



Topical review

Biological basis of visceral pain: recent developmentsElie D. Al-Chaer^{a,*}, Richard J. Traub^b^a*Departments of Internal Medicine and Anatomy and Neurosciences, University of Texas Medical Branch, Galveston, TX 77555-0632, USA*^b*Department of Oral and Craniofacial Biological Sciences, Dental School, Program in Neurosciences, University of Maryland, Baltimore, MD 21201, USA*

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1. Introduction

Visceral pain is caused by disorders of internal organs such as the stomach, kidney, gallbladder, urinary bladder, intestines and others. These disorders include distension from impaction or tumors, ischemia, inflammation, and traction on the mesentery, which can cause associated symptoms such as nausea, fever, malaise, and pain. The pain results from activation of sensory afferent nerves innervating internal organs and is often described in terms of five clinical characteristics (Cervero and Laird, 1999): (1) it may not be evoked from all visceral organs as not all viscera are innervated by sensory receptors or possibly because of the lack of an appropriate nociceptive stimulus; (2) it is not always linked to injury, hence the non-structural or functional properties of visceral pain; (3) it is referred to the body wall; this may be explained by the central convergence of visceral and somatic inputs; (4) it is diffuse and poorly localized, a possible consequence of the relative paucity of peripheral afferent fiber terminals in the viscera compensated for by the central rostrocaudal intraspinal arborization of visceral afferents; and (5) it is often accompanied by accentuated motor and autonomic reflexes, which are considered a reaction to a warning system.

In this review we will consider recent advances in our understanding of the biological basis of visceral pain, its characteristics and mechanisms, including recently developed animal models with focus on the gastrointestinal tract.

2. Causes of visceral pain

Visceral pain is, to a certain extent, dependent upon the

nature of the provoking stimulus. An adequate stimulus refers to the stimulus that produces a given sensation (Ness and Gebhart, 1990). Adequate stimuli that induce visceral pain are distension, ischemia, and inflammation (e.g. hollow organs such as the colon are sensitive to both luminal distension and inflammation but are quite insensitive to cutting or burning). However, the severity of the pain does not always reflect the severity of the condition causing the pain. Severe abdominal pain can be associated with mild conditions such as gas or the cramping of viral gastroenteritis, while relatively mild pain (or no pain) may be present with severe and life-threatening conditions such as cancer of the colon or early appendicitis. Solid organs are least sensitive, whereas the serosal membranes of hollow organs are most sensitive (Giamberardino and Vecchiet, 1996). On the other hand, mildly painful or even innocuous stimuli such as gas or passage of fecal material can be exquisitely painful (hyperalgesia/allodynia) when acting on inflamed or otherwise affected tissue (e.g. irritable bowel syndrome, IBS).

3. Animal models

As in other areas of pain research, the use of animal models is a necessary step to elucidate the underlying neurophysiological and neuropharmacological mechanisms of visceral pain. Until recently, much of what we knew about the basic mechanisms of pain derived from experimental studies of somatic nociception. However, over the past few years a number of animal models have been developed that, to a large extent, mimic the nociception originating in the viscera (e.g. Botella et al., 1998; Laird et al., 2001). These models helped advance our understanding of the acute physiological responses associated with mechanical or inflammatory visceral nociception and it has become apparent that visceral pain and somatic pain are different,

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although some similarities exist. Yet the visceral pain that leads a suffering patient to seek medical care is often associated with disease symptoms and is mostly chronic in nature.

Recently, animal models have been developed that closely mirror the symptom profile of visceral ailments with chronic prevalent hypersensitivity. Al-Chaer and collaborators have described an animal model of chronic visceral hypersensitivity in which neonatal insult to the colon can lead to adult visceral hyperalgesia long after the initial injury subsides (Al-Chaer et al., 2000). This visceral hyperalgesia is associated with motility disturbances (e.g. constipation or diarrhea) similar to the functional disorders often seen in patients with IBS (Ma et al., 2002). Preliminary studies of the underlying mechanisms of this chronic hypersensitivity indicate the presence of central sensitization demonstrated by heightened neuronal responses and increased c-Fos expression to colorectal distension in lumbosacral and thoracolumbar spinal cord segments (Al-Chaer et al., 2000; Park and Al-Chaer, 2001) as well as evidence of primary afferent sensitization seen in L6-S1 and T13-L2 dorsal roots (Lin and Al-Chaer, 2002). The pain-related behaviors and the disturbance in colonic motility seem to be aggravated by prior exposure to water-avoidance stress (unpublished observations). Stress-induced visceral hypersensitivity has also been reported in adult Long-Evans rats reared under conditions of maternal separation (Coutinho et al., 2002).

