Chapter 1

Neuroplasticity of Primary Sensory Neurons in Visceral Nociception

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http://dx.doi.org/10.5772/intechopen.73699

Abstract

Chronic visceral pain is the most common complication of many functional disorders that do not have a defined pathophysiological cause. Functional pain syndromes include common disorders, such as irritable bowel syndrome (gastroenterology), chronic pelvic pain (gynecology), interstitial cystitis/painful bladder syndrome (urology), fibromyalgia (rheumatology), across multiple medical disciplines. Patients suffering from functional diseases may progress to cognitive decline and depression through neuroplastic changes not only at the level of the central nervous system but also in the periphery. Moreover, most functional diseases are much more prevalent in women than men suggesting estrogen modulation of nociceptive pathways. Defining the etiology of functional diseases for possible therapeutic interventions will have a significant impact on our understanding of observed gender differences and on improving patient's quality of life.

Keywords: neuroplasticity, functional diseases, visceral pain, sensory neurons

1. Introduction

Despite considerable efforts made by the medical research community and pharmaceutical industry to develop effective therapeutical treatments aimed to treat chronic visceral pain resulted from functional disease, there is little progress to date. Functional syndromes are estimated to affect up to 15–20% of the population worldwide. Symptom description of interstitial cystitis/painful bladder syndrome (IC/PBS, urgency, frequency, and bladder pain generally relieved by voiding) is parallel to the description of irritable bowel syndrome-diarrhea (IBS-D) predominance (urgency, frequency and abdominal pain) relieved by defecation. IBS stands in contrast to a bowel's structural disorder: unlike ulcerative colitis and Crohn's

disease, which are forms of inflammatory bowel disease (IBD), it does not cause changes in bowel tissue. The cause of functional disorders is unknown. Chronic abdominal complaints are without a structural or biochemical cause. Bloating, mucous in stools, diarrhea, constipation or alternating diarrhea and constipation, depression, anxiety or stress are also common symptoms of IBS. Hypersensitivity of visceral primary afferent neurons could result from excessive production of different modulatory neurotransmitters in response to changes in their signal transduction pathways [1]. Nociceptors are small-to-medium size dorsal root ganglia (DRG) neurons, whose peripheral processes detect nociceptive physical and chemical stimuli. There is often no clear relationship between the severity of the chronic pelvic pain and pathology in the pelvic viscera, and there are also noticeable gender differences in the prevalence of functional diseases that affect more women than men. Most of studies in this area were focused on the central nervous system (CNS); however, our recent data that estrogen can gate primary afferent response to modulate nociception support the idea about the involvement of the peripheral nervous system (PNS) in the etiology of a wide range of the functional and inflammatory diseases [2]. This potentially could involve neuroplastic changes in primary sensory neurons and can be a novel target for therapeutic interventions for patients suffering from chronic visceral pain associated with functional diseases. Despite a successful reduction of pain using available analgesics, visceral pain relapses in most patients. Currently, it is a time for paradigm shift what we consider as visceral nociception, and in this report, author looks for possible new mechanisms of peripheral modulation of primary afferent sensory neurons in development of chronic pelvic pain.

2. Neuroplasticity in peripheral nervous system

Traditionally, the main mechanism involved in development of chronic visceral pain is thought to be neuroinflammation. This pathway effects peripheral and central nerve sensitization and/or dysfunction of inhibitory descending pathways [3]. However, in clinical studies, visceral nociception strongly affects negative sensations that difficult to correlate with visceral traumata. Most nociceptive systems involved in peripheral sensitization originate in free sensory nerve endings of target organs that send their signals toward primary afferent sensory neurons within the lumbar-sacral regions of dorsal root ganglia (L_1-S_3 DRG).

Visceral sensitization may develop as a result of interaction between the nervous and immune systems. All visceral afferents can be sensitized by proinflammatory mediators, such as serotonin, histamine, nitric oxide and ATP, leading to neuropathic hyperalgesia. During inflammation, mast cells and leukocytes secrete inflammatory mediators such as cytokines and prostaglandins that activate polymodal nociceptors triggering the response of normally silent mechano-insensitive receptors. Mast cell mediators can also activate vanilloid receptors (TRPV1), purinergic ($P2X_3$) and bradykinin (BK2) at PNS, causing hyperalgesia.

