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ORIGINAL ARTICLE

Clinical approach to visceral pain in irritable bowel syndrome – pathophysiology, symptoms, and treatment

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Abstract

Visceral pain has been defined as a pain resulting from activation of pain receptors localized in mucous membrane, serous membrane, and smooth muscles of hollow organs. The great majority of these organs are innervated by parasympathetic and sympathetic outflows. Afferent nerve fibres are involved in conduction of both acute and persistent pain and hyperalgesia. Visceral pain differs significantly from other types of pain in the way it originates and in clinical presentation. It can be misleading as a symptom, producing several problems in the diagnostic process. Sometimes, severe visceral pain is observed in the course of non-lifethreatening functional gastrointestinal disorders, while slight abdominal discomfort may be a first symptom of malignant tumours. For many years, the treatment of visceral pain has been considered as not satisfactory enough and covered a wide variety of pharmacological substances. For example, the complex therapy of pain and other manifestations associated with irritable bowel syndrome include psychotherapy/behavioural therapy, bulk-forming agents, probiotics, laxatives, antidiarrheals, antibacterial agents, antispasmodics, and antidepressants. The current knowledge about the pathogenesis of visceral pain gives a rationale for the development of new, more efficacious drugs with a positive benefit/risk ratio. Unfortunately, experience gained so far with the use of some agents affecting serotoninergic transmission in the gastrointestinal tract have shown a serious danger associated with their administration for patients with irritable bowel syndrome.

Key words

visceral abdominal pain, pathophysiology, treatment

INTRODUCTION

In the past, it had been thought that the visceral organs did not perceive any sensation. Although the pathophysiology of visceral sensory neurons is still not very well understood; nowadays. it is clear that visceral organs have sensory innervation. With the exception of the pancreas, the thoracic and abdominal visceral organs are innervated by parasympathetic (craniosacral) and sympathetic (thoracolumbar) outflows. Thoracic viscera and upper abdominal viscera are primarily innervated by the vagus (vagal afferents signal nonpainful sensations, such as hunger, satiety, fullness and nausea) and spinal thoracolumbar outflows. The lower abdominal viscera, including the small and the large intestine and the urogenital organs, are innervated by thoracolumbar and sacral outflows [1]. Visceral fibres can serve 'sensory' and 'afferent' functions; the former can evoke conscious sensations and the latter regulate autonomic flow [2]. It has been shown that primary visceral afferent neurons are involved in both acute and persistent pain and hyperalgesia, and have a low (1–5 mmHg) or high (about 30 mmHg) thresholds for response to the mechanical distension of the visceral organs. The fibre population with high thresholds represents a group of visceral nociceptors, the low threshold fibers encode distending pressures into the noxious range [3].

The receptors of primary visceral afferent neurons are located in mucosa, muscle, and serosa of hollow organs. Visceral afferent neuron terminals are placed to respond to luminal and local chemical stimuli and to mechanical stimuli. Visceral receptors apparently have no end organs or morphological specialization. They are associated with unmyelinated and thinly myelinated axons [3]. In the gastrointestinal tract, spinal afferents may by classified according to the location of the receptive endings. There are muscle or tension-sensitive, muscle/mucosal, serosal, and mesenteric afferents. The majority of these afferents are mechanosensitive and respond to a mechanical stimulus. However, Lynn et al. [4] found a small group of afferents in the colon mucosa that respond exclusively to chemicals. It is thought that multimodal mucosal afferents signal pain and discomfort due to a change in the luminal chemical

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environment, mucosal damage or inflammation. The muscle afferents also known as 'tension receptors' respond to distension and stretching of the hollow viscera. The results of Ozaki and Gebhart [5] showed that spinal afferents are also sensitive to hot and cold temperatures; however, the exact mechanism of the thermosensitivity of these afferents remains unknown. Thermospecific afferents could be located in the urothelium. Patients with painful bladder syndrome report significantly higher pain in the suprapubic area following ice-water instillation, compared with the same volume (100 ml) of distension with saline at room temperature, suggesting that cold temperature elicits a painful signal [6].

