

Institute of Experimental and Clinical Pharmacology and Toxicology

Chair of Pharmacology and Toxicology

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Research focus

- Signal transduction of cardiac rhythmogenesis and hypertrophy
- HCN channels in the nervous system
- Renal function and sepsis
- Pharmacological fMRI imaging

Structure of the Chair

Professorships: 2

Personnel: 24

- Scientists: 9 (thereof funded externally: 3)
- Graduate students: 5

Special structural feature

The position of the executive director of the Institute rotates between the Chair of Pharmacology and Toxicology and the Chair of Clinical Pharmacology and Clinical Toxicology on a two-year basis.

Research

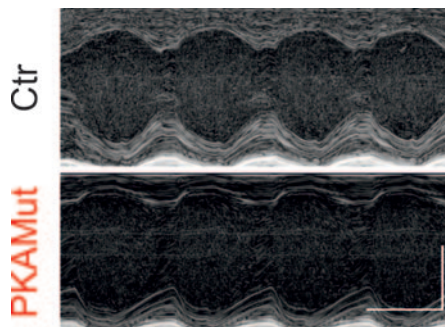
Various aspects of the cardiovascular system as well as of the central and peripheral nervous system in mammals are studied. Research foci are the mechanisms underlying the generation of the cardiac rhythm and signal transduction mechanisms in cardiac hypertrophy. Another research area is the pathogenesis of acute kidney injury under septic conditions. The role of HCN channels in the nervous system and in particular in nociception and in the thalamus is analyzed. Finally, brain function under various conditions (drugs, behavioral paradigms, diseases) is studied by non-invasive brain imaging using functional magnetic resonance imaging (fMRI).

Signal transduction of cardiac rhythmogenesis and hypertrophy

PI: PD Dr. J. Stieber, PD Dr. S. Herrmann, Prof. Dr. A. Ludwig

We found that ventricular RyR2 and CaV1.2-calcium channel mouse mutants develop a cardiac phenotype closely resembling human dilative

cardiomyopathy. Pathophysiological mechanism and new treatment strategies for this disease are studied in both mouse models. In another project, the role of protein kinase A (PKA) for cardiac function was examined by using a cardiac-specific inducible PKA-mutant. Mutant animals developed ventricular dysfunction, upregulation of cardiac stress markers and delayed sarcomere shortening and calcium-decay kinetics most likely due to an impaired phosphorylation of contractile proteins and phospholamban. We could show that under pathological conditions PKA activity plays a pivotal role in the beta1 adrenergic-signaling pathway and the cardiotoxic effects after its chronic activation. Furthermore, PKA activity is important for maintaining cardiac function under chronic pressure overload.



Echocardiograms depicting the left ventricular function of control (top) and PKA-mutant (bottom) animals. PKA mutants display a reduced ejection fraction and increased left ventricular volumes.

HCN channels in the nervous system

PI: PD Dr. S. Herrmann, Prof. Dr. A. Ludwig
Downstream targets of the cAMP-dependent signaling pathway in nociception are not well understood. We disabled the function of either HCN2 or PKA selectively in a subset of peripheral nociceptive neurons. A near-complete lack of sensitization was observed in both mutant strains during cAMP-dependent inflammation. The lack of HCN2 as well as the inhibition of PKA eliminated the cAMP-mediated increase of calcium transients in isolated dorsal root ganglion neurons. Facilitation of the Ih current via cAMP was abolished in neurons without PKA activity. These results show a significant contribution of HCN2 and PKA to inflammatory pain and suggest that PKA-dependent activation of HCN2 underlies cAMP-triggered neuronal sensitization. In collaboration with Prof. Dr. T. Budde (Westfälische Wilhelms-Universität Münster), the role of HCN4 ion channels in the thalamus was analyzed. We could show that HCN4 channels in different thalamic projection neurons are important for the production of rhythmic intrathalamic oscillations. In addition, thalamic HCN4 channels determine the regular thalamocortical oscillatory activity during alert states.

Renal function and sepsis

PI: Prof. Dr. K. Höcherl

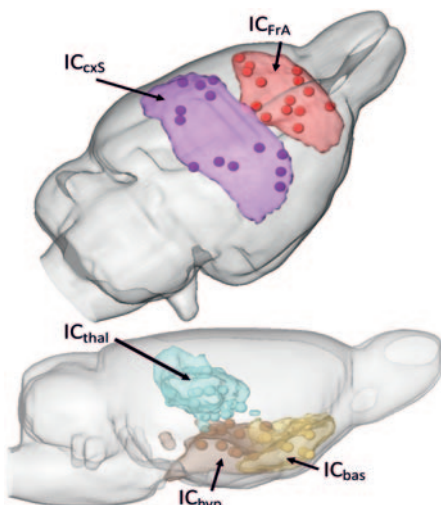
Decreased renal perfusion due to renal vasoconstriction seems to be a central factor in the pathogenesis of septic acute kidney injury. An increased production of vasodilator prostaglandins including prostaglandin E2 (PGE2) and prostacyclin (PGI2) may play an important role in maintaining renal function. By using an animal model of endotoxemia, we showed that the expression of EP2-, EP4-, and IP-receptors, which mediate the PGE2 and PGI2-induced vasodilation, was increased. In contrast, expression of EP1- and EP3-receptors, which transmit the vasoconstrictive effect of PGE2, was reduced. By using the isolated-perfused kidney model we found that the vasodilator effect of the above prostaglandins was much stronger in kidneys from lipopolysaccharide-treated animals as compared to controls. These results demonstrate an increased vasodilating effect of PGE2 and PGI2 during endotoxemia suggesting that these prostaglandins contribute to the maintenance of kidney function under endotoxemic conditions. Recently, the fibroblast growth factor-23 (FGF23) has been identified as an important regulator of calcium and phosphate homeostasis and the metabolism of vitamin D. FGF23 binds to the FGF-receptor-klotho-complex. Abnormal regulation of the FGF23-klotho-vitamin D signal transduction pathway and an altered expression of renal calcium and phosphate transporters may underlie the frequently observed hypocalcemia and changes in phosphate and vitamin D homeostasis during septic conditions. We showed that lipopolysaccharide induces hypocalcemia and hyperphosphatemia in an *in vivo* model. The plasma concentrations of FGF23, parathyroid hormone, and vitamin D3 were increased, whereas renal expression of klotho was reduced. In addition, we detected a change in the expression of various calcium and phosphate transporters. The renal expression of TRPV5, TRPV6, and Pit1 was stronger and the expression of calbindin-D28K, NCX1, NaPi-2a, und NaPi-2c was lower as compared to controls. Our results demonstrate that during endotoxemia a dysregulation in the FGF23-Klotho-vitamin D axis and alterations in various renal phosphate and calcium transporters take place.

