Institute of Physiology and Pathophysiology

Chair of Physiology

Address
Universitätsstraße 17
91054 Erlangen
Phone: +49 9131 8522295
Fax: +49 9131 8522497
www.physiologie1.fau.de

Director
Prof. Dr. med. Christian Alzheimer

Contact
Prof. Dr. med. Christian Alzheimer
Phone: +49 9131 8522400
Fax: +49 9131 8522497
Christian.Alzheimer@fau.de

Research focus

- Neurophysiologic substrates of higher brain functions
- Systems neurophysiology
- Transduction, integration and plasticity in primary nociceptive neurons
- Trigeminal nociception and headache generation
- Functional imaging of brain activity by fMRI

Structure of the Institute

Professorships: 3
Personnel: 40

- Scientists: 16 (thereof funded externally: 8)
- Doctoral students: 9

Special structural features
The Institute houses experimental set-ups of the Departments of Anesthesiology, Medicine 1 and 4, and Psychiatry, each with close methodical and thematic ties to the research groups of the Institute.

Research

The overarching research objective at our Institute is to understand the bioelectrical and neurochemical processes that constitute the basic language of the nervous systems and enable communication between nerve cells.
What factors elicit an electric impulse in a neuron, if, for instance, pain or temperature stimuli influence the body?
What mechanisms mediate signal transmission between nerve cells and how is information processed in neuronal networks? How do different brain regions communicate with each other? Answers to questions like these will also help to elucidate the underpinnings of cognition, emotion and action and of disorders thereof. We explore such issues with a broad spectrum of methods, ranging from modern electrophysiological, optical, cell and molecular biological techniques to fMRI in healthy volunteers and patients.

Neurophysiologic substrates of higher brain functions
PI: Prof. Dr. C. Alzheimer, Dr. F. Zheng, PD Dr. Dr. T. Huth
Our research focuses on the electric behavior of neurons and neuronal networks under normal and pathological conditions. Using high-resolution neurophysiological and optical techniques, we investigate functions and regulation of ion channels and synapses. Our aim is to understand fundamental neural processes that are essential for cognitive functions as well as for affective behavior and whose dysfunctions might give rise to neuropsychiatric disorders. In particular, we are studying the following topics:
1) Role of activin, a member of the Transforming Growth Factor-ß family, as a ”master molecule” tuning glutamatergic and GABAergic neurotransmission, and its impact on cognition, emotions, and neuroprotection
2) Interaction between BACE1, a crucial enzyme in the amyloid cascade of Alzheimer’s disease, and properties and expression of Na^+ and K^+ channels
3) Neuropsychiatric disease models and mechanisms of drug action (in collaboration with the Department of Psychiatry and Psychotherapy).

Systems Neurophysiology
PI: Prof. Dr. A. Ponomarenko
The motivation for our research is to uncover real-time interactions between neuronal ensembles in the brain supporting experience-dependent and innate behaviours. During these behaviours cortical and subcortical regions display various regimes of networks synchronization, which temporally coordinate neuronal ensembles and is often affected in neuropsychiatric disorders. Combining electrophysiological recording and optogenetic manipulations of neuronal activity in behaving rodents, mouse genetics and mathematical modeling, we study network oscillations and neural coding in brain regions involved in memory, navigation and adaptive behaviour. We further investigate the signaling between cortical and subcortical circuits supporting innate behaviors such as feeding, social interaction and sleep. A recent work focused on the functions of the relevant for obsessive-compulsive disorder coupling of fast and slow oscillations in the prefrontal - subthalamic pathway. Another project addressed the role of signaling between prefrontal cortical interneurons and astrocytes in oscillations, ensemble coding and decision-making.

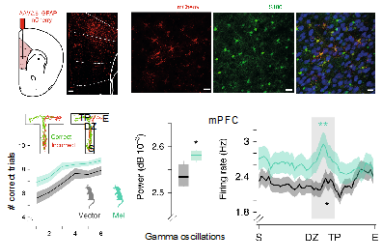

Fig.1: Optogenetic activation of medial prefrontal (mPFC) astrocytes by melanopsin (Mel) improves spatial working memory, facilitates gamma oscillations and increases firing rate of putative excitatory cortical neurons. S100 - astrocytic marker, S – start, DZ – decision zone, TP – turning point, E – end. Modified from Mederos et al., Nat. Neurosci., 2020

