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# Visceral pain from neuroanatomy to receptors – focus on gastrointestinal pain

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## ABSTRACT

The mechanisms and nervous structures involved in visceral pain are poorly understood, although visceral pain is one of the most debilitating clinical types of pain. We performed a literature review with the aim of identifying the distinct features of visceral pain and their potential use for identifying new therapeutic targets. In this article, we present the main structures involved in the generation and transmission of visceral pain, the main experimental techniques currently used for inducing and measuring visceral pain and the main mediators and receptors that play an essential role in this particular type of pain.

**Keywords:** visceral pain, visceral pain models, visceral pain mediators

Visceral pain is defined as pain arising from the internal organs of the body; it can be secondary to acute or chronic inflammation, infection, ischemia, benign or malignant tumors or neuropathy. Visceral pain is considered one of the most frequent and debilitating forms of pain encountered in the general population and in clinical practice; it is an umbrella term for heterogeneous conditions that affect different organs (Table 1).

***TABLE 1.*** *The main types of visceral pain (1)*

| Visceral pain | Incidence | Examples |
|---|---|---|
| **CHEST PAIN** | 20.4% | Musculoskeletal chest pain<br>Esophagi s<br>Costochondri s<br>Angina pectoris<br>Myocardial infarc on<br>Pericardi s<br>Herniated abdominal organs<br>Diseases of the diaphragm |
| **GASTROINTESTINAL PAIN** | 10%-20% | Abdominal wall pain secondary to herpe c infec on or neuralgia<br>Liver and gallbladder diseases<br>Pancrea c diseases<br>Abdominal pain syndromes secondary to systemic diseases (porphyria, abdominal migraine, fibromyalgia)<br>Affec ve disorders (anxiety and depression<br>Irritable Bowel Syndrome (IBS) |
| **CHRONIC PELVIC PAIN** | 1-7 % | Perineal pain Syndrome<br>Bladder pain Syndrome<br>Prostate pain Syndrome<br>Scrotal pain Syndrome<br>Urethral pain Syndrome<br>Vulvar pain Syndrome |

From a clinical point of view, visceral pain is a diffuse and poorly defined sensation. This feature is a consequence of the low density of visceral sensory innervation and divergence of visceral input within the central nervous system. Due to viscerosomatic convergences, the spatial discrimination of visceral pain is poor and it is often referred to superficial structures producing secondary hyperalgesia of the superficial or deep body wall tissues. Referred pain is sharper, better localized and less likely to be accompanied by autonomic signs, which makes it difficult to differentiate from pain of somatic origin (2).

When compared with somatic pain inducers, a noxious stimulus for the viscera is quite different, since life-threatening conditions accompanied by tissue destruction, such as perforation of hollow visceral organs or neoplastic processes, are frequently not painful, while some experimental stimuli which are painful for viscera (such as distension of the hollow viscera) do not necessarily damage the tissue.

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Visceral pain has some distinct features, such as: (a) the sensory afferents are thinly myelinated Aδ-fibers and unmyelinated C-fibers (3) (b) there is no clear distinction between nociceptive afferents and nonnociceptive afferents, (c) high-threshold receptors from viscera (heart, esophagus, colon, ureter, uterus, etc.) respond only to noxious mechanical stimuli (d) "low threshold receptors" are intensity-encoding and respond to both innocuous and noxious stimuli (e) viscera are innervated by so-called "silent" nociceptors, mechanically insensitive afferents which acquire mechanosensitivity following inflammation (4,5).

Visceral organs have a dual sensory innervation through autonomic sympathetic and parasympathetic nerves. The sympathetic innervation comes mainly through the spinal afferents that travel along hypogastric, lumbar colonic and splanchnic nerves (through both prevertebral and paravertebral ganglia) and ends in the thoracolumbar region (4). The vagal and pelvic afferents end in the brainstem and lumbosacral cord and contribute to parasympathetic innervation. Sympathetic preganglionic axons are therefore relatively short, and parasympathetic preganglionic axons are relatively long.

