Pain in RMDs

INFLAMMATION-INDUCED PAIN AND FATIGUE IN FIBROMYALGIA AND ME/CFS AND ROLE OF VARIANT CONNECTIVE TISSUE

Keywords: Fibromyalgia, Cytokines and chemokines, Patient reported outcomes

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Background: Fibromyalgia and ME/CFS are multifaceted conditions with overlapping symptoms(1); the pathophysiological mechanisms are under debate. It remains unclear whether dysregulated inflammation, induced either by an exogenous stimulus (eg a virus or other stressor), or autoimmunity, is of prime importance [2].

Objectives: 1. To determine in a novel human model the effects of an in vivo inflammatory challenge in the induction of pain and fatigue in fibromyalgia and ME/CFS compared to controls.

2. Explore potential mediators and moderators involved.

Methods: Data were available for 48 patients with confirmed diagnoses of Fibromyalgia and 22 matched controls, who had undergone a placebo controlled inflammatory challenge (typhoid vaccination) as part of ISRCTN78820481. Participants underwent full research diagnostic evaluation including a hypermobility assessment. Subjective pain and fatigue were assessed after saline injection and typhoid vaccination (VAS). Linear regression models were used to explore predictors, with adjustment for potential confounders (age/gender) and baseline levels as appropriate. Mediation analyses (looking for mechanistic effects) were conducted according to the method of Hayes (3) and mediation considered significant if bootstrapped confidence intervals of the estimated indirect effect did not cross zero. In these mediation analyses predictor variable was group membership (patient or control), outcome variable was change in 1) pain and 2) fatigue induced by challenge and mediators/moderators included change in IL-6 induced by inflammatory challenge and hypermobility features.

Results: Being a patient rather than control significantly predicted inflammation-induced fatigued (B=14.89 (95%CI 3.29-26.50), t=2.56, p=0.013) and pain (B=12.88 (95%CI 0.65-25.10), t=2.11, p=0.039) after adjusting for levels induced by placebo. Induced pain was independently predicted by level of IL-6 induced by inflammatory challenge (B=23.44 (95%CI 5.15-41.72),t=2.57, p=0.013) as was induced fatigue (B=10.63 (95%CI 2.84-18.41), t=2.73, p=0.008) Mediated moderation analyses suggested the link to induced pain and fatigue through induced inflammation was associated with hypermobility features (Index of moderated mediation 11.02 (95%CI 1.45-22.73) and 6.20 (95%CI 0.07-13.64) respectively))

Conclusion: To our knowledge this is the first human study to evaluate directly the effect of an exogenous inflammatory challenge (typhoid vaccination) in a combined group of Fibromyalgia and ME/CFS patients. IL-6 was shown to be a critical mediator. This work strongly supports the hypothesis that inflammation is key to the pathophysiology of ME/CFS. We are evaluating associated CNS inflammation in the model, as well as other associations, such as autonomic dysfunction and hypermobility. Further understanding the mediators involved in the condition should in future open the way to testing targeted anti-inflammatory therapy.

REFERENCES:


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TARGETED ABLATION OF KNEE-INNERVATING NOCICEPTORS HAS PROFONDED EFFECTS ON JOINT DAMAGE IN EXPERIMENTAL OSTEOARTHRITIS

Keywords: Osteoarthritis, Animal models

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Background: Sensory afferents abundantly innervate the knee joint. The vast majority of these are pain-sensing nociceptors, which express the voltage-gated sodium channel, NaV1.8. Using NaV1,8Cre-Tomato reporter mice, we have documented innervation changes that occur with experimental murine osteoarthritis (OA), including sprouting of nociceptors in the medial synovium and in subchondral bone [1]. Upon intra-articular (IA) injection into the mouse knee, adeno-associated virus serotype AAV.PHP.S is retrogradely transported to the lumbar dorsal root ganglia (DRG), where the cell bodies of sensory neurons reside [2].

Objectives: We leveraged this technique to selectively ablate knee-innervating nociceptors by IA injection of AAV.PHP.S carrying diphtheria toxin A (dtA), and determine the effect on joint damage after destabilization of the medial meniscus (DMM).

Methods: Expt. 1: AAV.PHP.S containing pAAV-EF1a-mCherry-flex-dtA (AAV-dtA) was injected into the right knee of 7-week old male C57BL/6 Na1.8Cre mice (3 µL, 1011 vp/mL). Three weeks later, the TLR2 ligand, Pam3CSK4 (3 µg), was injected into these same knees, followed by knee hyperalgesia measurement (using PAM) over 24-hours [3]. Na1.8Cre mice injected with AAV.PHP.S-EF1a-flex-GFP (AAV-Control) as well as wild type mice injected with AAV-dtA were included as controls (n=6 group). Expt. 2: AAV-dtA or AAV-Control was injected IA into the right knees of 7-week old male Na1.8Cre mice and 3 weeks later, DMM surgery was performed (n=19 mice/group). Mice were sacrificed 10 or 17 weeks after DMM, and knees collected for histology using a modified OARSI scoring system (toluidine blue, frontal plane). Expt. 3: Ten-week old male Na1.8Cre mice underwent DMM surgery, and 4 weeks later, AAV-dtA or AAV-Control was injected IA into the operated knees (n=12 mice/group). Knees were collected 17 weeks after surgery for histology.

Results: Expt. 1: Na1.8Cre mice injected with AAV-Control and WT mice injected with AAV-dtA responded to TLR2 stimulation, showing markedly decreased knee pain thresholds between 1 and 6 hours after IA injection of Pam3CSK4, as described [3]. In contrast, Na1.8Cre mice injected with AAV-dtA did not respond to Pam3CSK4, indicating functional effects of ablating knee-innervating nociceptors with AAV-dtA. Expt. 2: Ten weeks after DMM, all mice showed mild OA joint damage, with no difference between groups (Figure 1A). However, while AAV-Control injected joints showed markedly increased cartilage damage by week 17, AAV-dtA injected joints showed no progression of cartilage degeneration compared to week 10. Osteophytes were comparable between the groups. Expt. 3: Seventeen weeks after DMM, mice that had been injected with AAV-dtA 4 weeks post DMM showed markedly increased cartilage degeneration, total joint scores, and osteophyte sizes compared to AAV-controls (Figure 1B).

Conclusion: IA delivery of AAV-dtA into enables selective ablation of Na1.8+ neurons in the knee, as is evident from ablated pain responses to TLR2 stimulation. Experiments in the DMM model revealed a striking effect of ablation of joint nociceptors on joint damage. Nociceptron ablation before DMM significantly attenuated cartilage degeneration in late stage OA, while ablation of knee nociceptors