Pharmacological fMRI imaging

PI: Prof. Dr. A. Hess

This working group uses non-invasive functional magnetic resonance imaging (fMRI) to investigate dynamic-plastic processes in the central nervous system of rodents and humans. In the last two years, the group worked among other studies on two BMBF joint research projects (NeuroImpa and NeuroRad). In the NeuroImpa project, plastic brain processes were examined in var-

ious arthritis models (Prof. H.-G. Schaible and Prof. T. Kamradt, Universitätsklinikum Jena) as well as in bone healing (Prof. Dr. S. Grässel, Universität Regensburg). In the NeuroRad project, effects of different dosages of gamma-radiation on brain function of embryonic and postnatal mice were investigated in collaboration with Prof. Dr. M. Löbrich (TU Darmstadt) by using behavioral tests and fMRI. Further dynamic brain processes were investigated in rodent studies dealing with learning behavior (together with Prof. Dr. J. Braun, Otto-von-Guericke-Universität Magdeburg), depression (cooperation with Prof. D. Polak, Medizinische Universität Wien) and anxiety-associated brain structures (cooperation with Dr. W. Haubensak, Research Institute of Molecular Pathology, Vienna). In all these projects, the graph-theoretical network analyses that we have established over several years proved to be a very potent method for selectively analyzing dynamic processes in the brain. These techniques, which had been developed in preclinical studies, were also successfully applied to the analysis of fMRI data from patients. In cooperation with the departments of Medicine 1 and 3, Department of Neurology, and the Division of Neuroradiology), we used our methods for therapy validation in various diseases (Crohn's disease, rheumatoid arthritis, epilepsy). As part of the PreCePra study at the Department of Medicine 3, which examines an fMRT-based prediction of the therapeutic response to a TNF alpha-inhibitor in rheumatoid arthritis, we could include additional patient data from the participating international centers. Therefore, we soon will have reached the number of patients envisaged for the full analysis.



The picture shows the excellent overlap of the standard ICA components (big coloured areas) of the resting state activity in the rat brain with the much finer resolved structural analysis from our newly developed graph-theoretical methods (coloured balls). The surface of the rat brain is depicted in translucent grey.

Teaching

In addition to the teaching duties in the degree programs Medicine and Molecular Medicine, 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 as well as seminars and laboratory internships.

Bachelor's and Master's theses as well as MD and PhD theses are supervised.

Selected publications

Herrmann S, Rajab H, Christ I, Schirdewahn C, Höfler D, Fischer MJM, Bruno A, Fenske S, Gruner C, Kramer F, Wachsmann T, Wahl-Schott C, Stieber J, Biel M, Ludwig A. Protein kinase A regulates inflammatory pain sensitization by modulating HCN2 channel activity in nociceptive sensory neurons. *Pain* 2017, 158:2012-2024

Aziz Q, Finlay M, Montaigne D, Ojake L, Li Y, Anderson N, Ludwig A, Tinker A. ATP-sensitive potassium channels in the sinoatrial node contribute to heart rate control and adaptation to hypoxia. *J Biol Chem*. 2018, 293: 8921

Griessner J, Pasięka M, Böhm V, Grössl F, Kaczanowska J, Pliota P, Kargl D, Werner B, Kaouane N, Strobel S, Kreitz S, Hess A, Haubensak W. Central amygdala circuit dynamics underlying the benzodiazepine anxiolytic effect. *Mol Psychiatry*. 2018 Nov 30

Kreitz S, de Celis Alonso B, Uder M, Hess A. A new analysis of resting state connectivity and graph theory reveals distinctive short-term modulations due to whisker stimulation in rats. *Front Neurosci* 2018, 12: 334

Mendez-Torrijos A, Kreitz S, Ivan C, Konecny L, Rösch J, Pischetsrieder M, Moll G, Kratz O, Dörfler A, Horndasch S, Hess A. Snack food as a modulator of human resting-state functional connectivity. *CNS Spectr*. 2018 Oct;23(5):321-332

Meurer M, Ebert K, Schweda F, Höcherl K. The renal vasodilatory effect of prostaglandins is ameliorated in isolated-perfused kidneys of endotoxemic mice. *Pflugers Arch*. 2018, 470: 1691

International cooperations

Prof. D. Chetkovich, Northwestern University, Chicago: USA

Prof. C. Reid, Florey Institute of Neuroscience and Mental Health, Melbourne: Australia

Prof. A. Landstrom, Duke University, Durham: USA

Dr. W. Haubensak, Research Institute of Molecular Pathology, Vienna: Austria

Prof. I. Vetter, The University of Queensland, Brisbane: Australia