Preliminary evidence for small-fiber neuropathy in fibromyalgia patients

Roland Staud
University of Florida, McKnight Brain Institute, Department of Medicine, Gainesville, FL 32610-0221, USA
Tel.: +1 352 273 5346;
Fax: +1 352 392 8483;
staudr@ufl.edu

Kim SH, Kim DH, Oh DH, Clauw DJ: Characteristic electron microscopic findings in the skin of patients with fibromyalgia – preliminary study. *Clin. Rheumatol.* 27(3), 407–411 (2008). Peripheral tissue abnormalities may contribute to the increased pain sensitivity of fibromyalgia (FM) patients. To address this issue, the authors obtained skin biopsies from the deltoid region of 13 FM patients and five healthy, pain-free control subjects. After fixation, all tissues were examined using electron-microscopy (EM) by an investigator who was blinded to the participants' diagnosis. In contrast to healthy controls, the skin biopsies from nine out of 13 FM patients showed axons that were localized to the periphery of unmyelinated Schwann cell sheaths. These findings were associated with ballooning of Schwann cells, diminished folding of Schwann cell sheaths and smaller axonal size. Myelinated nerve fibers were unremarkable. The EM findings of this study show that the cutaneous nerve endings of FM patients possess unusual architecture, as well as ballooning of their associated Schwann cells. Similar changes were not detectable in skin biopsies of healthy pain-free controls.

The authors of this recently published study focused on peripheral tissue contributions to fibromyalgia (FM) pain, particularly axonal abnormalities of cutaneous nerve endings [1]. Tissue samples were obtained through punch biopsies and evaluated by electron microscopy. The results showed ballooning of Schwann cells, as well as lateralization of axons. The authors speculate that these findings could contribute to peripheral sensitization in FM. Although this study was small and its findings need to be interpreted with great caution, it raises many important questions related to the pathogenesis of FM; particularly, whether consistent abnormalities can be detected in peripheral tissues of FM patients that are associated with the increased pain sensitivity of these chronic pain patients. While much attention has been focused on muscles as an important source of abnormal pain processing, there is also some evidence for hypersensitivity of skin nociceptors in FM [2].

Small-fiber neuropathies

The differential diagnosis, clinical presentation, evaluation and treatment of small- or C-fiber neuropathies can be complex. Although such neuropathies are rare, their differential diagnosis is broad, and includes many components, including metabolic, toxic, inflammatory, infectious and genetic disorders. As small nerve fibers contribute to pain signaling and autonomic functions, these neuropathies usually present with touch or temperature deficiencies, painful dysesthesias, autonomic dysfunction, or a combination of each. These neuropathies are especially challenging to diagnose, as nerve conduction studies and electromyography, which help guide the evaluation of most peripheral neuropathies, may give normal results in patients with small-fiber neuropathies. Tests of autonomic function, intra-epidermal nerve-fiber analysis, microneurography and quantitative sensory testing are often required to confirm the presence of C-fiber neuropathies. Frequent causes of such neuropathies include diabetes mellitus, peripheral vascular disease, and toxins. Depending on the type of C-fiber neuropathy, autonomic dysfunction can be pronounced or minimal.

Pathogenesis of fibromyalgia

Fibromyalgia is a chronic, widespread pain syndrome that is associated with profound tenderness (hyperalgesia and/or allodynia) to pressure. As with C-fiber neuropathy patients, increased tenderness to additional stimulus modalities, including heat, cold, electric current and noxious chemicals, can be detected in FM. FM represents the extreme end of the spectrum of chronic widespread pain (CWP) disorders, but the difference between FM and CWP is mostly quantitative, not qualitative. The definition of FM through multiple continuous variables (such as pain and number of tender points) has created diagnostic difficulties similar to other medically relevant syndromes such as diabetes or hypertension (i.e., lacking characteristic features or clusters of features with a distribution clearly demarcating afflicted patients from the rest of

Keywords: chronic pain, fibromyalgia, neuropathy, nociception, Schwann cells

future medicine part of fsg

the population). Thus, it has been argued that FM does not represent a distinct clinical entity. However, FM clearly displays identifiable risk factors, as well as a characteristic natural course and prognosis. Additionally, this chronic pain syndrome has epidemiological and mechanistic features that are associated with important clinical outcomes such as organ dysfunction [3] or even death [4].

