K_{Na} and h) which were implemented across a detailed and realistic axon morphology.

Results: The model predicts that the small diameter of the axon can accumulate intracellular sodium when it is repeatedly activated in a similar fashion as during single fiber microneurography. This increase of intracellular sodium concentration can shift the balance between ion channel currents, shift the membrane potential and membrane input resistance, and thereby generate activity-dependent changes of velocity, such as ADS as well as recovery cycle supernormality.

Conclusions: Our results thus provide insight into how activity-dependent excitability changes can be generated in C-fibers. By identifying which ion channels are contributing to activity-dependent changes of velocity this could provide insight into ion channel alterations in neuropathic pain patients.

http://dx.doi.org/10.1016/j.sjpain.2017.04.062

Choice of rat strain in pre-clinical pain-research – Does it make a difference for translation from animal model to human condition?

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Aims: Translating preclinical drug-efficacy of analgesics from animal models to humans has proven challenging with many failures. Reasons are likely multifaceted, but lack of sufficiently rigorous study design, and phenotypical relevant animal models may be part of the explanation. Chronic pain is often associated with substantial comorbid burden, consisting of changes in affective state and cognitive impairment amongst other behavioral disturbances. Accordingly, many preclinical pain research activities have started to include assessment of comorbidity as a possible experimental outcome measure, but surprisingly, little consideration has been paid to the influence of animal-related factors to pain models. To address this essential issue, we have embarked on several comparative experiments in different pain-models, comparing Sprague Dawley's (SD) from two different vendors with different inbred rat strains (Lewis (LEW), Fisher (F344) and Wistar Kyoto (WKY)) selected based on reported stress, depression, inflammatory and pain phenotypes.

Methods: Male rats were characterized in acute (hot-plate), inflammatory (Complete Freund's Adjuvant (CFA)) and neuropathic (Spared Nerve Injury (SNI)) pain models, with dose-response to morphine (0.3–6.0 mg/kg) in hot-plate, CFA-induced hyperalgesia, and a locomotor motility-assay (LMA).

Results: F344 and SD's were sensitive to morphine in hot-plate and CFA (Minimum Effective Dose (MED) = 3.0 mg/kg). WKY rats developed a less robust mechanical hypersensitivity after CFA injection, and were less sensitive to morphine in both pain-tests (MED = 6.0 mg/kg). LEW rats were completely insensitive to morphine in the hot plate, in contrast to reversal of CFA-induced hyperalgesia (MED = 3.0 mg/kg). Additionally, neuropathic sensitivity developed with a later onset and less robustly in this strain after SNI. All strains tested in LMA exhibited sedative effects at 3.0 mg/kg.

Conclusions: Sensory phenotyping in response to acute, inflammatory and neuropathic pain, and sensitivity to morphine in these strains indicates that different pathophysiological mechanisms are engaged after injury. This could have profound implications for translating preclinical drug discovery efforts into pain-patients.

http://dx.doi.org/10.1016/j.sjpain.2017.04.063

Omics as a potential tool to identify biomarkers and to clarify the mechanism of chronic pain development

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Aims: The present study aims to identify the underlying mechanisms in the acute to chronic pain transition. Acute pain is a physiological response to an experience of noxious stimuli that can progress to chronic, becoming a disease. The negative consequences as personal suffering, reduction in physical function, maladaptive behaviours, reduction of productivity, make this condition a central and common problem affecting individuals and the society. After an acute damage, pain in some cases persists, being the process attributed to different causes, in particular persistent tissue and neuronal damages, central neuroplastic changes, psychosocial factors.

Methods: The techniques actually used to investigate acute and chronic pain offer only a partial explanation of the process and in addition, the obtained results are often far away from the possibility to lead some benefits in the clinical practice. Omics technologies could be the right way to detect biomarkers explaining these mechanisms. Our previous study examined epigenetic and pharmacogenetic aspects of acute and chronic pain in a large group of patients. Other omic approaches, such as metabolomics and glycomics, could help to (1) better identify metabolites that can serve as chronic pain development or side effects therapy biomarkers and to (2) better understand new insights involved into the pathophysiological mechanism that drives from acute to chronic pain. SNPs, DNA methylation, miRNA analyses, expression and protein assays on the identified pathway would than clarify the causative molecular mechanisms. In addition, linking these results to clinical evaluation of the central sensitization processes through algometry in nociceptive and neuropathic pain patients may reveal crucial clinical and pharmacological implications.

Conclusions: Our project will be implemented by omic technologies in different chronic pain patient cohorts (acute low back pain vs chronic low back pain patients and chronic postsurgical pain patients) in order to evaluate new possible pathophysiological mechanism with special focus in central sensitization.

http://dx.doi.org/10.1016/j.sjpain.2017.04.064