

Institute of Experimental and Clinical Pharmacology and Toxicology

Chair of Pharmacology and Toxicology

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Research Focus

- Mechanisms of cardiac pacemaking
- Ventricular Ion channels
- HCN-channels in neurons
- Pharmacological imaging and image analysis

Structure of the Department

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 together form 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 the heart and in the nervous system, in particular in pain generation. Another research field is small animal imaging, focusing mainly, but not exclusively, on mechanisms of pain processing. These areas are explored by combining methods from molecular biology, mouse genetics, electrophysiology, whole-animal studies and functional MRI. Research is supported by various grants from the DFG, EU and BMBF. Together with the chair of Clinical Pharmacology and Clinical Toxicology a drug information

service is provided for clinicians of the Universitätsklinikum Erlangen as well as for physicians in private practice.

Research

Mechanisms of cardiac pacemaking

Project managers: J. Stieber, S. Herrmann, A. Ludwig

The complex mechanisms of cardiac pacemaking in the sinoatrial node are analyzed by using a variety of knock-in and knock-out mouse models. We generated the first mouse model for age-dependent sick-sinus syndrome. Sinoatrial cells were deleted by using our sinus node-specific and inducible *Ki1-Cre* line. The resulting animals developed typical arrhythmias. Unexpectedly, sufficient atrial pacemaking was detected in the absence of any sinoatrial node cells. In addition, the role of *If* for cardiac pacemaking was analyzed. By generating a triple-knockout (*HCN1/2/4*), sinoatrial *If* was completely deleted resulting in severe bradycardia and lethality. Other projects examine the function of voltage-gated calcium channels and ryanodine receptors in the cardiac pacemaking and conduction system.

Ventricular Ion channels

Project managers: S. Herrmann, A. Ludwig, J. Stieber

Ventricular arrhythmias are frequently observed in cardiac diseases including heart failure and hypertrophie. The contribution of ventricular *If* to these arrhythmias is unclear. By inducing left ventricular hypertrophy in mice it could be shown that this current is increased in hypertrophied ventricular myocytes. Unexpectedly, cardiac-specific deletion of *HCN2+4* demonstrated that HCN channels contribute to the prolongation of repolarization observed in the hypertrophied heart. These results directly demonstrate that increased HCN channel activity augments the arrhythmic potential of hypertrophied hearts.

Another project used conditional mouse mutants to study the role of ryanodine receptors (*RyR2*) in different cardiac cell types. Lack of the channels in ventricular myocytes resulted in a severe dilatative cardiomyopathy. The selective deletion in the sinoatrial node led to sinus bradycardia with impaired heart rate modulation and low basal Ca^{2+} -levels in pacemaking cells.

HCN-channels in neurons

Project managers: S. Herrmann, A. Ludwig

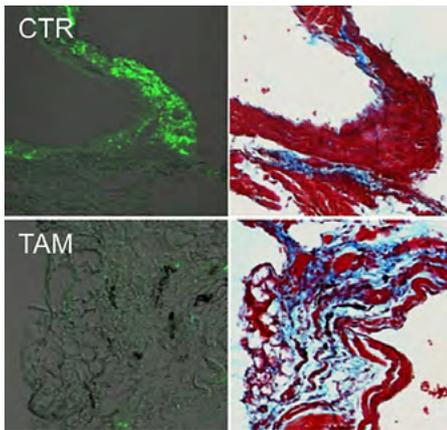
The detection and propagation of painful stimuli in the dorsal root ganglion involves several ion channels. We studied the potential role of HCN channels in this process by the generation and analysis of nociceptor-specific *HCN1*- and *HCN2* deletion mutants. These animals exhibit reduced pain responses in models of neuropathic and inflammatory pain. Single-fibre analysis in collaboration with the group of Prof. Reeh, Physiology, point in the same direction. The results suggest that HCN channels play an important role in the generation of pain signals in nociceptors.

The role of *HCN4* in thalamic regions is examined in a collaboration with the University of Münster by analysing a brain-specific *HCN4* deletion mutant.

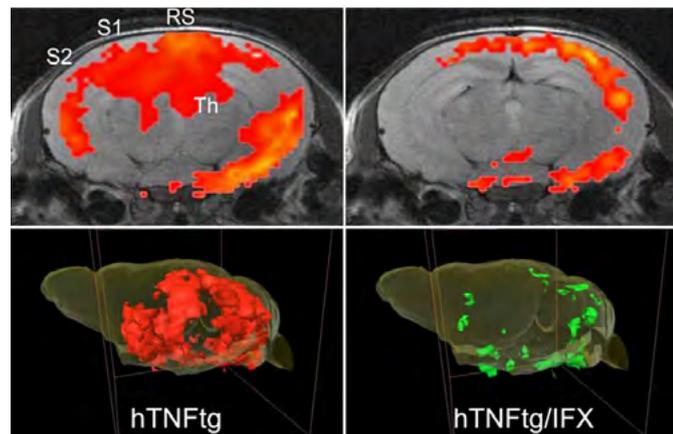
Pharmacological imaging and image analysis

