ADRB2, pain and opioids in mice and man

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Aims. We aim to characterize the effects of variation within *ADRB2*-gene on pain and opioid requirements in human patients. We will assess ADRB2-OPRM1-6TM heterodimer as a molecular mechanism, potentially explaining pronociceptive and antianalgetic effects, using preclinical *in vitro* and *in vivo* models. We will further assess clinical significance *via* its genetic proxy, rs563649 in humans.

Methods. In humans, experimental and postoperative pain and opioid responses were assessed in 1000 breast cancer surgery patients. Association of *ADRB2* (n = 40) and *OPRM1* (n = 1) polymorphisms was assessed using linear regression and analysis of variances (ANOVA). *In vitro* methods involved immunofluorescence microscopy (IF), cellular localization and translocation of 6TM/β2AR-heterodimers and Ca^{2+}-measurements. Behavioral *in vivo* characterization was performed in mice using formalin, von Frey, hot plate and cold plate tests after administration of morphine, specific OPRM1-6TM agonist IBNtxA and ADRB2-antagonist ICI118,551.

Results. In humans, several *ADRB2* SNPs were associated with pain and opioid phenotypes. The strongest associations were seen between cold pain phenotypes and rs17108817 & rs11957757 ($p < 0.0001$). *In vitro*, coexpression with β_2-Ars increased translocation of 6TM-MOR to plasma membrane and Ca^{2+}responses after treatment with selective 6TM-agonist, IBNtxA, compared with the cells expressing OPRM1-6TM alone. *In vivo*, co-administration of β_2AR selective antagonist ICI 118,551 increased analgesic efficacy of opioids in a synergistic manner and reduced opioid-induced hyperalgesia.

Conclusions. Our findings suggest that ADRB2 and genetic variation in *ADRB2*-gene are involved in the modulation of human pain and opioid responses. 6TM-MOR/β_2-AR heterodimerization represents a molecular mechanism causing excitatory cellular effects and sufficient explanatory potential to explain pronociceptive and antianalgesic effects. Our animal findings further confirmed the concept of β_2-AR and 6TM-MOR interaction *in vivo*. We suggest that co-administration of β-blockers with opioids might increase efficacy and safety of OPRM1 agonists.

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Retrospective analysis of pediatric patients with CRPS

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Aims: The aim of the study was to describe the clinical features and clinical pathway of pediatric CRPS patients in HUH Children's Hospital.

Methods: This retrospective study included patients admitted to the pediatric pain clinic for CRPS during six years 2008–2013. Data on time from the first symptoms to diagnosis, first appointment at the pain clinic, and symptom resolution, as well as demographic and clinical symptoms were extracted from patient records.

Results: Forty patients were clinically diagnosed with CRPS during the time period without using the Budapest Criteria. 75% of the patients were female, median age was 12, and in 90% of the cases the CRPS was localized in the lower extremity. The median time from first symptoms to the CRPS diagnosis was 8.5 weeks (range 0–47), to first appointment with the pain physician 10 weeks (range 2–47), and to symptom resolution 35 weeks (range 10–131). Eleven out of forty patients (27.5%) were not symptom-free at the end of the treatment period. Most common clinical finding was allodynia or hyperalgesia of the afflicted area (70%).

Conclusions: Compared to an earlier study performed in our hospital (retrospective study of seven years, $n = 18$), the number of patients has more than doubled, maybe due to better awareness of the syndrome. Our findings about demographics and localization of CRPS are in agreement with previous literature. Time to reaching diagnosis, the small number of consultations and radiographs show that CRPS is well known among pediatric orthopedic surgeons. Many Budapest criteria that are now considered important diagnostic findings were not highly prevalent in our patients (e.g. prior trauma, color changes of skin), although patient records were not always clear about the findings leading to diagnosis. The Budapest criteria should be used to standardize the diagnosis also in our pediatric patients.

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Activation of epidermal growth factor receptors (EGFRs) following disc herniation induces hyperexcitability in the pain pathways

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Aims: Low back pain and sciatica after disc herniation may be caused by mechanical compression of the nerve roots, but also by the release of pro-inflammatory agents including growth factors from the nucleus pulposus (NP).

Methods: Here, in an animal model mimicking the clinical situation following disc herniation, CLIA protein analyses, extracellular single-cell recordings in the spinal dorsal horn and qPCR were performed to examine the nociceptive signaling due to disc herniation.