4. Mechanisms of visceral pain

4.1. Peripheral mechanisms

Unlike somatic tissue, the viscera are innervated by two sets of primary afferent fibers that project to distinct regions of the neuraxis. Innervation of the gastrointestinal tract from the esophagus through the transverse colon is provided by vagal afferent fibers originating in the nodose ganglia and projecting centrally to the nucleus of the solitary tract. Pelvic nerve afferent fibers, originating in the sacral (human; lumbosacral in rat) dorsal root ganglia, projecting centrally to the sacral spinal cord innervate the remaining lower bowel. The entire GI tract is also innervated by afferent fibers in the splanchnic nerves projecting to the T5-L2 segments of the spinal cord. For example, colonic afferent fibers project in both the pelvic and the splanchnic nerves (Berkley et al., 1993; Traub et al., 1999). The peripheral terminals of these afferent fibers innervate all layers of a viscus (vagal/pelvic to mucosa; thoracolumbar, pelvic to muscle and serosa). In contrast to somatic afferent fibers, they have no end organs or morphological specialization.

Viscerosensory axons are almost exclusively thinly myelinated A-delta and unmyelinated C fibers. The receptors exhibit chemosensitivity, thermosensitivity and/or mechanosensitivity. Current research indicates that there

are two physiological classes of nociceptive viscerosensory receptors: 'high-threshold' receptors that respond to mechanical stimuli within the noxious range and 'low-threshold' receptors that encode the stimulus intensity in the magnitude of their discharges from innocuous stimuli into the noxious range (Sengupta and Gebhart, 1994). The distribution of these fibers varies among organs. High-threshold receptors exclusively innervate organs from which pain is the only conscious sensation (i.e. ureter, kidney, lungs, heart), but are relatively few in organs that provide innocuous and noxious sensations (e.g. colon, stomach, bladder). Experimental data suggest that the viscera also contain spinal nociceptive afferent fibers that are normally considered 'silent' and are sensitized by inflammation (McMahon and Koltzenberg, 1994).

Studies suggest that the two nerves that innervate a particular organ serve different functions. It is generally accepted that vagal afferents do not directly convey painful stimuli, but vagal activity does modulate nociceptive processing in the spinal cord (Ness et al., 2000; Randich and Gebhart, 1992). On the other hand, afferent fibers running in the pelvic nerve convey sensory information from the lower bowel and are the predominant pathway mediating physiological sensations from the rectum (see Jänig et al., 1993). However, the role of splanchnic rectal primary afferents projecting to the lumbar spinal cord remains poorly understood. It was recently suggested that inflammation alters the central processing of thoracolumbar afferent input, possibly by altering the magnitude of descending modulation (Traub, 2000). Similar observations were recently made in a model of chronic visceral hyperalgesia (Lin and Al-Chaer, 2002; Park and Al-Chaer, 2001).

4.1.1. Peripheral sensitization

In the presence of local inflammation or tissue injury or in the case of chronic hyperalgesia, visceral afferents become sensitized and respond to previously innocuous natural stimuli. Both low- and high-threshold receptors normally signal acute visceral pain. Additionally, local ischemia, hypoxia, and inflammation can cause pain by sensitizing these receptors as well as previously 'silent' or unresponsive receptors. Inflammatory mediators released locally lower the receptor firing threshold and, by peripheral sensitization, augment and perpetuate the transmission of noxious stimuli (Cervero and Laird, 1999; Sengupta and Gebhart, 1994; Traub and Gold, 2000; Gold et al., unpublished observations). This is partially mediated by TTX-resistant sodium channels (e.g. $Na_v1.8$). These channels are expressed in virtually all colonic and bladder afferents and the current density recorded from these channels increases following tissue inflammation or application of inflammatory mediators in vitro (Gold et al., unpublished observations; Yoshimura et al., 2001). In addition to acute sensitization of visceral afferent fibers, there are also long-term consequences after a visceral insult. For example, sensory-motor disturbances of the gut remain after peripheral inflam-

mation subsides, including primary afferent sensitization in adult rats treated as neonates (Lin and Al-Chaer, 2002).

