Visceral Pain

From Bench to Bedside

Ming Xia
Bifa Fan
Hong Jiang
Editors

Springer

Visceral Pain

Ming Xia • Bifa Fan • Hong Jiang
Editors

Visceral Pain

From Bench to Bedside

Springer

Editors
Ming Xia
Anesthesiology
Shanghai Ninth People's Hospital
Shanghai, China

Bifa Fan
Pain Medicine
China-Japan Friendship Hospital
Beijing, China

Hong Jiang
Anesthesiology
Shanghai Ninth People's Hospital
Shanghai, China

ISBN 978-981-99-9166-2 ISBN 978-981-99-9167-9 (eBook)
https://doi.org/10.1007/978-981-99-9167-9

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd. The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Paper in this product is recyclable.

Contents

Contributors

Editors

Ming Xia Department of Anesthesiology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Bifa Fan Department of Pain Medicine, China-Japan Friendship Hospital, Beijing, China

Hong Jiang Department of Anesthesiology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Associate Editors

Daying Zhang Department of Pain Clinic, The First Affiliated Hospital, Nanchang University, Nanchang, Jiangxi, China

Haipeng Liu Department of Pain Management, Gansu Provincial Hospital, Lanzhou, Gansu, China

Ningning Ji Department of Anesthesiology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Introduction

1

Hong Jiang

1.1 An Overview of Visceral Pain

1.1.1 Concept of Pain

Pain varies in intensity, quality, and duration, as well as in its pathophysiologic mechanisms and implications. It is therefore a challenge to define the concept of pain succinctly and accurately. The International Association for the Study of Pain (IASP) defines pain as an unpleasant sensory and emotional experience associated with tissue damage or injury [1], which has been widely and long accepted by the health care professionals. This definition suggests that pain has two important characteristics. One is that pain is an awareness that occurs in the brain and an experience that induced by the activity of multiple cortical sites. Nociception, on the other hand, refers to peripheral or central nervous system activities triggered by noxious stimuli. However, not all nociception brings the sensation of pain. Thus, pain requires the individual's autonomous consciousness, the participation of intact nervous system as well as the activity of the cortical nociceptive circuitry of the nervous system affecting specific cortical currents. The other is that pain has both sensory and emotional components which are supported by brain imaging studies of patients with specific brain injuries. Imaging results demonstrated that nociception can also lead to activation of corresponding cortical areas that process emotions, such as the amygdala and anterior cingulate cortex which can be controlled by the perceived experiment and further produces different sensations. In addition, patients who suffer from the above-mentioned cortical damage alone may also go through a loss of corresponding sensation, but not lead to the disappearance of pain. They may still feel a vague unpleasant experience when the corresponding brain is injured and the contralateral body part receives noxious stimuli.

Criticisms of the IASP definition have been prompted from different perspectives. For examples, some pointed out that the definition emphasizes the sensation of conscious human only, separating the connection between mind and body and being highly subjective. For other populations and species, such as neonates, animals and so on, they may be deprived of the right to develop pain since they are unable to report it verbally. Moreover, it neglects the cognitive and social factors that contribute to the pain experience, meaning that pain has certain intentionality which influences the patient's sensational and emotional experience [2]. Additionally, the term "unpleasant" has been debated as potentially trivializing the intense pain and suffering associated with many acute and chronic clinical pain states and failing to capture "all the words that can be used to describe the experience" and its associated pain [2,

H. Jiang (✉)
Department of Anesthesiology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

M. Xia et al. (eds.), *Visceral Pain*, https://doi.org/10.1007/978-981-99-9167-9_1

3]. In addition, it was disputed that pain is more than a symptom and that chronic pain may be a disease with its own clinical course, and therefore the definition should convey this view [4, 5].

A revised IASP definition of pain has been published based on the criticisms and discussions collected and researched and with tremendous deliberation. The definition is that pain is "An aversive sensory and emotional experience typically caused by, or resembling that caused by, actual or potential tissue injury" [6]. It reserves the emphasis on pain as an experience from the previous definition, while giving prominence to tissue injury-like experience which may be any sign of pain that requires no verbal description. The revised definition of pain highlights the pain as a critical health condition and is going to transform pain study and care [6].

1.1.2 Classification of Pain

Clinically, degrees, causes, and manifestations of pain vary from person to person. The classifications of pain involve different criteria or methods.

1. Classification of pain according to locations

   Pain belonging to this category includes somatic pain, visceral pain, and central pain.

   Somatic pain, also called superficial pain, refers to the pain that appears on the surface of the body, is localized, intense, mostly pins and needles, knife-like, sharp pain, and can clearly indicate the site of pain, such as frozen shoulder, arthritis, etc.

   Visceral pain, also known as deep pain, is usually hard to identify the site of the pain. The biliary colic, renal colic, stomach pain, etc. are examples of this type of pain, showing the nature of pain can be colic, pulling pain, vague pain, distension, etc.

   Central pain refers to pain caused by diseases in the nerve center, such as pain caused by brain hemorrhage and brain tumors.

2. Classification of pain according to characteristics

   Based on pain characteristics, pain can be divided into injury pain, inflammatory pain, neuropathic pain, cancer pain, neurological pain, and psychological pain. Injurious pain is pain caused by noxious stimuli. Inflammatory pain refers to pain mediated by inflammatory factors in the inflammatory response. Neuropathic pain is a lesion occurring anywhere in the nervous system that is burning-like, intense diffuse and persistent, and may be associated with nociceptive hypersensitivity and unusual pain. Cancer pain, also known as advanced cancer pain, generally refers to the pain that occurs with advanced tumors or tumor metastatic pain. Psychogenic and psychological pain is pain generally without organic lesions or other physical diseases, mainly caused by psychological or spiritual factors.