Pain in FM is consistently felt in deep tissues and is related to sensitization of peripheral and CNS pain pathways. Psychophysical testing of FM patients provides convincing evidence for peripheral [2], as well as central pain processing abnormalities, specifically increased temporal summation of pain in FM patients [5–9]. These abnormalities result in excessive amplification of painful signals from peripheral tissues and may be responsible for the often extreme clinical pain of FM patients. Although the initiation of central sensitization often requires strong and persistent nociceptive stimulation, much less is necessary for its maintenance [6].

Neurotrophins, such as nerve growth factor (NGF), and tachykinins, such as substance P (SP), are elevated in the cerebrospinal fluid of FM patients [10–12]. NGF and SP not only enhance the sensitivity of nociceptors, but are also associated with inflammatory regulation [13]. Specifically, administration of recombinant human NGF to pain-free volunteers can result in mild to moderate back pain [14]. Several neuropeptides, in particular SP, can induce the expression of cytokines that may sensitize peripheral nerve endings [15]. Not surprisingly, elevated levels of cytokines (including IL-1ra, -8 and -6) in peripheral blood and skin have been reported in FM patients [16,17]. Of these cytokines, IL-8 is of particular interest because it can not only increase nociceptive sensitivity, but is also involved in the activation of the sympathetic nervous system [18]. Cytokines, as well as SP, have been associated with inflammation and may very well contribute to the Schwann cell abnormalities discussed in this article.

Nevertheless, most FM pain appears to depend on impulse input from deep tissues, particularly muscles [19]. The source of peripheral pain input (so-called 'pain generators') is often difficult to detect, but can perpetuate chronic pain syndromes. Many, albeit inconsistent, tissue abnormalities have been reported in muscles of FM patients, including moth-eaten fibers, ragged red fibers and type II fiber atrophy [20–24]. In addition, the blood flow to muscles, particularly the trapezius, seems to be reduced in FM [25]. Muscle microcirculation can be measured by Doppler ultrasound [25,26], xenon-133 clearance [27] or oxygen multipoint electrodes on the muscle surface of FM patients [28]. The trapezius and brachioradialis muscles have been most frequently studied. Abnormal tissue oxygen pressures have been reported in FM patients compared with normal controls [29]. These results suggest abnormal capillary microcirculation, at least in the upper part of the body. In addition, decreased blood flow in the tender point areas of FM patients has also been reported using intramuscular needle electrodes. However, these blood-flow abnormalities do not appear to result from diminished capillary density. On the contrary, the capillary density of trapezius muscles [30] was increased compared with lower extremity muscles, including the vastus lateralis [31]. Other reported muscle abnormalities include increased thickness of the capillary endothelium of FM patients [32]. These changes may either be the cause or the effect of localized hypoxia. The microcirculation of muscles is not only regulated by locally produced metabolites and humoral factors, but also by the autonomic nervous system (ANS). This important role of the ANS for chronic muscle pain was demonstrated by stellate ganglion blockade, which abolished pain and tender points in FM patients, whereas sham blockade was ineffective [33].

Thus, muscular ischemia appears to be a relevant mechanism for chronic muscle pain, either focal or generalized. Hypoxia of muscle tissue, exacerbated by contraction, is highly effective in activating unmyelinated muscle nociceptors [34]. Furthermore, muscular blood flow in FM patients can not only be completely abolished by isometric or isokinetic exercise [25], but also seems to recover very slowly [35]. Such findings may explain why pain is abnormally increased for FM patients during and after exercise [27,36]. Several lines of evidence support the fact that strenuous or intensive exercise can contribute to FM patients' hyperalgesia and pain. For example, isometric contractions can increase the mechanical pain sensitivity of FM patients' exercised muscles (hyperalgesia), but render muscles of normal control subjects hypoalgesic [37]. Similarly, FM patients show increased heat hyperalgesia after exercise, whereas healthy controls become less sensitive [38]. These findings suggest that certain types of exercise can increase the tonic nociceptive input from FM muscles, resulting in peripheral and central sensitization. Whereas strenuous

exercise seems to activate powerful antinociceptive mechanisms in normal control subjects, this stress mechanism appears to be either dysfunctional or insufficient to overcome tonic muscle pain in FM.

