Institute of Experimental and Clinical Pharmacology and Toxicology

Chair of Pharmacology and Toxicology

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Research Focus
- Rhythm generation in the sinoatrial node
- HCN-channels in nociceptors and other neurons
- Immunological mechanisms in inflammatory liver and kidney injury
- Pharmacological imaging and image analysis

Structure of the Institution

The Chair of Pharmacology and Toxicology, the Chair of Clinical Pharmacology and Clinical Toxicology and the Doerenkamp-Foundation professorship for Innovations in animal and consumer protection form together the Institute of Experimental and Clinical Pharmacology and Toxicology.
The position of 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.The chair has a staff of 31 employees. Research is carried out by 8 PhD graduates, 7 postgraduate student and 6 research technicians.
Main areas of research are the function of various ion channels (HCN pacemaker channels, calcium channels, ryanodine receptors) in heart, brain and dorsal root ganglions, immunological mechanisms in liver injury and functional MR-Imaging. These areas are explored by combining methods from molecular biology, mouse genetics, electrophysiology, immunology and whole-animal studies. Research is supported by various grants from the DFG, EU and BMBF. In 2008 Prof. Gisa Tiegs left the institute to take over a position as director of the unit for experimental immunology and hepatology at the University Medical Centre Hamburg-Eppendorf.

Research

Rhythm generation in the sinoatrial node
Project manager: J. Stieber, S. Herrmann, A. Ludwig
The role of various ion channels for the generation of rhythmic cardiac activity is studied. One focus is the function of HCN pacemaker channels. These channels underly the If current and are thought to be essential for the generation of action potentials in the sinoatrial node. Since global deletion of HCN4-channels turned out to be embryonic lethal, we now deleted HCN4 selectively in the heart. If was severly reduced leading to the disturbed generation of action potenials and sinus pauses (Fig.). In contrast to earlier assumptions we found that HCN4 is not required for the sympathetic upregulation of heart rate. We currently attempt the complete deletion of sinoatrial If by generating double (HCN2/4) and triple (HCN1/2/4) knockout mice.
In addition, we generated the mouse line HCN4-KiT by "knock-in" of a Cre recombinase into the HCN4 locus. By using this line we are able to delete any gene selectively in the sinoatrial and atrioventricular node in a temporally controlled manner (Fig.). The line is currently used to analyse the exact mechanisms of action potenial generation in the cardiac conduction system. We focus on the physiological role of voltage-gated calcium channels and ryanodine-receptors.
Another project deals with the generation of arrhythmias in the hypertrophied heart. It was proposed that increased activtity and upregulation of ventricular HCN channels contributes to arrhythmogenesis. We study this hypothesis by induction of cardiac hypertrophy in HCN deficient mice.

HCN-channels in nociceptors and other neurons
Project manager: S. Herrmann, A. Ludwig
Various ion channels are involved in the generation and transmission of painful stimuli. Several reports suggest that HCN channels may play an important role in neuropathic and inflammatory pain. We found in earlier work that HCN1 and HCN2 are strongly expressed in dorsal root ganglions. We now study the exact role of these isoforms by generation of nociceptor-specific deletion mutants of HCN1 and HCN2. We also generated a brain-specific deletion of HCN4. In thalamocortical neurons of these mice, Ih was reduced by about 50 %. Contrary to expectations, brain specific HCN4-KOs do not show absence epilepsy, but a resistance towards seizures provoked by GABAA antagonists. In addition we could show that HCN4 is involved in the control of motor function during demanding motor tasks.

Immunological mechanisms in inflammatory liver and kidney injury
Project manager: G. Tiegs, G. Sass
The group addresses immunological mechanisms and signal transduction pathways in inflammatory liver and kidney disease. Based on TNFα- and TNFα-receptor signals which induce apoptosis but also cell proliferation, liver regeneration and the expression of "survival factors", the group worked on the identification of cytoprotective liver proteins. These proteins including heme oxygenase-1 exert mostly anti-apoptotic effects and are important for the protection of organ function but can also promote tumor growth. The RNAi-technology for the knockdown of genes *in vitro* and *in vivo* was established and used to downregulate the expression of pro- and antiapoptotic proteins.
Another research area focused on the mechanisms guiding the differentiation of adaptive tolerogenic T cells (Tregs and NKT cells) which can induce immune tolerance in the liver.
The group also studied interactions between immune and nervous system in animal models of hepatitis and nephritis. Based on the immunological mechanisms involved and the modulation of these mechanisms by neuropeptides and neurotransmitters new approaches for immunotherapy were developed.

Pharmacological imaging and image analysis
Project manager: A. Hess
The group uses non-invasive magnetic resonance tomography to study plastic nociceptive processes in the central nervous system of rodents. Further details can be found in the report of the Doerenkamp-Foundation professorship. In addition, various topics ranging from cardiology to lipid metabolism, imaging of vessels and in- vivo-tracing of marked cells are analysed in different cooperations (IZKF, DFG FG 661 Praeklinische Bildgebung, DFG KFG Postoperativer Schmerz). The combination of non-invasive MR imaging with the delineation of soft-tissue contrasts and state-of-the art image analysis proves to be highly effective and minimizes animal stress.

Teaching

Pharmacology and Toxicology is taught to medical students, students of molecular medicine and pharmacy students. The pharmacology course for medical students consists of lectures and a problem-based small group tutorial. Students of molecular medicine are trained by lectures, a seminar focusing on the molecular mechanisms of drug actions and laboratory internships.
In addition, the chair 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, seminars and laboratory internships.