The neurophysiological convergence of visceral and somatic afferent inputs to the central nervous system is thought to underlie referred visceral pain, where noxious stimulation of viscera triggers pain referred to somatic sites. Viscerosomatic convergence may occur as a result of the scarcity of visceral afferent fibres with spinal cord terminations somatic injury, and visceral inflammation can respectively alter central processing of visceral and somatic inputs. Axons can send peripheral terminals to anatomically distinct segments to produce pain sensations distant from the primary site [2].

Some of the recent molecular studies have provided new insights into the mechanisms of visceral pain. It has been known that there are many mediators involved in the pathways of visceral sensation, such as: serotonin (5-HT) and vasoactive intestinal peptide (VIP) which mediates functional reflexes, substance P and calcitonin gene related peptide (CGRP) which are responsible for basal nociception, protease-activated receptors-2 (PAR-2) and nerve growth factor (NGF) which sensitize the nerves terminals, transient receptor potential (TRP) channels and acid-sensing ion channels (ASIC) which are responsible for inflammatory and non-inflammatory nociception, and sodium channels which are involved in sensory nerve function and may transduce some aspects of mechanical stimuli to extrinsic afferents and the circular layer of smooth muscle in the human intestine [7]. The ability to modulate visceral pain has also been related to voltage-gated calcium and ATP-gated ion channels, N-methyl-D-aspartate (NMDA) and gamma-aminobutyric acid-B (GABA-B) receptors, receptors for bradykinin, somatostatin, and kappa receptors for opioids. Mutations in the genes encoding the proteins mentioned above may be responsible for pathological visceral sensation. It has been shown that some ion channels, such as: Nav 1.5, Nav 1.8, Nav 1.9 and channels contributing to mechanosensation in the gut, are associated with visceral pain [8]. Acid-sensing ion channels (ASIC1, ASIC2 and ASIC3), which mediate pain associated with tissue acidosis after inflammation or injury, may also be involved in colonic mechanical transduction [7]. Members of the transient receptor potential (TRP) family of ion channels are important sensors of environmental stimuli, and heightened responsiveness of these channels occurs during inflammatory diseases, causing pain. Transient receptor potential vallinoid receptor 4 (TRPV4) is expressed by neurosensory structures and sensory neurons where it responds to osmotic and mechanical stimuli, and has been identified as a channel that mediates somatic mechanosensation and inflammatory mechanical hyperalgesia [9].

There are also other factors that can cause or modify visceral pain sensation, such as persistent mental and social stress, a previous episode of infection or inflammation, genetic background, and early-life adverse events (e.g., abuse, trauma, and painful experience) [1].

Abdominal pain can be divided into 3 categories: visceral, parietal, and referred. Visceral pain, caused by stretching of the fibres which innervate the walls of hollow or solid organs, can be described as a steady ache or discomfort to excruciating or colicky, again, often making the diagnosis a challenge [10]. It may be acute, chronic, or recurrent in fashion, and some individuals may experience a combination of these manifestations.

The cause of visceral pain may be organic (identifiable structural change in an organ) or dysfunctional (an abnormal change in organ function without identifiable pathologic changes) [11]. Ischemia, inflammation, muscle contraction (spasm) or distension may be the primary underlying cause of visceral pain.

Abdominal pain may be classified in outpatients complaining of abdominal pain on their first visit to primary care physicians: whole abdominal; epigastric; right subcostal; left subcostal; right flank; left flank; periumbilical; right-lower; mid-lower; and left-lower.

Visceral pain is experienced by 40% of the population, and 28% of cancer patients suffer from pain arising from intra-abdominal metastasis or from treatment. Most abdominal pain is due to functional gastrointestinal disorders; irritable bowel syndrome, and functional dyspepsia [12]. Visceral abdominal pain may derive from the abdominal organs, i.e., gastrointestinal tract, upper-middle urinary tract, or organs located in the thorax or pelvis (reproductive organs, lower urinary tract) [13].

