Current Trends in Neurology
Vol. 14, 2020

Mini-Review

Peripheral modulation of chronic visceral pain

Victor V. Chaban[1,2,*]

[1]Department of Internal Medicine, Charles R. Drew University of Medicine and Science;
[2]Department of Medicine, University of California Los Angeles, USA.

ABSTRACT

Chronic visceral pain is a complex and often a serious burden on patients' life. It is strongly implicated in the etiology of many diseases, which often are complicated by co-morbid depression and other psychiatric disorders, all of which pose significant health risks. Understanding the mechanisms of nociception is an important step in treating pain-associated chronic diseases. The inflammatory process that is often associated with nociception produces a number of mediators, which activate nociceptors by interacting with ligand-gated ion channels, activation of different signal transduction pathways or by sensitizing primary afferent neurons located within the dorsal root ganglia (DRG). Primary afferents studied *in vitro* or *in vivo* are well-accepted models to examine various nociceptive and anti-nociceptive signals in peripheral nervous system. This review focuses on the recent work in the area of peripheral modulation of chronic pain at the level of visceral primary afferent neurons. Many studies intended to develop a coherent framework for a better understanding of heterogeneity of nociceptive neurons functioning as a gate for pain transmission and novel therapeutic tool for pain relief. Specifically, recent studies from the author's research group helped to define the role of ATP-sensitive purinergic and vanilloid-sensitive TRPV1 receptors in DRG-mediated nociceptive pathways. Tropic and physiological changes associated with chronic visceral pain indeed are mediated through different pathways; therefore, designing new and specific anti-nociceptive therapies will have a major impact on quality of life in patients by significantly reducing pharmacological and therapeutic interventions.

KEYWORDS: nociception, sensory neurons, functional diseases.

INTRODUCTION

Understanding the mechanisms of peripheral modulation of nociception is an important step in treating pain. Chronic pain symptoms account up to 50% of all visits to seek health care, and therefore development of appropriate therapies is of great clinical and societal importance. Pain is strongly associated with many diseases with significant pathology. Despite a successful reduction of pain with available medications, majority of treated patients were seeking professional help again [1]. The average time duration between the onset of pain symptoms and the diagnosis is couple of years despite the fact that majority of patients with chronic pain suffer every day. Efficacious and reliable therapeutic intervention is still unavailable despite the tremendous economic burden imposed on healthcare to treat many diseases associated with chronic pain. Frequently, chronic pain does not correlate with pathologic findings at the time of clinical assessment and pharmacological interventions are still largely unsatisfactory with many side effects outweighing therapeutic benefits. Even alternative to drugs such as simulation of spinal cord produces limited benefit to patients.

*Email id: chaban@ucla.edu

Recently, a potential benefit in designing a new generation of neuromodulatory therapeutical agents that target primary sensory neurons located within DRG has been acknowledged by the clinical community. These new strategies target aberrant afferent signaling, and thus offer promise in chronic pain treatment. Spinal cord stimulation that targets afferent and descending projections to the dorsal spinal cord has not been successful in relieving pain, but DRG modulates sensory information transmission from the viscera to the central nervous system, the attenuation of which has been shown to effectively alleviate chronic pain from internal (visceral) organs. Visceral pain often progresses to chronic with the most common diagnoses such as endometriosis, Painful Bladder Syndrome (PBS), Irritable Bowel Syndrome (IBS), Inflammatory Bowel Disease (IBD), pelvic floor tension myalgia, vulvar vestibulitis, vulvodynia and others. In addition, alterations in the limbic and sympathetic nervous systems and hypothalamic-pituitary-adrenal axis mediate a cycle of hypervigilance for pain sensations from different organs, which can lead to descending induction of pathologic changes in these organs [2]. Determining the neural encoding function, and selective neuromodulation of DRG neurons innervating different viscera will certainly guide the design of next-generation therapies for effective management of chronic visceral pain.

