



Centralized nociplastic pain causing fibromyalgia: an emperor with no cloths?

Manuel Martínez-Lavín¹

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Abstract

The leading school of thought views fibromyalgia as a central sensitization syndrome. Nociplastic pain is the recently proposed term to mechanistically explain central sensitization. Accumulating research suggests an alternate explanation; fibromyalgia can be conceptualized as a neuropathic pain syndrome and dorsal root ganglia (not the brain) as the primary fibromyalgia pain source. There is no need to propose nociplastic pain as new chronic pain mechanism.

Keywords Fibromyalgia · Dorsal root ganglia · Nociplastic pain · Central sensitization syndrome · Neuropathic pain · Dysautonomia

Fibromyalgia physiopathology is the subject of arduous debate. The predominant theory views fibromyalgia as a central sensitization syndrome defined as an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity [1]. A group of experts of the International Association for the Study of Pain has recently proposed “nociplastic pain” as a third pain generating mechanism other than nociceptive pain or neuropathic pain to explain the pathogenesis of fibromyalgia and similar maladies. The nociplastic pain concept intends to mechanistically explain central sensitization [2]. The centralized nociplastic pain paradigm disregards cumulative evidence suggesting fibromyalgia as stress-induced neuropathic pain syndrome [3]. The objective of this perspective is to constructively criticize the centralized nociplastic pain pathogenesis as applied to fibromyalgia.

Central sensitization in fibromyalgia

The proposal of central sensitization as the primary pathophysiologic mechanism for fibromyalgia and allied conditions is based mostly on brain abnormal functional neuroimaging and on increased pain excitatory neurotransmitter in the cerebrospinal fluid of fibromyalgia individuals. Magnetic

resonance imaging has clearly demonstrated that, when compared to controls, fibromyalgia patients have greater neuronal activation in the brain pain processing areas including the insula. Furthermore, fibromyalgia patients show increased connectivity between the network that becomes active when the brain is in default mode and the insula. There is also evidence of decreased functional connectivity in the descending pain-modulating system in fibromyalgia patients. The cerebrospinal fluid of fibromyalgia individuals contains high levels of excitatory neurotransmitters including substance P and glutamate. These brain imaging abnormalities, in the absence of known peripheral pain generators, led to the proposal that the central nervous system is the primary source of fibromyalgia pain [4]. In my opinion, this body of evidence demonstrate that fibromyalgia pain is real, but do not define the actual pain source. Similar increased neuronal activity in the brain pain processing areas is seen in humans and in animals with neuropathic pain [5, 6].

Nociplastic pain and fibromyalgia

Nociplastic pain was defined as “pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.” This purported third pain mechanism is intended to explain overlapping conditions such as fibromyalgia, complex regional pain syndrome, irritable

✉ Manuel Martínez-Lavín
drmartinezlavin@gmail.com

¹ Chief Rheumatology Department, National Institute of Cardiology, Mexico City, Mexico

bowel syndrome, and other “functional” visceral pain disorders [2]. The suggested mechanism underlying nociplastic pain is augmented central nervous system sensory processing with altered pain modulation [2, 7].

The Rheumatology and the Pain Research communities accepted the centralized nociplastic pain concept as valid fibromyalgia pathogenesis. Nevertheless, consistent clinical and experimental research suggests a different fibromyalgia paradigm. Accumulating evidence proposes fibromyalgia as a primary neuropathic pain syndrome [3] and dorsal root ganglia as the main fibromyalgia pain source [8].

Fibromyalgia as a neuropathic pain syndrome

This alternative theory views fibromyalgia as a stress-evoked, sympathetically maintained, neuropathic pain syndrome and puts dorsal root ganglia at the epicenter of fibromyalgia pathogenesis [3, 8]. Fibromyalgia pain has clear neuropathic features. It is a stimulus-independent pain state accompanied by paresthesias and allodynia. Nearly half of fibromyalgia patients display objective evidence of peripheral nerve damage. Skin biopsy and corneal confocal microscopy demonstrate unquestionable evidence of small nerve fiber pathology in these patients [3]. The suggestion that the peripheral denervation in fibromyalgia is the result of centralized pain [9] appears counterintuitive. Diverse diseases can induce peripheral denervation being diabetic neuropathy the best paradigm for small nerve fiber pathology; it would be difficult to conceive diabetic neuropathy as a centralized pain syndrome. Animal models are very clear; in rodents, different stressors, including unpredictable noise or forced swimming, induce dorsal root ganglia neuroplasticity and neuropathic pain [3, 8]. This body of evidence suggests that in fibromyalgia, central sensitization is secondary to peripherally originated painful stimuli.

Dorsal root ganglia unique physiopathology

Dorsal root ganglia distinctive pain generating capabilities cannot be overstated. These ganglia lying all along the spine contain the pain sensing fiber nuclei. Each individual nucleus is tightly enveloped by immune competent glial cells. Dorsal root ganglia lie outside the blood–brain barrier but are in direct contact with the subarachnoid space. These ganglia can actively trap antigen-specific antibodies and viruses including SARS-CoV-2. Psychological, physical, infective, and/or autoimmune stressors can inflame dorsal root ganglia thus inducing neuropathic pain [8].

Severe fibromyalgia is associated to particular dorsal root ganglia sodium channel gene variant [8]. IgG from

fibromyalgia patients injected to mice induces painful behavior and peripheral denervation. In these cases, IgG is exclusively deposited in the dorsal root ganglia [10]. The intimate contact of dorsal root ganglia with the subarachnoid space is an alternate explanation for the increased levels of excitatory neurotransmitter found in the cerebrospinal fluid of fibromyalgia patients.

Dorsal root ganglia are in direct anatomical connection with the paravertebral sympathetic chain. Small fibers also innervate internal organs and distal blood vessels. Autonomic (sympathetic) dysfunction provides a coherent explanation for the multiplicity of fibromyalgia symptoms [8]. There is clear evidence of sympathetic malfunction in individuals suffering from fibromyalgia.

Final remarks

Influential researchers have proposed the brain as the primary fibromyalgia pain source and nociplastic pain as new pain mechanism. Many clinicians and investigators have followed these directions. There is a coherent alternative explanation showing fibromyalgia as a stress-evoked sympathetically maintained neuropathic pain syndrome. Dorsal root ganglia, but not the central nervous system, are likely the primary fibromyalgia pain source.

The confusing nociplastic pain concept could be applied to the well-documented dorsal root ganglia neuroplasticity occurring after different stressful events [8]. But this phenomenon takes place outside the central nervous system and falls within the neuropathic pain realms. There is no need for a new pain descriptor.

The proposal of dorsal root ganglia as the key neural hub where different stressors can be converted in neuropathic pain opens new fibromyalgia research avenues. Advanced imaging techniques and tissue culture will be able to define if this hypothesis holds. Dorsal root ganglia pro-nociceptive molecules are attractive therapeutic targets. Sympathetic nervous system dysfunction demands multimodal holistic therapy [11].

Declarations

Disclosures None.

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