Transduction, integration, plasticity in primary nociceptive neurons
PI: Prof. Dr. S. Sauer, Prof. Dr. P.W. Reeh
The research focuses on primary nociceptive neurons, their electrophysiological and neurochemical responses to noxious and pruritogenic stimuli and chemical mediators. Isolated preparations and cultured dorsal root ganglion cells as well as transfected cell lines are used to study action potential discharge, ionic currents, calcium transients, and release of the neuropeptides substance P and calcitonin gene-related peptide. Aim is to elucidate nociceptive transduction and integration of stimuli as well as possible pharmacological interventions. Specific topics are sensitization by tissue acidosis, inflammatory mediators, metabolites as well as their intracellular signal transduction. Transgenic mouse strains lacking different metabotropic and ionotropic receptors or thermally activated ion channels (i.a. TRPV1, TRPA1) are studied. Voltage-controlled ion channels (NaV, Kv7.2, HCN, CaV3.2) came in focus because only few subtypes decide on excitability, i.e. on generation, frequency, and propagation of action potentials to the central nervous system. The group studies mechanisms of painful diabetic neuropathy. One project focus on reactive dicarbonyls, that cause glycation of TRPA1 receptors, the other investigates consequences of calcium channel (Cav3.2) glycosylation. Both processes increase excitability of nociceptors and could by that contribute to pain sensations of diabetes patients

Trigeminal nociception and headache generation
PI: Prof. Dr. K. Messlinger
Our group is working on nociceptive mechanisms in the cranial dura mater, the trigeminal ganglion, and the spinal trigeminal nucleus as the neurobiological basis for the generation of headaches. Extracellular recordings from single afferent fibers in the isolated rodent dura mater are performed to study the sensitivity and response of meningeal afferents and the role for receptors and ion channels that are probably involved in the generation of headaches in humans. In a similar preparation, we examine by which mechanisms the neuropeptide CGRP is released from the cranial dura mater as an indicator for trigeminovascular activation. Using immunohistochemical and molecular biological methods, we aim at detecting the intracellular signal pathways that are induced by these substances. To study the central processes of headache generation, we examine the response properties of neurons in the spinal trigeminal nucleus, record the peripheral and central blood flow, and assess the effects of potential headache therapeutics.

Functional imaging of brain activity by fMRI
PI: Prof. Dr. C. Forster
Functional magnetic resonance imaging (fMRI) is a well-established method to image the activity of the human brain during the processing of various stimuli and tasks. The method is used to identify brain regions involved in the central processing of pain and itch. By variation of the experimental paradigms, the function of various brain regions

and their contribution in the perception of the corresponding stimulus should be determined. Common projects with the Department of Medicine 1 analyze the central changes induced by chronic itch in patients suffering from cholestatic pruritus.

Teaching

In addition to its contribution to the preclinical curricula of students of Medicine, Dentistry, and Molecular Medicine, the Institute gives lectures, seminars, and practical courses in physiology for students of the Faculties of Engineering and of Sciences, in particular courses for the degree programs Medical Technology and Pharmacy. The Institute supervises Bachelor and Master theses as well as MD and PhD theses.

Selected publications

Becker AK, Auditore A, Pischetsrieder M, Messlinger K, Fleming T, Reeh PW, Sauer SK. Reactive dicarbonyl compounds cause Calcitonin Gene-related Peptide release and synergize with inflammatory conditions in mouse skin and peritoneum. J Biol Chem 295:6330-6343, 2020.

Dierich M, Hartmann S, Dietrich N, Moeser P, Brede F, Johnson Chacko L, Tziridis K, Schilling A, Krauss P, Hessler S, Karch S, Schrott-Fischer A, Blumer M, Birchmeier C, Oliver D, Moser T, Schulze H, Alzheimer C, Leitner M, Huth T. β-secretase BACE1 is required for normal cochlear function. J Neurosci 39: 9013-9027, 2019.

Dux M, Babes A, Manchen J, Sertel-Nakajima J, Vogler B, Schramm J, Messlinger K. Eur J Pain. 24:383-397, 2020.

Heikenfeld C, Mederos S, Chen C, Korotkova T, Schnitzler A, Ponomarenko A. Prefrontal - subthalamic pathway supports action selection in a spatial working memory task. Sci Rep 10: 10497, 2020. DOI: 10.1038/s41598-020-67185-1

Kasagarod VB, Pacios-Michelena A, Schaefer N, Zheng F, Bader N, Alzheimer C, Villmann C, Schindelin H. Pyridoxal kinase inhibition by artemisinins downregulates inhibitory neurotransmission. Proc Natl Acad Sci USA 117: 33235-33245, 2020.

Mederos S, Sánchez-Puelles C, Esparza J, Valero M, Ponomarenko A, Perea G. GABAergic signaling to astrocytes in the prefrontal cortex sustains goal-directed behaviors. Nature Neurosci, 2020, doi: 10.1038/s41593-020-00752-x.

International cooperations

Prof. S. Werner, Institute of Molecular Health Sciences, ETH Zürich: Schweiz,

Prof. S. Todorovic, U of Colorado School of Medicine, Aurora, CO: USA,

Prof. A. Babes, University of Bukarest, Bukarest: Rumänien,

Dr. M. Dux, Institute of Physiology, University of Szeged: Ungarn,

Prof. E. Jorum, Department for Neurophysiology, Rikshospitalet, University of Oslo, Oslo: Norwegen,

Dr. G. Perea, Instituto Cajal, Madrid: Spanien,

Prof. A.V. Tzingounis, University of Connecticut, Storrs, CT: USA