Project manager: A. Hess

The group uses non-invasive magnetic resonance tomography (fMRT) to study plastic nociceptive processes in the central nervous system of rodents and humans. The successful application of this technique to transgenic mice allowed for the first time the combination of modern genetic techniques with functional imaging. This achievement results in a unique position of the group documented by high-ranking publications. Together with the group of J. Penninger from the Institute of Molecular Biotechnology in Vienna it could be shown that an isoform of an accessory calcium channel subunit ($\alpha 2\delta 3$) contributes to the processing of nociceptive signals in the thalamus (Cell 2010). Another collaboration with the group of G. Schett, Medical Clinic 3 analyzed transgenic mice which overexpress human TNF α resulting in severe arthritis. It could be shown that treatment with the antibody infliximab alters the processing of pain signals in the central nervous system of the animals and thereby reduces painful conditions. In addition, similar effects were observed in the brain of patients with arthritis by using functional MRT imaging (PNAS 2011). The ability to perform non-invasive imaging in laboratory animals under minimal stress together with the development of image analysis techniques allowed acquisition of several research grants (DFG FG 661, DFG KFO 130, BMBF 3R, Baxter). Several different cooperations resulted in a variety of publications. In ad-



Sick sinus-mouse model: After induction with tamoxifen (TAM) sinoatrial node cells are completely eliminated



Infliximab (IFX) reduces the enhanced neuronal activity in the brain of TNF-transgenic mice (hTNFtg)

dition, the core-unit “Small animal imaging” of the IZKF was finished with several publications.

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, terminology and several seminars and laboratory internships.

Selected Publications

Heindl-Erdmann C, Axmann R, Kreitz S, Zwerina J, Penninger J, Schett G, Brune K, Hess A (2010) Combining functional magnetic resonance imaging with mouse genomics: new options in pain research. *Neuroreport*, 21: 29-33

Hofmann F, Ludwig A, Herrmann S (2010) The proarrhythmogenic role of I-f in cardiac hypertrophy. *Naunyn Schmiedebergs Arch Pharmacol*, 381: 49-49

Neely GG, Hess A, Costigan M, Keene AC, Goulas S, Langeslag M, Griffin RS, Belfer I, Dai F, Smith SB, Diatchenko L, Gupta V, Xia CP, Amann S, Kreitz S, Heindl-Erdmann C, Wolz S, Ly CV, Arora S, Sarangi R, Dan D, Novatchkova M, Rosenzweig M, Gibson DG, Truong D, Schramek D, Zoranic T, Cronin SJ, Angjeli B, Brune K, Dietzl G, Maixner W, Meixner A, Thomas W, Pospisilik JA, Alenius M, Kress M, Subramaniam S, Garrity PA, Bellen HJ, Woolf CJ, Penninger JM (2010) A genome-wide *Drosophila* screen for heat nociception identifies alpha2delta3 as an evolutionarily conserved pain gene. *Cell*, 143: 628-38

Stieber J, Ludwig A (2010) Complete deletion of I-f in the sinoatrial/AV-node results in lethal bradyarrhythmia in mice. *Naunyn Schmiedebergs Arch Pharmacol*, 381: 51-51

Herrmann S, Fabritz L, Layh B, Kirchhof P, Ludwig A (2011) Insights into sick sinus syndrome from an inducible mouse model. *Cardiovasc Res*, 90: 38-48

Hess A, Axmann R, Rech J, Finzel S, Heindl C, Kreitz S, Sergeeva M, Saake M, Garcia M, Kollias G, Straub RH, Sporns O, Doerfler A, Brune K, Schett G (2011) Blockade of TNF-alpha rapidly inhibits pain responses in the central nervous system. *Proc Natl Acad Sci U S A*, 108: 3731-6

International Cooperation

Dr. H. Wakimoto, Department of Genetics, Harvard Medical School, Boston, MA, USA

Prof. X. Wehrens, Molecular Physiology, Baylor College of Medicine, Houston, TX, USA

Prof. C. Zuker, Columbia University, New York, NY, USA

Prof. H. Sakano, Department of Biophysics and Biochemistry, University of Tokyo, Tokyo, Japan

Prof. R. Shigemoto, National Institute for Physiological Sciences, Okazaki, Japan

Prof. L. Cervetto, Dipartimento di Scienze Fisiologiche, University of Pisa, Pisa, Italy

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

Dr. M. Lei, School of Medicine, University of Manchester, Manchester, UK

Dr. M. Mangoni, Institut de Genomique Fonctionnelle, Université de Montpellier I et II, Montpellier, France

Research Equipment

Bruker 4,7 Tesla Small Animal MRT

Zeiss Confocal Laser Scanning Microscope LSM 5