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Editorial comment

Altered central pain processes behind fibromyalgia? Are they restored by antidepressants as indicated by an innovative fMRI-study?

Michele Curatolo*

University Department of Anaesthesiology and Pain Therapy, University Hospital of Bern, Inselspital, 3010 Bern, Switzerland

In this issue of the *Scandinavian Journal of Pain* Petzke and co-workers shed important light on the conundrum of pain mechanisms in fibromyalgia [1]. There is little doubt that fibromyalgia is one of the most challenging chronic pain syndromes. Widespread pain and disability are associated with lack of evident damage of the body areas at which pain is perceived. This leads to the general perception that the primary source of pain is not in the peripheral tissues. Accordingly, it seems unlikely that a pathological process of the peripheral tissues that initiate nociception can be the cause of this disease. An alternative explanation is that we may miss a peripheral pathological process due to lack of sensitivity of the currently available diagnostic tools. Nevertheless, while a peripheral pathological process cannot be ruled out, fibromyalgia is generally viewed as a pain syndrome that unlikely results from nociception arising from peripheral tissues.

The above considerations have led to the hypothesis that fibromyalgia may be caused by primary disturbances in central pain processing. This hypothesis is supported by several studies that explored central pain processes from different perspectives. The use of quantitative sensory tests consists in applying a stimulus to a healthy peripheral tissue and measuring a following response. If, for instance, pain can be evoked at a stimulus intensity that is painless in a control group of healthy volunteers, hypersensitivity is likely due to a central process, since no pathology is present at the stimulated tissue. This clearly remains an assumption, in the absence of direct measurements of the activities of the nociceptive pathways involved in the test. Several studies applying this paradigm have been performed and consistently showed enhanced pain responses in fibromyalgia, suggestive for central hypersensitivity (see e.g. [2]). Experimental procedures that explore endogenous inhibition have revealed alteration in groups of fibromyalgia patients, compared with healthy controls [3]. Measurements of nociceptive reflexes have provided evidence of spinal cord hyperreactivity [4,5]. Finally, studies using brain imaging have shown augmented cerebral activation of pain-related areas in patients with fibromyalgia following application of standardized stimuli [6]. Collectively, these studies show pain hypersensitivity that is likely due primarily to central processes, because: (a) pain is evoked after stimulation of healthy tissues; (b) endogenous inhibition is impaired; (c) spinal cord nociceptive processes are enhanced; and (d) pain-related brain areas are hyperactivated.

While the above evidence is convincing for altered pain processes within the central nervous system, a number of issues remain open. First, what are the primary mechanisms leading to the detected disturbances? For instance, when we say that patients with fibromyalgia display spinal cord hyperexcitability, what is the cause of the hyperexcitability? One can argue that impaired descending modulation can be involved, but, in turn, this would pose the question of the origin of altered descending modulation. Basically, we are observing a number of central phenomena that we can not place into a validated pathophysiological model.

Second, it is fundamentally wrong to generalize the above findings to all patients with fibromyalgia. All the positive studies have found a statistically significant difference between groups of patients and groups of healthy volunteers. However, a p-value less than 0.05 does not necessarily mean that all patients display the pathophysiologic phenomenon that has been studied. In fact, the analysis of the data shows substantial overlap between patients and healthy controls. An example can be seen in Fig. 1, showing the raw data of a study on nociceptive withdrawal reflex [4]. The two groups display statistically significant differences. However, the values for several patients lie in the middle of the cloud of the healthy controls. Seven out of 22 patient (32%) have values of reflex thresholds above the 5th percentile of the pain-free population examined by Scaramozzino et al. [7]. This means that they are unlikely to display spinal cord hypersensitivity, at least according to the method used. How should we interpret the findings of patients with high reflex thresholds? Do these patients lack spinal cord hypersensitivity, or is the methodology inadequate in part of the patients?

In the study by Petzke et al., published in the current issue of the *Scandinavian Journal of Pain* [1], a brain imaging analysis was undertaken to evaluate the effects of the antidepressant milnacipran. The investigation had the important aim to clarify the cerebral mechanisms of action of the drug, possibly allowing inferences on the mechanisms underlying the pain syndrome. Interestingly, brain regions involved in inhibitory processes were more activated by painful stimuli after drug treatment, compared to baseline. This indirectly suggests that endogenous inhibition is impaired in fibromyalgia, and that antidepressants may work by restoring it.

