Unraveling the Enigma of Visceral Pain

Victor V. Chaban

Pain and its Origins, Diagnosis and Treatments

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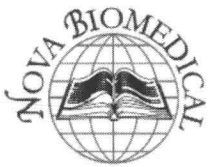
VICTOR V. CHABAN, PHD, MSCR



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Preface

The variations of symptoms and pain perception in a large percentage of patients diagnosed with various syndromes such as Irritable Bowel Syndrome (IBS), Painful Bladder Syndrome (PBS), Chronic Pelvic Pain (CPP) and others suggest the complex mechanism of etiology of visceral pain. Recent studies showed that modulation of visceral inputs of primary afferent nociceptors within lumbar-sacral dorsal root ganglia accounts for the observed changes in pain perception (nociception) and symptoms observed during the etiology of these syndromes. Patients diagnosed with these disorders frequently have pain from several organs. Moreover, for patients with IBS the most common co-morbid diagnoses include PBS or CPP. Even pain is strongly associated with the disease, the awareness to its pathology is further illustrated by the fact that the average time duration between the onset of pain and the diagnosis is 3 to 10 years. Viscero-somatic and viscero- viseral hyperalgesia and allodynia result in the spread of a perception of pain from an initial site to adjacent areas. Many patients may initially have only one pain source in the pelvis, but a multitude of mechanisms involving the peripheral and central nervous system can lead to the development of painful sensations from other adjacent organs resulting in pelvic pain. Pain research has uncovered important neuronal mechanisms that underlie clinically relevant painful states such as inflammation and neurodegeneration. The concept that the brain and other systems are closely connected in certain feeling states, especially in clinical presentations of chronic viscerally-associated nociceptive disorders, is widely accepted in scientific and clinical communities. Cells of the affected tissues may interact in cell-to-cell manner messages through the transfer of hormones, cytokines and prostaglandins that are released during pathological processes. Neurodegenerative diseases also accompanied by the concomitant decline in cognitive and motor performance therefore limiting normal body functions.

The complex interplay and balance between these diverse mediators, ageing, genetic background, and environmental factors may ultimately determine the outcome of the progression of chronic visceral pain. On a molecular level, these responses are highly complex, involving a vast array of messenger molecules interacting with 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 a considerable challenge.

Taking into the consideration a rapid growth of scientific knowledge the impact on society of a successful translation of a basic or clinical observation into new therapies is substantial. Today, understanding and meeting public concerns are as important as performing clinical studies. Despite many advances, the pathophysiological mechanism of visceral pain is still poorly understood comparing with its somatic counterpart and, as a result, the therapeutic efficacy is usually unsatisfactory. Even after tissue healing, pain may persist as chronic pain with a major impact on quality of life. To date, the majority of publications on chronic pain adopt an empirical approach to the treatment of visceral pain, primarily based on dealing with the putative nociceptive source of the pain. Most of the current data pertains to specific functional syndromes defined by medical subspecialties: IBS (gastroenterology); chronic pelvic pain: CPP (gynecology); interstitial cystitis/painful bladder syndrome: IC/PBS (urology); fibromyalgia (rheumatology) and others. Many reports describe the substantial overlaps between two or more of these syndromes. Moreover, clinical presentations of functional syndromes lack a specific pathology in the affected organ but may respond to a viscero-visceral 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) however the site of visceral cross-sensitivity is unknown. In this book, the author aims to challenge the traditional concept of many painful syndromes among different medical sub-disciplines for which therapies are developed by distinct divisions within pharmaceutical sciences to provide a systematic mechanism-orientated approach to the etiology of visceral pain and to present potential new therapies for various pain-associated disorders.

