Pathobiology of Visceral Pain: Molecular Mechanisms and Therapeutic Implications
IV. Visceral afferent contributions to the pathobiology of visceral pain*

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Gebhart, G. F. Pathobiology of Visceral Pain: Molecular Mechanisms and Therapeutic Implications. IV. Visceral afferent contributions to the pathobiology of visceral pain. Am J Physiol Gastrointest Liver Physiol 278: G834–G838, 2000.—Functional bowel and other visceral disorders exhibit multiple characteristics that suggest the presence of visceral hyperalgesia. The discomfort, pain, and altered sensations (e.g., to intraluminal contents) that define the hyperalgesia typically arise in the absence of tissue insult or inflammation. Visceral hyperalgesia thus differs from somatic hyperalgesia, which is commonly associated with tissue injury and inflammation. Hyperalgesia could develop and be maintained by either peripheral or central mechanisms; the altered sensations associated with functional visceral disorders are contributed to by both peripheral and central mechanisms. The relative contributions of peripheral and central mechanisms are not well understood, and the focus in this Themes article is on potential peripheral contributions: sensitization of visceral receptors, nerve injury, and ion channels.

The cell bodies of primary visceral afferent neurons are contained in the nodose ganglia (vagal afferents) and dorsal root ganglia (spinal afferents). Unlike somatic structures, the viscera receive dual innervation from vagal and spinal primary afferent neurons. The central terminals of vagal sensory neurons are in the brain stem, whereas the central terminals of spinal visceral afferent neurons are organized segmentally (although somewhat diffusely over several spinal segments). It has long been held that visceral pain is conveyed to the central nervous system by spinal afferents; vagal afferents are considered to play no role in visceral pain. A growing body of literature, however, suggests that perhaps most primary visceral afferents can contribute to altered sensations from the viscera in pathophysiological conditions.

The terminals (receptors) of primary visceral afferent neurons are located in mucosa, muscle, and serosa (mesentery) of hollow organs. Accordingly, visceral afferent neuron terminals are placed to respond to luminal and local chemical stimuli and to mechanical (usually distending) stimuli. Visceral receptors apparently have no end organs or morphological specialization (i.e., are unencapsulated). They are associated with unmyelinated and thinly myelinated axons, recording from which has provided the present understanding of the sensitivity and inferred function of visceral receptors. Receptors that respond to sugars, lipids, amino acids, and so forth (i.e., principally those associated with the mucosa) were an early focus of study (see Refs. 16 and 19 for overviews). Mechanical and nonnutrient chemical (irritant) stimuli have also been studied, with increasing emphasis on visceral nociceptive mechanisms. Improved understanding of the normal physiology of primary visceral afferent neurons has stimulated study of the mechanisms that contribute to development and maintenance of altered sensations from the viscera. These altered sensations, which characterize functional bowel disorders, interstitial cystitis, ureteric colic, and so forth, are considered to represent a vis-
VISCERAL HYPERALGESIA

The primary sensory neuron, innervating either somatic or visceral tissue, has been well established as contributing to the development of hyperalgesia (25). Primary visceral afferent neurons have been shown in the recent past to possess qualities that suggest a role in both acute and persistent pain and hyperalgesia.

Mechanosensitivity. Visceral afferent fibers innervating hollow organs have been documented, as summarized in Table 1, to have either low or high thresholds for response to mechanical distension, an adequate stimulus (in the Sherringtonian context) for hollow organs. There exists a proportion (~25%) of the mechanosensitive fiber population that has high thresholds for response (>30 mmHg) and likely represents a group of visceral nociceptors. The remaining ~75% of the mechanosensitive population of visceral afferent fibers has thresholds for response in the physiological range; most respond to distending stimuli between 1 and 5 mmHg. Unlike low-threshold cutaneous mechanoreceptors, low-threshold mechanosensitive visceral afferent fibers encode distending pressures into the noxious range and, as a group, give greater-magnitude responses throughout the noxious range of distending pressures than do high-threshold visceral afferent fibers (Fig. 1).

