of the sodium/calcium exchanger NCX1 in the sinoatrial node developed slowing of the heart rate and arrhythmias. Mutant cells displayed irregular spontaneous Ca^{2+} signals with a significantly reduced frequency. These results demonstrate that NCX1 in sinoatrial myocytes is essential for maintaining proper pacemaking. An inducible HCN triple-mutant (HCN1/2/4-KO) was further analyzed at the electrophysiological level by using isolated sinoatrial cells. The results demonstrate that sinoatrial If is generated by the combined activity of three HCN isoforms. We showed earlier that the activity of ventricular HCN channels is increased during cardiac hypertrophy. The potential enhanced arrhythmogenic propensity of isolated ventricular myocytes was analyzed in collaboration with Prof. Dr. F.U. Müller (Westfälische Wilhelms-Universität Münster). A collaboration with Prof. K.R. Chien (Karolinska Institutet, Stockholm) revealed that the cardiac pacemaker channel HCN4 unexpectedly constitutes a selective marker for the first heart field during cardiac development.



Conditional deletion of the sodium/calcium-exchanger NCX1 in the sinoatrial node. The sinoatrial node (SAN) is marked by staining of HCN4 (red, left). After induction of gene deletion, NCX1 (green, right) is eliminated selectively from the SAN region, but is still present in the superior vena cava (SVC) and other cardiac compartments.
(Herrmann S, Lipp P, Wiesen K, Stieber J, Nguyen H, Kaiser E, Ludwig A. The cardiac sodium-calcium exchanger NCX1 is a key player in the initiation and maintenance of a stable heart rhythm. Cardiovasc Res 2013, 99: 780-8. By permission of Oxford University Press).

HCN channels in the nervous system

Project managers: PD Dr. S. Herrmann, Prof. Dr. A. Ludwig
We could show that HCN channels are involved in the development of pathological pain including allodynia and hyperalgesia in acute inflammatory conditions. We now studied the role of HCN2 in a model reflecting chronic pain conditions. Our results demonstrate that the absence of HCN2 in primary sensory neurons reduces tactile hypersensitivity in chronic inflammatory conditions, but leaves heat hypersensitivity unaffected. Moreover, we showed that chronic inflammation results in an increased expression of HCN2 and causes sensitization in peripheral and spinal terminals of the pain transduction pathway. In addition, the role of HCN4 in thalamic nuclei was analyzed in collaboration with Prof. Dr. T. Budde (Westfälische Wilhelms-Universität Münster).

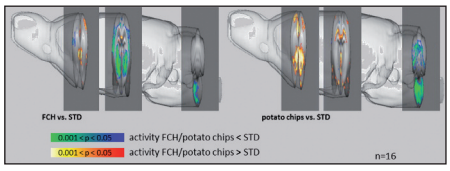
Renal function and sepsis

Project manager: Prof. Dr. K. Höcherl
The pathophysiology of septic acute kidney injury (AKI) is complex. Overall, renal hypoperfusion due to an imbalance between vasoconstriction and vasodilation seems to be a central pathogenetic factor in the development of septic AKI. Thus, the restoration of an adequate renal blood flow should be the primary goal in terms of renal protection in critically ill patients. Hyporeactivity to vasoconstrictors, such as angiotensin II, is commonly observed in patients and animal models of sepsis. The AT1 receptor-associated protein 1 (Arap1) is expressed in vascular smooth muscle cells and increases the surface expression of the AT1-receptor. We hypothesized that dysregulation of Arap1 may contribute to vascular hyporeactivity to angiotensin II during endotoxemia. During endotoxemia, mean arterial blood pressure decreased in Arap1-KO and in wildtype mice, with the time course of sepsis-induced hypotension being markedly accelerated in Arap1-KO as compared to wildtype mice. Following lipopolysaccharide (LPS) injections, Arap1 expression was successively down-regulated in the wildtype mice. The endotoxemia-related decline in Arap1 expression could be recapitulated in cultured mesangial cells by incubation with pro-inflammatory cytokines. Therefore, our data suggest that down-regulation of Arap1 expression during sepsis contributes to the development of hypotension by causing reduced vascular sensitivity to angiotensin II.