Several studies have examined the neurochemistry of colonic afferent fibers and soma. A greater percentage of colonic afferents contain neuropeptides, especially substance P, when compared with somatic afferents. In addition, colonic afferents contain other peptides including calcitonin gene-related peptide, somatostatin, and vasoactive intestinal peptide, and some are IB4-positive. To date, no differences have been reported in the neurochemistry of colonic afferents that project into the pelvic and splanchnic nerves. The same proportions of neurons in both nerves contain neuropeptides and colonic inflammation affects peptide levels in both nerves similarly (Traub et al., 1999). Colonic afferents in the pelvic nerve contain an array of receptors including excitatory amino acid receptors (McRoberts et al., 2001) and opioid receptors (Su et al., 1997). Colonic afferents are inhibited by kappa opioid agonists, but not mu or delta agonists, and peripheral administration of kappa agonists is antinociceptive. Studies suggest that this kappa opioid receptor may be unique to visceral afferents since the antinociceptive effects of kappa agonists were not attenuated by pretreatment with antisense to the cloned kappa opioid receptor, while the effect of kappa agonists on somatic nociception was reduced (Joshi et al., 2000). However, this unique receptor has not been cloned and there is no other evidence to suggest that there is a unique gene for an opioid receptor in visceral afferents.

4.2. Central mechanisms

Supraspinal projections: Upon entering the dorsal horn, visceral afferents terminate in spinal cord laminae I, II, V and X (Ness and Gebhart, 1990). Visceral afferents constitute 10% of all afferent inflow into the spinal cord. This is a relatively small number when considering the large surface area of some organs. Both anatomical and electrophysiological studies have demonstrated viscerosomatic convergence in both the dorsal horn and supraspinal centers (Al-Chaer et al., 1996, 1998a,b; Ness and Gebhart, 1990). There is also evidence of viscerovisceral convergence onto these second-order neurons. Examples include the convergence of pelvic visceral inputs such as colon/rectum, bladder, uterine cervix, and vagina (Ness and Gebhart, 1990; Berkley et al., 1993). Along with the low density of visceral nociceptors and the functional divergence of visceral input within the central nervous system, viscerovisceral convergence in the spinal cord may explain poorly localized visceral pain.

Visceral information carried by the pelvic nerve converges onto spinal neurons in the lumbosacral segments of the cord and those carried by the splanchnic nerves on thoracolumbar segments (see Traub, 2000). Centrally, ascending pathways reported to be involved in the transmission of visceral nociceptive information include the spinothalamic tract (STT), spinohypothalamic tract, spino-solitary tract, spinoreticular tract, spinoparabrachial tract,

and others. In addition, a number of recent studies have pointed to a possible role of the dorsal column (DC) in viscerosensory processing, opening the door for a new role of the DC in visceral pain (for review see Al-Chaer et al., 1998a; see also Willis et al., 1999).

One difference between the DC and the STT is that the DC axons ascend ipsilaterally near the midline before converging onto the DC nuclei (nucleus gracilis and nucleus cuneatus). From there, internal arcuate fibers transmit nociceptive input to the contralateral ventroposterolateral (VPL) nucleus of the thalamus. Experimental data from different groups (Al-Chaer et al., 1996, 1998b; Ness, 2000) have identified the DC as being more important in visceral nociceptive transmission than the spinothalamic and spinoreticular tracts. In monkeys, colorectal distension stimulates the firing of viscerosensitive VPL thalamic neurons. After a DC lesion at T10 level, the responses are dramatically reduced despite ongoing stimulation. Interestingly, a similar lesion of the STT at T10 does not achieve the same effect (Al-Chaer et al., 1998b). Further animal studies have recently reported that the DC also has a role in signaling epigastric nociception (see Willis et al., 1999). The DC, however, is not simply a conduit of viscerosensory information onto supraspinal centers, but may also facilitate visceral input upon other sensory channels originating in the spinal cord and rekindle spinal neuronal sensitization of visceral origin. A lesion of the DC was recently shown to suppress spinal neuronal responses to colorectal distension (CRD) and reduce spinal neuronal sensitization in Al-Chaer's model of chronic visceral pain (Broussard et al., 2000). This newly identified pathway has led to new clinical approaches in managing visceral cancer pain. For example, midline myelotomy has been used to treat visceral pain. Its success is clearly not due to interruption of the decussating fibers of the STT, as was previously thought. This procedure has been performed successfully for pelvic cancer pain and did not produce neurological sequels (Hirshberg et al., 1996; Kim and Kwon, 2000).