Table 1. Mechanosensitive visceral afferent fiber response thresholds

<table>
<thead>
<tr>
<th>Organ</th>
<th>Species</th>
<th>Response Threshold (% of sample)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus</td>
<td>Opossum</td>
<td>2.9 mmHg (63)</td>
<td>20, 21</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>Ferret</td>
<td>2.5 mmHg (68)</td>
<td>4</td>
</tr>
<tr>
<td>Colon</td>
<td>Cat</td>
<td>&lt;25 mmHg (68)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Rat</td>
<td>&gt;25 mmHg (32)</td>
<td>17</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>Cat</td>
<td>&lt;25 mmHg (70)</td>
<td>9, 10</td>
</tr>
<tr>
<td></td>
<td>Rat</td>
<td>&lt;30 mmHg (80)</td>
<td>18</td>
</tr>
<tr>
<td>Ureter (in vitro)</td>
<td>Guinea pig</td>
<td>8 mmHg (24)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Chicken</td>
<td>&lt;20 mmHg (36)</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;20 mmHg (64)</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Uterus</td>
<td>=20 mN (61)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>=35 mN (39)</td>
<td></td>
</tr>
</tbody>
</table>

There also exist visceral afferent fibers that are mechanosensitive, called "silent" or "sleeping" nociceptors, which acquire spontaneous activity and mechanosensitivity after tissue insult. Mechanically insensitive afferent fibers have been documented among the primary visceral afferent fiber population, although they have been more extensively characterized in somatic tissues (25). It is not known at present whether such afferent fibers, which are typically subjected only to experimental mechanical (distending) test stimuli, are truly mechanically insensitive or represent a group of chemonociceptors that become active after tissue insult and exhibit polymodal sensitivity. If such fibers are present in the viscosa in large number, they could contribute significantly to an increased barrage of afferent input to the central nervous system and thus to visceral hyperalgesia.

Polymodality. It is generally assumed that primary visceral afferent fibers are polymodal in character, but this has largely been inferred rather than documented experimentally. When mechanosensitive visceral afferent fibers have been tested for sensitivity to other modalities of stimulation, all have also been found thermosensitive and/or chemosensitive (22). Similarly, many chemosensitive mucosal afferent fibers also give evidence of mechanosensitivity when tested. Determination of the adequate stimulus for primary visceral afferent fibers has not been rigorously examined, but if the mechanosensitive population is representative of the visceral innervation in general, then polymodal sensitivity is the rule rather than the exception.

Sensitization. Another characteristic of the low-threshold group of mechanosensitive visceral afferent fibers that distinguishes them from their low-threshold cutaneous counterparts is the ability to sensitize after experimental organ inflammation. Sensitization means an increase in response magnitude, sometimes accompanied by an increase in spontaneous activity and/or a decrease in response threshold, after inflammation.
Sensitization of cutaneous nociceptors has long been recognized as an initial, important event in the development of cutaneous hyperalgesia. Mechanosensitive visceral afferent fibers, both those with low and those with high response thresholds, have the ability to sensitize and thus contribute to altered sensations arising from the visera (Fig. 2). Because low response threshold visceral afferent fibers encode well into the noxious range and sensitize when a viscus is insulted, both populations of mechanosensitive visceral neurons can contribute to visceral discomfort and pain.

The peripheral contributors to acute sensitization of mechanoreceptors or to awakening of silent nociceptors are not known. The chemical mediators derived from immune and nonimmune cells that potentially contribute to sensitization of the extrinsic (and intrinsic?) visceral sensory innervation include amines (e.g., histamine, serotonin), peptides (e.g., bradykinin, substance P), products of arachidonic acid metabolism (prostaglandins), cytokines, neurotrophins, reactive metabolites, and so forth (see Refs. 3, 6, and 7 for reviews). There has been limited direct investigation of the potential contributions of these mediators to mechanoreceptor sensitization, but a mixture of mediators (bradykinin, serotonin, histamine, prostaglandin E₂, and KCl) instilled acutely into the rat colon sensitizes responses of pelvic nerve afferent fibers to colonic distension (see Fig. 2 and Ref. 22).