Pharmacological imaging and image analysis

Project manager: PD Dr. A. Hess
Magnetic Resonance Imaging (MRI) plays an ever increasing role in research and clinical practice which is reflected in multiple collaborative research project of our group. In a collaboration with the Department of Medicine 2, we

could demonstrate an increased fat content in the aortic root of ApoE-deficient mice. Together with the Institute of Neuropathology, we could establish a new diagnostic method for hippocampal sclerosis. In addition, we analyzed the invasive growth of a craniopharyngioma. In a collaboration with Prof. Dr. J. Penninger (Institute of Molecular Biotechnology, Vienna), we could demonstrate that CLP1 mutant mice display microcephaly during embryonic development. We observed a markedly reduced cortical thickness in these CLP1 mutants. As part of the Emerging Fields Initiative "Neurotrition" of the FAU, we continued our collaboration with the Institute of Food Chemistry. We could demonstrate that craving for potato chips is not determined by their energy content, but is mainly dependent on an optimal food-to-carbohydrate ratio. In our main research field "pain mechanisms" we performed a translational fMRI study together with Prof. J.S. Mogil (McGill University, Montreal) and Prof. Dr. C. Maihöfner (Klinikum Fürth). By using graph-theoretical methods, we could show for the first time that pain induces a specific interaction pattern between the activated brain structures. In close collaboration with the Department of Medicine 3, the trial PreCePRA was started. This study investigates our hypothesis that fMRI is suitable to predict the effect of TNF-antagonists in the therapy of rheumatoid arthritis. In a collaborative project together with the Department of Medicine 1, we already could demonstrate that fMRI is principally able to predict the effect of an anti-TNF therapy in patients suffering from Crohn`s disease.



Activity patterns in the rat brain following ingestion of test food with an optimal fat-to-carbohydrate ratio (FCH, left) and potato chips (right) as compared to standard chow (STD). Regions displaying higher activity with the test foods are colored yellow – red; areas showing higher activity with standard chow are green – blue.

Teaching

Pharmacology and toxicology is taught to medical students, students of the degree program Molecular Medicine, and pharmacy students. The pharmacology course for medical students consists of lectures and problem-based small group tutorials. Students of the degree program Molecular Medicine are trained by lectures, a seminar focusing on the molecular mechanisms of drug actions, and various laboratory internships. In addition, the Chair of Pharmacology and Toxicology provides the complete training in pharmacology for pharmacy students (as required to acquire the license to practice pharmacy). This includes lectures covering pharmacology and pathophysiology as well as seminars and laboratory internships.

Selected Publications

Herrmann S, Lipp P, Wiesen K, Stieber J, Nguyen H, Kaiser E, Ludwig A. The cardiac sodium-calcium exchanger NCX1 is a key player in the initiation and maintenance of a stable heart rhythm. Cardiovasc Res 2013, 99: 780-8

Mederle K, Schweda F, Kattler V, Doblinger E, Miyata K, Höcherl K, Oike Y, Castrop H. The angiotensin II AT1 receptor-associated protein Arap1 is involved in sepsis-induced hypotension. Crit Care 2013, 17: R130

Später D, Abramczuk MK, Buac K, Zangi L, Stachel MW, Clarke J, Sahara M, Ludwig A, Chien KR. A HCN4+ cardiomyogenic progenitor derived from the first heart field and human pluripotent stem cells. Nat Cell Biol 2013, 15: 1098-106

Hoch T, Kreitz S, Gaffling S, Pischetsrieder M, Hess A. Manganese-enhanced magnetic resonance imaging for mapping of whole brain activity patterns associated with the intake of snack food in ad libitum fed rats. PLoS One 2013, 8: e55354

Karaca E et al. Human CLP1 mutations alter tRNA biogenesis, affecting both peripheral and central nervous system function. Cell 2014, 157: 636-50

Schnorr S, Eberhardt M, Kistner K, Rajab H, Käßer J, Hess A, Reeh P, Ludwig A, Herrmann S. HCN2 channels account for mechanical (but not heat) hyperalgesia during long-standing inflammation. Pain 2014, 155: 1079-90

International Cooperations

Prof. D.M. Chetkovich, Feinberg School of Medicine, Northwestern University, Chicago: USA

Prof. K.R. Chien, Department of Cell and Molecular Biology, Karolinska Institutet: Sweden

Prof. J. Mogil, Department of Psychology, McGill University, Montral: Canada

Prof. J. Penninger, Institute of Molecular Biotechnology, Vienna: Austria

Prof. A. Tinker, William Harvey Heart Centre, Queen Mary University of London, London: USA

Prof. X. Wehrens, Cardiovascular Research Institute, Baylor College of Medicine, Houston: USA

Prof. K.-W. Yau, School of Medicine, Johns Hopkins University: USA

Research Equipment

Bruker, 4,7 Tesla Kleintier-MRT

Zeiss, Konfokales Laserscanning-Mikroskop LSM 5