Clinical Rheumatology (2021) 40:783–787
https://doi.org/10.1007/s10067-020-05528-z

PERSPECTIVES IN RHEUMATOLOGY

Dorsal root ganglia: fibromyalgia pain factory?

Manuel Martínez-Lavín [1]

Received: 16 October 2020 / Revised: 25 November 2020 / Accepted: 26 November 2020 / Published online: 6 January 2021

Abstract

This *perspective* article focuses on dorsal root ganglia (DRG) as potential fibromyalgia main pain source. Humans possess 31 pairs of DRG lying along the spine. These ganglia have unique anatomical and physiological features. During development, DRG are extruded from the central nervous system and from the blood-brain barrier but remain surrounded by meningeal layers and by cerebrospinal fluid. DRG house the pain-transmitting small nerve fiber nuclei; each individual nucleus is tightly enveloped by metabolically active glial cells. DRG possess multiple inflammatory/pro-nociceptive molecules including ion channels, neuropeptides, lymphocytes, and macrophages. DRG neurons have pseudo-unipolar structure making them able to generate pain signals; additionally, they can sequester antigen-specific antibodies thus inducing immune-mediated hyperalgesia. In rodents, diverse physical and/or environmental stressors induce DRG phenotypic changes and hyperalgesia. Unfolding clinical evidence links DRG pathology to fibromyalgia and similar syndromes. Severe fibromyalgia is associated to particular DRG ion channel genotype. Myalgic encephalomyelitis patients with comorbid fibromyalgia have exercise-induced DRG pro-nociceptive molecules gene overexpression. Skin biopsy demonstrates small nerve fiber pathology in approximately half of fibromyalgia patients. A confocal microscopy study of fibromyalgia patients disclosed strong correlation between corneal denervation and small fiber neuropathy symptom burden. DRG may be fibromyalgia neural hub where different stressors can be transformed in neuropathic pain. Novel neuroimaging technology and postmortem inquest may better define DRG involvement in fibromyalgia and similar maladies. DRG pro-nociceptive molecules are attractive fibromyalgia therapeutic targets.

Keywords Dorsal root ganglia · Fibromyalgia · Myalgic encephalomyelitis/chronic fatigue syndrome · Small fiber neuropathy · Sodium channels

Significant advances in fibromyalgia knowledge have been gained in the last decade. The focus is being shifted from considering fibromyalgia a centralized pain syndrome to recognizing the role of autonomic and peripheral nociceptive nervous systems in the generation of widespread pain, fatigue, and insomnia. The description of small nerve fiber pathology in a sizable subgroup of fibromyalgia patients strongly supports the disease neuropathic-autonomic underpinning [1].

Fibromyalgia overlaps with other complex painful-dysautonomic syndromes including myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), postural orthostatic tachycardia syndrome, gulf war illness, macrophagic myofasciitis, and post-HPV vaccination syndrome. These overlapping syndromes may have common underlying pathophysiology [2].

Fibromyalgia is clearly a stress-related disorder. Psychological distress, physical trauma, and/or autoimmune illnesses are frequent fibromyalgia drivers. Dorsal root ganglia (DRG) have unique anatomical and physiological features making them able to convert varied afferent stressful impulses, including psychological distress, into neuropathic pain [3].

Previous publications from our department discussed the potential role of DRG sodium channels in fibromyalgia pain [4, 5]. The objective of this communication is to examine DRG unique pro-nociceptive anatomy, physiology, and immune competence, as well as to analyze recent clinical and experimental evidence linking DRG physiopathology to fibromyalgia pain. The focus on DRG as potential fibromyalgia pain factory in no way disregards other pathogenic proposals. Discussion of other hypotheses is beyond the scope of this perspective article.

✉ Manuel Martínez-Lavín
drmartinezlavin@gmail.com

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

Dorsal root ganglia unique anatomy

Human beings possess 31 pairs of DRG lying along the spine. The trigeminal ganglia share with DRG similar structure and physiology. Embryologically, DRG belong to the central nervous system. During the development process, DRG are extruded to the periphery but remain shrouded by meningeal layers and bathed in cerebrospinal fluid. Nevertheless, DRG lie outside the brain-blood barrier. Fenestrated capillaries irrigate DRG, so blood-borne molecules, antigens, or infecting agents can easily enter these ganglia interacting there with different metabolic and immune-competent cells. Herpes virus can lie dormant for years in these paravertebral nodules [6, 7].

