AG Name Stein/Machelska

AG Anesthesiology – Pain Research

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Homepage:
http://anaesthesie.charite.de/en/research/pain/

Forschungsgebiet:

Pain and inflammation are almost always associated with each other. Indeed, inflammation accompanies the majority of acute and chronic pain conditions. Examples are postoperative pain, trauma, arthritis, vasculitis, meningitis, invading cancer, visceral pain, and neuropathic pain (resulting from nerve damage). Our group is interested in mechanisms of inflammatory and neuropathic pain and its inhibition by opioids outside the central nervous system (CNS). This can be achieved by activation of opioid receptors on peripheral sensory neurons within injured tissue by exogenous or endogenous opioids. Endogenous opioid peptides (endorphin, enkephalins, dynorphin) are produced by immune cells infiltrating inflamed tissue. Activation of such cells by environmental stressful stimuli or releasing agents (corticotropin-releasing factor, catecholamines, cytokines, chemokines, bacterial components) releases the opioids from immune cells and ameliorates pain.

Projekte:

Macrophages in the regulation of neuropathic pain
In a mouse model of neuropathic pain (chronic ligation of the sciatic nerve), we found that opioid peptide-containing immune cells (CD45+ cells) accumulate at the site of nerve damage. Following stimulation (by corticotropin-releasing factor), immune cells secrete opioids and locally decrease pain. Interestingly, the majority of these cells are macrophages (60-70% of CD45+ cells). In this project we aim to in vitro and in vivo characterize macrophages and examine their contribution to the inhibition of pain.

Modulation of pain and inflammation in chronic arthritis by opioids
Together with a national consortium, the Division of Rheumatology CBF (J. Sieper) and the MDC (M. Lipp), this project aims at modulating pain and inflammation by stimulating the production and secretion, or by inhibiting the extracellular enzymatic degradation of endogenous opioids derived from immune cells. In animal models of inflammation and in patients with inflamed joints we will examine pain, inflammatory parameters, release and extracellular concentrations of opioid peptides, modulated by cytokines, chemokines and peptidase inhibitors. In patients we also compare effects of exogenous and endogenous opioids.
Contribution of opioid peptides and receptors in immune cells to exogenous opioid control of neuropathic pain

In this project we aim at elucidating the contribution of leukocytic opioid peptides and receptors to peripheral opioid analgesia in painful neuropathy. We will examine peripheral endogenous and exogenous opioid analgesia in pharmacologically and genetically immunosuppressed mice with injured sciatic nerves, employing adoptive transfer of leukocytes. The in vivo investigations will be accompanied by in vitro protocols examining the release of opioid peptides by activation of leukocytic opioid receptors. These studies will provide new insights into mechanisms of analgesic actions based on the interplay between endogenous and exogenous opioids acting at their receptors in immune cells.

The nociceptor pain model

Together with a national consortium, this project applies systems-medicine-based mathematical models of signalling switches involved in pain sensitisation, optimises and expands them by reflection on molecular, cellular as well as animal experiments, to finally translate this knowledge and test the predictive potential in humans. We hypothesize that opioids will inhibit cAMP-dependent and other pathways identified by computational simulation. Ultimately we aim at testing novel analgesic compounds in human patients identified as most suitable, aiming at mechanism-based therapy of inflammatory pain.

Computationally aided design of opioids

In collaboration with the Zuse Institute Berlin (M. Weber), this project uses modeling of opioid receptor conformations and docking of ligands to generate hypotheses to be tested in cell lines and animals expressing wild-type and mutated opioid receptors. We examine ligand binding, G-protein coupling, modulation of action potentials, transient receptor potential vanilloid receptor currents and cAMP formation. Ultimately, we test optimally designed synthetic agonists in animal models and patients with inflammatory pain in vivo.

Spezialtechniken:

Animal (rat and mouse) models of inflammatory and neuropathic pain, in vivo pain testing in animals (von Frey-, paw pressure-, Hargreaves-tests), pain assessment in patients (pain scales, patient-controlled analgesia), neuronal and immune cell cultures, electrophysiology (in vitro skin-nerve preparation, patch-clamp), calcium imaging, FRET, in vivo microdialysis, radioimmunoassay, ELISA, radioligand binding, western blot, histological assays (immunohistochemistry, immunofluorescence), DNA/RNA isolation, RT-PCR, transfections, gene and mRNA targeting.

Ausgewählte Publikationen:


Schreiter A, Gore C, Labuz D, Fournie-Zaluski MC, Roques BP, Stein C, Machelska H. Pain inhibition by blocking leukocytic and neuronal opioid peptidases in peripheral inflamed tissue.


**Laufende Drittmittelprojekte:**

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<thead>
<tr>
<th>Granting agency</th>
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<th>Duration</th>
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<tr>
<td>European Society of Anesthesiology</td>
<td>Bypassing Brain: Nanotechnology-enabled delivery of morphine for analgesia without central side effects</td>
<td>2010 – 2014</td>
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<tr>
<td>DFG MA 2437/4-1</td>
<td>Contribution of opioid peptides and receptors in immune cells to exogenous opioid control of neuropathic pain</td>
<td>2010 – 2014</td>
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<tr>
<td>BMBF, VIP0272/03V0364</td>
<td>Nebenwirkungsfreie Analgetika durch Modellierung pathologischer Rezeptorkonformationen (NAMPAR)</td>
<td>2012 – 2015</td>
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<td>Virtuelles Helmholtz Institut Multifunktionale Biomaterialien für die Medizin</td>
<td>Multifunctional Nanosystems for Selective Targeting of Inflammation and Pain</td>
<td>2012 – 2016</td>
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<tr>
<td>EU FP7-HEALTH-2013- INNOVATION-1; No. 602891-2</td>
<td>Neuropathic pain: biomarkers and druggable targets within the endogenous analgesia system (NeuroPain)</td>
<td>2013 – 2018</td>
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