The cell bodies of the ***vagal nerve,*** the largest sensory pathway in the body, reside in the ganglion nodosum and the central nerve endings terminate in the nucleus of the solitary tract in the dorsal medulla. Even though there are neurophysiological and anatomical data that show that vagal input reaches the cortical structures and can trigger sensations, there is no evidence that vagal input contributes to discomfort and pain. ***The pelvic nerves*** innervate mainly pelvic structures (colon, rectum, bladder, reproductive organs) and transmit visceral information to the spinal neurons in the lumbosacral segments L6-S2. The neuronal cell bodies are located in the lumbosacral dorsal root ganglia (DRG) and the afferents specialized in detecting circular stretch are present in the serosa, mucosa and muscular layer of the pelvic organs (6). ***The splanchnic nerves*** innervate the entire gastrointestinal (GI) tract and are the functional counterpart of the vagal and pelvic nerves. Visceral afferents located in the splanchnic nerves project in the spinal cord and onto thoracolumbar segments T10 – L2 in mice and rats (7). There are data suggesting that visceral spinal pathways convey nociceptive-specific information. Concordant with these data, splanchnic nerve resection was shown to abolish avoidance behavior in response to noxious gastric distension.

Because the GI pain is the best-studied type of visceral pain, our presentation will from now on focus only on this type of pain and we will refer to it as visceral pain.

Visceral functions (e.g. digestion, nutrient resorption, gaseous exchange, excretion) require complex regulation. The central nervous system (CNS) is the site where the information from the peripheral, enteric and hormonal systems is integrated. This neural pathway which links cognitive, emotional and autonomic centers in the brain to the neuroendocrine centers, enteric nervous system and immune system, has been called the "brain-gut axis". The "brain-gut axis" has, thus, an important contribution to autonomic dysregulation of the gut and is associated with pain and perceptual changes in visceral disorders (2).

Contrary to other internal organs, the digestive tract is exposed to a variety of physicochemical stimuli. As a consequence, the intestine has developed a network of coordinated movements to ensure the appropriate mixing and propulsion of contents during digestion, absorption, and excretion. The enteric nervous system (ENS) includes a number of neural circuits that control motor function, local blood flow, mucosal transport and secretion, and modulate immune and endocrine functions.

Noxious stimulation of visceral nociceptors generally produces hyperalgesia, which may lead to peripheral sensitization. However, inflammatory mediators can have noxious and ectopic activity, which will also promote excitability of the spinal cord and of the higher center neurons, i.e. central sensitization (8).

The enterochromaffin cells (ECC) are interposed between the epithelial cells of the GI tract and contain secretory granules with different types of peptides such serotonin, cholecystokinin and secretin (9). The mast cells are bone-marrow derived cells that circulate in the bloodstream as immature progenitors; after maturation, they reside within the mucosal wall. These cells also have a variety of mediators that can be rapidly released out of preformed granules – histamine, serotonin, serine proteases, and proteoglycans. Furthermore, mast cells can also synthesize prostaglandins, leukotrienes, platelet activating factor and cytokines (TNFα, IL-6) *de novo* (10,11).

Thus, both peripheral and central sensitisation are the consequence of enterochromaffin and mast cell activation by the inflammatory process (*e.g.*, tissue acidosis, cytokines, and metabolites of the arachidonic acid).

Although we know less about visceral pain than about somatic pain, available data indicate that the mechanisms involved are both central and perip-

heral. In order to better understand visceral pain, researchers use animal models of GI tract inflammation. Combining experimental pain studies and pharmacokinetic studies can improve the understanding of the pharmacokinetic-pharmacodynamic relationship between analgesics and, thus, provide valuable insight into optimal clinical treatment of visceral pain. The main experimental models used to evaluate visceral distention, hyperalgesia and pain in animals are presented in Tables 2 and 3.

Research performed in the past decade has led to the discovery of several channels that influence visceral pain. In the following pages, we will present the main channels and receptors that appear to be involved in GI visceral pain and are potential targets for novel analgesics.