DRG house the small and large sensory nerve fibers soma. Each ganglion contains approximately 100,000 nerve fiber nuclei. Every nucleus is tightly enveloped by immunologically active glial cells (Fig. 1). The robust DRG blood supply fulfills the metabolic needs of the extremely long and slender sensory nerve unit. The small unmyelinated DRG nerve fibers convey painful stimuli arising from the extensive skin area and from internal organs including the cardiovascular system, gastrointestinal tract, and bladder, among others [6, 7]. The eye cornea is the most pain-sensitive part of the body owing to the extremely dense small fiber innervation. This feature makes the cornea the ideal site to study small nerve fiber pathology [8].

DRG neurons have "pseudo-unipolar" structure (Fig. 1); a single axon projects from the cell body and bifurcates at the T-junction. The peripheral portion of the axon is responsible for afferent signaling [6]. The proximal portion of the axon extends into the central nervous system and shows considerable arborizations into the spinal cord spreading pain anatomical dermatomes. DRG are in direct connection with the sympathetic nerve chain via communicating nerves [7]. Owing to its pseudo-unipolar feature, DRG can generate and/or filtrate painful signals directed to the central nervous system. Epidurally inserted catheters can electrically stimulate DRG vicinity to treat different regional neuropathic pain syndromes [7].

Dorsal root ganglia pro-nociceptive micro-anatomy

Glial cells enveloping small nerve fiber nuclei have important metabolic and immunological function. These glial cells possess sizable amounts of transporters, glutamate receptors, and class I/II major histocompatibility complex molecules. DRG neurons have pro-nociceptive ion channels including voltage-activated sodium channels (NaV1.7, Nav1.8, and Nav1.9), calcium channels, and transient receptor potential channels. Nav1.7 and Nav1.8 sodium channels play an important role in the pathophysiology of inflammatory and neuropathic pain [6].