Results: The present data demonstrated that EREG may be released from NP – and that administration of EREG onto the spinal dorsal nerve roots increased spontaneous activity in nociceptive neurons. An up-regulation of EGFR and HER4 in the dorsal horn as

well as an up-regulation of HER3 in the DRG were demonstrated after application of NP onto the dorsal nerve roots.

Conclusion: Our findings suggest that EREG and signaling through its receptors may be involved in pain hypersensitivity and other sensory abnormalities after disc herniation.

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Pain rehabilitation with language interpreter, a multicenter development project

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Aims: To describe patients with persistent pain participating in multimodal rehabilitation with language interpreter (MMRI) with regard to demographic data, pain, anxiety, depression, fear of movement, health related quality of life before and after rehabilitation.

Methods: The university rehabilitation departments in Lund and Stockholm developed multimodal rehabilitation programmes for patients who cannot participate in ordinary programmes due to insufficient knowledge in Swedish. From 2014 to 2015, 50 patients participated in the MMRI. Data was collected at admission and discharge with instruments from the Swedish quality registry for pain rehabilitation. The assessments included health related quality of life (EQ5D), anxiety and depression (HADS), fear of movements (TSK), disability (PDI).

Preliminary results: Fifty patients participated in MMRI. Seventy-eight percent were women, and 88% were born outside Europe. Compared to patients participating in Swedish regular rehabilitation programmes (MMR), the level of education was low, 44% had finished high school (55% in MMR in Sweden) and 8% university (27% in MMR in Sweden). Also the distribution of pain differed; in MMRI 40% reported pain with varying localization compared to 33% in MMR. Both groups were frequent health care seekers, even though MMRI's patients reported a higher frequency of visits than MMR regular patients; 94% of MMRI's patients compared to 70% MMR patients were seeking physicians more than 4 times due to pain during the previous year. Both groups report very low health related quality of life. In the MMRI group, at admission, the EQ5Dindex was 0.088 (md) (MMR 0.157). This can be compared with 0.83, the value for the Swedish norm population.

Conclusions: Patients participating in MMRI, compared to patients participating in MMR, reported poorer health, higher rate of visit to physicians due to pain and less higher education than other, Swedish speaking pain patients attending to the country pain programmes.

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Trait-anxiety and pain intensity predict symptoms related to dysfunctional breathing (DB) in patients with chronic pain

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Aims: The purpose of this cross-sectional study was to investigate the occurrence of symptoms related to dysfunctional breathing (DB) in chronic pain patients and to examine factors associated with these symptoms.

Methods: A questionnaire was sent to 527 adults referred to outpatient pain clinics at Oslo university hospital. The questionnaire provided demographic data, Brief Pain Inventory, Spielberger state-trait anxiety inventory, and Nijmegen questionnaire (NQ). Multiple regression analyses were performed using SPSS.

Results: A total of 108 patients (20%) responded to the questionnaire and was included. Mean age was 49 years and two third of the participants were female. More than four out of ten had a NQ score $\geq$23 (a conservative cutoff value for DB). The median NQ score in the sample was 19. Trait-anxiety (Beta = .412, $p < 0.001$) and maximal pain intensity during the past week (Beta = .264, $p = 0.004$) predicted symptoms related to DB even when controlling for age and gender.

Conclusions: The study shows that a large portion of patients with chronic pain experiences symptoms that have been associated with hyperventilation and DB and at a higher level than previously reported. Although trait-anxiety is a strong predictor for symptoms related to DB, we find it interesting that maximal pain intensity during the last week also was associated with these symptoms. The cross-sectional design, low response rate, and lack of diagnoses limit our ability to draw conclusions about causal relationship and extrapolate to a larger populations of patients with chronic pain.

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Emla®-cream as pain relief during pneumococcal vaccination

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Background: Pneumococcal vaccination for children was introduced in Sweden in 2009. For more than two decades, previous studies have shown that anesthetic cream Emla® has good effect in reducing vaccine-related pain. Even today health care workers claim "children forget quickly, and it (the pain) goes away", this ignorance causes pain in children not treated or treated in one for the child and his guardians satisfactorily way.

Purpose: The purpose of this intervention study was to compare the effect of Emla® cream for pain relief or no pain relief