Scandinavian Journal of Pain 4 (2013) 109–110

Contents lists available at SciVerse ScienceDirect

Scandinavian Journal of Pain

journal homepage: www.ScandinavianJournalPain.com

Editorial comment

Amplification of osteoarthritis pain by peripheral and central nervous systems pain mechanisms

Cecilie Røe*

Department of Physical Medicine and Rehabilitation, Oslo University Hospital, Ulleval, Oslo, Norway

The mechanisms behind development of chronic pain are still not fully understood. Over the last years, evidence has emerged connecting sensitization in the peripheral and the central nervous system to amplification of pain experiences in osteoarthritis. However, few studies have tried to assess the contribution of these mechanisms directly to pain in the clinical situation.

In this issue of the *Scandinavian Journal of Pain*, Søren T. Skou and co-workers in Lars Arendt-Nielsen's research group report on their study of patients with unilateral knee osteoarthritis (OA) causing long duration knee pain. They explored relationship between experimentally assessed pain mechanisms and clinical measures of OA pain.

The authors induce temporal summation by computer controlled pressure algometry, spatial summation by cuff-algometer, and conditioning pain modulation by ischemic compression of the arm. Based on the multiple-regression model, they found that 55% of variance of the perceived maximal pain intensity in the osteoarthritic knee could be explained by quantitative experimental pain measures reflecting central pain mechanisms, in particular spreading sensitization and temporal summation. Conditioning pain modulation using ischemic arm pain as conditional pain stimuli, often termed top down pain regulation [2], was not associated with clinical OA-pain in these patients.

1. Peripheral and central pain mechanisms in knee osteoarthritis

The pathological joint changes in OA include cartilage destruction by pro-inflammatory cytokines, matrix metalloproteinases, and prostaglandins, all of which promote a catabolic environment with subchondral bone resorption. As a response subchondral bone remodeling, hypertrophic differentiation of chondrocytes, neovascularisation of synovial tissue; and focal calcification of joint cartilage take place. The source of pain likely stems from the richly innervated synovium, subchondral bone, and periostal components of the joint where tissue damage during joint degeneration generates nociceptive stimuli. Furthermore, the presence of inflammatory mediators, including bradykinin, prostaglandins, and leukotrienes, lowers the threshold of the Aδ and C pain fibers, resulting in increased response to painful stimuli- i.e. *peripheral sensitization* [3]. Im et al. [4], using a rat model showed that structural changes in the knee joint correlated with alterations in the dorsal root ganglion and spinal cord (*i.e. both peripheral and central sensitization*) and was related to behavioral hyperalgesia of the animal. They also suggested similarities between the sensitizations processes involved in OA and neuropathic pain [4].

2. Implications for understanding differences in patients' pain reports and outcome of treatment of OA-pain

It has been speculated that sensitization in knee OA could be important for the poor outcome after as well surgery as pharmacological interventions in subgroups of patients. Accordingly, Imamura et al. [5] found that patients with knee OA had significantly lower pain pressure thresholds than healthy controls, and the lower thresholds were correlated with higher pain intensity, higher disability scores, and with poorer quality of life. Also clinical pain level is markedly modified by sociodemographic and psychological factors [6], which may contribute to the lack of success of total knee arthroplasty. Hence, there may be large individual variations between the components of pain explained by joint degeneration and central sensitization. This also may explain the often large discrepancy between joint destruction visualized by radiography and clinical pain reports from patients with high pain sensitivity compared with patients with low pain sensitivity as evaluated by quantitative sensory tests [7]. The results of the Skou et al. study [1] agree well with these observations.

However, based on previous studies of knee OA, altered "top down" regulation or conditioning pain modulation could be expected [8]. Conditioning pain modulation has been suggested to be involved in the transition from localized to generalized pain, and it is shown to be dysfunctional in fibromyalgia patients [9]. The unilateral and localized pain in the patients studied by Skou et al. [1] may represent a selection of subjects robust to changes in conditioning pain modulation. The conditioning pain stimuli used by Skou et al. [1] were ischemic arm pain. Other conditioning pain stimuli, such as cold pressure pain, may have given different results. Further studies of knee OA patients are therefore needed.

DOI of refers to article: http://dx.doi.org/10.1016/j.sjpain.2012.07.001.
* Corresponding author.
E-mail address: e.c.t.roe@medisin.uio.no

http://dx.doi.org/10.1016/j.sjpain.2012.10.001

3. Associations between experimentally induced pain and clinical pain intensity

These have been reported previously in several musculoskeletal condition including low back pain and fibromyalgia [10,11]. Staud et al. [12] found that mechanical spatial summation, aftersensations, and wind-up aftersensations predicted up to 64% of the variance of fibromyalgia patients' clinical pain when number of painful body areas was included in the model. However, other studies failed to demonstrate associations between pain sensitivity and clinical pain. These studies have typically applied pain pressure threshold or other single sensitivity measures [13,14]. Hence, as Skou et al. [1] suggest, future research may need a battery of tests including different sensory modalities reflecting both peripheral and central sensitization processes in order to reveal the differentiated pain processes in diagnostic subgroups.

