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Mini-Review

Visceral nociception and functional diseases

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ABSTRACT

This mini-review summarizes the different pain-associated diseases and potential mechanisms that may help to achieve a deeper understanding of gender differences presented in clinical aspects of the functional syndromes. 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), Interstitial Cystitis/Painful Bladder Syndrome (Urology), Fibromyalgia (Rheumatology), and Chronic Pelvic Pain (Gynecology) and cross multiple medical disciplines. Patients suffering from functional diseases may progress to cognitive decline and depression through neuroplastic changes not only at the level of central nervous system but also in the periphery. Pain pathways are activated in virtually all human diseases and only a thorough understanding of the mechanism implicated in the functional, painful disorders can truly contribute to more efficient therapeutic interventions.

KEYWORDS: sensory neurons, functional diseases, visceral nociception.

INTRODUCTION

The incidence of persistent, episodic or chronic visceral pain disorders is more prevalent in female patients. Disorders such as Irritable Bowel Syndrome or Painful Bladder Syndrome are 2-3 times more prevalent in women than men but there is a significant lack of translational research that explores their basic mechanisms [1]. The published literature also suggest that many patients with functional disorders have co-morbidity with other conditions such panic disorder, generalized anxiety disorder, social phobia, posttraumatic stress disorder, and major depression or inflammatory-induced endometriosis [2]. Both physiological and psychological variables appear to play significant roles in the development of functional syndromes; therefore cognitive-behavioral therapy has received increased attention in the conceptualization of these diseases. The fact that cognitive or physiological changes are similar in all functional disorders suggests a model in which alteration in the central nervous system circuits in predisposed individuals is triggered by the similar pathophysiology in affected patients.

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The influence of gonadal hormones on visceral pain perception

Most functional syndromes are associated with pain, which is the symptom that patients list as the most depressing and it is a major factor for consulting a physician. Estrogen receptor alpha (ERα) plays a significant role in modulating pain signaling. In females, 17β-estradiol (E2) that activates ERα receptor is involved in inflammation and pain. The pain originating from the pelvic structures often overlaps, manifesting a diffuse peritoneal pain. Typically, this type of pain is functional in nature without any clear pathological manifestation in the organ. However, the pain due to dysfunction of a specific pelvic organ, such as inflammation, obstruction or stricture, can overlap with other organs. Commonly, the overlapping of pelvic pain occurs between the urinary bladder, lower gut and uterine inflammation. This pelvic

cross-organ pain can occur: i) due to cross-signaling (chemical and electrical) between the cell somas and satellite glial cells (SGC) at the level of dorsal root ganglion (DRG), ii) dichotomy of peripheral processes of one primary afferent fiber supplying two pelvic structures [3], iii) common convergence of two visceral primary afferents from two pelvic organs onto one spinal secondary neuron transmitting pain signal to the supraspinal nuclei and *via* circulating humoral and pro-inflammatory components including cytokines. These substances can either sensitize or attenuate intrinsic cellular functions *via* the activation or inactivation ionic channels such as ATP-sensitive purinergic P2X3/2, and capsaicin-sensitive TRPV1 receptors of the primary sensory neurons [4]. The main focus of future studies will be to identify how estrogen and other sex-steroid hormones can produce endogenous analgesia by acting peripherally at the level of DRG and how this can manage cross-organ pain sensitization that may contribute a gender-specific therapeutic target to manage visceral pain.

Role of primary afferent neurons in nociception

The cell bodies of primary visceral spinal afferent neurons are located within dorsal root ganglion (DRG). Direct activation of chemosensitive receptors and ion channels on their peripheral terminals and modulation of neuronal excitability activates extrinsic primary afferent nerves. Nociceptors belong predominantly to small-diameter DRG neurons whose peripheral processes detect different and potentially damaging physical and chemical stimuli. The terminals of primary visceral afferent neurons are described as having no specific morphological specialization. Viscerally labeled C-fibers originating from DRG activated by ATP released by noxious stimuli from cells in target organs have been implicated as mediators of noxious stimulus intensities. Visceral nociceptive capsaicin-sensitive C-fibers are activated by ATP and excitatory amino acids that are released by noxious stimuli from cells in target organs (paracrine action), from afferent terminals themselves (autocrine action), or in sensory ganglia [1].

Alteration in signal transduction of primary afferent neurons can result in enhanced perception of the visceral sensation that is common in patients with different disorders, resulting in elevated pain perception. Peripheral sensitization can develop in response to sustained stimulation, inflammation, and nerve injury. Visceral pain is different from cutaneous pain, based on clinical, neurophysiological and pharmacological characteristics. The pathophysiology of visceral hyperalgesia is less well-known than its cutaneous counterpart, and our understanding of visceral hyperalgesia is colored 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 of spinal neurons.

Modulation of nociception at the level of primary afferent sensory neurons

Neuroinflammation is thought to be a main mechanism involved in development of chronic visceral pain. During inflammation, immune cells secrete inflammatory mediators such as cytokines and prostaglandins that activate nociceptors triggering the response of normally silent vanilloid (TRPV1), purinergic (P2X3), bradykinin (BK2) receptors at the level of peripheral nervous system, causing hyperalgesia. However, in clinical studies, visceral nociception strongly affects negative sensations that are 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. Visceral sensitization may also develop as a result of interaction of nervous and immune systems. All visceral afferents can be sensitized by pro-inflammatory mediators such as serotonin, histamine, nitric oxide and ATP, leading to neuropathic hyperalgesia. Nociceptive mechanisms involved in the progression of functional diseases are complicated by both components of pain, discriminative and affective, that concomitantly affect motor and cognitive systems. These systems can be gated by estrogen to modulate perception of pain, pain threshold and tolerance, potentially leading to neuroplastic changes at the level of DRG. Such a novel mechanism has recently been proposed in the etiology of Irritable Bowel Syndrome [5].

CONCLUSION

Sex is a biological variable that is frequently ignored in study designs and analyses, leading to

an incomplete understanding of potential sex-based differences in basic science mechanisms during the disease processes. Estrogen has a significant role in modulating visceral sensitivity, indicating that sex steroid alterations in sensory processing may underlie sex-based differences in functional pain symptoms. However, reports of estrogen modulation of visceral and somatic nociceptive sensitivity are inconsistent. To help resolve these inconsistencies, the clinical and scientific community needs to focus on sex steroid actions on nervous system. Little is known about estrogen-mediated mechanisms in peripheral nervous system, but the fact that DRG neurons express both estrogen receptors (ERα and ERβ) and respond to estrogen treatment by modulating different nociceptive pathways suggest a potential target for pain treatment. Pain accounts for nearly 25% of all primary health care visits worldwide and contributes substantially to high medical costs as well as excess personal suffering and disability, especially for women. Studies in this domain have the potential to transform our understanding of visceral health. New discoveries of the pathways through which intra-organ interactions are biologically embedded in the individual‘s constitution will lead to a better understanding of the etiology of functional diseases associated with visceral nociception.

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CONFLICT OF INTEREST STATEMENT

There is no conflict of interest to disclose for this manuscript.

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