Genetic variation in *P2RX7* and pain

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Background and aims: P2X7 is a purinoceptor and non-selective cation channel that is activated by extracellular ATP, especially in immune and glia cells. Activation of P2X7 triggers the secretion of several pro-inflammatory substances, such as IL-1β, IL-18, TNF-α, and nitric oxide. P2X7 activation contributes to the pro-inflammatory response to injury or bacterial invasion and mediates apoptosis. It has been implicated in physiological and pathological conditions such as bone tissue remodelling, inflammation, oncogenesis, depression, and inflammatory, neuropathic and chronic pain. Here, we aim to characterize the effects of variation within the *P2RX7* gene, which encodes the P2X7 receptor, on pain and opioid requirements in human patients.

Methods: Pain was assessed in Norwegian and Finnish cohorts. The Norwegian cohort represents the 6th wave of the Tromsø Study, a longitudinal and cross-sectional population based study ($N = 3700$), whereas the Finnish cohort (BrePainGen) consists of patients who underwent breast cancer surgery ($N = 1000$). For both cohorts, experimental pain data were analyzed. Pain intensity and tolerance were assessed with cold pressor test and after standardized noxious heat stimulation in both cohorts. In addition, data on acute postoperative pain and opioid requirements were analyzed in the BrePainGen cohort. Postoperative pain and opioid responses were followed during 20 h after surgery. In total, 29 single nucleotide polymorphisms (SNPs) in *P2RX7* were genotyped and their association with outcome variables was assessed using linear regression and analysis of variances (ANOVA).

Results: Several *P2RX7* SNPs were associated with the pain phenotypes. The strongest associations were seen with cold pain intensity and tolerance. The results of this study will be presented at the meeting.

Conclusions: Our results suggest that P2X7 and genetic variation in the *P2RX7*-gene are involved in the modulation of human pain responses.

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Reversal of thermal and mechanical allodynia with pregabalin in a mouse model of oxaliplatin-induced peripheral neuropathy

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Aims: Chemotherapy-induced peripheral neuropathy (CIPN) is a dose limiting side effect in the use of the platinum-based anti-neoplastic drug oxaliplatin as a treatment for colorectal cancer. Currently there is no treatment available to reverse the neurotoxicity which presents as pain, sensory loss and cold allodynia in up to 80% of patients. The aim of this study is to investigate if pregabalin can reverse the allodynia caused by oxaliplatin in CIPN.

Methods: CIPN was induced in 10 male C57BL/6 mice (6 weeks-old) with a single intraperitoneal injection of oxaliplatin (15 mg/kg i.p.). Signs of thermal and mechanical allodynia were assessed from baseline to 20 days after injection by Cold/Hot plate (Bioseb, France) at 20 °C and hand-held von Frey (vF) hairs of gradually increasing weights. Pregabalin (3 mg/kg and 10 mg/kg p.o.) was administered to treat CIPN.

Results: Mechanical and thermal allodynia were established 3 days post-oxaliplatin injection and remained stable for 14 days. At day 15, pregabalin (3 mg/kg p.o.) reversed mechanical allodynia to baseline scores at 2 h (H) post-dosing and thermal allodynia at 1 and 2H post-dosing. Following a 2-day wash out where scores returned to neuropathic baseline, pregabalin (10 mg/kg p.o.) reverted scores for mechanical and thermal allodynia to baseline scores at both 1 and 2H. Thermal testing was performed either immediately after vF or alone and our results were similar, showing no iatrogenic effects of vF on thermal sensitivity. Correlation analysis of the responses to thermal and mechanical stimuli showed no significant trend, indicating that oxaliplatin- induced peripheral neuropathy affects the mechanical and thermal modalities in different ways.

Conclusion: Oxaliplatin-induced peripheral neuropathy as measured by thermal and mechanical allodynia is reversible by a single dose of pregabalin.

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