3. Classification of pain according to courses

   According to the course of the disease, pain can be divided into acute pain, chronic pain, intractable pain, and special pain categories. Acute pain refers to acute injury pain in soft tissues and joints, post-surgical pain, obstetric pain, acute herpes zoster pain, gout, etc. Chronic pain is generally soft tissue and joint strain pain or degenerative pain, discogenic pain, neurogenic pain, etc. Intractable pain mainly includes trigeminal neuralgia, post-herpetic neuralgia, disc herniation, intractable headache, etc. Special pain mainly refers to thrombotic vasculitis, intractable angina pectoris, idiopathic chest and abdominal pain, etc.

   Though the above classification standard can be referred to, clinical pain is not necessarily bound to these criteria when it comes to specific situations, as pain may fall into one of several categories together at the time of occurrence, or be superimposed by several different types of pain.

1.2 Concept and Classification of Visceral Pain

Visceral pain has a significant systemic impact, accounting for a large proportion of all forms of chronic pain [7]. Surveys have shown that the prevalence of chest pain among adults was 20%, intermittent abdominal pain was 25%, and pelvic pain in women was 16–24% [8]. Visceral pain, despite its ubiquity, is poorly understood due to the complexity of the interactions between the visceral organs, the autonomic nervous system, and the central nervous system. For instance, not all visceral organs respond to stimuli as some organs are more sensitive than others, and not all stimuli cause pain. Besides, emotions and stress can affect visceral pain via the hypothalamic-pituitary-adrenal axis. Thus, multiple factors play a role in the development of visceral pain. Visceral pain signals can be transmitted to multiple locations within the central nervous system and can converge with somatic afferent nerves, which may lead to modulation of referred pain and signals within the central nervous system. Dysregulation may also happen, resulting in hyperalgesia. Physical responses to visceral pain such as spasticity may also be produced. Recent studies have manifested that the gut microbiome can modulate pain and that probiotics can lead to improvements in pain in irritable bowel syndrome (IBS) patients. While in contrast, pathogenic bacteria may contain or secrete substances that cause inflammation and pain [9].

There are various classifications of visceral pain [8, 10]. The classification criteria include nerve conduction mechanisms, etiology, anatomy, and manifestation modalities. According to nerve conduction mechanisms, visceral pain can be divided into nociceptive conduction through visceral afferent nerves, conduction through spinal nerve afferent fibers such as mural pleura, peritoneum, mediastinum and mesentery, and visceral pain produced through distal sites with certain types of somatic pain or nociceptive hypersensitivity, i.e., true visceral pain, pseudo-visceral pain, and visceral referred pain. According to the etiologies, visceral pain can be classified as functional, inflammatory, and cancerous visceral pain. And according to the anatomical features, visceral pain includes thoracic pain, abdominal pain, and pelvic pain. Last but not least, pain originating from internal organs may manifest in several different ways. The main phenomena associated with visceral nociception can be schematically summarized as: (a) true visceral pain; (b) referred pain without hyperalgesia; (c) referred pain with hyperalgesia; (d) visceral hyperalgesia; and (e) viscero-visceral hyperalgesia. Careful assessment of the characteristics of the symptoms and accompanying signs is essential for a correct diagnosis.

1.3 Clinical Features of Visceral Pain

1.3.1 Clinical Visceral Pain

Visceral pain is characterized by the lower density innervation of visceral structures comparing with the sensory innervation of other tissues and the differentiation of sensory input in the peripheral and central nervous systems, resulting in less diffuse and localized pain. In clinical practice, the mechanisms behind visceral pain vary widely, including distension or muscle contraction of hollow organs, ischemia, traction of the mesentery, chemical irritants, and nerve compression due to malignant tumor [11].

The abdominal viscera are innervated by two systems: the vagus nerves and the spinal visceral sensory nerves. Most viscera receive dual afferent innervation via sympathetic and parasympathetic nerves, which ultimately project to the central nervous system. In noxious events, the spinal tract and dorsal column are two main ascending fiber tracts in the spinal cord that transmit sensory input from the viscera to the brain. Subsequent projections to the medial thalamus are closely associated with pain-triggered emotional and autonomic responses, whereas projections to the lateral ventral thalamus are associated with pain perception, both in terms of location and intensity. Visceral pain also preferentially increases activity in the anterior cingulate cortex, which may explain the strong emotional response

to visceral pain. In addition, in response to ongoing injury or inflammation, visceral afferents lead to peripheral and central sensitization due to increased neuronal excitability, finally bringing increased sensitivity, such as hyperalgesia, and an enlargement of the metastatic pain areas seen in some visceral pain syndromes, such as IBS, dyspepsia, and interstitial cystitis [11].

Visceral pain usually has a temporal evolution and varies in clinical features at different stages of pathology. "True visceral pain" is a diffuse, ill-defined sensation, usually perceived in the midline, lower sternum or upper abdomen of the body. Pain in visceral organs may present in different areas, such as the bladder pain may present in the perineal region, the heart pain may present in the left arm and neck, and the left ureter pain may present in the left lower abdomen and low back. This diffusivity and difficulty in localizing visceral pain is due to the low density of visceral sensory innervation and the extensive differentiation of visceral input within the central nervous system. Thus, visceral pain is more diffuse than noxious cutaneous stimuli in terms of location and timing [12].

Subsequent symptom development may require the transfer of pain to parietal somatic structures within the same metadomain as the affected organs. Thus, spatial discrimination of visceral pain usually involves superficial structures, producing secondary hyperalgesia in superficial or deep body wall tissues due to the fusion of visceral sensations (discussed later). Referred pain with or without hyperalgesia is more acute, more precisely localized, and less likely to be accompanied by autonomic signs, making it difficult to distinguish from pain of somatic origin. Unlike somatic or superficial pain, the main characteristic of visceral pain is that it is more sensitive to stimuli such as mechanical pulling, organ ischemia or spasm, and inflammation, while it is insensitive to stimuli such as cutting and burning [13].

Visceral pain is often associated with marked autonomic phenomena, including pallor, profuse sweating, nausea, digestive disturbances, and changes in body temperature, blood pressure, and heart rate [13]. Pain occurs slowly but persists for a long time, is difficult to localize and often accompanied by referred pain, emotional or defensive reactions.