In addition to acute sensitization of mechanosensitive visceral afferent fibers, there are also long-term consequences after visceral insult. For example, there remain sensory-motor disturbances of the gut after inflammation subsides (see Ref. 6 for review), including an adult visceral (colonic) hyperalgesia in rats treated as neonates (1). These outcomes suggest that persistent sensitization of visceral receptors or awakened, now active silent nociceptors can contribute to the initiation and maintenance of visceral hyperalgesia by peripheral and central nervous system mechanisms. In such circumstances, the potential peripheral mediators are likely either to be a subset of those mentioned above or to include none of them and instead reflect function of visceral receptors changed by a previous event. That is, the disorder now labeled “functional” had some antecedent peripheral initiating event (e.g., acute inflammation, infection, and so forth) that contributed to changes in the behavior of mechanosensitive, chemosensitive, and/or thermosensitive visceral receptors that did not revert to “normal” after resolution of the insult.

**PERIPHERAL MECHANISMS OF PERSISTENT VISCERAL HYPERALGESIA**

If this is so, what possible changes in the periphery could be responsible? What follows is speculative, and experimental evidence is scant. However, all propositions are testable.

Enhanced sensitivity to normal intraluminal contents. Our own work has shown that bile salts instilled acutely into the colon significantly increase the activity of mechanosensitive (polymodal) colon sensory fibers (see Fig. 2). Response magnitude to colonic distension

![Fig. 2. Responses of pelvic nerve low-threshold and high-threshold fibers before (control) and after (treated) intracolonic instillation of an irritant. Responses are illustrated as peristimulus time histograms (1-s bin-width); colonic distending pressures are illustrated at bottom. After control responses to graded distension were determined, inflammatory soup (bradykinin, serotonin, histamine, prostaglandin E₂, and KCl at 10⁻⁵ M, pH 5.5) or bile salt (1%) was instilled into the colon, and responses to graded distension of the colon were studied 60 min later. Inflammatory soup increased response magnitude and resting activity of the low-threshold fiber. Bile salts decreased response threshold, increased response magnitude, and significantly increased resting activity of the high-threshold fiber. Data from X. Su and G. F. Gebhart (unpublished).](http://ajpgi.physiology.org/ by 10.220.33.6 on March 31, 2017)
was not increased for all fibers tested (22), but resting activity was significantly increased for all fibers studied. Bile salts in the gut thus can contribute an exaggerated afferent input to the spinal cord in the absence of colonic inflammation. When mechanoreceptors previously insulted (infection or inflammation) are exposed to bile salts (and/or other substances normally present), effects greater than those illustrated in Fig. 2 could result and lead to discomfort and pain. The effect of other normally present substances on mechanosensitive visceral afferent fibers has not been widely studied.

How bile salts (or other normally present intraluminal substances) might affect mucosal chemosensitive (polymodal?) receptors, such as those exposed in the past to an acute infection or inflammation, is not known. One could imagine, however, that chemosensitive mucosal receptors in patients with functional bowel disorders may give enhanced responses and contribute exaggerated input to the central nervous system when exposed to normal content or secreted chemicals in response to food intake. For example, peptides such as CCK are released from mucosal endocrine cells in the presence of intraluminal nutrients. Amines like serotonin are also present, and serotonin, CCK, or both CCK and serotonin could act on their respective receptors located on the terminals of primary visceral afferent neurons. Furthermore, potentially important interactions between the intrinsic and extrinsic primary afferent populations of neurons have not been characterized. The anatomical proximity and the richness of the chemical soup in which their terminals reside suggest an interface and potential contribution to altered sensations that has yet to be explored.