In genetically susceptible individuals, tonic impulse input from muscles and other tissues can result in peripheral sensitization as well as neuroplastic changes of the CNS, termed central sensitization. During central sensitization, a cascade of transcriptional and translational events leads to heightened sensitivity (hyperalgesia and/or allodynia) of second and higher order neurons and expansion of their receptive fields. It is unclear at this time why such changes are long-lasting or even permanent in FM patients. One likely mechanism is the abnormal response of FM patients to stressful events. Specifically, altered neuroendocrine and ANS function appears to play an important role in the pathogenesis of FM [39–41]. Disturbances of neuroendocrine and ANS function can trigger many symptoms that are commonly observed in FM, including pain, fatigue, insomnia, mood disorders, weakness and orthostatic intolerance. A number of studies that have examined coordinated hypothalamic–pituitary–adrenal axis and ANS functioning showed hyporeactivity to applied stress in FM [12,42–46]. This altered neuroendocrine responsiveness seems to result from changes in hypothalamic function and not from a primary adrenal defect. Thus, neuroendocrine alterations are most likely involved in the pathophysiology of FM and contribute to its ongoing symptomatology. Owing to the fact that pain is not only worsened by chronic stress, but is also an important stressor in its own right, reductions in stress will likely have a positive effect on chronic pain and FM.

Future perspective

The study by Kim *et al*. [1] reported novel and possibly clinically relevant cutaneous C-fiber abnormalities in patients with FM. As many metabolic or toxic factors can contribute to peripheral nerve damage in chronic pain patients, more detailed future evaluations will be necessary. In particular, the correlation of small-fiber changes in skin and other tissues with clinical pain and pain sensitivity of FM patients would be of great interest.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- C-fiber changes, including ballooning of Schwann cells, were found in the skin of fibromyalgia (FM) patients by Kim *et al*.
- As small, unmyelinated nerve fibers play a very important role in pain signaling, these abnormalities are of great interest, in particular for FM.
- Although increasing evidence points towards the contribution of muscle nociceptors for FM pain, cutaneous nerve fibers could also be involved in the abnormal pain processing of this chronic pain syndrome.
- Future larger studies of patients with FM or other chronic pain syndromes are needed to clarify these issues.

Bibliography

1. Kim SH, Kim DH, Oh DH, Clauw DJ: Characteristic electron microscopic findings in the skin of patients with fibromyalgia – preliminary study. *Clin. Rheumatol.* 27(3), 407–411 (2008).
2. Granot M, Buskila D, Granovsky Y, Sprecher E, Neumann L, Yarnitsky D: Simultaneous recording of late and ultra-late pain evoked potentials in fibromyalgia. *Clin. Neurophysiol.* 112, 1881–1887 (2001).
3. Kuchinad A, Schweinhardt P, Seminowicz DA, Wood PB, Chizh BA, Bushnell MC: Accelerated brain gray matter loss in fibromyalgia patients: premature aging of the brain? *J. Neurosci.* 27, 4004–4007 (2007).
4. Macfarlane GJ, Jones GT, Knekt P *et al*.: Is the report of widespread body pain associated with long-term increased mortality? Data from the Mini-Finland Health Survey. *Rheumatology* 46, 805–807 (2007).
5. 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* 91, 165–175 (2001).
6. Staud R, Price DD, Robinson ME, Mauderli AP, Vierck CJ: Maintenance of windup of second pain requires less frequent stimulation in fibromyalgia patients compared to normal controls. *Pain* 110, 689–696 (2004).