This book represents an attempt to review the most recent knowledge concerning nociceptive processes occurring in the visceral organs. At present, the available information concerning the regulation of nociception have been dramatically multiplied. Paradoxically, proposed therapeutic intervention is

sometimes complicated by new data. Some of these data, even being correct, are contradictory due to different models and methodological approaches used for their collection. I hope this book can help health care providers, researchers and students in various disciplines of medicine or basic sciences to increase their knowledge concerning all aspects of visceral pain, as well as look for new concepts and approaches in this important topic. Reaching further than the concrete basic science contribution, this project is a liaison between the basic science work and the clinical aspects that are addressed through other disciplines such as anesthesiology (pain management), gastroenterology, urology and gynecology. Over the last decade, medical literature has carefully documented the undertreatment of all types of pain by physicians especially in vulnerable populations in medically underserved areas that receive almost no attention from the medical community. From a public health prospective, a substantial impact on our knowledge of nociceptive diseases can help to achieve a better quality of life for patients affected by visceral pain, leading to the discovery of new therapeutic interventions.

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Introduction

The concept of the brain's close connection to pelvic viscera plays an important role in certain feeling states especially in clinical presentations of chronic viscerally-associated nociceptive disorders. This concept is now widely accepted in scientific and clinical communities. Moreover, the fact that primary afferent neurons modulate nociception supports the idea about the involvement of the peripheral central system in the etiology of a wide range of functional and inflammatory gastrointestinal diseases that may potentially lead to new interventions and therapies.

Chest pain from coronary heart disease, endometriosis, acute and recurrent/chronic pelvic pain or abdominal pain from irritable bowel syndrome are all visceral pain sensations that may result in part from sensitization or sensory neurons. As we begin the investigation of particular problems that underlie visceral pain in the central nervous system (CNS) and peripheral nervous system (PNS), it may be asked - just what is so special about primary afferents? These nerve cells have two special properties that distinguish them from all other cells in the body. First, they conduct an input from the internal or external environment for long distances without any loss of signal strength. Second, they possess an intercellular connection within the ganglia or with other neurons that determine the type of information (sensation) and range of responses they can yield toward the CNS. Sensitization of primary afferent neurons to stimulation may play a role in the enhanced perception of visceral sensation and pain. Mechanisms of peripheral sensitization may involve increased transduction, which is secondary to repeated stimulation or an increase in the excitability of the afferent nerves by molecules that decrease the excitation threshold. Sensitization can also develop in response to inflammation although basic mechanisms of this process are poorly understood.

Pain is a protective mechanisms that alerts the individual to a condition or experience that is harmful to the body. Somatic pain is superficial and originates from the areas close to the surface of the body. Visceral pain originates in internal organs, the abdomen or the skeleton. The accumulation of disabilities and nociceptive diseases that limit normal body functions is a major risk factor for the quality of life. Many nociceptive diseases accompanied by the concomitant decline in cognitive and motor performance share the same pathophysiological changes. Pain is one of the body's most important adaptive mechanisms, and all current definitions suggest it is a complex phenomenon that cannot solely be explained as a response to injury. Different systems interact to produce pain sensation. The sensory system processes information regarding the strength, intensity, and temporal/spatial aspects of nociception. The affective system determines the individual's conditioned avoidance behavior. The evaluative system overlies the individual's learned experience of pain. The afferent pathways which begin in the PNS at the level of dorsal root ganglion (DRG) send information to the spinal gate in the dorsal horn and then ascend into the CNS centers. The sensory process leading to the perception of pain is called nociception. Nociceptors are free nerve endings that respond to thermal, mechanical or chemical stimuli. Because they are not distributed evenly in the body, the sensitivity to pain differs according to the body area. Some of the triggering mechanisms of nociception initiate release of neuromodulators and lymphokines, and chronic inflammatory mediators. Most common excitatory (pro-nociceptive) neuromodulators include substance P, glutamate, somatostatin, VIP (vasoactive intestinal peptide), CGRP (calcitonin-gene-related peptide) and ATP (adenosine- triphosphate). Most common inhibitory (anti-nociceptive) neuromodulators include GABA (γ-aminobutyric acid), glycine, serotonin, norepinephrine and endorphins. Endorphins (endogenous morphines) inhibit transmission of pain by binding to mu, delta and kappa opioid receptors. Cells of the affected tissues may interact in a cell-to-cell manner messages through the transfer of hormones, cytokines, and autacoids such as histamine, serotonin, kinins and prostaglandins released in pathological processes. The complex interplay and balance between these diverse mediators, ageing, genetic background, and environmental factors may ultimately determine the outcome of progression of neurodegeneration, one of a major clinical problem associated with nociception. On a molecular level, these responses are highly complex, involving a vast array of messenger molecules in addition to neuromodulators interacting with enzymes and receptors of virtually every class, directing the recruitment of many types of

cells to recover the healthy state of individual. Indeed, a balance between the messengers with the inherent redundancy of the different body systems makes therapeutic intervention a considerable challenge.

