INTRODUCTION

All viscera within the body have a complex sensory innervation, with afferent nerves from most organs projecting through two anatomically distinct pathways. Many physiological studies showed that these sensory nerves respond to mechanical, chemical or thermal stimuli. Yet, despite the ongoing afferent input, humans typically perceive very little sensory input from the viscera, even though some may even reach cortical structures (1). Thus, if a person consciously processes information from different visceral structures, the sensation is often described using negative attributes, such as palpitations, heartburn, fullness, bloating or urgency. Patients and physicians alike typically interpret such symptoms, especially when associated with discomfort or pain, as alarm signals, which trigger physician visits and often extensive evaluations. Recent studies indicate that abdominal pain or discomfort leads to more than 12 million outpatient consultations annually in the United States (2). However, in a substantial number of patients, work up does not demonstrate any structural or biochemical abnormalities, leading to the diagnosis of a functional disorder. In such functional disorders, the persistent or repeated negative sensory experiences, primarily pain or discomfort, have become the disorder rather than functioning as a physiologically meaningful warning sign of an underlying problem. This review will describe our current understanding of mechanisms that may contribute to the development of abnormal visceral sensation, potential diagnostic strategies to identify affected individuals and therapeutic options.

BASIS OF GASTROINTESTINAL SENSATION AND PAIN

The gastrointestinal system has a complex innervation with intrinsic and different extrinsic nerves projecting to each layer from mucosa to serosa. The intrinsic or
**enteric nervous system**, comprised of about as many neurons as the spinal cord, certainly plays an important role in the regulation of normal gut function. However, its sensory neurons do not project to the central nervous system and thus do not directly contribute to conscious sensation. The extrinsic nervous system, with two distinct pathways, provides the anatomic correlate for this brain gut axis. Based on their association with efferent pathways, visceral afferents have traditionally been divided into vagal (parasympathetic) and sympathetic systems. Yet, anatomically and functionally, these sensory pathways are not simply a part of the autonomic nervous system. Therefore, they are now typically referenced based on the location of their cell bodies as vagal (located in the nodose ganglion and projecting to the brain stem) and spinal pathway (located in the dorsal root ganglia and projecting to the spinal cord). Less than 10% of dorsal root ganglion neurons project to visceral structures, resulting in a relatively low innervation density. Some of the peripheral axons branch extensively and send processes to several distinct areas within the same organ or even to more than one organ. Such dichotomizing axons limit the specificity of afferent input, which is often vague and poorly localized. Another phenomenon, further confounding visceral sensation is the fact that visceral afferents respond to different modalities, such as mechanical, thermal and/or chemical stimuli. The polymodal character of visceral sensory neurons also contributes to the poor ability to discriminate input from the viscera. These physiological findings have clinical correlates. For example, esophageal distension triggers a sensation of heartburn in about one third of healthy volunteers. This observation may explain why quite a few patients with achalasia early in their disease receive treatment for presumed gastroesophageal reflux disease.

In the gastrointestinal tract, changing luminal contents require frequent adjustment in function. In this context, the epithelium plays an important role in mediating information about luminal contents to the nervous system. Specialized enteroendocrine cells release a variety of mediators into the subepithelial space, where they can activate sensory terminals of intrinsic and extrinsic neurons. Serotonin has gained special prominence as a paracrine mediator released by enteroendocrine cells. Most of the body’s serotonin is indeed found within the gut, most prominently within the epithelial layer. Mechanical and chemical stimuli can trigger release of serotonin, which can interact with receptors that have been identified on intrinsic and extrinsic neurons (3–5). Finally, serotonin agonists and antagonists significantly alter gut function, including sensory input, and thus attract significant attention to this signaling pathway (3,6).