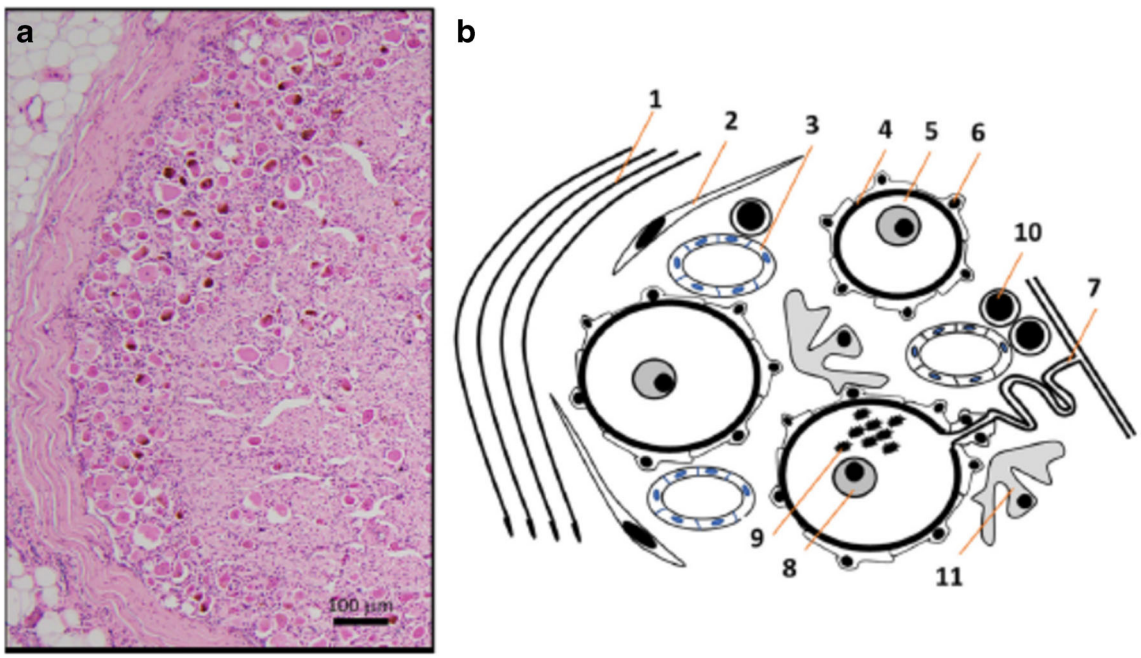

Fig. 1 **a** Micrograph section of a thoracic human dorsal root ganglia in higher magnification showing neuronal nuclei of different sizes in the periphery of DRG, next to the thick connective tissue covering. **b** Schematic representation of the micrograph figure highlighting the variety of different structures and cell types in human dorsal root ganglia. 1 = connective tissue layers, 2 = fibroblasts, 3 = capillaries, 4 = basement membran, 5 = nerve, 6 = satellite glial cells, 7 = pseudo-unipolar process originating from sensory neurons with prominent nuclei containing a singular nucleolus (8) and sometimes lipofuszin (9). 10 = Non-neuronal cells including T and B lymphocytes and macrophages (11). Reproduced from Haberberger et al. Human dorsal root ganglia [6]. This open access publication explicitely allows reproduction of the figures providing the appropiate credit is given

Other DRG pro-nociceptive compounds include neuropeptides such as calcitonin gene-related-peptide, substance P, and galanin, as well as neurotrophins including nerve growth factor, brain-derived growth factor, and N-acetylaspartate [6, 9]. In summary, DRG contain large pain-inducing arsenal.

Dorsal root ganglia immune competence

Lymphocytes and macrophages populate DRG (Fig. 1). Macrophages play a major role in the initiation and maintenance of the mechanical hypersensitivity that characterizes neuropathic pain. After peripheral nerve injury, there is proliferation of macrophages around DRG-injured sensory neurons [10]. DRG do not have the machinery to produce antibodies; nevertheless, an important discovery describes how these paravertebral nodules play a key role in the immune-nociceptive crosstalk. DRG Nav1.8 sodium channels modulate lymphocyte trafficking [11]; DRG sensory neurons can sequester antigen-specific antibodies released by antibody-secreting plasma cells [12]. These important findings could enlighten the physiopathology of immune-mediated hyperalgesia.

Hypothetical mechanisms whereby dorsal root ganglia may induce chronic pain in fibromyalgia and similar maladies

Psychological distress, physical trauma, and autoimmunity are well-established fibromyalgia drivers. Similar stressful impulses induce hyperalgesia in animal models; DRG play a central role in this phenomenon [3].

In rodents, physical trauma (sciatic nerve ligation) leads to DRG sympathetic sprouting via nerve growth factor overexpression establishing abnormal connections between the sympathetic nervous system and the nociceptive system. In such circumstances, norepinephrine induces pain [13].

Diverse animal models show stress-induced DRG inflammation; females are more vulnerable. Prolactin, estrogens, and progesterone favor DRG inflammation [3]. After sound stress exposure, mice developed long-lasting hyperalgesia. Affected mice had lysophosphatidylcholine 16:0 overexpression, which triggered nociceptive signaling via activation of acid sensing ion channel 3 and upregulated expression of DRG phosphorylated extracellular signal-regulated kinase [14].

Hashimoto's thyroiditis, Sjogren's syndrome, lupus, and other autoimmune disorders often coexist with fibromyalgia. Dorsal root ganglionitis with neuropathic pain is a well-recognized Sjogren's syndrome complication [15]. In rare instances, vaccination may induce severe fibromyalgia-like illness [16]. As already stated, DRG neurons are able to sequester antigen-specific antibodies [12]. Human DRG neurons express SARS-CoV-2 angiotensin converting enzyme receptor2, speculatively explaining post-COVID-19 chronic pain and fatigue [17]. These aggregated pieces of evidence suggest that, in given instances, environmental stress, retained immune complexes, viruses, or vaccine-derived antigens may induce DRG inflammation and chronic pain.

Unfolding clinical evidence favoring dorsal root ganglia involvement in fibromyalgia and similar maladies

Several lines of investigation link DRG dysfunction to fibromyalgia and ME/CFS development. We described the association of DRG Nav1.7 rs6754031 GG genotype with severe fibromyalgia [4, 5]. In a different study, we learned that fibromyalgia patients have norepinephrine-evoked pain [18].