As both the patients' daily pain and the responses to painful stimulation are based on subjective responses, one could question if the results in the study by Skou et al. [1] merely reflect a common trait of increased pain response across experimental situations and daily life. However, genome-wide association studies have uncovered genes influencing both extracellular matrix components and neurotrophin regulation of cell motility of the peripheral nervous system [15]. Thus, combined influence on degenerative joint processes and nociception is likely. Only large prospective studies relating the genetic epidemiology to pain responses and development of OA and clinical pain caused by OA will provide more insight into the interactions between these mechanisms.

4. Pharmacological treatment of OA should target central as well as peripheral pain mechanisms

I agree with the implications of their study suggested by Skou et al. [1] that insight into the specific components contributing to the clinical pain in OA patients is likely to be important for development of better treatment strategies. Therefore, their study indicates the need of combining treatment strategies addressing both central and peripheral pain components of OA. The majority of guidelines and traditions of pharmacological treatment strategies for OA target the peripheral component, adding an opioid when pain intensity is high. The study by Frakes et al. [16] represents an exception, targeting the central component by duloxetine and the nociceptive component by NSAIDS, documenting an additive effect of the combined therapy in knee OA. As duloxetine is thought to strengthen descending inhibition, the treatment effect is a bit surprising regarding the lack of altered conditional pain modulation in the study by Skou et al. [1]. Adding quantitative sensory testing and experimental pain provocations to treatments studies could be an interesting follow up of the Skou et al. study [1].

References

[1] Skou ST, Graven-Nielsen T, Lengsoe L, Simonsen O, Laursen MB, Arendt-Nielsen L. Relating clinical measures of pain with experimentally assessed pain mechanisms in patients with knee osteoarthritis. Scand J Pain 2013;4:111–7.
[2] Le Bars D, Dickenson AH, Besson J-M. Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn convergent nerurones in the rat. Pain 1979;6:283–304.
[3] Adatia A, Rainsford KD, Kean WF. Osteoarthritis of the knee and hip. Part I: aetiology and pathogenesis as a basis for pharmacotherapy. J Pharm Pharmacol 2012;64:617–25.
[4] Im HJ, Kim JS, Li X, Kotwal N, Sumner DR, van Wijnen AJ, Davis FJ, Yan D, Levine B, Henry JL, Desevrè J, Kroin JS. Alteration of sensory neurons and spinal response to an experimental osteoarthritis pain model. Arthritis Rheum 2010;62:2995–3005.
[5] Imamura M, Imamura ST, Kaziyama HH, Targino RA, Hsing WT, de Souza LP, Cutait MM, Fregni F, Camanho GL. Impact of nervous system hyperalgesia on pain, disability, and quality of life in patients with knee osteoarthritis: a controlled analysis. Arthritis Rheum 2008;59:1424–31.
[6] Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. Lancet 2011;377:2115–26.
[7] Finan PH, Buenaver LF, Bounds SC, Hussain S, Park RJ, Haque UJ, Campbell CM, Haythornthwaite JA, Edwards RR, Smith MT. Quantitative sensory tests of central sensitization are associated with discordance between pain and radiographic severity in knee osteoarthritis. Arthritis Rheum 2012 September 2012, http://dx.doi.org/10.1002/art.34646 [Epub ahead of print].
[8] Quante M, Hille S, Schofer MD, Lorenz J, Hauck M. Noxious counterirritation in patients with advanced osteoarthritis of the knee reduces MCC but not SII pain generators: a combined use of MEG and EEG. J Pain Res 2008;1:1–8.
[9] Lee YC, Nassikas NJ, Clauw DJ. The role of the central nervous system in the generation and maintenance of chronic pain in rheumatoid arthritis, osteoarthritis and fibromyalgia. Arthritis Res Ther 2011;13:211.
[10] Staud R. Predictors of clinical pain intensity in patients with fibromyalgia syndrome. Curr Rheumatol Rep 2004;6:281–6.
[11] Clauw DJ, Williams D, Lauerman W, Dahlman M, Aslami A, Nachemson AL, Kobrine AI, Wiesel SW. Pain sensitivity as a correlate of clinical status in individuals with chronic low back pain. Spine (Phila Pa 1976) 1999;24:2035–41.
[12] Staud R, Robinson ME, Vierck Jr CJ, Cannon RC, Mauderli AP, Price DD. Ratings of experimental pain and pain-related negative affect predict clinical pain in patients with fibromyalgia syndrome. Pain 2003;105:215–22.
[13] Kamper SJ, Maher CG, Hush JM, Pedler A, Sterling M. Relationship between pressure pain thresholds and pain ratings in patients with whiplash-associated disorders. Clin J Pain 2011;27:495–501.
[14] Curatolo M, Arendt-Nielsen L, Petersen-Felix S. Evidence, mechanisms, and clinical implications of central hypersensitivity in chronic pain after whiplash injury. Clin J Pain 2004;20:469–76.
[15] Chapman K, Valdes AM. Genetic factors in OA pathogenesis. Bone 2012;51:258–64.
[16] Frakes EP, Risser RC, Ball TD, Hochberg MC, Wohlreich MM. Duloxetine added to oral nonsteroidal anti-inflammatory drugs for treatment of knee pain due to osteoarthritis: results of a randomized, double-blind, placebo-controlled trial. Curr Med Res Opin 2011;27:2361–72.