**The Voltage-Gated Sodium Channel (VGSC)** plays an important role in somatic pain transmi-

***TABLE 2.*** *Tests used for assessing visceral pain*

| Investigation | Purpose of the test | Principle of the test |
|---|---|---|
| Electromyography of the neck muscles | To evaluate nocicep ve response to gastric distension. | Afferent neurons project from different spinal sites to the colorectal area and the stomach; gastric distension does not induce abdominal contrac ons, but results in stretching of the body and raising of the head, ac vity that can be recorded |
| Arterial blood pressure and heart rate | To evaluate visceral distension | In anaesthe zed rodents, visceral distension increases arterial blood pressure and causes tachycardia; in deeply anaesthe zed rats, there is a depressor response and bradycardia |
| Behavior | To evaluate colorectal distension | A er mechanical or chemical colonic irrita on, behavior is assessed as follows<br>1 – brief head movement followed by immobility,<br>2 – contrac on of abdominal muscles,<br>3 – li ing of the abdomen<br>4 – body arching and li ing of pelvic structures |
| von Frey hairs test | To evaluate referred soma c hyperalgesia | The applica on of von Frey hairs with forces 1 – 32 mN on the abdomen and the assessment of subsequent behavioral response |
| Electrophysiology | Visceral distension | Recording of the neuronal ac vity of afferent or second-order neurons located in the superficial spinal dorsal horn of the T13– L2 vertebrae in anaesthe zed animals |
| Immunohistochemistry | Nocicep ve visceral responses | Long-term neuronal responses increase the expression of proteins such as c-fos. For example, mechanical colorectal s mula on evokes c-fos expression in different areas of the spinal cord, including the dorsal horn. |
| Experimental inflamma on | To evaluate hypersensi vity and/ or inflamma on secondary to distension & chemical irrita on | The experimental induc on of inflamma on by a chemical agent<br>• HCl – for lower esophageal irrita on<br>• 0.1% iodoace c acid (oral inges on) for stomach inflamma on (12)<br>• trinitrobenzenesulfonic acid or ace c acid (intracolonic) for colon inflamma on<br>• zymosan (intracolonic) for inducing colonic hypersensi vity in the absence of inflamma on (13)<br>• cyclophosphamide for urinary bladder inflamma on (intraperitoneal administra on). Cyclophosphamide metabolizes to acrolein, an irritant that produces cys s (14)<br>• mustard oil (intrauterine administra on) for uterine inflamma on (15) |

***TABLE 3.*** *Main visceral pain models in animals*

| Visceral pain models | Principles | Technique |
|---|---|---|
| Intraperitoneal administra on of irritants | Administra ons of irritants such as ace c acid, hypertonic saline or phenylquinone intraperitoneally do not act selec vely on the viscera; moreover, they produce a reproducible behavior (writhing) that is inescapable. | The ace c acid writhing test is mostly used to study the nociceptors lining the peritoneum and measures spontaneous pain. Ace c acid (0.6% v/v) is given by i.p. injec on and the number of writhing events (stretching, retrac ng, or pressing the belly against the floor) is counted over a 30 minute period (16) |
| Hollow organ distension | Hollow organ distension produces several types of responses, including contrac on of skeletal (non-visceral) muscles (termed the visceromotor response) and increases in blood pressure and heart rate.<br>Electromyography (EMG) recordings of muscle contrac on and blood pressure and heart rate measurement are used as measures for assessing distension. | The most commonly used model is colon distension, where a balloon inserted into the colon is inflated and the abdominal muscles ac vity evoked is measured by means of electromyography (visceromotor response).<br>A number of insults to the bowel are associated with enhanced visceromotor responses to colorectal disten on. These include butyrate, hypertonic saline acidified with 2,4,6-trinitrobenzene sulfonic acid, capsaicin, mustard oil, dextran sodium sulfate or zymosan administra on. The insults are meant to mimic disease states such as irritable bowel syndrome.<br>These tests have been validated as painful in human subjects (17). |

ssion and there is enough evidence that suggests it is involved in visceral pain as well. Thus, the NaV1.9 subtype seems to be an important regulator of afferent sensitivity in visceral pain secondary to mechanical and inflammatory stimuli (18); however, the most important type of VGSG, involved in both noxious visceral pain and visceral hypersensitivity seems to be the tetrodotoxin-resistant channel NaV1.8 (19,20); its importance was demonstrated in bladder hypersensitivity and colitis experimental models (21); also, in patients with rectal hypersensitivity, NaV1.7 channel immunoreactive nerve fibers increased significantly in those with IBS (22). Moreover, morphine tolerance and visceral hyperalgesia were interconnected with the tetrodotoxin-resistant Na(+) channel (23). Lidocaine is a drug that binds to voltage-gated sodium channels and prevents the flow of sodium ions through the channel pore. In humans, intrarectal lidocaine administration decreased rectal sensitivity and abdominal pain in patients with IBS (24).

**Voltage-gated calcium channels (CaVs)** are considered the major route of Ca2+ supply from the extracellular environment to the cytosol of electrically excitable cells; CaVs are encoded by 10 human genes. Depending on the α1 subunit of CaVs, there are three distinct subfamilies: CaV1 (1.1-1.4) conducting L-type currents; CaV2 (2.1-2.3), conducting N-type, P/Q- and R-currents; CaV3 (3.1-3.3) conducting T-type currents. In animal studies, it has been demonstrated that CaV1.2 and CaV2.3 from colonic primary sensory neurons play an important role in visceral inflammatory hyperalgesia (25) and that CaV3.2 seems to be involved in acute, somatic, visceral and tonic inflammatory insults (26); also, Q-type CaVs were found to play an important role in acute bladder nociception (27). Both pregabalin and gabapentin, by binding to the α2δ-1 subunit of voltage-gated calcium ion channels, have been shown to reduce visceral hypersensitivity in experimental animals as well as symptoms of IBS in humans.