When the internal organ system is in a healthy state, it may cause a minimal level of sensation. During daily activities, fullness, belching, and venting derive from digestion or excretion process will not cause discomfort. In general, they often lead to minor discomfort, but when lesions or inflammation of internal organs occur, stimuli that normally induce no harmful reaction may be amplified and cause serious effects on the patient, further leading to more severe discomforts or pain. In visceral pain, there is a high incidence of nausea, in addition to possible autonomic reactions such as night sweats, profuse sweating, and shortness of breath. The strong emotional response that accompanies visceral pain is also one of the challenges, and the occurrence rate often depends on the patient's perception of pain. Strong emotional changes induced by visceral sensations may be accompanied by further changes in visceral sensations, generating anxiety due to pain and in turn, anxiety causes more severe pain, thus potentially creating a positive feedback pathway that further exacerbates the pain level. Therefore, the correlation between the degree of pathological changes in visceral pain and the intensity of the pain they cause is poor [14].

1.3.2 Specific Types of Visceral Pain or Abdominal Pain Syndrome

Many surveys indicated that most of chronic and recurrent pain occurred in the chest, abdomen, and pelvic regions. For example, intermittent abdominal pain was present in about 25% of adults and chest pain in about 20%, while more than 24% of women were often bothered by pelvic pain [15]. For more than 23% of patients, pain was considered part of daily life and symptoms were often managed by patients themselves; while a smaller percentage sought medical help. Visceral pain conditions are strongly associated

with declined quality of life, and both the cost of medical care and the impaired ability to work due to the disease place a significant burden on the patient's life.

Abdominal pain is the most common clinical form of visceral pain and may be a manifestation of a specific disease, but in many patients, all diagnostic tests may turn out to be normal or negative. This pain of visceral origin usually presents as vague sensation, spasmodic pain, and indefinite localization. Surgeons call it non-specific abdominal pain, older textbooks just called it non-organic pain, and abdominal pain in children is mostly recurrent abdominal pain (RAP). Currently, the majority of patients have simple abdominal pain, but some patients who visit health care institutions with severe pain may be diagnosed as chronic functional abdominal pain syndrome.

The general incidence of abdominal pain is as high as 22–28%, with more women than men, and only about 20% of all abdominal pain patients select to seek medical attention [10]. A significant proportion of those surveyed, however, suffer from pain that influences their daily life, and there is no significant gender difference in the degree of impact. This also means that in many undiagnosed populations, abdominal pain is also an important factor that interferes daily life. The natural course of abdominal pain in adults is largely unknown. In a follow-up study on the recurrence and remission of abdominal manifestations in populations, it was found that the overall incidence of recurrence remained constant, being approximately 10%, but the symptoms of the vast majority of patients got improved. The remission rate was 35%, and the ratio of overall incidence versus remission rate were unchanged [10].

Functional abdominal pain is the main clinical presentation of patients admitted to hospital with abdominal pain. Back decades ago, abdominal pain without a clear cause ranked tenth among the most common causes of hospitalization in men and sixth in women. This situation has not been improved to date, with up to 67% of consecutive admissions to surgical wards in hospitals being "non-specific" abdominal pain [10].

1. Irritable bowel syndrome (IBS)

   IBS represents a group of symptoms including abdominal pain and altered bowel movement patterns, but lacks any evidence of an underlying organic injury. These symptoms can persist for a long time, often up to several years. Depending on whether constipation or diarrhea occurs, IBS can be divided into four main types, namely diarrheal IBS, constipated IBS, mixed IBS (diarrheal and constipated), or uncertain IBS. Disorders such as anxiety, major depression, and chronic fatigue syndrome are also common in patients with IBS.

   Currently, the etiology of IBS is not fully understood. Related theoretical studies include altered brain-gut axis, intestinal dysmotility, changes in pain sensitivity, infections (including small intestinal bacterial overgrowth, neurotransmitters, genetic factors, and food sensitivities), etc.

   The diagnosis of IBS is based on signs and symptoms, and high-risk factors include age over 50 years, weight loss, fecal blood loss, or a family history of inflammatory bowel disease. However, similar symptoms may be seen in other conditions, including celiac disease, colitis, inflammatory bowel disease, bile acid malabsorption, and colon cancer.

   Currently, IBS is incurable, and its treatments target at relieving symptoms. Lifestyle modification, changes in diet, medications, pain management, probiotics, and psychological counseling are adopted to treat IBS patients. Among them, dietary treatment methods include increasing the intake of soluble fiber and limiting the intake of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. Pharmacological treatment includes antidiarrheal, laxatives, and antidepressants.
2. Chest pain

   In the clinical setting, chest pain is a common symptom and one of the most common reasons for seeking medical care in emergency department. Chest pain caused by cardiovascular disease should be considered first. Acute chest pain is often considered a warn-

ing sign of myocardial ischemia. However, chest pain that mimics angina may be non-cardiac in nature. The most common causes of chest pain in adults include gastrointestinal disease (42%), coronary artery disease (31%), musculoskeletal disease (28%), pericarditis (4%), and pulmonary embolism (2%). Other less common causes include pneumonia, lung cancer, and aortic aneurysm. In addition, panic attack is one of psychological causes of chest pain. It can be seen that non-cardiogenic factors may trigger more chest pain situations than cardiogenic factors. Functional chest pain is also called non-cardiac chest pain (NCCP), and it has been reported that the incidence of NCCP in China was as high as 13.9%, but the research and investment on it was relatively small and much lower than that of cardiac chest pain [16].

In children, the most common causes of chest pain are musculoskeletal disorders (76–89%), exercise-induced asthma (4–12%), gastrointestinal disorders (8%), and psychological causes (4%). In addition, chest pain in children may also be caused by congenital factors [10].

It is currently believed that non-cardiogenic chest pain should also be treated with different strategies in clinical practice according to its etiologies. Therefore, a correct understanding of the source of the disease that contributes to a correct diagnosis, is a key prerequisite for effective treatment of NCCP.