The present book is written at the basis of available publications and several authors' recent reviews (Chaban 2012-2015) and my research experience in this field. It also includes novel ideas, not previously published. Data are summarized in separate chapters with references to corresponding manuscripts and reviews. The text gives a lucid view of novel aspects of pain generation and perception. It is recommended to students, scientists, health care providers and patients who seek a fundamental understanding of neuronal modulatory systems. This book is not intended to be a comprehensive review of all currently known regulatory mechanisms associated with nociception, but rather aims to provide a framework for understanding the most significant signaling processing in order to unravel the enigma of visceral pain.

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Contents

Chapter 1

Pathways of Nociception

Abstract

This chapter provides basic knowledge concerning different mechanisms of pain transmission- nociception. The pain field has been advocating for some time for the importance of teaching people how to live well with pain and we might again consider the possibility that we can help people live well without pain. This refers to a range of educational interventions that aim to change one's understanding of the biological mechanisms associated with nociception. Pain is a hallmark of almost all bodily ailments and can be modulated by agents, including analgesics and anesthetics that suppress pain signals in the nervous system. Defects in the modulatory systems, including the endogenous pain-inhibitory or pain- excitatory pathways, are a major factor in the initiation and chronicity of pain. The Gate Control Theory is presented with discussion on the capacity of pain modulation to cause both hyper- and hypoalgesia. An emphasis has been given to highlight receptors and their ligands involved in visceral pain.

Etiology of Pain

International Association for the Study of Pain defines pain as "unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." McCaffery (1980) defined pain as "whatever the experiencing person says it is, existing whenever he says

it does." Pains that are evoked by noxious sensory inputs have been meticulously investigated by scientists, and their signal transduction mechanisms are generally well understood. In contrast, visceral pain syndromes, which are often characterized by severe pain associated with little or no discernible injury or pathology, remain a mystery. Unrelieved pain has major negative effects on the lives of millions of people worldwide, and is associated with huge societal costs. Breakthroughs in pain therapy have been rare in the past 50 years, but there is increasing hope that advances in multiple areas of pain research could lead to the introduction of much-needed novel and more effective analgesics (Melzak 2008).

The specificity theory of pain was described by Descartes in the seventeenth century and proposes that the intensity of pain is directly related to the amount of associated tissue injury. Later, specificity theory proposes that a mosaic of specific pain receptors in body tissue projects to a pain centers in the brain. It is useful to explain acute pain but does not account for chronic or cognitive and psychological contributions to nociception. The traditional theory of pain, which evolved during the twentieth century, states that pain is a specific sensation produced by a direct-line pain pathway from pain receptors in the body to a pain center in the brain. The gate control theory of pain, proposed in 1965 by Melzak and Wall, focused on chronic pain and postulated that neural gates in the spinal cord can be opened or closed by signals descending from the brain, as well as by sensory information ascending from the body. This theory also highlighted the psychological functions of the brain and produced an explosive growth of knowledge related to pain. Brain research, especially in neuropharmacology and cognitive neuroscience, has led to the development of new drugs, as well as several psychological techniques that produce substantial relief from chronic pain. The gate control theory also stimulated a shift away from the traditional direct-line pain pathway to the concept of parallel neural networks in the brain associated with the sensory, affective and cognitive dimensions of pain (Melzak 2005). New approaches to reveal the nociceptive functions of the brain will hopefully lead to the relief of the pain and suffering that is currently endured by millions of people.