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* Tel.: +41 31 632 0133; fax: +41 31 632 3028.
E-mail address: michele.curatolo@insel.ch

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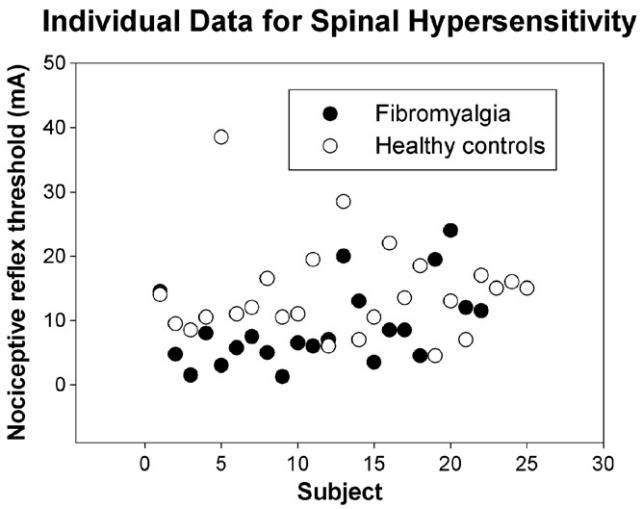

Fig. 1. Nociceptive withdrawal reflex. The graph shows the individual data of patients with fibromyalgia and healthy controls from a previous study [4]. The test used was the reflex threshold to single transcutaneous electrical stimulation of the sural nerve, recorded by electromyography of the biceps femoris muscle (nociceptive withdrawal reflex). The graph shows a difference between the two groups, with a *p*-value for the difference between the two groups of 0.001. However, there is evident data overlap between the two groups.

While part of the results was statistically significant, the authors pointed out that corrections for multiple comparisons were not performed and the statistical effects were not very robust. They mentioned that their sample size (70 patients completing the study) was likely insufficient. I would rather argue that the sample size should actually be fully sufficient, if the changes in modulatory processes applied to all fibromyalgia patients, the drug consistently worked in all patients and the imaging methodology were sensitive enough to detect the changes that occur. Evidently, one or more of these conditions are not fulfilled, which still leaves us with a number of open questions. Perhaps, the most important one is: do all patients with fibromyalgia have altered endogenous pain modulation?

Nevertheless, these kinds of studies are very important and should be performed more frequently. So far, research has mostly concentrated on describing differences between patients and controls in measurements of nociception or pain perception. Investigating the pathophysiology of fibromyalgia by interventions that modulate the possible underlying mechanisms may allow further steps in the pathway leading to the clarification of the pathophysiology of this disabling pain condition, and eventually in more effective treatment.

References

[1] Petzke F, Jensen KB, Kosek E, Choy E, Carville S, Fransson P, Williams SCR, Marcus H, Mainguy Y, Ingvar M, Gracely RH. Using fMRI to evaluate the effects of milnacipran on central pain processing inpatients with fibromyalgia. Scand J Pain 2013;4:65–74.
[2] Staud R, Vierck CJ, Cannon RL, Mauderli AP, Price DD. Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. Pain 2001;91:165–75.
[3] Kosek E, Hansson P. Modulatory influence on somatosensory perception from vibration and heterotopic noxious conditioning stimulation (hncs) in fibromyalgia patients and healthy subjects. Pain 1997;70:41–51.
[4] Banic B, Petersen-Felix S, Andersen OK, Radanov BP, Villiger PM, Arendt-Nielsen L, Curatolo M. Evidence for spinal cord hypersensitivity in chronic pain after whiplash injury and in fibromyalgia. Pain 2004;107:7–15.
[5] Desmeules JA, Cedraschi C, Rapiti E, Baumgartner E, Finckh A, Cohen P, Dayer P, Vischer TL. Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. Arthritis Rheum 2003;48:1420–9.
[6] Giesecke T, Gracely RH, Grant MA, Nachemson A, Petzke F, Williams DA, Clauw DJ. Evidence of augmented central pain processing in idiopathic chronic low back pain. Arthritis Rheum 2004;50:613–23.
[7] Scaramozzino P, Neziri AY, Andersen OK, Arendt-Nielsen L, Curatolo M. Percentile normative values of parameters of electrical pain and reflex thresholds. Scand J Pain 2013;4:120–4.