3. Functional abdominal pain syndrome (FAPS)

FAPS differs from other functional bowel disorders in that it is less common. Its symptoms are mostly irrelevant to food intake and bowel movements, and there is a high rate of comorbidity with psychiatric disorders. Its etiology and pathophysiology are not fully understood. Because FAPS may represent a heterogeneous group of disorders, peripheral neuropathic pain mechanisms, alterations in the endogenous pain modulation system, or a combination of these may show together in one patient. The diagnosis of FAPS is based on positive symptom criteria and a long history of symptoms; in the absence of alarm symptoms, an extensive diagnostic evaluation is not required. Treatment is determined by a therapeutic relationship between physician and patient and an empirical treatment algorithm using various types of centrally acting medications, including antidepressants and anticonvulsants. The choice, dosage, and combination of medications are influenced by psychiatric comorbidities. Psychotherapy options include psychotherapy, relaxation techniques, and hypnosis. Patients with refractory FAPS can benefit from a multidisciplinary outpatient approach to pain [17].

4. Recurrent abdominal pain in children (RAP)

Abdominal pain is one of the most common symptoms in children. The pain is often acute and the possible causes are classified as gastrointestinal or extraintestinal factors, specifically including gastrointestinal infections, dietary mydriasis, urinary tract infections and other more dangerous surgical conditions, such as acute appendicitis. If properly managed, this acute abdominal pain usually does not lead to long-term sequelae. However, there are often some difficulties in the treatment of pediatric abdominal pain. First, in young children, the history of pain is usually "second-hand", i.e., children are unable to describe the location and nature of the pain precisely and it is often relayed by the parents or caregivers. Fortunately, most parents can be helpful in providing information about the cause of their child's abdominal pain. In addition, the physical examination of pediatric abdominal pain is often difficult due to factors such as the child's poor cooperation.

RAP is very common in children and can affect up to 10–20% of school-age children. In the mid-twentieth century, RAP in children was first reported by Apley and Naish, who noted that in the vast majority of cases RAP has no definite etiology and was therefore thought to be the result of psychological influence in children [18]. In young children, abdominal pain is often vaguely localized, with the child usually indicating that the pain comes from the central region of the abdo-

men. Moreover, the severity and frequency of pain are not associated with the cause. The term "recurrent" refers to the duration and frequency of the pain, which is usually considered to be at least 3 months, during which at least three episodes of pain are severe enough to interfere with the child's daily activities. Over the years, with advances in medical technology and a better understanding of the pathophysiology of abdominal pain, an increasing number of organic causes have been identified. However, it is currently believed that the most common etiology of RAP in children remains functional.

5. Chronic pelvic pain (CPP)

Pelvic pain is broadly defined as pain in and around the pelvic area and is usually more common in acute pain than in chronic pain. When the pain persists for more than 6 months, it is considered to be CPP. Relatively speaking, CPP is associated with comorbidities such as IBS, major depressive disorder, or pelvic inflammatory syndrome. CPP is not only common in female patients, but also common in male patients. Reviewing the literature, Sibert et al. published in 2010 a prevalence of chronic pelvic pain syndrome (CPPS)/chronic prostatitis in men of approximately 10%; bladder pain syndrome/interstitial cystitis (in both sexes) 0.24–0.31%; post-vasectomy, testicular and epididymal pain 15–20%; and ejaculation or orgasm-related pain in men 1–9% [19].

CPP is a form of concentrated pain in which the body produces a low threshold for pain, which is often the result of chronic pain. For example, if a woman has endometriosis, over a period of 3–6 months, the acute pain associated with this condition may become concentrated pain, as the pain becomes chronic. In concentrated pain, previously mild to moderate pain is experienced as severe pain (hyperalgesia), or tenderness can be interpreted as pain (ectopic sensation). In addition, CPP is strongly associated with previous physical or emotional trauma. Therefore, the etiology of CPP may also be related to functional somatic pain syndromes.

The diagnosis of CPP is made after 3–6 months of pelvic pain and is usually based on history or physical examination; there are many associated symptoms or precipitating factors that help establish the diagnosis. Although imaging and laboratory findings are often inconclusive in the diagnosis of CPP, they are often helpful in diagnosing comorbidities that contribute to the development of CPP.

Treatment of CPP is often complex, with limited evidence-based options. Treatment usually focuses on suspected causes of CPP, such as treatment of comorbid mood disorders, neuropathy, or uterine dysfunction. The prevalence of CPP is estimated to be 5.7–26.6% [20]. Given its prevalence, patients experiencing CPP must be treated with a high degree of suspicion. The management of CPP requires an interprofessional team approach; collaboration between multiple specialties is needed to provide adequate pain relief. Some patients with CPP may benefit from cognitive behavioral therapy and hormone replacement. Conversely, others may require more invasive therapeutic interventions such as spinal cord stimulation or total hysterectomy. Pelvic pain is broadly defined as pain in and around the pelvic area and is usually more common in acute pain than in chronic pain. When the pain persists for more than 6 months, it is considered CPP. Relatively speaking, CPP is associated with comorbidities such as IBS, major depressive disorder, or pelvic inflammatory syndrome.

6. Cancer visceral pain

Cancer visceral pain is a special type of visceral pain caused by tumor, which is more complicated than general visceral pain, and is easily affected by patients' emotion, cognition and other spiritual factors, and spiritual factors are influenced by culture and religion, so it is still very difficult to diagnose or treat. According to incomplete statistics, about 50% of cancer patients have inadequate pain treatment, and in a few types of tumor patients, the proportion of inadequate pain treatment is even higher, which greatly affects the survival

quality of cancer patients and is one of the important reasons why many patients are afraid to talk about cancer. Contrary to the public perception, untreated pain is not insignificant, but long-term chronic pain can change the immune system and even organ function, increase patients' anxiety and depression, which can seriously affect health and quality of life, and may even accelerate patients' death.