The common causes of acute abdominal pain are appendicitis, biliary colic, cholecystitis, bowel obstruction, visceral perforation, pancreatitis, peritonitis, salpingitis, mesenteric adenitis, and renal colic. Other examples of visceral pain include: cardiac angina, uretheral stones, endometriosis, diverticulitis, peptic ulcer disease, Crohn's disease/ulcerative colitis, functional abdominal pain, primary cancer tumours, hepatic metastases, biliary obstruction, retroperitoneal adenopathy, mesenteric infiltration, chemotherapy and radiation effects.

Clinical presentation of visceral pain. Visceral pain can be misleading as a symptom, being vague, poorly defined, more a sense of malaise and discomfort than real 'hurt', accompanied by marked neurovegetative signs and emotional reactions, and perceived indistinctly at the same site (usually the midline, in the lower sternal region or epigastrium) whatever the organ involved. Visceral pain is connected with the autonomic nervous system: pallor, sweating, nausea, change in vital signs, anxiety. Intensity of the pain has little correlation to the extent of internal injury i.e., IBS may present with significant pain and disability, and metastic disease may have little or no pain.

Pain from the internal organs or viscera is often difficult to localize and is rated as more unpleasant than somatic pain. It is described in more emotive language and can result in quiescence and withdrawal as opposed to the active motor 'fight-or-flight' response usually illicited by somatic pain [14].

An example of functional abdominal pain is Irritable Bowel Syndrome (IBS), characterized by increased pain sensitivity at gut level, in the absence of any detectable organic cause ('visceral hyperalgesia'). Therapies include psychotherapy/behavioural therapy, bulking agents, antidiarrheals,

antispasmodics, tricyclic antidepressants, and also recently agents that affect the serotonergic pathways [15].

Visceral pain results from the activation of nociceptors (pain receptors) in the thoracic, abdominal or pelvic viscera. Somatic is pain caused by the activation of nociceptors in either the body surface or musculoskeletal tissues. i.e. skin, muscle, joints, bone. Neuropathic is pain caused by injury or malfunction to the spinal cord or peripheral nerves.

True visceral pain is usually perceived during the initial episodes, or initial phases of first episode, of a painful visceral disease. This pain is usually felt at the same site, whatever the viscous in question. In fact, whether the pain is from the heart, oesophagus, stomach, duodenum, gallbladder, or pancreas, it is always in this area. The symptom is generally perceived as a deep, dull, vague, and poorly defined sensation; in most cases, it cannot even be clearly described, being a sense of discomfort, malaise, or oppression rather than real pain. Visceral fibres enter the spinal cord at several levels, leading to a poorly localized, poorly characterized pain (dull, cramping, aching).

Visceral pain can be localized by the sensory cortex to an approximate spinal cord level determined by the embryologic origin of the organ involved. Foregut organs (stomach, duodenum, biliary tract) produce pain in the epigastric region; midgut organs (most small bowel, appendix, cecum) cause periumbilical pain; hindgut organs (most of the colon, including sigmoid), as well as the intraperitoneal portions of the genitourinary tract, cause pain initially in the suprapubic or hypogastric area.

Physicians should pay attention to the cardiac and lung examination in the patient with upper abdominal pain because they could suggest pneumonia or cardiac ischaemia [16].

Diagnosis of visceral pain. Physical examination of the abdomen in patients with abdominal pain should include inspection, auscultation, palpation and percussion, as well as rectal and pelvic examinations.

