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Irritable Bowel Syndrome: Functional Gastrointestinal Disease Regulated by Nervous System

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Abstract

A functional disorder is a medical condition that impairs the normal function, but without major organic cause such as irritation or inflammation and where the organ or part of the body looks completely normal under medical examination. The accumulation of abnormalities that limit body functions is a major risk factor for patients with irritable bowel syndrome (IBS), defined as a gastrointestinal disorder with abdominal pain or discomfort that is associated with a change in bowel habit. Often, this disorder is accompanied by the concomitant decline in cognitive or motor performance. Pain that in some patients is out of proportion to identifiable pathology is the most immediate and dramatic consequence of IBS and is responsible for a highly negative impact on quality of life and substantial workforce loss. For patients with IBS, the most common comorbid diagnoses include painful bladder syndrome (PBS) or chronic pelvic pain (CPP). Cells of the affected tissues may interact in cell-to-cell manner messages through the transfer of hormones, cytokines, and other mediators that influence normal functioning. The complex interplay and balance between these diverse mediators, ageing, genetic background, and environmental factors may ultimately determine the outcome of the progression of the functional disorder. On a cellular level, these responses are highly complex, involving a vast array of enzymes and receptors of virtually every class, directing recruitment of many types of cells to recover the healthy state. Indeed, a balance between the messengers with the inherent redundancy of the different body systems makes therapeutic intervention of functional disorders a considerable challenge.

Keywords: sensory neurons, extrinsic primary afferents, nociception

1. Introduction

The response properties of pelvic extrinsic primary afferent nerves (EPANs) play an important role in etiology of irritable bowel syndrome (IBS). Hypersensitivity of visceral

mechanoreceptors could result from excessive production of modulatory neurotransmitters. In addition to direct stimulation of stretch-activated channels on primary afferent neurons located in dorsal root ganglia (DRG), chemicals produced by different target cells (such as smooth muscle cells and interstitial cells of Cajal) in response to stretch or inflammation play an important role in the neuromodulation of nociception. The incidence of persistent, episodic, or chronic visceral pain is more prevalent in females, which also suggests hormonal regulation. Despite extensive research of the properties of pelvic and splanchnic afferent nerves, little is known about the mechanisms underlying normal and pathological signal transduction pathways underlying many functional diseases. Despite considerable efforts by the scientific community and the pharmaceutical industry to develop novel pharmacological treatments aimed at chronic visceral pain, the traditional approaches to identifying and evaluating novel drugs for this target have largely failed to translate into effective IBS treatments [1]. A better understanding of these processes has direct implications for the development of more effective therapies. During the last decade, we identified that DRG neurons can be affected by ATP, NO, estrogen, and other mediators producing neuronal hyper- or desensitization that may unravel the enigma of the development of chronic pelvic pain associated with IBS. Moreover, our recent data that estrogen can gate primary afferent response to modulate nociception support the idea about involvement of peripheral central system in etiology of a wide range of the functional and inflammatory gastrointestinal diseases [2].

2. Role of EPANs in the mechanisms of visceral neurotransduction and modulation

Pelvic nerve afferent fibers innervating the visceral organs of the lower colon have been well characterized (reviewed in Ref. [3]). In general, during colonic distension, a large number of pelvic EPANs show static levels of discharge. Stretches that lead to the opening of stretch-activated (SA) channels on the plasma membrane lead to the selective or nonselective opening of different cation and anion channels in nodose ganglia and DRG neurons. Thus, depending on the cell type and channel type, EPANs activation may result in hyperpolarization, depolarization, or primarily Ca^{2+} influx. The function of SA channels in the plasma membrane differs between various cell types. Influx of Ca^{2+} may repolarize the plasma membrane via activation of K_{ca} channels and inactivating of voltage-gated calcium channels (VGCCs), and thus influence adaptation rates of sensory neurons during ongoing stimulations.