Globally, the degree of treatment for cancerous visceral pain is highly inconsistent; even in China, patients with the same degree of pain may receive widely varying pain-related treatments due to economic factors, patients' education level, psychological factors influence, and physicians' cognitive factors. A few patients and elderly people may be more reluctant to talk about their pain with their doctors, believing that pain is a sign of cancer deterioration, convinced that pain cannot be relieved, unresolved concerns about addiction and side effects of medication, and possibly because they cannot afford to pay for the treatment of analgesic drugs. In fact, the prevalence of cancerous visceral pain varies depending on the location of the primary tumor. The incidence and extent of pain also vary at different stages of tumor development. Usually, the more advanced the cancerous visceral pain is, the higher the incidence of pain and the greater the intensity of pain, and it is often the most difficult to control pain at the advanced stage of the disease. In addition, pain caused by tumor metastasis is also very common, and is more common and severe in progressive and end-stage cancer. However, regardless of the degree and nature of cancer pain caused by any of these causes, patients have the right to safe, effective pain treatment with few side effects, and this requires that all physicians should properly understand and treat cancer visceral pain in order to treat every patient with cancer visceral pain with the most optimal method available.

1.4 Summary

This chapter focuses on a review of several commonly seen visceral pain disorders in clinical practice and their epidemiology. As opposed to the detailed and specific coverage in subsequent chapters, the main purpose of this chapter is to provide a preliminary understanding of visceral pain-related disorders and research, to lay the initial foundation for future in-depth understanding and research, and to help the reader quickly understand the general scope of the coverage in the subsequent sections of this book. Although the diagnosis of visceral organic pathology has not been ruled out in many patients, current studies in the literature mostly suggest that most patients do have functional problems. Because of the difficulty in classifying and treating these diseases, it is important to further understand the etiology and pathogenesis of visceral pain, and then to investigate and explore the corresponding treatment countermeasures and their clinical efficacy, in order to reduce patients' suffering and introduce unnecessary medical costs. Meanwhile, in addition to the specific types of visceral pain or abdominal pain mentioned above, many different types or mixed occurrence of visceral-related pain in clinical practice will be illustrated in detail in subsequent relevant chapters from multiple perspectives based on the etiology and mechanism, epidemiology, diagnosis and treatment, and research progress of various types of visceral pain and visceral pain-related disorders, respectively.

References

1. Merskey H, Bogduk N. Classification of chronic pain. 2nd ed. Seattle: IASP Task Force on Taxonomy, IASP Press; 1994. http://www.iasp-pain.org/Education/content.aspx?ItemNumber=1698
2. Williams AC, Craig KD. Updating the definition of pain. Pain. 2016;157:2420–3.
3. Cohen M, Quintner J, van Rysewyk S. Reconsidering the International Association for the Study of Pain definition of pain. Pain Rep. 2018;3:e634.

4. Loeser JD, Treede RD. The Kyoto protocol of IASP Basic Pain Terminology. Pain. 2008;137:473–7.
5. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). Pain. 2019;160:19–27.
6. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, Keefe FJ, Mogil JS, Ringkamp M, Sluka KA, Song XJ, Stevens B, Sullivan MD, Tutelman PR, Ushida T, Vader K. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161(9):1976–82. https://doi.org/10.1097/j.pain.0000000000001939. PMID: 32694387; PMCID: PMC7680716.
7. Halder SLS, Locke GR. Epidemiology and social impact of visceral pain. In: Visceral pain. Oxford University Press; 2009. p. 1–8.
8. Giamberardino MA. Visceral pain. Oxford University Press; 2009.
9. Katz BL, Van Houten T, Sassan Sabouri A. Chapter 2—Neuroanatomy and mechanisms of visceral pain. In: Pak DJ, Yong RJ, Shah KB, editors. Interventional management of chronic visceral pain syndromes. Amsterdam: Elsevier; 2021. p. 5–15.
10. Zhijie L. Visceral pain—basic and clinical. Beijing: Science Publishing House; 2018.
11. Ahmed HS, Shah KB, Pak DJ. Chapter 1—Epidemiology of chronic visceral pain syndromes. In: Pak DJ, Jason Yong R, Shah KB, editors. . Interventional management of chronic visceral pain syndromes: Elsevier; 2021. p. 1–3.
12. Procacci P, Zoppi M, Maresca M. Visceral sensation. In: Cervero F, Morrison JFB, editors. Progress in pain research. Amsterdam: Elsevier; 1986. p. 21–8, 39.
13. Sikandar S, Dickenson AH. Visceral pain: the ins and outs, the ups and downs. Curr Opin Support Palliat Care. 2012;6:17–26.
14. Millham FH. Acute abdominal pain. In: Sleisenger and Fordtran's gastrointestinal and liver disease, vol. 11. Amsterdam: Elsevier. p. 144–57.
15. Kapural L, et al. Chronic abdominal pain: an evidence-based, comprehensive guide to clinical management, vol. 13. New York: Springer Science+Business Media; 2015. https://doi.org/10.1007/978-1-4939-1992-5_2.
16. Wong WM, Lam KF, Cheng C, et al. Population based study of non-cardiac chest pain in southern Chinese: prevalence, psychosocial factors and health care utilization. World J Gastroenterol. 2004;10(5):707–12.
17. Clouse RE, Mayer EA, Aziz Q, Drossman DA, Dumitrascu DL, Mönnikes H, Naliboff BD. Functional abdominal pain syndrome. Gastroenterology. 2006;130(5):1492–7. https://doi.org/10.1053/j.gastro.2005.11.062. PMID: 16678562.
18. Feuerstein M, Dobkin PL. Recurrent abdominal pain in children. In: Gross AM, Drabman RS, editors. Handbook of clinical behavioral pediatrics. Applied clinical psychology. Boston, MA: Springer; 1990. https://doi.org/10.1007/978-1-4613-0505-7_18.
19. Sibert L, Rigaud J, Delavierre D, Labat JJ. Chronic pelvic pain: epidemiology and economic impact. Prog Urol. 2010;20:872–85.
20. Ahangari A. Prevalence of chronic pelvic pain among women: an updated review. Pain Physician. 2014;17(2):E141–7. PMID: 24658485.