Visceral pain is the most common form of pain caused by varied diseases and a major reason for patients to seek medical consultation. Despite decades of extensive research and the availability of several therapeutic options, management of patients with chronic visceral pain is often inadequate, resulting in frustration for both patients and physicians. This is, most likely, because the mechanisms associated with chronic visceral pain are different from those of acute pain. For years, treatment recommendations for visceral

pain were the same as that for somatic pain. However, it is widely accepted that visceral pain processing is distinctly different from somatic pain and as a result it should be treated differently (Kannampalli and Sengupta 2015). It also known that the pathophysiology of the visceral pain is extremely complex. The gate control theory's most important contribution to biological and medical science was its emphasis on central nervous system (CNS) mechanisms. In this book the author will present new scientific evidence of regulation of visceral pain in peripheral nervous system (PNS) at the level of primary afferent neurons located in dorsal root ganglia (DRG). DRG neurons have very characteristic cytoplasmic organelles regardless of their size. Neuronal cytoplasm in the perikaryon is reach in smooth and rough endoplasmic reticulum connoting an emphasis on their secretory activity. These neurons are rich in mitochondria, connoting their dependence on high rates of adenosine-triphosphate (ATP) generation. Neuronal processes (neuritis) exhibit prominent microtubules to maintain their polarized shapes.

Primary order neurons: nociceptors bare nerve endings in skin, muscle, joints, arteries, and the viscera that respond to chemical, mechanical, and thermal stimuli. They can detect a wide range of stimuli through A-delta fibers or unmyelinated C polymodal fibers. These neurons communicate to second and third order neurons in spinal cord and primary somatosensory cortex providing segmental regulation of nociception. Neuromodulation of pain provides diffuse noxious control and integration of peripheral sensory axon terminals, spinal interneurons by top-down control pathways. PNS stimuli converge on the spinal dorsal horns. Additionally, threshold depolarization from inflammatory mediators after nociception leading to hyperalgesia and allodynia. Historically, it was believed nervous system fails to mount an inflammatory response due to its protection from the systemic immune system mediated by blood-brain barrier. However, in the last decades it became more evident role of inflammatory response induced within CNS and PNS. Various cytokines possess a significant role in nerve pathology and their presence is fundamental for the repair, regeneration and neurological recovery. The most interesting aspect of this recovery is the new concept that the concentration of cytokine seems to be criteria for determining their function and possible physiological response, Progress has been made in understanding the mechanisms underlying the action of cytokines in pain. To date, several direct and indirect pathways are known that link cytokines with nociception or hyperalgesia. Cytokines may act via specific cytokine receptors inducing downstream signal transduction cascades, which then modulate the function of other receptors like the ionotropic glutamate receptor, the transient vanilloid

receptors, or sodium channels. This receptor activation, either through amplification of the inflammatory reaction, or through direct modulation of ion channel currents, then results in pain sensation. Complete understanding of the basis for nociceptive signal transduction initiated by primary afferent neurons requires knowledge of all the molecules involved. Before we can deal with the critical details of molecules that regulate the function of DRG neurons, we must consider how these cells are differ from the other cells in the body. They are excitable and capable of communication. Contrary to what one might assume, the more we learn about intercellular communication within DRG, the more complicated the situation appears. Many chemicals and neurotransmitters involved in this neuromodulation: pain excitatory (glutamate, aspartate) or pain inhibitory (serotonin, GABA, endorphins). Evidence from extensive clinical and basic research in the last decade have shown the involvement of several receptors and ion channels in the development and maintenance of chronic visceral pain conditions (Table 1.1). On the basis of their functional actions, amino acid neurotransmitters have been divided into two categories: excitatory (glutamate, aspartate) which depolarize neurons and inhibitory (γ- aminobutyric acid: GABA, gycine, taurine) which hyperpolarize neurons. Among them are GABA, the major inhibitory transmitter and glutamate, the major excitatory in the brain, and glycine, important inhibitory transmitter in the brain stem and spinal cord. GABA produces neuronal inhibition by acting on a diversity of membrane-bound receptors. These receptors can be divided into two major types: ionotropic receptors that are ligand-gated ion channels (GABA-a receptors), and metabotropic receptors that are G-protein coupled receptors (GABA-b receptors).

