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
- Regulation of renal function
- Pharmacological fMRI imaging

Structure of the Chair

Professorships: 2
Personnel: 23
- Scientists: 9
- 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

The chair of pharmacology and toxicology studies physiological and pathophysiological mechanisms in the cardiovascular system as well as in the central and peripheral nervous system of mammals. Research foci are the mechanisms underlying the generation and modulation of the cardiac rhythm and the signal transduction in cardiac hypertrophy. In addition, mechanisms of acute renal failure and other aspects of renal function were analyzed. The role of HCN channels in the nervous system and in particular in nociception and in epilepsy is studied. 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, Dr. S. Jamra, Prof. Dr. A. Ludwig
Mice expressing HCN4-channels with a mutant, cAMP-resistant cyclonucleotide-binding domain were characterized. These animals showed a loss of the circadian modulation of the heart rate and an increased arrhythmia propensity. The results suggest that basal cAMP stabilizes the cardiac rhythm by direct binding to HCN4. The role of protein kinase A (PKA) for cardiac function was examined by using a cardiac-specific and inducible mouse mutant of a specific PKA isoform. Mutant animals developed ventricular dysfunction and delayed sarcomere shortening and calcium-decay kinetics. At least part of this phenotype is due to an impaired phosphorylation of contractile proteins and phospholamban. In models of cardiac hypertrophy and failure, we found that the function of this PKA is critical for mediating long-term detrimental adrenergic signal transduction mechanisms. Another important target protein may represent the L-type calcium channel. Therefore, measurements of the L-type calcium current in ventricular myocytes were performed.

HCN channels in the nervous system
PI: PD Dr. J. Stieber, Prof. Dr. A. Ludwig

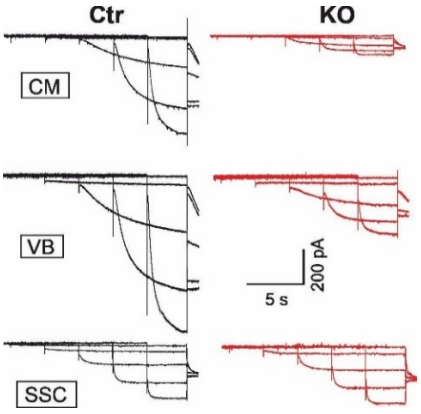

Fig. 1: Ih current in various regions in brain-specific HCN4-deficient mice. The current is strongly reduced in the thalamic centromedial (CM) and ventrobasal (VB) nucleus of knockout animals as compared to controls. In contrast, Ih is unchanged in the somatosensory cortex (SSC) (Zobeiri et al., 2019).

We could show that HCN channels play an important role for pain processing in nociceptive dorsal root ganglion cells. The results indicated that a PKA-mediated activation of HCN2 channels is responsible for the cAMP-dependent sensitization of nociceptors. To directly examine this mechanism, various phosphorylation-deficient HCN2 channels were generated and characterized electrophysiologically. A channel lacking a particular phosphorylation site showed indeed a reduced response to cAMP. Several results regarding the relationship between HCN channels and epilepsy were published. In a cooperation with Prof. M. Biel (LMU München) it was found that the deletion of HCN2 in the ventrobasal complex of the thalamus induced generalized absence epilepsy. Together with Prof. Dr. T. Budde (Westfälische Wilhelms-Universität Münster), we could define the function of HCN4 in the brain. Lack of HCN4 in the thalamus did not result in the occurrence of absence seizures. We determined the specific contribution of HCN4 to the Ih-current in various brain regions and demonstrated, that this isoform is essential for the generation of rhythmic intrathalamic activity. In a collaboration with Prof. C. Reid (University of Melbourne), it was shown that HCN4 constitutes a potential pharmacologically relevant target for anti-seizure drugs.

Renal function and sepsis
PI: Prof. Dr. K. Höcherl
The expression of protease-activated receptors (PARs) has been described in different renal cell types, but the significance of these receptors for renal function is not known yet. We could demonstrate that PAR2-receptors control the secretion of renin in the context of inflammation. However, PAR2 receptors are not involved in the typical physiological regulations of renin secretion and renin gene expression. In addition, pathomechanisms underlying the tubular dysfunction in acute renal failure were examined. In a mouse model of endotoxemia, we studied the metabolism of Mg^{2+}. The results suggest that the observed hypermagnesemia is due to an LPS-induced decrease in renal function. In a renal ischemia/reperfusion model, alterations in the expression of various renal Ca^{2+}-, Mg^{2+}-, and phosphate-transporters in connection with increased fibroblast growth factor FGF23 were characterized.

Pharmacological fMRI imaging
PI: Prof. Dr. A. Hess
Dynamic plastic processes in the central nervous system of laboratory animals (rodents) and humans are analyzed. Brain function is studied primarily by using non-invasive functional magnetic resonance imaging (fMRI). It has been shown repeatedly by our group that fMRI represents an ideal technique for translating experimental findings from laboratory animal to humans and patients. We are working mainly on two neurobiological research areas. Neurotrition, the interaction of food and brain function, was analyzed together with the groups of Prof. M. Pischetsrieder (Food Chemistry, FAU) and Prof. C. Müller (Psychiatry). We could demonstrate that snack food (potato chips) significantly increased the food intake of rats and mice. Together with the Child Psychiatry unit functional brain imaging data from certolizumab in rheumatoid arthritis) was successfully completed. In collaboration with the department of Medicine 1, various patients could be highly specifically differentiated from probands by using newly developed analytical methods which are based on "machine-learning" algorithms and multimodal MRI. This differentiation was most successful when functional markers were used in the brain image analyses. In contrast, a brain signature specific for the fatigue-syndrome of Crohn's disease was observed primarily in anatomical characteristics. All clinical MRI projects were performed in close cooperation with the Division of Neuroradiology. Several additional projects in the pain research field were performed anorectic patients during food intake are collected and analyzed, these results are currently published. In the pain research field, the phase 3-study PreCePra (prediction of treatment success of the TNF-alpha antagonist with various external