4.2.1. Central sensitization

In somatic tissue, NMDA receptors contribute to the generation of central sensitization following tissue injury and inflammation. They do not signal acute nociceptive stimuli or innocuous stimuli. In contrast, recent studies suggest that NMDA receptors signal acute noxious stimuli in the absence of inflammation as well as contributing to the central processing of innocuous colorectal stimuli. Transient distension of the ureter evokes a pressor response that is inhibited by NMDA receptor antagonists (Olivar and Laird, 1999). Likewise, NMDA receptor antagonists attenuate primary afferent (McRoberts et al., 2001) and spinal neuron responses to acute noxious and innocuous colorectal stimuli (Zhai and Traub, 1999; Ji and Traub, 2001; Traub et al., in press). The contribution of NMDA receptors to the signaling of innocuous colonic stimuli leads to speculation that excessive activity at these receptors in the absence of inflamma-

tion could produce central sensitization leading to visceral hyperalgesia associated with IBS (Ji and Traub, 2001; Traub et al., in press). This needs to be examined in models of chronic hyperalgesia in the absence of inflammation such as Al-Chaer's.

Similar to somatic tissue, NMDA receptors and neurokinin receptors mediate inflammatory visceral pain. Recent studies indicate that NK-1 receptors and NK-3 receptors partially mediate spinal responses to colonic distension. However, the particular receptor involved in the signal transduction depends upon the mechanism for producing inflammation. NK-1 receptors signal neurogenic inflammation, but not non-neurogenic inflammation (Laird et al., 2000). Likewise, a different inflammagen works through NK-3 and/or NMDA receptors (Coutinho et al., 2002; Kamp et al., 2001). Since most visceral afferents contain substance P, the natural ligand at the NK-1 receptor, a role for NK-1 receptors would be expected (Kawasaki et al., 2000). The reason for appearing less so needs further examination.

5. Future directions

Scientific advances within the field of pain in general – mainly somatic – reflect a new understanding of pain as something not just felt or experienced, but also something that can be modeled and visualized, through the structures, chemistry, and microanatomy of the nervous system. These advances are helping researchers to understand pain better and in so doing, to select potential targets for new therapeutic agents. These include ion channels, neurotransmitter receptors, trophic factors that affect the survival and function of cells, and targeted genetic mutations that can change pain sensitivity and behavioral responses to pain. A cardinal feature of chronic pain is the plastic changes seen throughout the nervous system. These changes are best studied in animal models amenable to experimentation. These models can be designed to mimic the human condition (e.g. Al-Chaer's) or genetically engineered to lack a certain gene suspected in pain processing (knockouts). These models offer a necessary and useful tool to unravel the pathobiology of pain and eventually develop new treatments that take into consideration the different pains associated with different symptoms.

Today, visceral pain management focuses on both pharmacological and interventional techniques. Combinations of opioids, NSAIDs, and adjuvant medications form the mainstay of therapy (see Berkley, 1997). Recent studies on spinal (neurokinin and NMDA receptors) and primary afferent (kappa opioid receptors and sodium channels) mechanisms suggest further avenues to be explored for pharmacological targets of therapeutic intervention. When pharmacological therapies prove ineffective or are limited by side effects, regional anesthesia techniques or neurosurgical techniques are considered. These involve the administration of local anesthetics, opioids, or neurolytic agents to the neural axis

or visceral plexi. The goals of these interventional procedures are to provide superior analgesia with optimal opioid consumption. Ablative neurosurgical techniques continue to be used albeit to a lesser extent than in the past, but for patients with refractory unilateral cancer pain, percutaneous cordotomy may still be useful. The recently described dorsal column pathway may also offer therapeutic options for the future.

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