Anatomy of the Visceral Nerves

2

Bifa Fan

To give a clear and concise description of visceral pain, it is necessary to start by introducing the anatomy of the visceral nerves which are complicated and closely related to the activation of sensations. The visceral nerves are divided into visceral motor nerves and visceral sensory nerves. A comparison of visceral motor nerves and somatic motor nerves will be made to reveal the unique features of visceral motor nerves. Then, sympathetic nerve, parasympathetic nerve, visceral plexuses, and enteric nervous system will be introduced, as they all play an indispensable and crucial role in consisting of the visceral motor nerves. The visceral sensory nerves section covers the concepts of interoceptor and neural pathways. Besides, referred pain is also illustrated as it is an important physiological characteristic of visceral sensation. It is a sensory hypersensitivity or nociception phenomenon in a certain area of the body surface. The detailed classification and explanation of visceral nerves will lay a solid foundation for further discussion of visceral pain and diseases.

The visceral nervous system is a component of the entire nervous system and can be divided into central and peripheral parts according to their distribution.

The central part of the visceral nervous system is located in the spinal cord, brainstem, mesencephalon, and cerebral cortex. Visceral stimulus signals are transmitted to the central nerve, triggering two different physiological responses in the organism, one that does not cause subjective sensations but is accessible by scientific means, such as blood pressure fluctuations, lung expansion, intestinal peristalsis, etc., i.e., autonomic activity in the traditional sense. These reflex activities can be achieved, in part, by short-circuit reflex arcs within the visceral wall. Another visceral signaling impulse transmitted to the central nervous system causes sensory awareness in the brain, the most typical of which is visceral pain.

The peripheral part is mainly located in the visceral, cardiovascular, and glandular areas, hence named as visceral nerves. Visceral nerves, like somatic nerves, can be divided into sensory and motor fiber components according to the nature of the fibers. The visceral motor nerves regulate visceral and cardiovascular movements and glandular secretion, which are usually not controlled by human will and are not random, so they are also called the autonomic nervous system; because they mainly control and regulate the metabolic activities of substances common to plants and animals, they do not govern the movements of skeletal muscles unique to animals. Therefore, they are also called the vegetative nervous system. According to the morphological, functional, and pharmacological characteristics, the visceral motor nerves can be divided into two parts: sympathetic and parasympathetic nerves. The enteric nervous system is structurally and

B. Fan (✉)
Department of Pain Medicine, China-Japan Friendship Hospital, Beijing, China

M. Xia et al. (eds.), *Visceral Pain*, https://doi.org/10.1007/978-981-99-9167-9_2

functionally distinct from the sympathetic and parasympathetic nervous systems, but it is also part of the autonomic nervous system as it participates in and mediates the voluntary movements of the intestine. The primary sensory neurons of the visceral sensory nerves are also located in the cerebral nerves and spinal ganglia, while the peripheral branches are distributed in the visceral and cardiovascular internal sensory apparatus, transmitting the perceived information to the centers at all levels and also reaching the cerebral cortex. This plays an important role in maintaining the dynamic balance of the internal and external environment of the organism and maintaining normal life activities.

2.1 Visceral Motor Nerves

2.1.1 Differences Between Visceral Motor Nerves and Somatic Motor Nerves

Generally speaking, somatic motor nerves are under volitional control, while visceral motor nerves are not. There are also major structural and functional differences between them, which are summarized in Table 2.1.

Table 2.1 Differences between visceral motor nerves and somatic motor nerves

Differences	Visceral motor nerves	Somatic motor nerves
Innervated organs	Smooth muscle, cardiac muscle, and glands	Skeletal muscle
Fiber composition	Sympathetic nerves and parasympathetic nerves	Only one type
Number of neurons from low-level centers to effectors	Two neurons: the preganglionic neuron and the postganglionic neuron	Only one
Fiber thickness	Thin medullary (pre-nodal fibers) and non-medullary (post-nodal fibers) thin fibers	Thick medullary fiber
Postganglionic fiber distribution form	Climbing of organs or blood vessels to form plexuses, which in turn branch to effectors	Distribute in the form of nerve trunks
Controlled by will or not	No	Yes

2.1.2 Sympathetic Nerve Anatomy

The sympathetic nerve is part of the visceral motor nerve, and together with the parasympathetic nerve and the enteric nervous system, it forms the autonomic nervous system.

1. Physiological functions of sympathetic nerve

   The main function of sympathetic nerves is to stimulate the "fight or flight" response of the body. Sympathetic excitation will cause pupil dilatation, increased heart rate, skin and visceral vasoconstriction, coronary artery dilation, increased blood pressure, small bronchial diastole, gastrointestinal peristalsis, bladder wall muscle relaxation, reduced saliva secretion, sweat gland secretion, and contraction of the erector spinae. When the body is in a state of nervous activity, sympathetic nerve activity plays a major role.
2. Composition of sympathetic nerves

   The low-level center of sympathetic nerves is located in the lateral nucleus of the middle band (preganglionic neuron) in the T_1–$L_{2/3}$ segment of the spinal cord. The preganglionic neurons send preganglionic fibers out of the intervertebral foramen via the anterior roots, which terminate in the corresponding postganglionic neurons (sympathetic ganglia), which then send postganglionic fibers to the effectors. The peripheral part of the sympathetic nerve includes the sympathetic trunk, the sympathetic ganglion, and branches from the ganglion and the sympathetic plexus. Depending on their location, sympathetic ganglia can be divided into paravertebral ganglia and prevertebral ganglia.

   (a) Paravertebral ganglia: The ganglia of the sympathetic trunk is located on both sides of the spine and is connected to the left and right sympathetic trunks by the interganglionic branch. The sympathetic trunk

is distributed from the base of the skull to the coccyx, and the two trunks merge in front of the coccyx. The sympathetic trunk is divided into five parts: cervical, thoracic, lumbar, sacral, and caudal. The number of sympathetic ganglia in each part is similar to the number of vertebrae in each part, except for 3–4 ganglia in the cervical part and 1 ganglion in the caudal part, and the total number of sympathetic ganglia on each side is 19–24. The sympathetic trunk ganglion consists of multipolar neurons of different sizes, and some of the postganglionic fibers of the sympathetic nerve originate from these cells.