Spinal afferents enter the spinal cord to project to the brain. Neurons within the spinal cord typically receive converging input from many structures, somatic and visceral. This viscero-somatic or viscero-visceral convergence onto higher order sensory neurons explains the referral of visceral sensation and pain to other areas of the body. As physicians, we use the referral pattern of visceral pain to identify potential underlying problems. Abdominal pain radiating to the periumbilical or lower abdominal areas suggests a gastrointestinal etiology, while radiation to groin or inner thigh indicates renal or ureteral causes.

Neuroimaging studies show typical patterns of central activation during visceral stimulation. In addition to important relay stations within the brain stem and thalamus, the cingulate cortex (ACC) and insula are most consistently activated (Figure 1). These areas appear to play an important role in the central representation of pain, as they are also activated during painful somatic stimuli and even during the anticipation of a painful somatic or visceral stimulus (7–9). The cingulate cortex is part of the phylogenetically older limbic system, which plays an important role in emotional processing. The complex experience of pain includes a strong affective dimension, often described as unpleasantness. Interestingly, similarly intense visceral pain triggers stronger emotional reactions than cutaneous pain, which has been linked to a strong activation of the anterior cingulate cortex in response to visceral, but not somatic stimulation (10,11).

Our sensory innervation exhibits significant functional and even structural plasticity. Injury or insult can sensitize nerve fibers, lowering the threshold for activation and increasing the information flow to higher centers. This process is typically referred to as sensitization, and results in hyerperalgesia (exaggerated pain response to a painful stimulus) or allodynia (pain in...
response to an innocuous stimulus). This peripheral sensitization contributes to symptoms during an acute disease process, such as inflammation of the gut wall. The increased afferent input in turn alters the properties of neurons within the spinal cord or brain (central sensitization), which may outlast the time of the original insult. Such a sequence of events has been demonstrated in experimental animals and humans and may explain the increased incidence of functional gastrointestinal disorders after episodes of acute gastroenteritis (12). Modulation of visceral sensory input is a two-way road. Descending inputs from the central nervous system project to the spinal cord and facilitate or inhibit the flow of nociceptive input to the brain. Changes in the descending modulatory system typically affect afferent inflow independent of its source. Thus, individuals with impaired descending inhibitory system display increased pain responses to somatic and visceral stimuli, which may explain the common coexistence of different functional syndromes characterized by pain, such as irritable bowel syndrome, interstitial cystitis and fibromyalgia (Table 1).

### DIAGNOSIS OF VISCERAL HYPERSENSITIVITY

More than 30 years ago, Ritchie first suggested that irritable bowel syndrome may be characterized by abnormal sensation rather than being a disorder of motility (13). This notion has since entered the mainstream and is accepted as one of the important mechanisms underlying the development of functional gastrointestinal disorders (14). However, gastrointestinal sensory testing has not yet made it into an accepted routine tool for clinical use. In the following section, we want to discuss some of the remaining questions related to gastrointestinal sensory testing.

An ideal stimulus should be physiologically relevant, innocuous, provide a broad intensity spectrum, allow repeated administrations and provide reproducible results. While a variety of modalities from chemical to electrical stimuli has been employed, distension of hollow organs using air-filled balloons best

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**Table 1**

**Clinical Implications**

- The low innervation density and polymodal character of visceral sensory neurons explain the poor discriminatory ability of sensory input.
- Convergence of different afferent input to higher order sensory neurons is responsible for pain referral to somatic areas and may contribute to coexistence of different functional disorders.
- Sensitization of sensory pathways during acute episodes of gastroenteritis contributes to the development of postinfectious functional gastrointestinal disorders.
meets these criteria. Unfortunately, the test is invasive, requiring insertion of a balloon mounted on a catheter into the proximal or distal gastrointestinal tract. Early studies used simple latex balloons that were inflated with large air-filled syringes. However, latex balloons conform very poorly to the surrounding tissues and require significant pressures to overcome the significant elasticity, thus not allowing reliable filling rates. As results depend on the rate and sequence of distensions, most investigators rely on a barostat, a computer-controlled pump system that controls balloon volume and/or pressure. As pressure rather than balloon volume is the more reproducible measure, most studies indicate values for different sensory thresholds in mmHg.