The cell bodies of primary visceral spinal afferent neurons are located in the lumbosacral (L1-S1) DRGs that transmit information about chemical or mechanical stimulation from the periphery to the spinal cord. Nociceptors are small- to medium-size DRG neurons whose peripheral processes detect potentially damaging physical and chemical stimuli. Until recently, ATP release from nonneuronal cells was thought to be exclusively as result of injury. It is now clear that certain integral membrane proteins contain an ATP-binding cassette so this

neurotransmitter can act as signaling molecule modulating sensory afferent nerve terminals. Six P2X receptors are expressed in DRGs. Significantly, the P2X3 receptor is found exclusively in a subset of small diameter capsaicin sensitive peripheral sensory neurons (presumably nociceptors) [4]. Today, multiple lines of evidence suggest that ATP signaling via P2X receptors contribute to different pain phenotypes, therefore P2X antagonists may be useful analgesics. The availability of P2X receptor-specific antagonists also holds the promise of revealing the cellular and molecular neurobiology underlying pain states underlying functional diseases [5]. With sufficiently high levels of ATP, P2X and SA channels (which has a greater permeability for Ca^{2+} than Na^{+}) would depolarize nerve terminals directly producing action potentials and leading to sensation of pain. On the other hand, the response of EPANs may be tonically inhibited by NO produced by peripheral nerve terminals. The peripheral sensitization of nerve fibers is transient depending on the duration of stimuli and the presence of visceral (colonic) inflammation.

3. Estrogen receptors and visceral nociception associated with functional diseases

Changes in pain perception and variations of symptoms throughout the menstrual cycle, as well as sexual intercourse triggering symptoms in a significant portion of females diagnosed with irritable bowel syndrome (IBS), painful bladder syndrome (PBS), chronic pelvic pain (CPP), and other function syndromes, points to a connection with sex steroids. Several lines of evidence indicate that 17β -estradiol (E2) directly influence the functions of primary afferent neurons. Both subtypes of estrogen receptors ($\text{ER}\alpha$ and $\text{ER}\beta$) are present in DRG neurons including the small-diameter putative nociceptors [4]. In vitro, ATP-sensitive DRG neurons respond to E2 [6, 7], which correlated well with the idea that visceral afferents are E2 sensitive: (i) visceral pain is affected by hormonal level in cycling females; (ii) there are sex differences in the prevalence of functional disorders involving the viscera; and (iii) putative visceral afferents fit into the population of DRG neurons that are sensitive to E2 [7]. These data suggest that in addition to the CNS actions, E2 can act in the periphery to modulate nociception [6, 7]. E2 modulates cellular activity by altering ion channel opening, G-protein signaling, and activation of trophic factor-like signal transduction pathways. These effects have been ascribed to membrane-associated receptors [8]. The results from our laboratory and others indicate that E2 acts in DRG neurons to modulate L-type VGCC and through group II metabotropic glutamate receptors [6].

E2 has a significant role in modulating visceral sensitivity, indicating that E2 alterations in sensory processing may underlie sex-based differences in functional pain symptoms [9]. Indeed in most clinical studies, women report more severe pain levels, more frequent pain, and longer duration of pain than men [10]. Little is known about E2-mediated mechanisms in peripheral nervous system, but the fact that DRG neurons express ERs and respond to E2 treatment suggest that they are a potential target for mediating nociception. E2 modulation of

nociceptive response depends on the type of pain, its durations, and the involvement of other nociceptive-mediated mechanisms.

E2 (both short-term and long-term exposure) significantly decreased the nociceptive signaling in viscerally labeled DRG neurons [6, 7]. Thus, in addition to central regulation, estrogen may affect nociception associated with IBS peripherally.

4. Primary afferent neurons and viscerovisceral cross-sensitization: emerging model for functional gastrointestinal disorders

Most of the current literature pertains to specific functional syndromes defined by medical subspecialties. These include: IBS (gastroenterology); CPP (gynecology); PBS (urology); fibromyalgia (rheumatology); and others. Many reports described the substantial overlaps between two or more of these syndromes [11, 12]. Moreover, clinical presentations of functional syndromes lack a specific pathology in the affected organ but may respond to a viscerovisceral cross-sensitization in which increased nociceptive input from an inflamed organ (i.e., uterus) sensitizes neurons that receive convergent input from an unaffected organ (i.e., colon or bladder). The site of visceral cross-sensitivity is unknown.