The serotonergic pathway, one of the main inhibitory mechanisms in the CNS, may also be functionally important in facilitating peripherally mediated visceral pain [4]. Most antidepressants gradually increase serotonin level in the brain. Indeed, depression has been reported to be associated with immunosuppression. Serotonin plays a major role in the gut-brain axis by

http://dx.doi.org/10.5772/intechopen.73699

modulating intestinal movement and the perception of visceral pain. An imbalance of serotonin in the gut, an improper reaction of the digestive system to serotonin, or a faulty serotoninergic network between the gut and the brain may be a cause of depression associated with functional diseases. Enteric nervous systems that innervate gastrointestinal tract include differentiated (visceral) primary afferent neurons that innervate intrinsic and extrinsic pathways implicated in the pathology of many inflammatory as well as functional diseases. There is a noticeable correlation between inflammation induced by gut infection and symptom occurrence of functional disorders such as IBS [5]. New data changed the previous paradigm that each primary afferent neuron innervates only one viscus. The concept of viscero-visceral cross-sensitization is well accepted and has been documented clinically [6]. Inflammation in one organ can induce peripheral (in addition to central) sensitization affecting another viscera. Therefore, nociceptive mechanisms involved in the progression of functional diseases are complicated by comorbid disorders. Both components of pain—discriminative and affective—concomitantly affect motor and cognitive systems. These systems can be gated by estrogen to modulate perception of pain, pain threshold and tolerance.

3. Gender differences in visceral pain

The chronic pelvic pain (CPP) from pelvic structures is more prevalent in female subjects compared to males. In clinical studies, this sexual dimorphism is well recognized: the incidence of functional disorders is 2–3 times higher in women with IBS and even greater with IC/PBS. A large body of literature supports that concept indicating estrogen modulation of different nociceptive pathways [2]. In our previous studies, we found that estrogen receptors (ERα and ERβ) are present in small-to-medium size DRG neurons (presumably nociceptors) and ATP-sensitive DRG neurons respond to 17β-estradiol (E_2) [7], which correlated well with the idea that visceral afferents are E_2 sensitive. Our data clearly suggest that in addition to CNS actions, E_2 can act in the periphery to modulate nociception [1]. Specifically, E_2 acts in DRG neurons to modulate L-type VGCC and through group II metabotropic glutamate receptors [8]. One prominent way E_2 modulates neuronal excitability is through the interaction with antinociceptive opioids such as enkephalins, β-endorphin and pronociceptive nociceptin/orphanin. Furthermore, our hypothesis is that increased nociceptive input from an inflamed organ (i.e. uterus) sensitizes neurons that receive convergent input from an unaffected organ (i.e. colon). In summary, our data suggest that potential site of visceral cross-sensitivity is the dorsal root ganglion [9]. DRG neurons could be responsible for changes observed in the perception of pain during the etiology of different functional syndromes associated with pain.

Several lines of evidence indicate that E_2 directly influences the functions of primary afferent neurons. Both estrogen receptors (ERα and ERβ) are present in DRG and visceral pain is affected by hormonal level in cycling females [1, 2]. Even a large body of literature supports the idea that E_2 modulates nociceptive responses in pelvic pain syndromes, the exact mechanism remains unresolved. Within the context of our hypothesis, E2 modulation of nociceptive response depends on the type of pain, its durations and the involvement of other nociceptive-mediated mechanisms.

4. Primary afferent nociceptors as target in modulation of nociception

Visceral nociceptive signal transduction depends on type of pain (type of sensory fiber), severity, duration and effects of other endogenous nociceptive-mediated molecules. Extrinsic primary afferent fibers can be directly modulated by activation of different chemosensitive or mechanosensitive receptors in target organs. There are 31 pairs of polymodal nerves carrying sensory motor and autonomic signal transduction in human spinal cord. This information is further transferred to the CNS by the spinothalamic ascending pathways to the primary sensory motor cortex for integration and analysis. In DRG neurons, afferent and efferent processes function as a single axon-proximal and distal part connected to somata as an offshoot. DRG first synapses with a dorsal horn neuron through the contralateral spinothalamic tract. These primary sensory neurons have been studied intensively in pain sensory physiology. Small-to-medium size DRG neurons express a variety of receptors involved in pain perception such as ATP-sensitive P2X3, capsaicin-sensitive TRPV1 or acid-sensitive ASIC channels. Since DRG neurons are responsive to estrogen [10] through ERα type [11] and show sensitization, it makes them a suitable model to study gender differences in nociception. Interestingly, TRPV1 and P2X3 transduction is significantly altered during inflammatory response. DRG is also an important site for primary afferent fiber convergence and visceral organ cross-sensitization. Even the role of DRG in neuromodulation of nociception is a novel topic in visceral and chronic pain, we hope to convince the scientific community that the DRG is an active structure rather than passive. The future studies may reveal more neuroplastic changes at the level of first-order sensory neurons. New hypotheses will drive translational research that should improve the outcomes of clinical interventions to relive patients from suffering.