**Acid-sensing Ion channels (ASICs)** are an H+-gated subgroup of the degenerin/epithelial sodium channel (DEG/E NaC) family of proteins. Literature data support the hypothesis that ASICs contribute to acid-evoked pain; however, is not clear whether ASICs transduce or modulate painful stimuli. Of the 3 channels containing acid-sensing subunits, only the subunit 1 and 3 appear to be important in peripheral nociception. Animal studies have shown that ASIC3 is responsible for cardiac pain, pain accompanying gastritis, inflammatory bowel disease, and other GI pain disorders and for fibromyalgia (28). ASICs are likely to be promising candidates as clinical targets for esophageal pain provoked by acid, but further human studies are warranted.

**Transient receptor potential ion channels** (TRPs) are so named because when activated, they allow the influx of positive charges into the cell which sometimes generates an action potential and always generates a transient depolarization called "transient receptor potential". The TRP superfamily is divided into two groups: group 1 has five subfamilies (TRP-C, -V, -M, -N and -A) and group 2 has 2 – TRP-P and -ML. Those implicated in visceral pain are TRPV and TRPA. TRPV is activated by capsaicin, anandamide, protons and endogenous cannabinoids and TRPA is activated by mustard. TRPV is involved in visceral inflammation and hypersensitization (29) and has been shown to play a role in pancreatitis, gastro-esophageal reflux, Crohn's colitis, cystitis and inflammatory bowel disease (30,31). TRPV1 receptors are co-expressed with calcitonin gene-related peptide and substance P in 60-80% of visceral afferents. TRPA has been shown to be involved in colitis and is a key element in visceral hypersensitivity (32).

**Gamma Aminobutyric Acid Receptors**. Γ-aminobutyric acid (GABA) is a well-known mediator within the enteric nervous system that acts as a modulator for both motor and secretory GI activity; its effect depends on whether ionotropic (GABAA and GABAC receptors) or metabotropic (GABAB) receptors are activated. The real importance of GABAergic signaling in the gut is still a matter of debate. Current data show that GABA receptor B agonists can reduce visceromotor responses that occur in experimental models of colorectal distension or bladder irritation (33,34). Moreover, volatile anesthetics such as halothane, isoflurane, sevoflurane or propofol block visceral nociception via augmentation of GABA-B.

**Opioid Receptors.** The effects of opioid receptor agonists (ORAs) are mediated by one of the three opioid receptors: μ, δ, or κ; the visceral afferents contain only the κ and μ opioid receptors. While the first one does not modify GI motility, the activation of the second one has been associated with symptoms like nausea, vomiting or myoclonus. Targeting kappa receptors can actively reduce the number of writhes in experimental animal models, and also alleviate visceral pain in patients (35). On the other hand, μ receptor agonists (such as fentanyl) reduce responses to colorectal distension; it is hypothesized that the main role in modulating visceral pain in played by the central μ recep-

tor agonists rather than the peripheral μ receptor agonists (36). These data generated the hypothesis that administering both κ and μ agonists might have a synergic effect on visceral pain. However, in a PET study that used carfentanil as a radioligand, Ly et al showed that there is no opioid release in the brain during sustained visceral pain (37).

**N-Methyl-D-Aspartate (NMDA) Receptors** are ligand-gated ion channels that play an important role in long-term potentiation and memory processing. NMDA receptors are activated by colon distension but do not require the presence of inflammation. While NMDA receptors appear to be involved in signaling acute innocuous and noxious visceral pain and inflammatory visceral pain in animals, they do not appear to signal innocuous stimuli in humans during esophageal stimulation (1). Because their inactivation is slow, it has been linked with chronic visceral pain. In animal studies, ketamine, an NMDA receptor antagonist, reversed acid-induced esophageal hypersensitivity (38). However, although peripheral NMDA receptors are important in normal visceral pain transmission, there is no other evidence that NMDA antagonists are efficient in visceral pain. In fact, there is solid evidence that certain associations of NMDA antagonists that are efficient in the management of somatic pain do not have any effect on visceral pain (39).