Light et al. found that moderate exercise increases expression for sensory, adrenergic, and immune genes in patients with ME/CFS and comorbid fibromyalgia, but not in normal subjects. Patients showed greater increases than controls in gene expression for metabolite detecting DRG receptors including acid-sensing ion channel 3, and P2X purinoreceptor 4 and 5. Furthermore, ME/CFS patients also had increased expression of sympathetic receptors αlpha-2A, βeta-1, βeta-2, and catechol-o-methyltransferase, as well as for immune system genes for Interleukin 10 and toll-like receptor 4 [19]. A pilot postmortem inquest of 4 ME/CFS patients disclosed DRG inflammation in 3 of them [20].

A preliminary publication authored by recognized neuropathic pain investigators describes how fibromyalgia pain can be passively transferred from patients to mice. Immunoglobulin G (IgG) from fibromyalgia patients induces hyperalgesia in mice. Immunohistochemical analysis of tissues from mice that had been injected with patients IgG using anti-human IgG antibodies revealed robust staining in DRG. In contrast, IgG from control subjects generated only low levels of immunoreactivity in DRG. Western blood analysis detected fibromyalgia patients IgG in DRG, but not in brain or spinal cord tissue. The fibromyalgia patients IgG was primarily located in DRG satellite glial cells, fiber tracts entering the DRG and macrophages [21].

The most robust evidence linking fibromyalgia with DRG pathology comes from the description of small fiber neuropathy in approximately half of fibromyalgia patients [22]. Small fiber neuropathy is a denervating disease. Fibromyalgia patients without marked anxiety or depression display strong correlation between corneal denervation and small fiber neuropathy symptom burden [8]. A tentative explanation for the peripheral denervation seen in small fiber neuropathy is DRG nuclear degeneration. Damaged nuclei may become unable to maintain the long-slender nerve unit metabolic needs, resulting in distal nerve atrophy.

Future directions

Novel neuroimaging techniques are able to define DRG metabolic activity. Magnetic resonance imaging (MRI) of human DRG shows significantly increased permeability and interstitial leakage compared to spinal nerves. Permeability is significantly higher in DRG nuclei–rich area than in the nerve fiber–rich area. Female gender is associated with a significantly increased vascular permeability within the DRG compared to male [23].

Magnetic resonance neurography has consistently demonstrated increased DRG perfusion in patients with painful neuropathy associated to Sjogren's syndrome [15], Fabry disease [24], and oxaliplatin-induced polyneuropathy [25]. In contrast, MRI assessment of DRG volume has not shown adequate clinical-pathological correlation [25]. Proton nuclear magnetic resonance spectroscopy can recognize DRG pro-nociceptive amino acids [9].

Future studies may define if fibromyalgia patients have increased DRG metabolic activity and if this hypermetabolism correlates with disease severity. Systematic postmortem examination of fibromyalgia cases will provide direct information on DRG histology.

There is much to be learned about DRG stimulation as therapeutic tool. A recent report describes that DRG stimulation reduces sympathetic muscle traffic [26]. This lowered sympathetic outflow may benefit fibromyalgia patients. In a rat model, after hind-limb injury, DRG stimulation leads to decreased blood oxygen level–dependent functional magnetic resonance imaging in pain-related brain areas [27]. Nevertheless, it seems unlikely that focalized DRG stimulation may be useful treatment for widespread pain syndromes.

Autoimmune fibromyalgia may require different therapeutic approach including immunoglobulin infusion or plasmapheresis [28].

Conclusions

DRG have unique anatomic and physiologic features allowing transformation of diverse stressful signals, including psychological distress, into neuropathic pain. DRG may be fibromyalgia main pain source. These ganglia possess multiple inflammatory, autoimmune, and nociceptive mediators. DRG are in direct contact with the paravertebral sympathetic nervous chain. The recent recognition of small nerve fiber pathology in fibromyalgia patients supports DRG involvement in this painful illness. The proposed link between DRG and fibromyalgia can be tested using modern neuroimaging technology and postmortem inquest. DRG ion channels and other pro-nociceptive receptors are attractive targets to explore in the development of novel analgesic medications for fibromyalgia.

Compliance with ethical standards

Declarations The author declares no conflict of interest. This *perspective* article did not require funding.