5. Discussion

Pain is a complex and personal experience. Chronic visceral pain affects mood, and social and professional life. A delicate balance between biochemical and physiological changes and cognitive approaches is the most appropriate strategy to study clinical aspects of nociception. Pain in women can originate due to inflammation of a pelvic organ (gut, uterus and bladder) that can heighten the sensitivity of noninflamed organ that are innervated by the same afferent neuronal pathway [12]. Commonly, the overlapping of pelvic pain occurs between the lower gut, uterus and urinary bladder. Common convergence of different visceral primary afferents onto one spinal secondary neuron transmitting signals to the supraspinal nuclei can either synthesize or attenuate intrinsic cellular functions via activation of $P2X_3$ receptors by ATP and TRPV1 receptors by capsaicin within the L_1-S_3 DRG neurons. Furthermore, in addition to ATP, prostaglandin E2 (PGE2) is synthesized and realized during distention and contributes to hyperalgesia. We showed that PGE2 enhanced calcium responses induced by pronociceptive molecules such as ATP and capsaicin [2]. Together, our studies opened up a new paradigm of neuroplasticity: modulation of primary sensory neurons by sex steroids that may lead to structural changes within DRG. Estrogen can gate primary afferent nociceptors to enhance or decrease nociception.

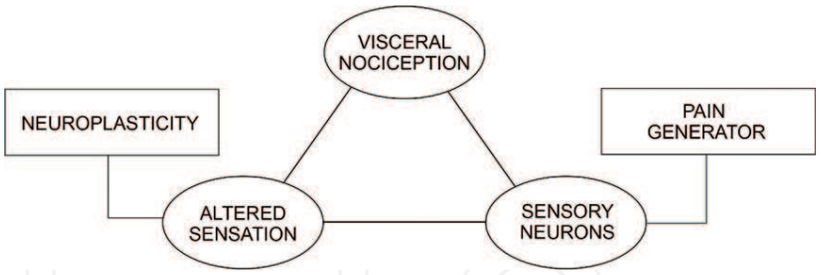

Figure 1. Conceptual model of regulatory mechanisms mediating neuroplasticity of visceral nociception at the level of primary afferent sensory neurons.

Pelvic pain is very subjective and thus difficult to standardize for any scientific modeling since its etiology affects different systems. In addition to nervous, urinary, gastrointestinal, reproductive and psychological systems are involved. Nociceptive behavior is highly complex: the affective experience leads to avoidance and often protective escape. New data will hopefully lead to the development of effective gender-specific therapies. Involvement of peripheral nervous system in mediating and/or regulating chronic visceral pain associated with nociception through structural and physiological changes at the level of DRG is confirmed. The new principle of neuroplasticity at the level of peripheral nervous system is important to understand the etiology of many chronic diseases associated with visceral pain (**Figure 1**). Peripheral sensitization at the level of primary afferent neurons (pain generator) leads to neuroplastic changes with major structural alterations. The observation that 17β-estradiol increased survival of DRG neurons [13] put this sex steroid hormone as potential neuroplastic modulator of sensory afferent neurons. Estradiol may act as transmitter molecule by changing excitability of DRG [14]. DRG neuroplasticity also contributes to hyperalgesia [15]. Noteworthy, treating pain can restore normal nervous system function. As with all new stories, the unusual concept gets most attention of medical and clinical communities. We convey the message by driving translational science into the new horizon and propose a multicomponent conceptual model of neuroplasticity associated with functional disorders.

Acknowledgements

This work is supported by National Institute of Health grant: SC1 NS 063939 (PI—Victor Chaban).

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