(b) Prevertebral ganglia: Irregular nodular masses located anterior to the spine, at the root of the visceral branch of the abdominal aorta. The prevertebral ganglia include celiac ganglia, superior mesenteric ganglion, inferior mesenteric ganglion, and aorticorenal ganglia.

3. Communicating branch between sympathetic nerve and spinal nerve

Each sympathetic ganglion is connected to the corresponding spinal nerve by a communicating branch. The communicating branch is divided into the white communicating branch and the gray communicating branch. The white communicating branch is mainly composed of preganglionic fibers with myelin sheath and is white in color, so it is called the white communicating branch. The cytosol of preganglionic neurons exists only in the lateral horn of the spinal cord in $T_{1–12}$ and $L_{1–3}$ segments, and the white communicating branch also exists only between the anterior branches of each spinal nerve from T_1 to L_3 and the corresponding sympathetic trunk ganglion. The gray communicating branch is connected between the sympathetic trunk and 31 pairs of anterior spinal nerve branches, and consists of postganglionic fibers emanating from the sympathetic trunk ganglion cells, which are mostly unmyelinated and grayish in color, hence the name gray communicating branch.

4. The general itinerary of sympathetic nerves

(a) The preganglionic fibers of the sympathetic nerve: The preganglionic fibers emanate from the lateral nucleus of the intermediate zone of the spinal cord and enter the sympathetic trunk via the anterior spinal nerve roots, the spinal nerve trunk, and the white communicating branch, and then have three kinds of destinations:

- Terminating in the corresponding paravertebral ganglion and changing neurons.
- Ascending or descending within the sympathetic trunk to terminate in the paravertebral ganglion above or below.

It is generally believed that preganglionic fibers from the middle band of the lateral nucleus in the upper thoracic segment of the spinal cord ($T_{1–6}$) ascend within the sympathetic trunk to the cervical region and exchange elements in the cervical paravertebral ganglion; those in the middle thoracic segment ($T_{6–10}$) ascend or descend within the sympathetic trunk to exchange elements in the sympathetic ganglion of the other thoracic segments: those in the lower thoracic and lumbar segments (T_1–L_3) descend within the sympathetic trunk and exchange elements in the lumbosacral sympathetic ganglion.

- After crossing the paravertebral ganglion, it goes to the prevertebral sympathetic ganglion for neurons.

(b) The destination of postganglionic fibers of sympathetic nerves:

- Postganglionic fibers originating from the sympathetic trunk ganglia return to the spinal nerves via the gray communicating branch and are distributed with the spinal nerves to the blood vessels, sweat glands, and erector spinae of the head and neck, trunk, and extremities. Thirty-one pairs of spinal nerves are connected to the sympathetic trunk by the gray communicating branch, and their branches

generally contain postganglionic fibers of sympathetic nerves.

- Climbing arteries travel, forming corresponding plexuses in the arterial epicardium, such as the internal and external carotid plexus, the ventral plexus, and the superior mesenteric plexus, and distributing with the arteries to the organs they innervate.
- Directly distributed by sympathetic ganglia to the innervated organs.

5. Local distribution of sympathetic nerves
   (a) Neck: The cervical sympathetic trunk is located posterior to the carotid sheath and anterior to the transverse processes of the cervical vertebrae. Generally, there are 3–4 sympathetic ganglia on each side, and as many as 6, which are called superior, middle, and inferior cervical ganglia. The superior cervical ganglion is the largest, shuttle-shaped, and is located anterior to the $C_{2,3}$ transverse process and posterior to the internal carotid artery. The middle cervical ganglion is the smallest, sometimes absent, and is located at the C_6 transverse process. The inferior cervical ganglion is located anterior to the C_7 transverse process and posterior to the beginning of the vertebral artery, and often merges with the T_1 ganglion to form the cervicothoracic ganglion (also known as the stellate ganglion).

   The distribution of postganglionic nerve fibers emanating from the cervical sympathetic ganglion is as follows:

   The cervical nerve joins eight pairs of cervical nerves via the gray traffic branch, and distributes with the cervical nerve branches to the blood vessels, sweat glands, and lissencephalic muscles of the head, neck, and upper limbs.

   Branches from the ganglion to the internal and external carotid arteries, subclavian artery and vertebral artery, etc., climbing on the surface of the arteries and forming the corresponding arterial plexus, accompanying the branches of the arteries to the glands of the head and neck (lacrimal glands, salivary glands, mucosal glands in the oral and nasal cavities, thyroid gland, etc.), the erector spinae, blood vessels, pupil opening muscle, smooth muscle of the eye and face, etc.

   The pharyngeal branches from the ganglion, which enter the pharyngeal wall directly, together with the pharyngeal branches (containing parasympathetic fibers) from the vagus and swallowing nerves, form the pharyngeal plexus, which is distributed in the pharyngeal wall and has branches to the glottis of the larynx and carotid artery.

   Three pairs of cervical sympathetic ganglia give off separate branches of the supracardiac, cardiac, and subcardiac nerves, respectively, which enter the thoracic cavity and participate in forming the cardiac plexus.

   (b) Thorax: There are 10–12 (11 are most common) thoracic ganglia on each side. They are connected upward to the cervical sympathetic trunk and continue downward through the diaphragm to the lumbar sympathetic trunk. The upper thoracic sympathetic ganglia are located on both sides of the spine, anterior or slightly lateral to the head of the ribs, crossing in front of the intercostal vessels and nerves, and gradually moving downward to the front of the vertebral body. The paravertebral ganglia of the thoracic sympathetic trunk are small in size. The thoracic sympathetic trunk emits the following branches:

   - Via the gray traffic branch, it is connected to 12 pairs of thoracic nerves and distributed with them to the blood vessels, sweat glands, and lissencephalic muscles of the thoracic and abdominal walls.
   - From the upper five pairs of thoracic sympathetic trunk ganglia, many branches are sent out to participate in

the thoracic aortic plexus, esophageal plexus, pulmonary plexus and cardiac plexus, etc.