References

1. Martínez-Lavín M (2018) Fibromyalgia and small fiber neuropathy: the plot thickens! Clin Rheumatol 37(12):3167–3171. https://doi.org/10.1007/s10067-018-4300-2
2. Shoenfeld Y, Ryabkova VA, Scheibenbogen C, Brinth L, Martinez-Lavin M, Ikeda S, Heidecke H, Watad A, Bragazzi NL, Chapman J, Churilov LP, Amital H (2020) Complex syndromes of chronic pain, fatigue and cognitive impairment linked to autoimmune dysautonomia and small fiber neuropathy. Clin Immunol (Orlando, Fla) 214:108384. https://doi.org/10.1016/j.clim.2020.108384
3. Martínez-Lavín M (2020) Fibromyalgia in women: somatisation or stress-evoked, sex-dimorphic neuropathic pain? Clinical and experimental rheumatology. Advance online publication
4. Martinez-Lavin M, Solano C (2009) Dorsal root ganglia, sodium channels, and fibromyalgia sympathetic pain. Med Hypotheses 72:64–66. https://doi.org/10.1016/j.mehy.2008.07.055
5. Vargas-Alarcon G, Alvarez-Leon E, Fragoso JM, Vargas A, Martinez A, Vallejo M, Martinez-Lavin M (2012) A SCN9A gene-encoded dorsal root ganglia sodium channel polymorphism associated with severe fibromyalgia. BMC Musculoskelet Disord 13:23. https://doi.org/10.1186/1471-2474-13-23
6. Haberberger RV, Barry C, Dominguez N, Matusica D (2019) Human dorsal root ganglia. Front Cell Neurosci 13:271. https://doi.org/10.3389/fncel.2019.00271
7. Esposito MF, Malayil R, Hanes M, Deer T (2019) Unique characteristics of the dorsal root ganglion as a target for Neuromodulation. Pain Med (Malden, Mass) 20(Suppl 1):S23–S30. https://doi.org/10.1093/pm/pnz012
8. Ramírez M, Guerra-Juárez A, Miyake DY et al (2020) Correlation between corneal nerve density and symptoms of small fiber neuropathy in patients with fibromyalgia: the confounding role of severe anxiety or depression [published online ahead of print, 2020 Oct 10]. J Clin Rheumatol. https://doi.org/10.1097/RHU.0000000000001592
9. Bhakoo KK, Williams IT, Williams SR, Gadian DG, Noble MD (1996) Proton nuclear magnetic resonance spectroscopy of primary cells derived from nervous tissue. J Neurochem 66:1254–1263. https://doi.org/10.1046/j.1471-4159.1996.66031254.x
10. Yu X, Liu H, Hamel KA, Morvan MG, Yu S, Leff J, Guan Z, Braz JM, Basbaum AI (2020) Dorsal root ganglion macrophages contribute to both the initiation and persistence of neuropathic pain. Nat Commun 11(1):264 Published Jan 14. https://doi.org/10.1038/s41467-019-13839-2
11. Hanes WM, Olofsson PS, Talbot S, Tsaave T, Ochani M, Imperato GH et al (2016) Neuronal circuits modulate antigen flow through lymph nodes. Bioelectron Med 3:18–28. https://doi.org/10.15424/bioelectronmed.2016.00001
12. Gunasekaran M, Chatterjee PK, Shih A, Imperato GH, Addorisio M, Kumar G, Lee A, Graf JF, Meyer D, Marino M, Puleo C, Ashe J, Cox MA, Mak TW, Bouton C, Sherry B, Diamond B, Andersson U, Coleman TR, Metz CN, Tracey KJ, Chavan SS (2018) Immunization elicits antigen-specific antibody sequestration in dorsal root ganglia sensory neurons. Front Immunol 9:638. https://doi.org/10.3389/fimmu.2018.00638
13. McLachlan EM, Hu P (2014) Inflammation in dorsal root ganglia after peripheral nerve injury: effects of the sympathetic innervation.