Nerve injury. Irritation of peripheral nerve trunks (neuritis) or frank damage (neuropathy) both contribute altered input to the central nervous system. In animal models of somatic nerve mononeuropathy or neuritis, hyperalgesia is characteristically produced and is long lasting. There is little experimental evidence that similar insult to spinal visceral afferent nerve trunks produces exaggerated responses to stimuli applied to the visera. Visceral neuropathy has been associated principally with altered function (e.g., pseudoobstruction, slow transit constipation) but has not been studied as a possible contributor to the altered sensations that characterize functional bowel disorders. In preliminary studies of a model of pelvic nerve neuritis in the rat, response magnitude at low distending (physiological) pressures and spontaneous activity are clearly increased (Fig. 3), suggesting that a visceral nerve neuritis could contribute significantly to the afferent barrage arriving at the spinal cord.

Ion channels. Ligand- and voltage-gated channels in sensory neurons may be altered subsequent to insult to a viscus or nerve injury and thus contribute to the discomfort and pain present in functional visceral disorders. Candidate channels include voltage-gated sodium and calcium channels, acid-sensing and temperature-sensing ion channels, and ion channels gated by endogenous ligands such as serotonin or ATP. The presumed changes in such channels occur at the nerve terminal in the viscus as well as in the cell body in the nodose or spinal dorsal root ganglia. Because it is not possible to interrogate directly the peripheral nerve terminal, ion channels in sensory neuron cell bodies are studied as representative of peripheral events. Many ion channels have been cloned, and there now exist molecular and pharmacological probes with which to study them.

The nodose or dorsal root ganglia cell bodies of specific visera can be labeled by injection into the viscus of a retrogradely transported dye and subsequent identification with fluorescence microscopy. With the use of such a strategy, we know that colon sensory neurons contain both tetrodotoxin-sensitive and tetrodotoxin-resistant voltage-gated sodium channels, capsaicin-sensitive cation channels (the VR1 receptor, a temperature-sensing channel), and stretch-activated potassium channels (23, 24). It is not known at present how the number, subunit composition, or biophysical properties of such channels may change (and remain changed?) after a visceral insult, but it has been shown that a tetrodotoxin-resistant sodium current is increased by putative inflammatory mediators, consistent with a role in peripheral sensitization and hyperalgesia (8).

**SUMMARY**

The physiology of visceral afferent pathways was the emphasis of study in the recent past, and we now understand much better how mechanoreceptors contribute to acute noxious events in the visera. The pathophysiology of visceral sensory neurons is not as well understood, but it is clear that they share with their somatic counterparts the ability to sensitize. In the cutaneous sensory realm, however, only nociceptors sensitize, whereas both low- and high-threshold mecha-
nosensitive visceral sensory neurons sensitize. Accordingly, both mechano-sensitive populations in the viscera can contribute to discomfort and pain. Knowledge about the potential contribution of the nonmechano-sensitive population of visceral receptors in mucosa, muscle, and/or serosa to visceral pain and visceral hyperalgesia is limited at present. However, given the approximately fourfold greater size of the low-threshold population of mechano-sensitive afferent fibers, acute inflammatory events in the viscera are conceivably represented in the central nervous system by a greatly increased afferent input relative to normal. Because these receptors are polymodal, intraluminal chemical or mechanical visceral stimuli in the physiological range have the potential to contribute significantly to altered sensations arising from the viscera.

Mechanisms by which primary visceral afferent neurons contribute to functional visceral disorders, which often exist in the absence of detectable insult to the viscus, are not known. Several avenues of investigation were presented above. The functional visceral disorders, characterized by discomfort and pain, could be a consequence of visceral nerve neuritis or nerve damage or could arise from changes in the number and behavior of one or several neuron ion channels, initiated and maintained by presently unknown means. It is known that there are long-term consequences (e.g., changes in sensory-motor function, visceral hyperalgesia) following resolution of acute visceral inflammation (see, e.g., Refs. 1 and 6). Because normally non-pain-producing stimuli, such as eating or drinking, often precipitate discomfort and pain, functionally disordered visceral receptors respond inappropriately. Inappropriate visceral receptor(s) transduction or amplification of these physiological stimuli or normally present luminal contents contributes an exaggerated peripheral input to the central nervous system. This input could initiate in a normal central nervous system interpretation of the event as inappropriately painful. More likely, however, is that the peripheral input adds to central nervous system mechanisms that also contribute significantly to the visceral hyperalgesia.

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