Determining the cause of abdominal pain commonly requires laboratory testing. Complete blood count, comprehensive metabolic panel (CMP), amylase, lipase and UA (Urine Analysis) are routinely ordered as 'belly labs' but should not be ordered blindly. Complete blood count may show lekocytosis, indicating an inflammatory condition. Microcytic anaemia raises the possibility of bleeding from the gastrointestinal system. Elevated serum amylase and lipase are observed in acute pancreatitis. Elevated levels of bilirubin or alkaline phosphatase suggests disease of the pancreas or biliary tract. Aminotransferase elevations indicate hepatocellular disease. Urinalysis may show erythrocytes or crystals suggesting calculi, leukocytes or bacteria, suggesting infection.

Three-position plain abdominal radiographs should be performed to determine the presence of perforation signs, ileus and bowel obstruction. Another routine test is abdominal ultrasonography (abdominal USG), which may reveal a disrupted hepatobiliary system, urinary tract or gynaecologic tract. Ultrasonography of the abdominal cavity is recommended when a patient presents with right upper quadrant pain. Ultrasonography is repeatable, cheap, and can be used in pregnancy. Nowadays, other imaging tests such as gastrointestinal endoscopy, abdominal CT-scan, MRI CT arteriography are being increasingly used.

Drug management of visceral pain. Paracetamol is commonly used for pain, but little is known about visceral pain responses since most studies have not focused on visceral pain. Several studies involving animal models of visceral pain have confirmed the benefits of NSAIDs plus paracetamol combinations [17].

Diclofenac blocks acetylcholine-induced smooth muscle contraction [18]. NSAIDs are superior to anticholinergics in relieving biliary colic. Baclofen reduces visceral nociception in multiple models which makes it attractive to use with opioids and nonopioid analgesics (NSAIDS or paracetamol) [19]. NSAIDs were superior to opioids in reducing renal colic [20].

Morphine is still the standard drug for the treatment of severe cancer pain [21]. This is a hydrophilic opioid and a pure opioid agonist that acts predominantly through the activation of μ-opioid receptors. Morphine may accumulate, especially in patients with renal failure, leading to possible intense adverse effects associated with the accumulation of metabolites. Morphine often causes constipation; therefore, the use of laxative prophylaxis is recommended.

Pain associated with cancer may be somatic, visceral, or neuropathic in origin. When visceral structures are stretched, compressed, invaded, or distended, a poorly localized noxious pain is reported. Neurolysis of the sympathetic axis has been shown to be an effective and safe method for treating this visceral pain. The goals of performing a neurolytic block of the sympathetic axis are to maximize the analgesic effect of opioid and nonopioid agents, and to reduce the dosage of these agents to alleviate untoward side-effects [22]. Indications for celiac plexus block include pain from acute or chronic pancreatitis [23] and visceral pain from cancer in the upper abdomen [24]. Pelvic pain associated with both cancer and chronic nonmalignant conditions may be alleviated by blocking the superior hypogastric plexus [25]. Visceral pain in the perineal area associated with pelvic cancer may be effectively treated with neurolysis of the ganglion impar [26].

Irritable Bowel Syndrome. One of the most common presentations of visceral pain is associated with Irritable Bowel Syndrome (IBS), a complex disorder with its background in biological (including infectious), psychological, and social factors, characterized by increased pain sensitivity at gut level, in the absence of any detectable organic cause ('visceral hyperalgesia') [27, 28]. Patients with IBS experience altered bowel movements with chronic pain, the transient alleviation of which usually takes place after defecation [29]. In some individuals, the most predominant complaint is diarrhea, whereas others suffer mostly from constipation. The periodical change in frequency of defecation and stool consistency can lead to the diagnosis of mixed IBS, and in the case of un-subtyped IBS a stool consistency does not allow clear diagnosis of the previously mentioned types of IBS [30].