While it requires insertion of balloon catheters, sensory testing has become a useful tool in clinical research. When thresholds for urgency, discomfort, or pain are determined, results are reproducible (15,16). Analgesic therapy increases sensory thresholds, supporting the validity of the approach (17,18). Conversely, the intragastric administration of capsaicin, the active ingredient of chilli peppers, triggers discomfort and lowers sensory thresholds (19). Many studies have examined visceral sensitivity since Ritchie’s initial publication, with most, but not all showing an enhanced sensitivity in patients with functional bowel diseases (Figure 2).

So, why has sensory testing not yet become a routine test? First, there is an extensive overlap of results obtained in healthy volunteers and patients, raising questions about the clinical utility of the test in individual patients (Figure 2). Second, phenotypic differences, most notably severity of reported symptoms, do not correlate with sensory thresholds (20). Third, time-dependent changes in sensory threshold poorly reflect the natural history of the disorder or effect of interventions, as experimental determined thresholds increase in healthy controls and patients with repeated testing, even if symptoms remain stable (21). Similarly, changes in sensory thresholds determined during acute pharmacologic interventions do not predict the results of long-term treatment (22,23). Fourth, despite sophisticated testing, we can not currently differentiate increased attention to visceral stimulation (central cause) from increased sensitivity of afferent nerves (peripheral cause). Thus, test results cannot distinguish between peripheral sensation of visceral stimuli or their central processing. Finally, there are practical considerations in that sensory testing requires dedicated personnel and is quite time-consuming and invasive, further slowing its introduction into clinical practice (Table 2).

**TREATMENT OF VISCERAL HYPERSENSITIVITY**

Ever since Ritchie’s initial description of increased sensitivity as a contributor to functional bowel disorders, we have gained significant insight into the normal physiology of visceral sensation as well as its role in disease. However, the wealth of basic and clinical research has not yet translated into an effective and specific visceral analgesic therapy. Treatment of pain,
specifically gastrointestinal pain, is fraught with problems. Symptoms are typically associated with physiologic changes, such as diarrhea or vomiting. The clinical efficacy of drugs is often limited and adverse effects (e.g., nausea and constipation with opioids; dyspepsia with non-steroidal anti-inflammatory drugs) exacerbate the already existing abnormalities of gut function. In the previous section, we described peripheral and central processes involved in the conscious perception of visceral stimuli. Using this conceptual framework, we will discuss therapeutic approaches targeting either one or both of these theoretically distinct sites (Figure 3).

While much of modern medicine focuses on evidence-based decisions, we still largely rely on empiric therapies when treating patients with visceral hyperalgesia. Appropriately designed and powered randomized-controlled trials have only tested some of the strategies and yielded at times conflicting results. These apparent discrepancies in treatment trials likely reflect the heterogeneity of patients with symptoms meeting the definition of irritable bowel syndrome or functional dyspepsia despite at times significant phenotypic differences and, likely, underlying mechanisms.

Table 3

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<th>Clinical Implications</th>
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<td>• Muscarinic receptor antagonists and the 5-HT₄ receptor agonist tegaserod alter gastrointestinal function and, thus, indirectly improve visceral discomfort and pain.</td>
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<td>• The peripherally acting 5-HT₃ receptor antagonist alosetron improves urgency and discomfort at least in part by decreasing afferent neuron responses to visceral distension.</td>
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<td>• Tricyclic antidepressants and perhaps selective serotonin reuptake inhibitors appear to provide some benefit in patients with functional gastrointestinal disorders.</td>
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<td>• While labor-intensive and costly, different psychological treatments lead to significant and apparently longer lasting improvement in overall symptoms of pain and discomfort.</td>
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Local anesthetics, such as lidocaine, block voltage-dependent sodium channels and, thereby, inhibit the generation of action potentials. Considering the efficacy as local anesthetics, topical application of lidocaine enemas has been examined in patients with irritable bowel syndrome. While conceptually appealing, the results are inconclusive, as different groups obtained different results (24–26). Perhaps more importantly, the inconvenient route of application will limit the practical utility of this approach. Systemic application of related agents (e.g., mexilitine) has been tried in patients with neuropathic pain and showed limited beneficial effects (27). Considering the different characteristics and mechanisms of neuropathic and functional gastrointestinal pain, it is unlikely that this approach will have a positive effect in patient with common visceral pain syndromes.