Nociceptive pathways associated with chronic visceral pain

Patients with visceral pain frequently have multiple diagnoses because vicero-somatic and viscero-viseral hyperalgesia and allodynia result in the spread of a perception of pain from an initial site to adjacent areas. Pain may initially have only one pain source in the viscera, such as the uterus in dysmenorrhea or tissue implants in endometriosis but multitude mechanisms involving the peripheral and central nervous system modulation can lead to the development of nociceptive sensations from other adjacent organs. Often the etiology of visceral pain is not clear, as many symptoms from the reproductive system, gastrointestinal and urinary tracts, musculoskeletal, neurological systems co-occur in the same patient. Therefore, the treating clinician is often tempted to take a unidimensional approach to focus on specific organ system and to ignore the other systems involved as well as behavioral manifestations. For example, the manifestations of endometriosis-induced nociceptive signaling in some cases can be exacerbated by co-morbidity with other diseases such as IBS, PBS, vulvodynia and fibromyalgia. It has also been shown that ectopic implants can develop their own sensory nerve supply both in patients and animal models. Sensory input arriving from the visceral organs to the spinal cord divergences at the level of DRG which modulate sensory input from periphery to the central nervous system. Visceral pain may be manifestation from a single organ such as colon, urinary bladder or uterus (in females) or may arise from algogenic conditions affecting more than one visceral organ [3]. Cross-sensitization in the pelvis implies the transmission of noxious stimuli from one organ to another through an adjacent non-affected tissue resulting in functional changes without identifiable inflammatory mediator(s). It is quite possible to modulate pain from one visceral organ to another: treatment of the endometriotic lesions results in the improvement of spontaneous and referred urinary symptoms. Pelvic organ cross-sensitization can be considered as one of the factors contributing to chronic visceral pain [4, 5].

Chronic pelvic pain (CPP) syndrome affects up to a quarter of reproductive age women and results in dysmenorrhea, menstrual irregularities, and back pain as the most common clinical presentation of chronic pain. One of the causes of CPP is indeed endometriosis. In addition, CPP patients report adverse mood, difficulties in their social and professional life. Assessing the impact of chronic visceral pain on patient's wellbeing has become an important focus in the therapeutic and biobehavioral management. Most women with complaints of pelvic pain will undergo laparoscopy that often is unsuccessful due to lack of intraperitoneal pathology. Pain out of proportion is the most identifiable and dramatic consequence of CPP and is responsible for a highly negative impact on quality of life or subsequent workforce loss. Up to 15% of women in the US have experienced CPP buy only 10% of these consulted a gynecologist and overwhelming majority did not consult any physician from other medical disciplines.

Due to unmet needs, many health care providers have launched a call for more focused research and treatment of CPP [6].

Our understanding of visceral hyperalgesia is less obvious by comparison to cutaneous hyperalgesia, which is believed to arise as a consequence of the sensitization of peripheral nociceptors due to long-lasting changes in the excitability. Endometriosis is currently defined as a chronic functional syndrome characterized by recurring nociceptive symptoms. In the context of visceral pain, the vanilloid receptor (TRPV1) is a DRG-specific cation channel to determine thermal- and inflammatory-induced nociceptive signals. Mice lacking TRP1 receptor gene have deficits in thermal- or inflammatory-induced hyperalgesia [7]. Various inflammatory mediators such as prostaglandin E2 (PGE2) and bradykinin potentiate TRPV1. The potentiation of TRPV1 activity can be quantified by measuring the differences of capsaicin- induced Ca^{2+} concentration changes before and after receptor activation. Significantly, a subset of DRG neurons respond to both capsaicin and ATP indicating that there may be cross-activation of these receptors that may underlie the sensitization of visceral nociceptors. Capsaicin-induced TPRV1 receptor-mediated changes in $[Ca^{2+}]_i$ may represent a level of DRG activation to noxious cutaneous stimulation while ATP-induced changes in $[Ca^{2+}]_i$ may reflect the level of DRG neuron sensitization to noxious visceral stimuli since ATP is released by noxious stimuli from tissue damage near the nerve terminals [8].