**Toll-Like Receptor 4 (TLR4).** Current evidence suggests the involvement of the TLR4 in innate immunity. The TLR4 fusion with CD2 appears to be responsible for a constitutively active version of TLR4, which results in the expression of B7.1 (the co-stimulatory ligand of CD28) and inflammatory cytokines. TLR signaling involves at least two distinct pathways: a MyD88-dependent pathway that leads to the production of inflammatory cytokines, and a MyD88-independent pathway associated with the stimulation of IFN-β and the maturation of dendritic cells (40). More and more data point to a key role for TLR4 in chronic pain states of somatic origin. Both central and peripheral administration of a TLR4 specific antagonist (TAK-242) attenuated visceral pain sensation in animals (41). Furthermore, the same team recently published the results of another murine study that showed an increase of the TLR4 expression and microglia activation in brain areas related to visceral pain such as the prefrontal cortex and the hippocampus; also, they noted that long-term exposure to high-fat diet was followed by an increase in peripheral TLR4 activity with a subsequent increase in pro-inflammatory cytokine levels. The authors concluded that TLR4 has an important role in visceral pain modulation and it could be a potential therapeutic target for visceral hypersensitivity associated with fat diet consumption (42).

**Serotonin (5-HT) receptors.** 5-HT is an important neurotransmitter. More than 90% of the human body's serotonin is produced and stored in enterochromaffin cells in the intestinal epithelium. 5-HT is responsible for bloating, nausea, vomiting, and chemotherapy associated pain. From the seven types of 5HT receptors, the 5-HT4 receptor is involved in rectal distension and visceral perception of sensations, while the 5-HT7 receptor participates in nociception, particularly in visceral pain and the 5-HT3 receptor seems to modulate gut sensitivity. Ondansetron, a 5-HT3 antagonist, was shown to improve abdominal pain and increase evacuation in patients with IBS. Selective serotonin-reuptake inhibitors (SSRIs), such as paroxetine, fluoxetine, and citalopram, have also been reported as effective in patients with IBS (22). Tegaserod, a 5-HT4 partial agonist, appears to improve the overall symptomatology of IBS, but there are few data on its effect on life quality. In addition, oral administration of 5-hydroxytryptophan in human volunteers induced an alteration in systemic 5-HT metabolites and was accompanied by increased visceral perception of pain (43).

**Prostaglandin (PG) Receptors.** PGs are synthesized in response to tissue injury. They sensitize afferents to mechanical and thermal stimuli and contribute to spinal processing of pain. PGs act by reducing the activation threshold of sensory afferents via PKA pathways. In the GI tract, constitutive COX1 is involved in gastric mucosal protection and inducible COX2 contributes to afferent sensitization. Thus, nonsteroidal anti-inflammatory drugs inhibit prostaglandin synthesis and attenuate inflammation and pain, but unfortunately they also damage the gastric mucosa.

**Tachykinin receptors**. The tachykinin NK1-, NK2- and NK3G-protein-coupled receptors are activated by peptides such as substance P (SP), neurokinin A (NKA) and neurokinin B (NKB). The tachykinin receptors are located throughout the autonomic and central nervous system and are involved in visceral hypersensitivity. SP and calcitonin-related gene peptide (CGRP) are abundant in human GI sensory afferents suggesting a role in human GI visceral pain. In animal models, NK1 receptor antagonists reduce hyperalgesia and the use of a CGRP antagonist was shown to reverse the sensitizing effects of acetic acid intracolonic administration in a rat model. Experimental colitis

studies suggest that SP is involved in visceral hyperalgesic mechanisms.

**Purinergic receptors**, also known as purinoceptors play an important role in inflammation and can be activated by ATP released via pannexin channels and/or connexin hemichannels. Extracellular ATP can act on purinergic receptors in the GI system to mediate a variety of effects depending on the receptor type and localization. The ATP involved in excitatory neurotransmission within the enteric nervous system (ENS) acts as both an autocrine and paracrine molecule, altering ion transport, cell-cell communication, and inflammation (44). There are two types of receptors: the ATP-gated P2X, also known as purinergic; and the G-protein coupled – the P2Y receptor. ATP-gated ion channels were identified in afferent nerve endings of the large intestine and seem to be involved in mediation of the nociception secondary to inflammation, infection and digestive cells lesion. In animal studies, visceral hypersensitivity was observed after activation of purinergic receptors P2X3. Also, the P2X7 receptors located on the macrophages seem to play an important role in intestinal inflammation and in visceral hypersensitivity.