7. Staud R, Robinson ME, Price DD: Temporal summation of second pain and its maintenance are useful for characterizing widespread central sensitization of fibromyalgia patients. *J. Pain* 8, 893–901 (2007).
8. Staud R, Bovee CE, Robinson ME, Price DD: Cutaneous C-fiber abnormalities of fibromyalgia patients are specifically related to temporal summation. *Pain* (2008) (In press).
9. Desmeules JA, Cedraschi C, Rapiti E *et al.*: Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. *Arthritis Rheum.* 48, 1420–1429 (2003).
10. Giovengo SL, Russell IJ, Larson AA: Increased concentrations of nerve growth factor in cerebrospinal fluid of patients with fibromyalgia. *J. Rheumatol.* 26, 1564–1569 (1999).
11. Russell IJ, Fletcher EM, Vipraio GA, Lopez Y, Orry MA: Cerebrospinal fluid (CSF) substance P (SP) in fibromyalgia (FMS): changes in CSP SP over time parallel changes in clinical activity. *Arthritis Rheum.* 41, S256 (1998).
12. Vaeroy H, Helle R, Forre O, Kass E, Terenius L: Elevated CSF levels of substance P and high incidence of Raynaud phenomenon in patients with fibromyalgia: new features for diagnosis. *Pain* 32, 21–26 (1988).
13. Lewin GR, Mendell LM: Nerve growth factor and nociception. *Trends Neurosci.* 16, 353–359 (1993).
14. Petty BG, Cornblath DR, Adornato BT *et al.*: The effect of systemically administered recombinant human nerve growth factor in healthy human subjects. *Ann. Neurol.* 36, 244–246 (1994).
15. Fu KY, Light AR, Maixner W: Long-lasting inflammation and long-term hyperalgesia after subcutaneous formalin injection into the rat hindpaw. *J. Pain* 2, 2–11 (2001).
16. Wallace DJ, Linker-Israeli M, Hallegua D, Silverman S, Silver D, Weisman MH: Cytokines play an aetiopathogenetic role in fibromyalgia: a hypothesis and pilot study. *Rheumatology* 40, 743–749 (2001).
17. Salemi S, Rethage J, Wollina U *et al.*: Detection of interleukin 1β (IL-1 β), IL-6, and tumor necrosis factor-α in skin of patients with fibromyalgia. *J. Rheumatol.* 30, 146–150 (2003).
18. Cunha FQ, Lorenzetti BB, Poole S, Ferreira SH: Interleukin-8 as a mediator of sympathetic pain. *Br. J. Pharmacol.* 104, 765–767 (1991).
19. Wall PD, Woolf CJ: Muscle but not cutaneous C-afferent input produces prolonged increases in the excitability of the flexion reflex in the rat. *J. Physiol. (Lond.)* 356, 443–458 (1984).
20. Bengtsson A, Henriksson KG, Larsson J: Muscle biopsy in primary fibromyalgia. Light-microscopical and histochemical findings. *Scand. J. Rheumatol.* 15, 1–6 (1986).
21. Bartels EM, Danneskiold-Samsoe B: Histological abnormalities in muscle from patients with certain types of fibrositis. *Lancet* 1, 755–757 (1986).
22. Kalyan-Raman UP, Kalyan-Raman K, Yunus MB, Masi AT: Muscle pathology in primary fibromyalgia syndrome: a light microscopic, histochemical and ultrastructural study. *J. Rheumatol.* 11, 808–813 (1984).
23. Pongratz DE, Spath M: Morphologic aspects of fibromyalgia. *Z. Rheumatol.* 57, 47–51 (1998).
24. Drewes AM, Andreasen A, Schroder HD, Hogsaa B, Jennum P: Pathology of skeletal muscle in fibromyalgia: a histo-immuno-chemical and ultrastructural study. *Br. J. Rheumatol.* 32, 479–483 (1993).
25. Elvin A, Siosteen AK, Nilsson A, Kosek E: Decreased muscle blood flow in fibromyalgia patients during standardised muscle exercise: a contrast media enhanced colour Doppler study. *Eur. J. Pain* 10, 137–144 (2006).
26. Larsson SE, Alund M, Cai H, Oberg PA: Chronic pain after soft-tissue injury of the cervical spine: trapezius muscle blood flow and electromyography at static loads and fatigue. *Pain* 57, 173–180 (1994).
27. Bennett RM, Clark SR, Goldberg L *et al.*: Aerobic fitness in patients with fibrositis. A controlled study of respiratory gas exchange and 133xenon clearance from exercising muscle. *Arthritis Rheum.* 32, 454–460 (1989).