According to current strategies, the core of the treatment is to help patients in understanding the nature of the chronic, inconvenient, and embarrassing but not life-threatening disease with the use of psychotherapy/behavioural support as needed, and to include proper dietary modifications, usually with a daily intake of dietary fibre [31, 32]. The relief of pain is believed to be associated with restoration of proper gastrointestinal tract motility [29]. The majority of drugs used in patients suffering from IBS do not directly influence

receptors engaged in visceral pain transmission, but, e.g. they influence smooth muscle tone in the intestines, which in turn decreases the pain sensation at the site of origin, not where it is conducted. In theory, pharmacological treatment has been considered rather as supportive, although many patients require chronic drugs intake to control symptoms. The main approach for the treatment aims at modulation of intestinal function, while in some cases therapy of accompanying diseases, like anxiety or depressive disorders, can lead to improvement in IBS [27]. Although symptoms-free periods are observed, pain and defecation problems persistently return for the lifetime, impairing every day activity [32]. Due to the lack of satisfactory results in the treatment of IBS, the development of new efficacious and safe in long-term use drugs is urgently needed. Very recently, the European Medicines Agency (EMA) has even released a draft Guideline on the evaluation of medicinal products for the treatment of irritable bowel syndrome to give formal advice on how to conduct a scientific programme leading finally to the introduction of a new drug for the treatment of IBS [33].

Today's therapies, although with their efficacy not always unequivocally confirmed in clinical studies, include bulk-forming agents, probiotics, laxatives, antidiarrheals, antibacterial agents, antispasmodics, and antidepressants [32, 34, 35, 36]. New therapeutic indications for IBS have been e.g. proposed for well known antiepileptic drugs (gabapentin, pregabalin) [36], which is probably consistent with their GABAergic mechanism of action. The attention paid to agents affecting serotoninergic pathways [37] led to the introduction of some new agents for the treatment that were later restricted in their use due to emerging adverse reactions [38, 39].

Bulk-forming agents, like psyllium hydrophilic mucilloid, are indigestible substances that by absorbing water produce an increase in the stool volume. This in turn enhances the pressure in the lumen of gastrointestinal tract and stimulates bowel peristalsis, facilitating defecation in case of constipation and leading to pain relief. By the same mechanism, i.e. by restriction of free water volume in the intestines, bulk-forming agents can be useful in the treatment of diarrhea [40]. They are considered to be generally very safe, but some patients with IBS can experience exacerbation of symptoms [32]. Unfortunately, there is no convincing evidence that bulk-forming agents are efficacious in IBS [35].

The mechanism of action of probiotics is complex. Primarily, their administration inhibits the excessive growth of pathogenic bacteria, the occurrence of which has been proposed to be involved in the pathomechanism of IBS. Probiotics can help to restore proper gastrointestinal tract motility and sensitivity to various stimuli. It has also been suggested that probiotics exert anti-inflammatory effects, and some strains are even able to increase the expression of analgesic opioid receptors in the intesintal wall, thereby influencing the severity of pain associated with IBS [41]. Not all probiotics have been shown to be equally effective. The effectiveness of Lactobacillus, Bifidobacterum, and Streptococcus strains has been proved in meta-analysis [42], but some authors still have doubts about their real usefulness in the treatment of IBS [32].

Osmotic laxatives consist of poorly absorbed substances, e.g. magnesium oxide or lactulose. These substances have the ability to retain water in the intestines and increase osmotic pressure; thus, osmotic laxatives stimulate intestinal motility and defecation. The main threat associated with their use is the risk of electrolytes and fluids imbalance, leading to several complications. Fortunately, these adverse reactions are transient [40]. The very unique laxative, lubiprostone, is available in USA to treat IBS with constipation [36], but the drug has been formally approved in Europe only for the treatment of chronic idiopathic constipation and associated symptoms in adults, when response to diet and other non-pharmacological measures (e.g., educational measures, physical activity) are inappropriate.

Lubiprostone is a prostone that activates the chloride Cl-C2 channel in the apical membrane of the intestinal epithelium. It increases intestinal fluid secretion rich in chloride ions. Activation of fluid secretion increases intestinal movements facilitating defecation and decrease the severity of symptoms associated with constipation [36, 40].