partners including analysis of cerebral pain processing in arthritis models (Prof H.-G. Schaible, Universitätsklinikum Jena), bone healing (Prof. S. Grässel, Universität Regensburg) and incision pain (Prof. E. Pogatzki-Zahn and Prof. C. Faber, Universität Münster). Proteom-based analyses were performed together with Prof. M. Schmidt, University of Vienna. In the research field of function MRI, we published in cooperation with Prof. J. Grandjean (Radboud University, Nijmegen) an international multicenter study about the identification of resting-state networks in the mouse brain.

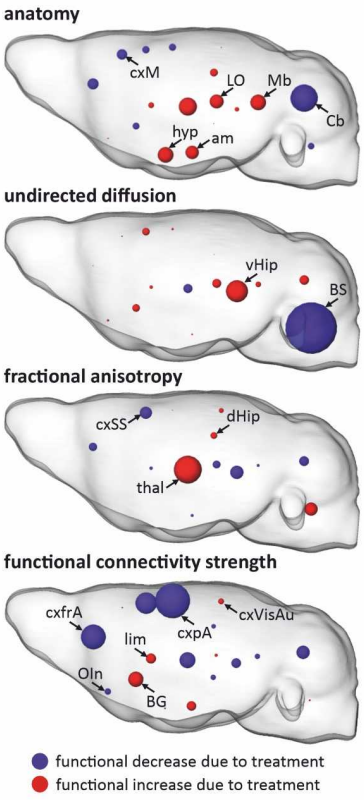

Fig. 2: Depiction of functional brain areas behaving differently in offspring from dams with maternal immune activation as compared to control mice. Shown are significantly changed areas, increases and decreases of relative changes in MRI modalities are indicated by red and blue circles, respectively. Relevant brain regions including brain stem (BS), thalamus (thal), frontal association cortex (cxfrA), etc. are labelled accordingly (Kreitz et al., 2020).

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

Zobeiri M, Chaudhary R, Blaich A, Rottmann M, Herrmann S, Meuth P, Bista P, Kanyshkova T, Lüttjohann A, Narayanan V, Hundehege P, Meuth SG, Romanelli MN, Urbano FJ, Pape HC, Budde T, Ludwig A. The Hyperpolarization-Activated HCN4 Channel is Important for Proper Maintenance of Oscillatory Activity in the Thalamocortical System. Cereb Cortex. 2019, 29:2291-2304.

Kharouf Q, Phillips AM, Bleakley LE, Morrisroe E, Oyrer J, Jia L, Ludwig A, Jin L, Nicolazzo JA, Cerbai E, Romanelli MN, Petrou S, Reid CA. The hyperpolarization-activated cyclic nucleotide-gated 4 channel as a potential anti-seizure drug target. Br J Pharmacol. 2020, 177:3712-3729.

Meurer M, Höcherl K. Endotoxaemia differentially regulates the expression of renal Ca2+ transport proteins in mice. Acta Physiol (Oxf). 2019, 225(1):e13175.

Kreitz S, Zambon A, Ronovsky M, Budinsky L, Helbich TH, Sideromenos S, Ivan C, Konerth L, Wank I, Berger A, Pollak A, Hess A, Pollak DD. Maternal immune activation during pregnancy impacts on brain structure and function in the adult offspring. Brain Behav Immun. 2020, 83:56-67.

Grandjean J, Canella C, Anckaerts C, Ayrancı G, Bougacha S, Bienert T, Buehlmann D, Coletta L, Gallino D, Gass N, Garin CM, Nadkarni NA, Hübner NS, Karatas M, Komaki Y, Kreitz S, Mandino F, Mechling AE, Sato C, Sauer K, Shah D, Strobelt S, Takata N, Wank I, Wu T, Yahata N, Yeow LY, Yee Y, Aoki I, Chakravarty MM, Chang WT, Dhenain M, von Elverfeldt D, Harsan LA, Hess A, Jiang T, Keliris GA, Lerch JP, Meyer-Lindenberg A, Okano H, Rudin M, Sartorius A, Van der Linden A, Verhoye M, Weber-Fahr W, Wenderoth N, Zerbi V, Gozzi A. Common functional networks in the mouse brain revealed by multi-centre resting-state fMRI analysis. Neuroimage. 2020, 205:116278.

Hess A, Kress S, Rakete S, Muench G, Kornhuber J, Pischetsrieder M, Müller CP. Influence of the fat/carbohydrate component of snack food on energy intake pattern and reinforcing properties in rodents. Behav Brain Res. 2019, 364:328.

International cooperations

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

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

Prof. A.Tinker, Queen Mary University, London:UK

Prof. M. Schmidt, Pharmacology and Toxicology, University of VIenna: Austria

Prof. J. Grandjean, Radboud University, Nijmegen: The Netherland