Specialized ion channels in nerve terminals transduce the stimulus energy (e.g., stretch) into an electrical signal within the nerve terminal that may trigger action potentials.

Figure 3. The schematic drawing shows currently used therapies for visceral pain and their site of action. Blockers of TRPV1 and P2X channels as well as peripherally acting κ opioid receptor agonists are under development (for details see text).

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potentials. Some of these ion channels are primarily activated by potentially noxious stimuli and have thus generated significant interest, as they may function as targets for drugs that could blunt pain sensation. Blockers of the capsaicin receptor (TRPV1 channel) and purinergic P2X receptors have been developed, show some promise in animal experiments and may find their way into clinical applications in the future.

Serotonin (5-HT) released from enteroendocrine cells is an important signaling molecule within the gastrointestinal tract. Interestingly, some studies have demonstrated an increase in the number of these enteroendocrine cells in patients with postinfectious and diarrhea-predominant irritable bowel syndrome (28,29). Several functionally distinct 5-HT-receptors are found on different cells within the gastrointestinal tract and contribute to sensation, motility and secretion. Thus, drugs interacting with serotoninergic signaling may directly affect sensory neurons or indirectly alter sensation through changes in secretion and/or motility. The peripherally acting 5-HT3-receptor antagonist alosetron significantly improved symptoms including pain in patients with diarrhea-predominant irritable bowel syndrome (30,31). While indirect effects on motility and secretion likely contributed, the agent blunted discomfort, urgency and pain during isobaric rectal distension, suggesting a direct effect on afferent pathways (32,33). The potent antiemetic effect and diarrhea-predominant irritable bowel syndrome (30,31). While indirect effects on motility and secretion likely contributed, the agent blunted discomfort, urgency and pain during isobaric rectal distension, suggesting a direct effect on afferent pathways (32,33). The potent antiemetic effect of the 5-HT3-receptor antagonists ondansetron and granisetron show the importance of this signaling pathway for the proximal gastrointestinal tract. However, alosetron does not affect gastric sensation in response to distension (34). Thus, independent of its adverse effects with the increased incidence of ischemic colitis, alosetron and related agents do not meet the profile of an effective visceral analgesic. The 5-HT4-receptor agonist tegaserod improves bloating and discomfort in conjunction with constipation (35). While tegaserod alters a reflex response to rectal distension in humans, it did not affect conscious sensation (36). When tested in vitro, 5-HT4-receptor agonists enhance rather than decrease excitability of visceral sensory neurons, suggesting that its beneficial effect is largely due to acceleration of gastrointestinal transit (5). Meta-analyses show that 5-HT3-receptor antagonists and the 5-HT4-receptor agonist are superior to placebo. However, the effect is only moderate with an odd ratio favoring the active agent over placebo between 1.8 and 2.0, translating to a number-needed-to-treat of about 7 (37,38). Consistent with frequent patient descriptions of painful spasms, strong gastrointestinal contractions can actually be perceived as painful or uncomfortable (39). These findings provide the rationale for smooth muscle relaxants. Theoretically, adrenergic agonists, muscarinic antagonists, nitric oxide donors or L-type calcium channel blockers can be used. However, only muscarinic antagonists have consistently demonstrated efficacy when compared to placebo (40). Moreover, frequent and significant systemic side effects, most notably hypotension, limit the clinical utility of the other agents. As is true for tegaserod, the effect is largely due to alterations of gastrointestinal motility rather than direct changes in sensory function.