Antidiarrheal agents commonly used for IBS are opioid receptors agonists. Among them, loperamide and diphenoxylate are recommended, as they poorly penetrate to the brain and with therapeutic doses should not evoke any central nervous system adverse reactions [43]. They are believed to act more locally in the gastrointestinal tract, where they induce contractions of smooth muscles, increase muscle tone, and finally produce inhibition of peristalsis. Although opioids are in general very strong drugs for relieving pain, the use of loperamide and diphenoxylate is associated with very weak analgesic activity [40]. Since the analgesic action of opioids depends primarily on the activation of the descending inhibitory pathways in the spinal cord and brain to inhibit the neurotransmission of pain, drugs that can quite selectively activate opioid receptors in intestinal smooth muscle are deprived of these properties. Thus, pain relief in IBS after opioids is much more attributed to diarrhea restriction and decreased hyperactivity of intestines [43].

The discovery of a post-infectious type of IBS led to the concept of using locally acting antibacterials [29]. But not only an infection but altered microbial flora in the intestines can also cause the symptoms of IBS. Rifaximine is an antibacterial drug that has shown some clinical efficacy in the treatment of IBS without constipation. The drug is taken orally, but undergoes almost no absorption from the gut, therefore, is relatively free of systemic adverse reactions. Rifaximine is particularly useful in the treatment of IBS with pain associated with the presence of bloating [34].

There is much data available to support the statement that antispasmodics are effective for the treatment of IBS [35]. The majority of antispasmodics are muscarinic receptor antagonists, such as dicyclomine, hyoscyamine or scopolamine [30]. These drugs, used to treat intestinal spasms and pain, are among the most widely used drugs by patients irrespective on the subtype of IBS. They produce gastrointestinal tract muscles relaxation, except sphincters. Because they can inhibit peristalis and increase intestinal transit time, especially when used in excessive doses, they must be used with caution in people suffering from IBS with constipation. Patients are usually told to use them in order to reduce the severity of abdominal pain associated with meal intake [32].

A spasmolytic drug believed to be relatively free of anticholinergic adverse reactions is mebeverine, a musculotropic antismasmodic drug affecting directly and selectively the smooth muscles of the intestines [44]. Quite unusual properties are characteristic for trimebutine, which is known to be a regulator of gastrointestinal tract motility.

The drug can block muscarinic receptors and is an agonist to enkephalin receptors in the intestines. This is responsible for its ability to activate hypokinetic smooth muscles, on one hand, and to decrease contractility of hyperkinetic smooth muscles on the other hand [43]. With restoration of proper motility, trimebutine helps to relieve pain associated with IBS [35].

The latter symptom can be also reduced with the use of simethicone or dimethicone [32]. These agents are anti-foaming substances that help facilitate the passing of flatulence and reduce bloating-related pain in IBS. Due to some law regulations, oral preparations containing simethicone or dimethicone are sometimes not considered as medicinal products, but as medical devices.

Interestingly, the analgesic and antispasmodic effects of peppermint oil have been considered to be proved in clinical settings, with favourable outcomes on the quality of life [45].

Antidepressants and anxiolytics are particularly recommended in the treatment of IBS in the case of concomitant depressive disorders or anxiety. Sometimes, benzodiazepines are believed to be able to produce benefits for patients with IBS [46], and the benefits have been suggested to be asscociated with use of venlafaxine [47]. The most convincing evidence about their effectiveness concern tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). Drugs like amitriptyline or imipramine (TCAs) and fluoxetine or citalopram (SSRIs) have been shown to produce a significant benefit for improvement of abdominal pain, as well as for some other disturbances in the course of IBS [35]. It is worth to noting that in addition to their behavioural central effects, these drugs improve serotoninergic transmission, and disturbances in serotoninergic transmission has been shown to exacerbate symptoms of IBS.