28. Lund N, Bengtsson A, Thorborg P: Muscle tissue oxygen pressure in primary fibromyalgia. *Scand. J. Rheumatol.* 15, 165–173 (1986).
29. Strobel ES, Krapf M, Suckfull M, Bruckle W, Fleckenstein W, Muller W: Tissue oxygen measurement and 31P magnetic resonance spectroscopy in patients with muscle tension and fibromyalgia. *Rheumatol. Int.* 16, 175–180 (1997).
30. Bengtsson A, Henriksson KG, Larsson J: Muscle biopsy in primary fibromyalgia. Light-microscopical and histochemical findings. *Scand. J. Rheumatol.* 15, 1–6 (1986).
31. Lindh M, Johansson G, Hedberg M, Henning GB, Grimby G: Muscle fiber characteristics, capillaries and enzymes in patients with fibromyalgia and controls. *Scand. J. Rheumatol.* 24, 34–37 (1995).
32. Lindman R, Hagberg M, Bengtsson A, Henriksson KG, Thornell LE: Capillary structure and mitochondrial volume density in the trapezius muscle of chronic trapezius myalgia, fibromyalgia and healthy subjects. *J. Musculoskelet. Pain* 3, 5–22 (1995).
33. Bengtsson A, Bengtsson M: Regional sympathetic blockade in primary fibromyalgia. *Pain* 33, 161–167 (1988).
34. Mense S, Stahnke M: Responses in muscle afferent fibres of slow conduction velocity to contractions and ischaemia in the cat. *J. Physiol.* 342, 383–397 (1983).
35. Qiao ZG, Vaeroy H, Morkrid L: Electrodermal and microcirculatory activity in patients with fibromyalgia during baseline, acoustic stimulation and cold pressor tests. *J. Rheumatol.* 18, 1383–1389 (1991).
36. Mengshoel AM, Vollestad NK, Forre O: Pain and fatigue induced by exercise in fibromyalgia patients and sedentary healthy subjects. *Clin. Exp. Rheumatol.* 13, 477–482 (1995).
37. Kosek E, Ekholm J, Hansson P: Modulation of pressure pain thresholds during and following isometric contraction in patients with fibromyalgia and in healthy controls. *Pain* 64, 415–423 (1996).
38. Vierck CJ, Staud R, Price DD, Cannon RL, Mauderli AP, Martin AD: The effect of maximal exercise on temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. *J. Pain* 2, 334–344 (2001).
39. Sarzi-Puttini P, Atzeni F, Diana A, Doria A, Furlan R: Increased neural sympathetic activation in fibromyalgia syndrome. *Ann. NY Acad. Sci.* 1069, 109–117 (2006).
40. Crofford LJ: The relationship of fibromyalgia to neuropathic pain syndromes. *J. Rheumatol. Suppl.* 75, 41–45 (2005).
41. Gerwin RD: A review of myofascial pain and fibromyalgia – factors that promote their persistence. *Acupunct. Med.* 23, 121–134 (2005).
42. Adler GK, Kinsley BT, Hurwitz S, Mossey CJ, Goldenberg DL: Reduced hypothalamic–pituitary and sympathoadrenal responses to hypoglycemia in women with fibromyalgia syndrome. *Am. J. Med.* 106, 534–543 (1999).

43. Torpy DJ, Papanicolaou DA, Lotsikas AJ, Wilder RL, Chrousos GP, Pillemer SR: Responses of the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis to interleukin-6 – a pilot study in fibromyalgia. *Arthritis Rheum.* 43, 872–880 (2000).
44. Russell IJ, Orr MD, Littman B *et al.*: Elevated cerebrospinal fluid levels of substance P in patients with the fibromyalgia syndrome. *Arthritis Rheum.* 37, 1593–1601 (1994).
45. Bradley LA, Alarcon GS, Sotolongo A *et al.*: Cerebrospinal fluid (CSF) levels of substance P (SP) are abnormal in patients with fibromyalgia (FM) regardless of traumatic or insidious pain onset. *Arthritis Rheum.* 41, S256 (1998).
46. Neeck G: Neuroendocrine and hormonal perturbations and relations to the serotonergic system in fibromyalgia patients. *Scand. J. Rheumatol.* 29, 8–12 (2000).

Affiliation

• *Roland Staud*
University of Florida, McKnight Brain Institute, Department of Medicine, Gainesville, FL 32610–0221, USA
Tel.: +1 352 273 5346
Fax: +1 352 392 8483
staudr@ufl.edu