Recent studies from our laboratory demonstrated that hormonal modulation of visceral inputs of primary afferent nociceptors located in the dorsal root ganglia (DRG) is responsible for changes observed in the perception of pain during the etiology of functional pain syndromes [2]. Individuals suffering from CPP frequently have pain emanating from several visceral organs. Viscero-somatic and viscerovisceral hyperalgesia and allodynia lead to the perception of pain spreading from an initial site to adjacent areas. Patients with CPP may at first have only one source of pain in the pelvis, but numerous mechanisms involving the central and peripheral nervous systems may result in the development of painful sensations in adjacent organs, such as IBS being associated with lower colonic pain.

5. Summary

Similar to other chronic diseases, a multicomponent conceptual model of IBS, which involves physiologic, cognitive and behavior factors will be necessary for developing new therapies. The different systems such as neuroendocrine regulation, pain modulation, and autonomic response will affect ascending aminergic systems (**Figure 1**).

From a public health perspective, a substantial impact on our knowledge of nociceptive diseases such IBS will help achieve a deeper understanding of data presented in clinical aspects of these symptoms. Only a thorough understanding of the mechanism implicated in these phenomena can truly contribute to the designing of new and more efficient therapies.

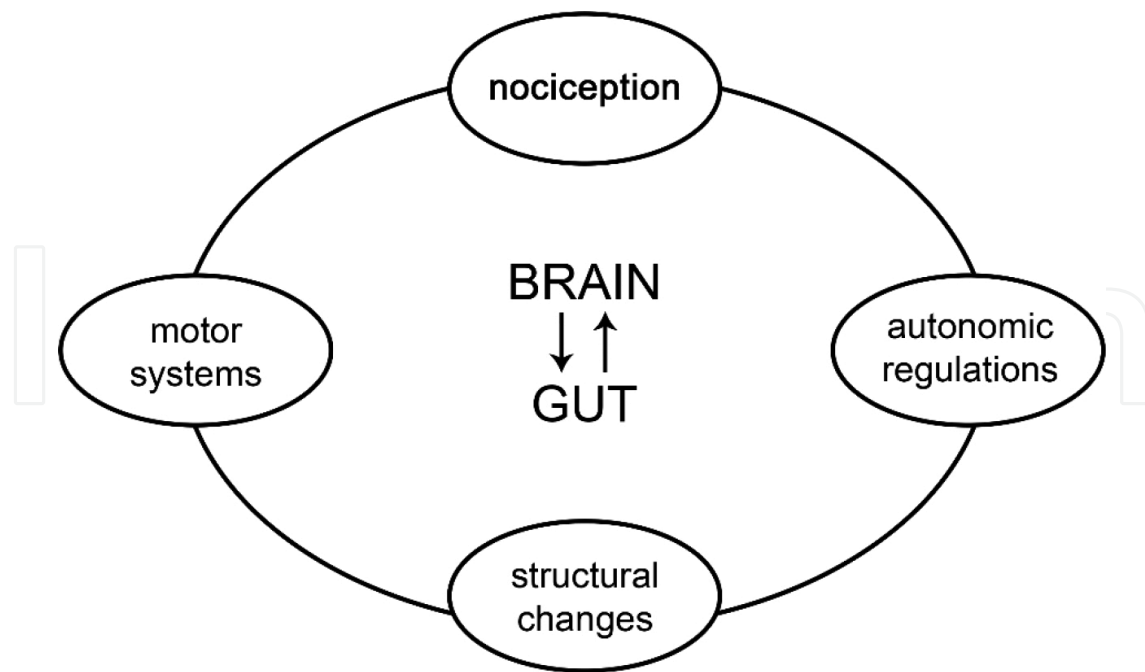


Figure 1. Different regulatory mechanisms involved in irritable bowel syndrome.

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