Tegaserod, first approved in the USA in 2002, represents a novel mechanism of action in the treatment of IBS. Tegaserod is an agonist to serotonin 5-HT4 receptor [48]. By stimulation of intestinal peristalsis the drug helps to relieve constipation, while suppression the pain-sensing nerves reduces abdominal pain. Clinical trials with tegaserod enrolled predominantly women [37]. The small number of male participants in studies pivotal for registration gave no opportunity to judge equivocally about its effectiveness in men. Thus, the drug has been initially introduced onto the market with an indication for the treatment of women with IBS whose predominant symptom is constipation. Subsequent trials produced emerging results concerning cardiovascular adverse reactions. Analysis of safety data found an increase in the frequency of angina pectoris, myocardial infarction, and stroke among patients taking tegaserod. The increase was considered to be small but statistically significant and the use of a drug that can cause potentially fatal adverse reactions in the treatment of a non-lifethreatening condition like IBS was considered no longer justified [39, 49]. In 2005, the EMA refused to grant a marketing authorization for tegaserod in Europe, and in 2007, the manufacturer of tegaserod decided to withdraw the drug from the US market. However, it is still available in USA, but only in exceptional cases and under a special investigational protocol for patients who cannot be effectively treated with any other agent [40]. What should be noticed is that although tegaserod has been described in many scientific sources as a drug available for the treatment of IBS, it has never been available in Europe.

Alosetron is another drug influencing serotoninergic transmission, the introduction of which gave hope for new therapeutic options in IBS. Alosetron blocks a serotonin 5-HT3 receptor in the gastrointestinal tract [50]. Antagonism to these receptors decreases intestinal stool passage and helps reduce visceral pain in patients with IBS. Similarly to the case of tegaserod, but this time due to reported incidences of ischemic colitis as an adverse reaction of alosetron, which have been even fatal in few cases [51], the use of drug is now restricted to women with IBS whose predominant symptom is diarrhea, suffering from severe symptoms of IBS, including abdominal pain, causing disability or restriction of daily activities in whom standard treatment proved to be ineffective [52].

In the second half of 2012, a completely new drug, linaclotide, with a very unique mechanism of action, was approved almost simultaneously in Europe and the USA for the symptomatic treatment of moderate to severe IBS with constipation in adults [30]. Linaclotide is a guanylate cyclase-C (GC-C) receptor agonist on the luminal surface of the intestinal epithelium. Activation of GC-C receptor enhances intestinal movements and increases the transit time through the large bowel, increases the volume of intestinal fluid, as well as reducing nerves sensitivity and visceral pain. Linaclotide is a promiscuous agent, but with a lesson learnt from the case of tegaserod and alosetron, further safety data seem to be necessary in order to constitute a proper place for the drug in the management of IBS with constipation.

SUMMARY

The mechanism of visceral pain is still less understood compared with that of somatic pain. This is primarily due to the diverse nature of visceral pain compounded by multiple factors such as sexual dimorphism, psychological stress, genetic trait, and the nature of the predisposed disease. Visceral pain is a frequent reason for gastroenterological referrals. It is diffuse and can be difficult to localize. As several viscera can converge onto the same spinal segment, patterns of referred sensations can overlap considerably, causing problems with differential diagnosis. Irritable bowel syndrome represents a condition with still elusive pathogenesis, producing visceral pain sensations. The diagnosis of IBS is usually given after careful exclusion of other organic diseases in the gastrointestinal tract. Due to multiple factors possibly involved in the disease, its treatment is complex and on many occasions cannot bring satisfactory results. Currently available therapeutic agents influence gastrointestinal tract motility rather than directly interact with receptors engaged in visceral pain transmission. In most cases, the relief of pain is believed to be associated with restoration of proper gastrointestinal tract motility, and not with the inhibition of pain conduction. Some new drugs are still under investigation for their usefulness in the treatment of IBS. A better understanding of the mechanisms leading to pain sensations can hopefully give patients suffering from IBS and other diseases characterized by visceral pain a long-awaited, efficacious and safe agent in the future.

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