Primary DRG neuron culture has been a useful model system for investigating sensory physiology and putative nociceptive signaling [9]. ATP-induced intracellular calcium concentration ($[Ca^{2+}]_i$) transients in cultured DRG neurons have been used to model the response of nociceptors to painful stimuli. Visceral nociception and nociceptor sensitization appear to be regulated by P2X3 and TRPV1. Sensory neurons' response to ATP and capsaicin suggest that visceral afferent nociceptors can be modulated by Ca^{2+} changes at a new site at the level of primary afferent neurons. Several lines of evidence indicated that there is a close relationship between nerve fiber density and associated pain. There is a significant increase in nerve fiber density in women with inflammation who reported pelvic pain, suggesting these nerve fibers may play an important role in the mechanisms of pain generation. Accumulating literatures described that Substance P (SP) is involved in the inflammatory and pain responses, suggesting a possible role of SP nerve fibers in the generation of pain-related sensations. SP, which is synthesized and contained in 20-30% of DRG neurons, is involved in the transmission of nociceptive information to the central nerve system. SP is contained primarily in, and co-released from, small-diameter primary afferent fibers upon noxious stimulation. Activation of nociceptive C and Aδ primary afferent fibers by electrical, chemical, or mechanical stimulation has been reported to release SP. Visceral nociceptive C-fibers can be activated by SP, representing an endogenous system regulating inflammatory, immune responses, and visceral hypersensitivity. SP afferent fibers play an important role in the pathogenesis of visceral hyperalgesia, suggesting critical role of SP in regulation of visceral nociception. ATP is a peripheral mediator of pain, which contributes to the activation of sensory afferents by activating ATP receptors following inflammation or nerve injury. It may correlate with SP release and play an important role in modulating nociception in primary sensory neurons [2].

The response properties of visceral extrinsic primary afferent nerves play a significant role in the etiology of nociception. Hypersensitivity of visceral nociceptors could result from excessive production of modulatory neurotransmitters. In addition to direct stimulation of stretch-activated channels on primary afferent neurons located in DRG, chemicals produced by different target cells that respond to inflammation also modulate the nociception. The incidence of persistent, episodic, and chronic visceral pain is more prevalent in females, which suggests hormonal regulation of visceral nociception. Despite extensive research on the properties of pelvic and splanchnic afferent nerves, little is known about the mechanisms underlying normal and pathological signal transduction pathways underlying chronic pain. Considerable efforts were made by the scientific community and the pharmaceutical industry to develop novel pharmacological treatments aimed

at chronic visceral pain, but the traditional approaches to identify and evaluate novel drugs have largely failed to translate into effective therapeutic treatments.

DRG neurons in short-term culture retain the expression of receptors (P2X and TRPV1) which mediate the response to putative nociceptive signals. In general, depending on the channel activation activity of primary afferent neurons may result in hyperpolarization, depolarization or primarily Ca^{2+} influx. DRGs transmit information about chemical or mechanical stimulation from the periphery to the brain. They continue to respond to different agonists *in vito* mimicking *in vivo* activation. Nociceptors are small to medium size DRG neurons whose peripheral processes detect potentially damaging physical and chemical stimuli. The peripheral sensitization of nerve fibers is transient and depends on the duration of stimuli and presence of inflammation. An important advantage is that these neurons can be studied apart from endogenous signals. Available data clearly showed the new role of nociceptors in pathophysiological aspects of chronic pelvic pain [9]. A multicomponent conceptual model for developing new therapies for nociceptive disorders in addition to physiologic should involve cognitive and behavior factors since these systems may affect chronic visceral pain.