The excitatory amino acid, glutamate, is a major neurotransmitter in the CNS and plays an important role in nociceptive processing via a diverse set of membrane receptors which include both ionotropic and metabotropic. Activation of these receptors is responsible for basal excitatory synaptic transmission and many forms of synaptic plasticity such as long-term potentiation (LTP) and long-term depression. Glutamate acts on three ionotropic receptor subtypes: N-methyl-D-aspartate receptor (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), and kainite receptors that are widely reported to be involved in plasticity, brain development, learning, excitatory synaptic transmission, and LTP. NMDA receptors are calcium channels activated by glutamate and are slowly desensitized once activated. These high-calcium permeable channels generate

synaptic neuroplasticity, wide dynamic range neuronal responses and gene expression.

Table 1.1. List of Receptors Involved in Visceral Nociception and Their Ligands

Receptor		Agonist	Antagonist
P2X3		ATP, αβ-met ATP	AF 219
GABA A receptor		GABA, Muscimol, HZ166	Baclofen
GABA B receptor		GABA, Baclofen, gamma-hydroxybutyrate, CGP7930	Phaclofen, CGP-35348
NMDA receptor		NMDA, glutamate, aspartic acid	AP-5, AP-7, Ketamine
Kainate receptor		Kainic acid	LY382884, CNQX, DNQX
AMPA receptor		AMPA, glutamate	NBQX, Kynurenic acid
Opioid receptor			
MOR		Morphine, oxycodone	-
KOR		Oxycodone, asimadoline	-
DOR		Enkephalin, cannabidiol, tetrahydrocannabinol	Buprenorphine
Cannabinoid (CB) receptor	CB1	Dronabinol	-
	CB2		
Serotonin (5-HT) receptor	5-HT_1	DPAT	-
	5-HT_3	-	Alosetron
	5-HT_4	Tegaserod	-
TRP channels	TRPV1	-	SB 366791
	TRPA1	-	-
	TRPV4	-	RN1734
	TRPC4	-	ML-204

ATP, adenosine-tri-phosphate; GABA, gamma aminobutyric acid; NMDA, N-methyl-D-aspartate receptor; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; MOR, μ-opioid receptor; KOR, κ-opioid receptor; DOR, δ-opioid receptor; DPAT, 8-hydroxy-DPAT hydrobromide; TRP, transient receptor potential.

Our previous data showed involvement of NMDA (Chaban et al. 2004) and group II metabotropic glutamate receptors (Chaban et al. 2011) in modulation of nociception in PNS by modulating DRG neuronal activity. In addition, NMDA receptors appear to have a pivotal role in long-term depression (LTD), long-term potentiation (LTP), and developmental plasticity. However, overactivation or prolonged stimulation of NMDA receptors can damage and eventually kill neurons via process called excitotoxicity. AMPA and kainic acid (KA) receptors mediate fast excitatory synaptic transmission and are associated primarily with voltage-independent channels that gate a depolarizing current carried by the influx of sodium ions.

Opioid receptors are a group of G protein-coupled receptors with opioids as ligands. Kappa and mu opioid receptors are found on visceral afferents. Moreover, kappa opioid receptor expression is functionally up-regulated during inflammation and chronic visceral hypersensitivity. The cannabinoid (CB) receptors in mammals are CB1 and CB2, both members of the superfamily of G protein-coupled receptors. CB1 receptors are found primarily in neurons of the brain and GI tract extrinsic and intrinsic nervous system while CB2 receptor is expressed mainly in the immune system. Both receptors are G-protein- coupled. The role of CB receptors in visceral pain is unclear and their role in modulation of nociception is a subject of intense research. The transient receptor potential (TRP) family of ion channels is TRPV1, TRPV2, TRPV3, TRPV4, TRPM 8, and TRPA1. These channels are, in general, thermoreceptors found on poorly myelinated and nonmyelinated afferents arising from CNS and PNS (dorsal root and nodose ganglia). TRPA1 is highly expressed on primary afferents. Another potential target receptor in regulating nociception is purinergic P2X3 receptors (Burnstock 2013). Over the last decade author of this book was involved in research studies that confirmed that both TRPV1and purinoregic- mediated mechanosensory transduction are involved in the initiation of visceral pain (Chaban et al. 2003; Chaban 2008; Cho and Chaban 2012a; Cho and Chaban 2012b). I believe the great challenge ahead of us is to further explore the role of known and discover new signal transduction pathways of visceral pain.

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