**Connexins** are gap junctions formed from connexon hemichannels. The connexins are expressed throughout different types of mammalian tissues. In non-excitable cells, gap junctions provide a means for the exchange of regulatory molecules less than 1 kDa such as ATP, NAD, IP3, cAMP and ions. Among the types of connexins found within the intestine, the Cx: 26, 32, 36, 37, 43, and 45 are the most frequent. From these, only Cx43, Cx37 and Cx 45 have been intensely studied. As such, Cx43 seems to be involved in intestinal inflammation and motility; this connexin is linked to inflammation of the intestine and to diarrhea caused by bacterial infection. The Cx37 and Cx45 are involved in immune responses and some authors suggest they might also be involved in IBS pathology (45).

**Pannexin channels** are a class of newly identified ATP release channels. The pannexin is a glycoprotein that forms a pore directly between the cytosol and the extracellular space; this pore has a good conductance and is large enough so that, when it is open, it allows large molecules such as ATP to pass through classic ion channel. In mammals, there are three types of pannexin channels: Panx1, ubiquitous in mammalian tissues; Panx2, localized to the central nervous system and recently found in enteric neurons; and Panx3 expressed in skin and cartilage, that seems to act as an ATP release channel in these tissues (45, 46).

Unlike connexin channels, the pannexin channels do not join together to form gap junction pores between neighboring cells. However, similar to connexins, pannexins are expressed in the ENS within the enteric ganglia and other cells involved in the immune response, making thus the pannexin channels potential players alongside connexins in ATP-associated dysmotility and inflammation. The role of pannexin and connexin channels in gut inflammation is an emerging and exciting topic of research. Current available data cannot fully explain the expression profile of Panx1 in intestinal tissues and further studies are necessary to confirm if pannexin and connexin channels really contribute to extracellular ATP signaling in IBS pathophysiology.

**Adenosine receptors** modulate neuronal and synaptic function through adenosine $A_1$, $A_{2A}$ and $A_3$ receptors (P1 family). Adenosine is a potent anti-inflammatory agent and its actions are mediated partly through A3A receptor activation. Adenosine receptors are being investigated as therapeutic targets for chronic inflammatory disorders including IBS, autoimmune disorders and cancer. In rodent models of IBS and inflammatory pain, among the drugs considered to be effective are the $A_1$AR agonists (Paeoniflorin, FK352, DPCPX), the $A_{2A}$AR antagonists (STW5 (Iberogast), ATL-313) and the $A_{2B}$AR antagonist ATL-801 (47).

Purinergic drugs such as methotrexate, sulfasalazine, adenocard (adenosine), dipyridamole or caffeine seem to work in diseases associated with visceral inflammation. Moreover, newer generation drugs developed as a result of progresses in biochemistry (targeting $A_3$, $A_{2A}$, $P2Y_{12}$, $P2X_{2/3}$, $P2X_3$, $P2X_7$ receptors) and several phytopharmaca such curcumin have an excellent safety/efficacy profile for potential future clinical trials in IBS and inflammatory diarrhea.

**Ovarian hormones.** Epidemiological studies show that IBS affects twice more women than men in western countries, suggesting that sex hormones might play a part in IBS pathophysiology. Moreover, the prevalence of visceral pain disorders (IBS, gastroesophageal reflux disease, gallbladder and biliary tract diseases) is significantly higher in women (48). Also, there is a strong positive correlation between IBS and dysmenorrhea and most of the GI tract symptoms, including abdominal pain, motility/transit and/or visceral sensitivity, decline around menses. Women experience more abdominal symptoms at the beginning of the follicular phase compared to the early luteal phase. The

mechanism by which sex hormones influence visceral pain is not clear, but estrogens seem to have a modulatory effect on GI pain by slowing down intestinal motor activity via mechanisms that likely involve the 5HT system (49). Interactions between the 5HT system and ovarian hormones have also been involved in differential peripheral pain processing. Even though the link between menstrual and bowel symptoms suggests there may be a common physiological basis involving both peripheral and central mechanisms, further studies are needed to characterize the multiple locations at which dynamic changes in ovarian hormones modulate contractility, transit, visceral sensitivity, and immune function.

Taking into account the multiple receptors and mediators involved in visceral pain, it is highly unlikely that a single analgesic or targeted agent could significantly influence clinically relevant visceral pain. Most likely, the future of visceral pain analgesia relies on combinations of the analgesics which, through synergy, will be more effective than current available therapeutic options.

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