New research concepts for therapeutic interventions of chronic visceral pain

Visceral pain is one of the most prevalent human health problems that can be associated by the concomitant decline in cognitive and motor functions. The complex interplay between diverse group of nociceptive mediators, genetic imprint and environmental factors may ultimately determine the outcome of clinical etiology or progression of therapy. Pain is a subjective feeling that is difficult to standardize for traditional scientific analysis. The causes of visceral pain are often not clear, as there are many symptoms of dysfunction from the neurological, psychological, reproductive, gastrointestinal, urinary and musculoskeletal systems in the same patient without a clear relationship between the severities. There is no clear relationship between the severity of the visceral pain and pathology in the different visceral organs. Compared with non-visceral ('somatic') pain, visceral pain is difficult to localize and is referred to other tissues. Sensory input from healthy viscera gives rise to little conscious sensation, and stimuli that evoke pain from the somatic tissue fail to be noticeably perceived from the viscera. Afferent sensitization (i.e., increase in excitability) is manifested by a reduced response threshold, and enhanced response magnitude to mechanical stimulation [10]. There are two essential components of pain: discriminative and affective. The discriminative component includes the ability to identify the stimulus as originating from specific visceral tissue, and determine some of the properties of the stimulus such as localization in space, timing and a continuum of intensities. The affective component is the experience that motivates escape, and protective behavior. All of these components of chronic visceral pain must be considered to understand the basis of visceral nociception.

Because of the inherent subjectivity to pain, there is a wide disparity among patients in their experience. There is also a tension between the subjectivity of the patient's pain tolerance and the findings of the clinician that are proportionate to the patient's complaints. Therefore, an important focus of pain management must include the deep assessment of a patient's health history and quality of life that include their emotional, physical, and cognitive states. There is a growing concern that not enough emphasis is placed on a clinical validity to balance between biomedical and cognitive approaches in view of the maintenance of chronic pain syndromes. Since nociceptive responses involve vast messenger molecules and receptors of different signal transduction pathways, a balance between these messengers and various physiological body systems presents major difficulties for appropriate therapeutic management.

Visceral nociception and nociceptor sensitization appear to be regulated by ATP/capsaicin. The medium (diameter < 40 microns) and small (diameter < 25 microns) diameter DRG neurons in short-term culture respond to ATP/capsaicin, indicating that there may be cross-activation of these receptors that may underlie the pain perception of visceral nociceptors [9]. Furthermore,

the prostaglandin (PGE2) is synthesized and released in response to damaged tissues, contributes to hyperalgesia, and is involved in the chronic inflammatory reactions. The sensitizing actions of PGE2 on retrogradely labeled visceral DRG neurons are mediated through the pain signaling pathway such as cAMP/PKA. The abdominal pain related with IBS and acute and chronic/repeated pelvic pain are good examples of this type of sensitization [11]. Patients who have pain related to IBS are mostly depressed and seek professional biobehavioral therapy. Only clear understanding of implicated physiological and psychological mechanisms can lead to more efficient therapies in treating chronic pain.

Pharmacologic management of visceral pain has been notoriously difficult and unsatisfactory. Trials with conventional analgesics (e.g., NSAIDs, acetaminophen, aspirin, opioids) did not significantly improve patient's symptoms [12]. IBS patients with comorbid anxiety and/or depression may benefit from anxiolytic (benzodiazepine) or antidepressant drugs (TCAs, SSRI and SNRI) [13]. Drugs used to manage neuropathic pain (gabapentin, pregabalin) require confirmation of their efficacy in managing visceral pain [14]. Despite the recent moderate successes of eluxadoline and linaclotide, most drugs are either ineffective in relieving visceral pain or cause excessive GI-related side effects (e.g., lubiprostone, loperamide, and the 5-HT3 antagonists alosetron, granisetron, and ondansetron) [12].