Gastroenterologists very commonly use the centrally-acting opioids during procedural evaluations and acute illnesses, such as pancreatitis. While they are potent analgesics for visceral pain, µ opioid receptor agonists typically cause gastrointestinal side effects, such as nausea, vomiting, and constipation. Moreover, concerns about abuse potential, central nervous system side effects and potential long-term use of these agents limit their utility in patients with chronic, non-malignant visceral pain. More recently, peripherally acting κ-opioid agonists were developed, as the κ-opioid receptor is expressed on primary visceral afferent neurons (41). Consistent with the theoretical advantage of a peripheral side of action, adverse effects were limited. However, so was the analgesic effect, as the benefit in patients with functional gastrointestinal disorders was rather small compared to placebo (18,42,43).

Tricyclic antidepressants are commonly used in patients with functional gastrointestinal disorders. Several rationales explain their potential efficacy. First, even low dosages decrease neuropathic pain, which has been attributed to a use-dependent block of voltage-sensitive sodium channels (44). Second, pain, especially visceral pain, has a significant affective component. Considering the high prevalence of mood disorders in patients with functional bowel disorders, the antidepressant effect itself may improve the overall quality of life. While effects on perception of visceral

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stimulation under experimental conditions were inconsistent, controlled trials show a benefit of the active agent over placebo (37). Interestingly, while dosage and plasma levels correlate with treatment response in psychiatric disease, a per-protocol analysis of the tricyclic antidepressant desipramine did not demonstrate any significant dose-response relationship in women with functional bowel disease, leaving some questions about its mechanism of action (45). However, frequent adverse effects pose a significant problem. Theoretically, serotonin reuptake inhibitors offer an attractive alternative, especially if mood-altering properties are indeed the primary mechanism of action. However, the results of randomized controlled trials are mixed (22,46,47), which may be at least partly due to the resulting increase in peripheral serotonin, as the agents inhibit serotonin reuptake in brain and gut.

Sensory disorders may be seen as disorders of the gut-brain axis. Thus, different treatments have been developed targeting the brain as the site of processing rather than the gut as the presumed site of stimulation. The theoretical roots for this shift in treatment focus are expressed in the biopsychosocial model of illness, which suggests that an individual’s biology, behavior and cognitive processes influence somatic diseases through their interaction with each other as well as early life experiences and social environment (48,49). A higher prevalence of mood disorders, perhaps associated with or triggered by experiences of abuse, provides a frame of mind that may favor selective attention to gastrointestinal phenomena. Two conceptually distinct approaches try to modify such potentially maladaptive behaviors through psychological therapy. Relaxation techniques, hypnosis or biofeedback teach patients to decrease vigilance and arousal in response to visceral stimuli, while cognitive therapies attempt to change a patient’s pattern of thinking which leads to excessive emotional and physiological reaction to visceral symptoms (49). A recent meta-analysis shows an impressive rate of global symptom improvement in actively treated patients with a pooled odds ratio of 12 and a number-needed-to-treat of two (49). Despite these impressive results, cost, availability and labor-intensive demands of treatments such as cognitive-behavioral therapy, often requiring 10–12 weekly sessions, limit their clinical utility.

CONCLUSION

Pain and discomfort are the defining manifestations of the very common functional disorders of the gastrointestinal tract. Altered visceral sensation and sensory processes certainly contribute to their pathogenesis. However, we do not yet have practical methods allowing us to easily identify patients with abnormal visceral sensation. Perhaps more importantly, currently available methods cannot distinguish between central or peripheral mechanisms underlying such hypersensitivity. The results of different treatment trials show that therapies must be comprehensive and target mind and body, if we want to improve disorders of the gut-brain-axis.

References

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Sensation in the GI Tract

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