

EDITORIAL

Are Peripheral Pain Generators Important in Fibromyalgia and Chronic Widespread Pain?

Fibromyalgia (FM) is a chronic widespread pain syndrome (CWPS) that is generally considered to be the result of a dysfunctional central pain modulating system. It is thought to importantly involve the descending pain inhibitory system. FM is known to be associated with multimodal hypersensitivity: mechanical, thermal, visual, and auditory. It is associated with a variety of comorbid conditions including irritable bowel syndrome, painful bladder, migraine headache, and temporo-mandibular joint syndrome. The relationship of the comorbid conditions to FM has not been clear. They can be considered to be the result of hyper-effective ascending central pain transmission resulting from deficient descending pain inhibition, or they can be considered as clinical entities in themselves, whose importance in FM lies in their acting as peripheral pain generators that enhance or initiate central sensitization, thereby contributing to chronic widespread pain. There may, of course, be some truth in both of these concepts. The presence of peripheral pain generators that lead to central sensitization initiating or maintaining CWPS or FM remains controversial, however. This question is addressed in a masterful study by Albrecht et al. [1], published in this issue.

Albrecht et al. [1] investigated the innervation of arteriole-venule shunts (AVS) that are located deep in the dermis of hypothenar glabrous skin, an area that is often painful in FM patients. The function of these AVS, as the authors note, is to increase or decrease blood flow to glabrous skin as part of the body's thermoregulatory mechanism. Under thermal stress conditions, as much as 60% of the cardiac output is distributed to skin, and a high proportion of this is directed to glabrous skin. They hypothesized that FM patients may have a disorder involving the sensory and sympathetic innervation of the arterioles and AVS in glabrous skin, leading to or exacerbating the pain of FM. They performed an immunofluorescent examination of arteriole and AVS innervation, using immunofluorescent labeling to identify unmyelinated peptidergic C fibers, lightly myelinated peptidergic A δ , and lightly myelinated non-peptidergic A δ fibers. The skin biopsies were double labeled to differentiate C fiber, A δ sensory fibers, and noradrenergic sympathetic fibers. Noradrenergic sympathetic fibers were identified by being positive for neuropeptide Y and negative for calcitonin-gene-related-peptide (CGRP). The relative proportions of sensory and sympa-

thetic nerve innervation of arterioles and AVS and the density of innervation of arterioles and AVS were also measured. AVS were significantly larger in the FM patients than in the controls. The increased size of the AVS correlated with increased tortuosity to some degree but more significantly to an increase in the innervation of the AVS. The overall innervation area was 4x greater in FM patient AVS than in control subjects AVS. Peptidergic (CGRP-containing) C-fiber sensory axons made up the largest component of the increased AVS innervation. The CGRP-containing vasodilatory sensory innervation was far greater in proportion to noradrenergic vasoconstrictive sympathetic innervation than the ratio of the two types of innervation was in control subjects. In summary, the authors found that AVS in palmar glabrous skin of FM patients had increased sympathetic and sensory innervation compared to control subjects, whereas arteriole and venous innervation was normal. This study suggests, as the authors point out that changes in blood flow and increased thermal sensitivity may each contribute to local palmar pain, a common complaint of FM patients. By so doing, they contribute to peripheral nerve sensitization which gives rise to local (peripheral) pain as well as contributing to central sensitization and central pain. These findings contribute importantly to our concept of the nature of pain in CWPS or FM. Previous studies in this area showed that lidocaine injections into tender points in the trapezius muscle in FM patients result in decreased local tenderness, and also decreased heat hyperalgesia at points remote from the injection sites, showing that peripheral nociceptive input is important in maintaining central sensitization [2]. Myofascial trigger points were not specifically mentioned as the pain source in the trapezius muscles in that study, but subsequently, in other studies, myofascial trigger points were identified as sources of peripheral nociceptive pain that caused local tenderness [3–6]. The association and reproduction of pain in FM patients produced by stimulating peripheral nociceptive sites is suggestive, but not proof of a cause and effect relationship. It is the reduction in local and widespread pain in FM in response to treatment of the peripheral nociceptive sites that is most convincing in determining that peripheral nociceptive sites play an important role in initiating and maintaining pain [7,8]. It is unlikely that chronic changes in central pain modulation would produce the changes seen in innervation patterns of AVS.

Gerwin

Pain is not a simple sensation, and is rarely the result of a disorder in one system only. It is complex, involving multiple interactions. CWPS and FM cannot be considered to be solely a disorder of central pain modulation, and perhaps not even primarily so. Pain is the outcome of a complex interplay between the central modulation and peripheral pain input. That balance between inhibition and facilitation of incoming pain impulses determines the pain that we experience, as shown when descending pain modulation shifts from inhibition to facilitation following sustained isometric contraction sufficient to cause muscle nociception in FM patients [9]. The work of Albrecht et al. [1] advances our understanding of this interplay with their elegantly done study of AVS in FM patients that emphasizes the importance of peripheral pain generators in determining the clinical expression of pain.

ROBERT GERWIN, MD
*Johns Hopkins University JHOC
Baltimore, Maryland, USA*

References

- 1 Albrecht P, Hou Q, Argoff C, et al. Excessive peptidergic sensory innervation of cutaneous arteriole-venule shunts (AVS) in the palmar glabrous skin of fibromyalgia patients: Implications of wide-spread deep tissue pain and fatigue. *Pain Med* 2013;14:895–915.
- 2 Staud R, Nagel S, Robinson ME, Price DD. Enhanced central pain processing of fibromyalgia patients is maintained by muscle afferent input: A randomized, double-blind, placebo-controlled study. *Pain* 2009;145:96–104.
- 3 Ge HY, Nie H, Madeleine P, et al. Contribution of the local and referred pain from active myofascial trigger points in fibromyalgia syndrome. *Pain* 2009;147:233–40.
- 4 Ge HY, Wang Y, Danneskjold-Samsøe B, et al. The predetermined sites of examination for tender points in fibromyalgia syndrome are frequently associated with myofascial trigger points. *J Pain* 2010;11:644–51.
- 5 Alonso-Blanco C, Fernandez-de-las-Peñas C, Morales-Cabezas M, et al. Multiple active myofascial trigger points reproduce the overall spontaneous pain pattern in women with fibromyalgia and are related to wide-spread mechanical hypersensitivity. *Clin J Pain* 2011;27:405–13.
- 6 Ge HY, Wang Y, Fernandez-de-las-Peñas C, et al. Reproduction of overall spontaneous pain pattern by manual stimulation of active myofascial trigger points in fibromyalgia patients. *Arthritis Res Ther* 2011;13(2):R48. doi: 10.1186/ar3289.
- 7 Affaitati F, Costantini R, Fabrizio A, et al. Effects of treatment of peripheral pain generators in fibromyalgia patients. *Eur J Pain* 2011;15:61–9.
- 8 Giamberardino MA, Affaitati G, Fabrizio A, Costantini R. Effects of treatment of myofascial trigger points on the pain of fibromyalgia. *Curr Pain Headache Rep* 2011;15:393–9.
- 9 Ge HY, Nie H, Graven-Nielsen T, et al. Descending pain modulation and its interaction with peripheral sensitization following sustained isometric muscle contraction in fibromyalgia. *Eur J Pain* 2012;16:196–203.