The lumbosacral DRG is a promising neuromodulation target for treating visceral pain

Due to the sparse nature of visceral organ innervation, knowledge of the topologic distribution of visceral neurons in the DRG is crucial for managing visceral pain *via* selective DRG modulation. Data from the author's research group suggest that visceral DRG express nociceptive ATP-sensitive purinergic (P2X3) and capsaicin-sensitive vanilloid (TRPV1) receptors [2, 9, 11]. DRG neurons express mGluR2/3 receptors indicating that glutamate could have a substantial inhibitory effect of primary afferent function, reducing and/or fine-tuning sensory input before transmission to the spinal cord. Glutamate toxicity and dysfunction of ligand-gated Ca^{2+} channels can also cause neuronal damage. Increased glutamate level may lead to an excessive Ca^{2+} influx that causes misfolding of proteins facilitating their toxic aggregation. An increased cytosolic Ca^{2+} level may impair the buffer systems of the endoplasmic reticulum causing Ca^{2+} leak. Therefore, different Ca^{2+}-release channels such as ATP-gated P2X, P/Q-type voltage-gated Ca^{2+} channels and TRPA1 (transient receptor potential) non- selective cation channels are localized to the cytoplasm [15].

In DRG neurons innervating different pelvic viscera have a greater $[Ca^{2+}]_i$ response to subsequent ATP and capsaicin and N-methyl-D-aspartate (NMDA) stimulation than somatic afferents [9]. These data may indicate that viscerally specific neurons express receptors with higher permeability to Ca^{2+}, which can modulate transduction of nociceptive signals and suggest that visceral afferents are functionally different from somatic afferents. Sensitization of primary afferent neurons may play a role in the enhanced perception of visceral sensation leading to pain. Acute and recurrent/chronic pelvic pain from IBS, PBS and CPP are all visceral pain sensations that may result in part from sensitization. Within the context of the cross-sensitization hypothesis, inflammation sensitizes non-inflamed viscera that are innervated by the same DRG, and/or cross-sensitization occurs as a result of intra-DRG release of sensitizing mediators such as ATP within the DRG [2]. Sensitization of primary afferent neurons to stimulation may play a role in the enhanced perception of visceral sensation and pain. Compared with dorsal spinal cord and peripheral nerve therapies, relatively few neuromodulatory strategies have been employed to target visceral DRG for the treatment of chronic pain. However, there are several obvious advantages to targeting the DRG. First, the confined location of DRG in inter-vertebral foramina can significantly increase chances of successful neuromodulation, Second, DRG are located outside the enclosure of cerebrospinal fluid. Third, unlike direct stimulation of spinal nerves that contain both motor efferent and sensory afferent fibers, DRG contain the somata

of sensory afferent neurons only, thus permitting selective neuromodulation of the sensory innervation. Fourth, afferent sensitization correlates with pathophysiology of the somata in the DRG, including changes in excitability, gene expression, membrane and cytosol protein levels, and glial cell functions. Thus, DRG neuromodulation could have profound therapeutic impact.

Chronic visceral pain is not the result of a single mediator activity such as prostaglandin PGE-2, or the activity of a single channel protein such as P2X or TRPV1. The maintenance of central sensitization depends on persistent, ongoing peripheral nerve activity at the original injury site. The physiology of the sensory system is dynamically changing and adapting through molecular and cellular dialog within and between cells that modulate nociception. In the peripheral nervous system, nerve injury models like chronic constriction injury reveal a highly dynamic process in the transition from acute to chronic pain, which results from a dialog between neurons, glia and the infiltrating immune cells. However, the fundamental physiology of peripheral modulation of nociception also involves changes in gene expression for hundreds of genes, and hence more expansive approach is needed. Comprehensive assessment of the transcriptome of the dorsal root ganglia viewed across the transition from acute to chronic pain will be necessary to understand this complicated pathway.

