Modellierung von peripheren Schmerzschaltern (MoPS)

Modelling of Pain Switches (MoPS)

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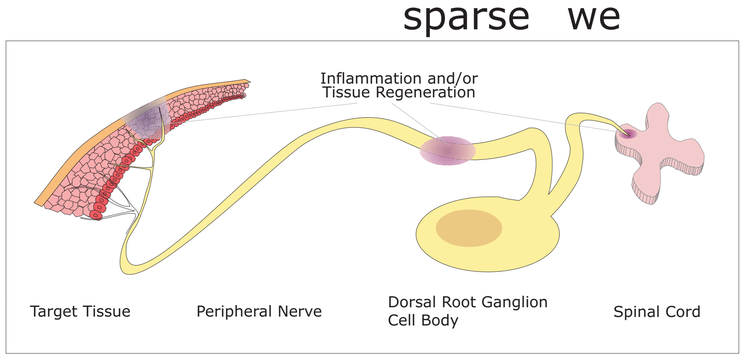
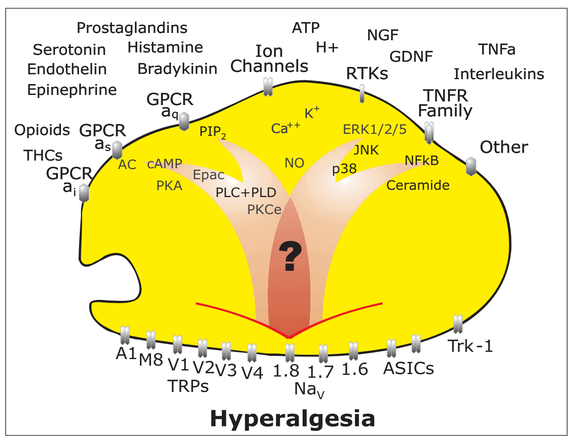
Characterisation of "Pain" Modules

In clinical practice pain is among the most prevalent symptoms. Treatment of 50-70% of chronic pain patients is insufficient. The current approach of therapy guided by the concurrent/symptomatic disease shows highly variable success. Thus, a shift toward a "mechanism-based" therapy is urgently needed.

Progress in elucidation of molecular components involved in sensitization of peripheral neurons activated by painful stimuli is enormous. Nevertheless, the fundamental question, if these components are part of a network converging onto one or few pain, i.e. "nociceptive modules", or if they constitute discrete paralele mechanisms has hardly begun to be addressed

Our project combines mathematical modelling of pre-existing data with novel data collection of a comprehensive number of signalling components to feedback into the mathematical models. Thus, we will be able to identify differential nociceptive modules. These data in turn will allow us to test the derived mathematical models electrophysiologically on primary sensory neurons and in vivo animal models.

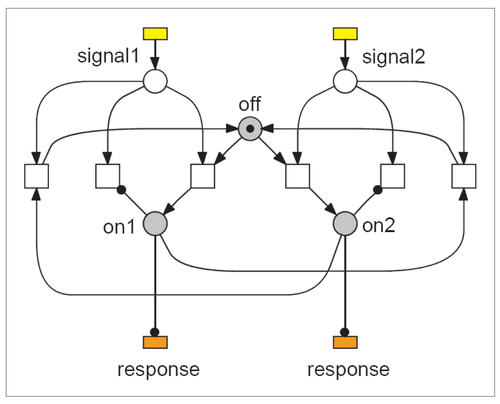


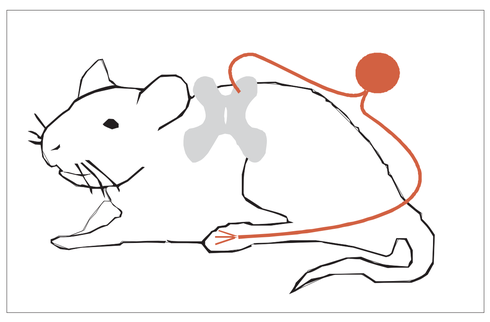


Mathematical Modelling

The consortium includes molecular scientists, cell biologists, electrophysiologists, behavioural scientists, clinicians as well as mathematicians. Accordingly a wide variety of data qualities will have to be combined. The modelling of the data has therefore to be versatile as well as intuitively accessible for all coworkers. Thus, we use the easily visualizable approach of Petri Nets.

Classicle transition nets as well as stochasticle and continous nets will be applied for qualitative and quantitative analysis of the signaling networks. Painful stimuli activated neurons are not homogenous. Instead, multiple subgroups of neurons can be differentiated. Thus, tools will be constructed for subgroup specific data analysis. As the modelling should serve as base for wet lab hypothesis building and experimental design, further tools allowing temporary partial network "knock out" and/or disturbances will be developed.





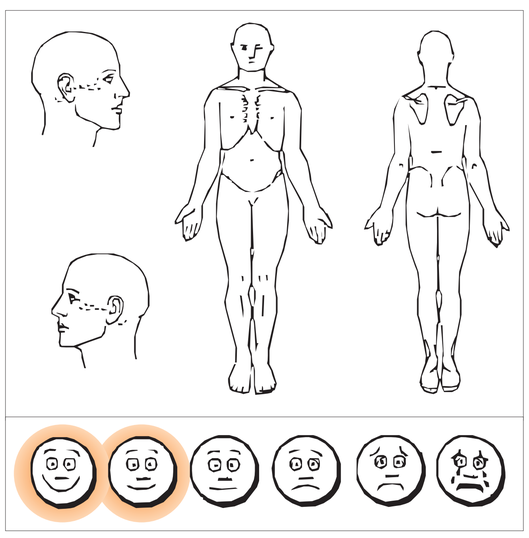
Cellular/Molecular Data Aquisition

Knowledge about intracellular signalling underlying sensitization of painful- stimuli-activated neurons is still only starting to emerge. One aspect, which has hampered progress is the lack of an experimental cell line system. Thus we will investigate signalling events directly in primary sensory neurons. As the starting material is sparse we apply highly efficient current techniques such as BIAcore interaction measurements, FRET/BRET technologies, cell lysate spotting and high content immunofluorescent single cell analysis. Focussing first on enzymes regulated by phosphorylation, their activation, activity kinetics as well as the relationships of various signaling molecules in response to various extracellular stimuli will be characterized.

The signaling network will be nucleated by studying well described signalling components such as cAMP, the MAP-kinases Erk1/2, PKCε, as well as PKA before enlarging the focus onto as many as possible components, known as well as novel to pain signalling. As modules around these components are in part also modelled in other cellular systems, only a minimal number of timepoints and conditions is required for the transfer to sensory neurons. This analysis will give first indications if signaling cascades converge or if they act seperately.

Validation on Animal Models and Humans

Pain modules identified through cellular as well as modelling approaches will be tested in vertebrates. Animal behaviorural studies as well as electrophysiological studies for example on nerve skin preparations will be performed to validate the cellular results. These studies will be then extended to suitable human experimental/clinical conditions. For the latter a powerful quantitative standardized sensory testing tool developed by the BMBF financed "Deutsche Forschungsverbund neuropathischer Schmerz (DFNS)" is available.



Overal Aims

1) Definition of peripheral nociceptive signalling modules

2) Mechanism based differentiation between pain states

3) Guide for mechanism based therapy of current therapeutics

4) Initiation of development of novel therapeutics