Selected Publications

Erhardt A, Biburger M, Papadopoulos T, Tiegs G (2007) IL-10, regulatory T cells, and Kupffer cells mediate tolerance in concanavalin A-induced liver injury in mice. Hepatology, 45: 475-85

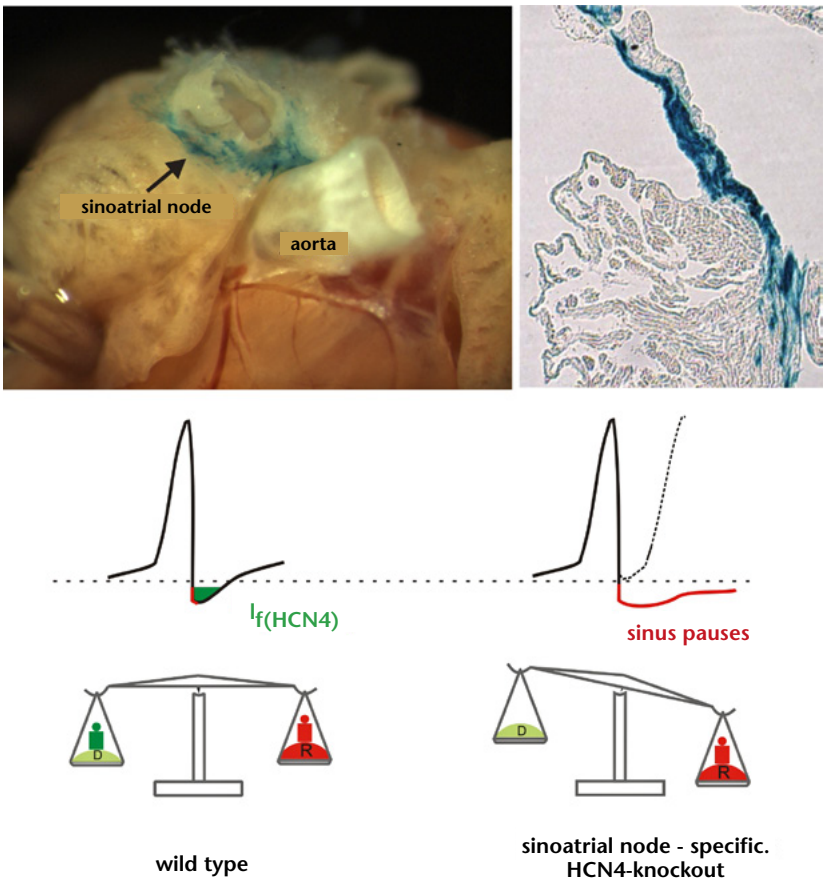
Herrmann S, Stieber J, Stoeckl G, Hofmann F, Ludwig A (2007) HCN4 provides a ‚depolarization reserve' and is not required for heart rate acceleration in mice. EMBO J, 26: 4423-32

David R, Brenner C, Stieber J, Schwarz F, Brunner S, Vollmer M, Mentele E, Mueller-Hoecker J, Kitajima S, Lickert H, Rupp R, Franz WM (2008) MesP1 drives vertebrate cardiovascular differentiation through Dkk-1-mediated blockade of Wnt-signalling. Nat Cell Biol, 10: 338-45

Hoesl E, Stieber J, Herrmann S, Feil S, Tybl E, Hofmann F, Feil R, Ludwig A (2008) Tamoxifen-inducible gene deletion in the cardiac conduction system. J Mol Cell Cardiol, 45: 62-9

Knabl J, Witschi R, Hoesl K, Reinold H, Zeilhofer UB, Ahmadi S, Brockhaus J, Sergejeva M, Hess A, Brune K, Fritschy JM, Rudolph U, Moehler H, Zeilhofer HU (2008) Reversal of pathological pain through specific spinal GABAA receptor subtypes. Nature, 451: 330-4

Ludwig A, Herrmann S, Hoesl E, Stieber J (2008) Mouse models for studying pacemaker channel function and sinus node arrhythmia. Prog Biophys Mol Biol, 98: 179-85



Temporally controlled gene deletion in the sinoatrial node
Top, A target gene is deleted selectively in the sinoatrial node after administration of tamoxifen to HCN4-KiT mice. Blue staining indicates successful recombination (left, whole-mount; right, section). Middle, Lack of HCN4 channels in the sinoatrial node results in disturbed action potential generation and sinus pauses. Bottom, Diagram of proposed mechanism. HCN4-deficient animals have difficulties counter-balancing hyperpolarizing currents.

International Cooperation

Prof. Kenneth Chien, Harvard Medical School, Boston, USA

Prof. L. Cervetto, Dipartimento di Scienze Fisiologiche, Università di Pisa, Italy

Dr. Ming Lei, Cardiovascular Research Group, University of Manchester, Great Britain

G. Fishman, MD, Division of Cardiology, NYU Department of Medicine, New York, USA

Prof. Jeffrey Holt, Department of Neuroscience, University of Virginia, Charlottesville, USA

Meetings and International Training Courses

01.08.2008: DFG Forschergruppe 923 – Molecular Dissection of Cardiovascular Functions, Erlangen

Research Equipment

Bruker 4,7 Tesla Kleintier-MRT

Zeiss Konfokales Laserscanning-Mikroskop LSM 5