CONCLUSION

Chronic pain impacts many patients and is responsible for a staggering healthcare cost. Patients with visceral pain may at first have only one source of pain, but numerous mechanisms involving the central and peripheral sensitization may result in the development of painful sensations in adjacent organs. Individual response may affect ascending somatosensory and descending efferent systems. Similar to other chronic diseases, a multicomponent conceptual model, which involves physiologic, cognitive and behavior factors is necessary to understand chronic visceral pain. Central sensitization is an important underlying contributor to chronic pain states, but it remains poorly understood how sensitization persists when the inciting injury has apparently resolved. Despite the wealth of knowledge about critical players that induce peripheral sensitization upon injury, it remains poorly understood how this sensitization is maintained. This critical gap in knowledge is a major obstacle hindering the development of new effective therapies. Chronic pain is also the root cause of the national opioid health crisis, which adds to health care costs and deaths. Thus, new pain therapies based on detailed understanding of chronic pain mechanisms are needed as alternatives to opioid analgesics.

Chronic pain management is a major scientific and public health care challenge, as current analgesic drugs rarely provide sufficient efficacy without serious side effects. Sensitivity to pain remains long after tissue healing. The discovery of the neurochemical mechanisms that maintain chronic pain hypersensitivity is needed for a better treatment. Current treatment options are often limited, and significant side effects include risk of addiction. A multicomponent conceptual model of chronic visceral pain must involve physiologic, cognitive and behavior factors necessary for developing new effective therapies.

ACKNOWLEDGEMENTS

This work was supported by National Institute of Health NS 063939 (PI- V. Chaban). Research reported in this publication was supported by the National Institute on Minority Health and Health Disparities of the National Institutes of Health under award number S21 MD000103. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

CONFLICT OF INTEREST STATEMENT

There is no conflict of interest to disclose for this manuscript

REFERENCES

1. Gatchel, R. J., McGeary, D. D., McGeary, C. A. and Lippe, B. 2014, American Psychologist, 69(2), 119-130.
2. Chaban, V. 2020, Calcium Signaling and Nervous System. Overview and Directions for Research. Nova Medicine and Health, New York.

3. Malykhina, A. 2007, Neuroscience, 149(3), 660-672.
4. Giamberardino, M., Costantini, R., Affaitati, G., Fabrizio, A., Lapenna, D., Tafuri, E. and Mezetti, A. 2010, Pain, 151(2), 307-322.
5. Pezzone, M., Liang, R. and Frasier, M. 2005, Gastroenterol., 128(7), 1953-1964.
6. Yosef, A., Allaire, C., Williams, C., Ahmed, A., Al-Hussaini, T., Abdellah, M., Wong, F., Lisonkova, S. and Yong, P. 2015, Am. J. Obstet. Gynecol., 6, 760.e1-760.e14.
7. Petruska, J., Napaporn, J., Johnson, R, Gu, J. and Cooper, B. 2000, J. Neurophysiol., 84(5), 2365-2379.
8. Burnstock, G. 2001, Tren. Pharmacol. Sci., 22(4), 182-188.
9. Chaban, V. 2016, Unraveling the Enigma of Visceral Pain, Nova Publishers, New York.
10. Bielefeldt, K. and Gebhart, G. 2015, Wall and Melzack's Textbook of Pain, M. Koltzenburg and S. McMahon (Eds.), Churchill-Livingstone: Saunders, Philadelphia.
11. Chaban, V. (Ed.). 2017, Irritable Bowel Syndrome: Novel Concepts for Research and Treatment, InTech, London.
12. Chen, L., Ilham, S. and Feng, B. 2017, Anesthesiol. Pain Med., 7, e42747.
13. Rahimi, R., Nikfar, S., Rezaie, A. and Abdollahi, M. 2009, World J. Gastroenterol., 15, 1548-1553.
14. Houghton, L., Fell, C., Whorwell, P., Jones, I., Sudworth, D. and Gale, J. 2007, Gut, 56, 1218-1225.
15. Tadeschi, V., Petrozziello, T. and Secondo, A. 2019, Cell, 8(10), 1216-1231.