Auton Neurosci 182:108–117. https://doi.org/10.1016/j.autneu.2013.12.009
14. Hung CH, Lee CH, Tsai MH, Chen CH, Lin HF, Hsu CY, Lai CL, Chen CC (2020) Activation of acid-sensing ion channel 3 by lysophosphatidylcholine 16:0 mediates psychological stress-induced fibromyalgia-like pain. Ann Rheum Dis. annrheumdis-2020-218329. https://doi.org/10.1136/annrheumdis-2020-218329
15. Birnbaum J, Duncan T, Owoyemi K, Wang KC, Carrino J, Chhabra A (2014) Use of a novel high-resolution magnetic resonance neurography protocol to detect abnormal dorsal root ganglia in Sjögren patients with neuropathic pain: case series of 10 patients and review of the literature. Medicine 93(3):121–134. https://doi.org/10.1097/MD.0000000000000024
16. Blitshteyn S, Brinth L, Hendrickson JE, Martinez-Lavin M (2018) Autonomic dysfunction and HPV immunization: an overview. Immunol Res 66(6):744–754. https://doi.org/10.1007/s12026-018-9036-1
17. Shiers S, Ray PR, Wangzhou A, Sankaranarayanan I, Tatsui CE, Rhines LD, Li Y, Uhelski ML, Dougherty PM, Price TJ (2020) ACE2 and SCARF expression in human dorsal root ganglion nociceptors: implications for SARS-CoV-2 virus neurological effects. Pain. 161:2494–2501. https://doi.org/10.1097/j.pain.0000000000002051
18. Martinez-Lavin M, Vidal M, Barbosa RE, Pineda C, Casanova JM, Nava A (2002) Norepinephrine-evoked pain in fibromyalgia. A randomized pilot study [ISRCTN70707830]. BMC Musculoskelet Disord 3:2. https://doi.org/10.1186/1471-2474-3-2
19. Light AR, White AT, Hughen RW, Light KC (2009) Moderate exercise increases expression for sensory, adrenergic, and immune genes in chronic fatigue syndrome patients but not in normal subjects. J Pain 10:1099–1112. https://doi.org/10.1016/j.jpain.2009.06.003
20. https://meassociation.org.uk/research/research-projects/pathology-of-me-cfs/. Accessed 15 Oct 2020
21. Goebel A, Gentry C, Cuhadar U et al (2019) Passive transfer of fibromyalgia pain from patients to mice. BioRXiv. https://doi.org/10.1101/713495
22. Grayston R, Czanner G, Elhadd K, Goebel A, Frank B, Üçeyler N, Malik RA, Alam U (2019) A systematic review and meta-analysis of the prevalence of small fiber pathology in fibromyalgia: implications for a new paradigm in fibromyalgia etiopathogenesis. Semin Arthritis Rheum 48(5):933–940. https://doi.org/10.1016/j.semarthrit.2018.08.003
23. Godel T, Pham M, Heiland S, Bendszus M, Bäumer P (2016) Human dorsal-root-ganglion perfusion measured in-vivo by MRI. Neuroimage 141:81–87. https://doi.org/10.1016/j.neuroimage.2016.07.030
24. Godel T, Köhn A, Muschol N, Kronlage M, Schwarz D, Kollmer J, Heiland S, Bendszus M, Mautner VF, Bäumer P (2018) Dorsal root ganglia in vivo morphometry and perfusion in female patients with Fabry disease. J Neurol 265:2723–2729. https://doi.org/10.1007/s00415-018-9053-y
25. Apostolidis L, Schwarz D, Xia A, Weiler M, Heckel A, Godel T, Heiland S, Schlemmer HP, Jäger D, Bendszus M, Bäumer P (2017) Dorsal root ganglia hypertrophy as in vivo correlate of oxaliplatin-induced polyneuropathy. PLoS One 12:e0183845. https://doi.org/10.1371/journal.pone.0183845
26. Sverrisdottir YB, Martin SC, Hadjipavlou G, Kent AR, Paterson DJ, FitzGerald JJ, Green AL (2020) Human dorsal root ganglion stimulation reduces sympathetic outflow and long-term blood pressure. JACC Basic Transl Sci 5(10):973–985
27. Pawela CP, Kramer JM, Hogan QH (2017) Dorsal root ganglion stimulation attenuates the BOLD signal response to noxious sensory input in specific brain regions: insights into a possible mechanism for analgesia. Neuroimage 147:10–18
28. Oaklander AL, Klein MM (2013) Evidence of small-fiber polyneuropathy in unexplained, juvenile-onset, widespread pain syndromes. Pediatrics 131(4):e1091–e1100