- The visceral greater splanchnic nerve starts from the T_5 or $T_{6–9}$ sympathetic trunk ganglia and consists of preganglionic fibers that pass through these ganglia, synthesizes a trunk in the anterior and inferior course, and descends along the anterior inclination of the vertebral body, penetrates the foot of the diaphragm into the abdominal cavity, and terminates in the ventral ganglia. The lesser splanchnic nerve originates from the preganglionic fibers of the sympathetic trunk ganglia from T_{10} to T_{12}, descends through the pedicle of the diaphragm into the abdominal cavity, and terminates in the aorto-renal ganglion. The postganglionic fibers after the neuron exchange in the celiac ganglion and the aorticorenal ganglion are distributed to the substantive organs such as the liver, spleen, kidney, and the digestive tube above the left flexure of the colon.

  It is noteworthy that the visceral major and minor nerves, although passing through the paravertebral ganglion, do not change neurons in that ganglion, but go to the abdominal cavernous ganglion and the aortic renal ganglion to change neurons, respectively, and then innervate the corresponding visceral organs. Therefore, they belong to the preganglionic fibers of the sympathetic nerves.

(c) Lumbar: The lumbar sympathetic travels downward between the anterolateral aspect of the lumbar vertebral body and the medial border of the psoas major muscle, and the lower end enters the pelvis via the posterior aspect of the common iliac vessels. The right side is located lateral to or partially covered by the inferior vena cava: the left side is located lateral to the abdominal aorta. The lumbar paravertebral ganglia are usually four per side, but can be as few as two, irregular in shape and all small. The branches are as follows:

- The gray communicating branch connects five pairs of lumbar nerves and is distributed among the lumbar nerves.
- The lumbar splanchnic nerve consists of preganglionic fibers that pass through the lumbar ganglion and terminate in the prevertebral ganglion in the abdominal aortic plexus and the inferior mesenteric plexus, and replace the neurons. The postganglionic fibers are distributed to the alimentary canal and pelvic organs below the left curvature of the colon, and some fibers are distributed to the lower extremities along with the blood vessels. When lower extremity vasospasm is present, the lumbar sympathetic trunk can be surgically removed to obtain relief.

(d) Pelvis: The pelvic sympathetic trunk descends medially along the anterior sacral foramen to the front of the coccyx, with two to three pairs of sacral ganglia and one ganglion impar. Its branches are as follows:

- The gray communicating branch, joining each neighboring sacral nerve, distributes to the blood vessels, sweat glands and lissencephalic muscles of the lower limbs and perineum.
- Some small branches join the pelvic plexus and distribute to the pelvic organs.

  It can be seen that the sympathetic preganglionic and postganglionic fibers are distributed with some regularity. The preganglionic fibers from the middle lateral nucleus of $T_{1–5}$ segments of the spinal cord, after neuron replacement, innervate the head, neck, thoracic organs and blood vessels of the upper limbs, sweat glands, and the erector spinae. The preganglionic fibers from the lateral nucleus of the middle band of the upper lumbar segment of the spinal cord, after replacing

neurons, innervate the digestive ducts below the left curvature of the colon, the pelvic organs and the blood vessels of the lower limbs, sweat glands, and the erector spinae.

2.1.3 Anatomy of Parasympathetic Nerves

1. Physiological functions of the parasympathetic nerve

   The role of the parasympathetic nervous system is opposite to that of the sympathetic nerve, and the two are in mutual balance. The parasympathetic nervous system can maintain the physiological balance of the body in a quiet state, and its role is threefold: first, to enhance gastrointestinal activity, secretion of digestive glands, promote the discharge of urine and feces, and maintain the body's energy; second, to narrow the pupils to reduce stimulation and promote the production of liver glycogen to save energy; third, to slow down heart rate, lower blood pressure and narrow bronchial tubes to save unnecessary consumption, and to assist reproductive activities, such as causing dilation of reproductive blood vessels and increased secretion of fluids from sexual organs.
2. Composition of parasympathetic nerves

   The parasympathetic nerves include preganglionic neurons, preganglionic fibers and postganglionic neurons, postganglionic fibers, and their low-level centers are located in the parasympathetic nucleus of the brainstem and the sacral parasympathetic nucleus (preganglionic neurons) in the gray matter of segment $S_{2–4}$ of the spinal cord. The peripheral parasympathetic ganglia, called parasympathetic and intra-organ ganglia, are located in the cranial region and are larger and visible to the naked eye, including the ciliary ganglion, submandibular ganglion, pterygopalatine ganglion, and auricular ganglion. The preganglionic fibers of the cranial parasympathetic nerves exchange neurons in these ganglia, and then send out postganglionic fibers to the innervated organs with the corresponding brain nerves. Sympathetic and sensory nerve fibers pass through the ganglia (without exchanging neurons) and are called sympathetic and sensory roots, respectively. The parasympathetic ganglia located in other parts of the body are so small that they can only be seen with the aid of a microscope. For example, ganglia are located in the cardiac plexus, pulmonary plexus, bladder plexus, and uterovaginal plexus, as well as ganglia located in the walls of the bronchi and digestive tubes.
3. Distribution of parasympathetic nerves
   (a) Cranial parasympathetic nerves: Their preganglionic fibers travel within the III, IX, and X pairs of cerebral nerves, as outlined below.
   - The parasympathetic preganglionic fibers from the parasympathetic nucleus of the oculomotor nerve exit the cranium with the oculomotor nerve, enter the orbital cavity and reach the ciliary ganglion to exchange neurons, and their postganglionic fibers enter the wall of the eye and distribute to the pupillary sphincter and ciliary muscle.
   - The parasympathetic preganglionic fibers from the superior salivary nucleus exit the cranium with the facial nerve, and part of the preganglionic fibers exchange neurons via the great rocky nerve to the pterygopalatine ganglion in the pterygopalatine fossa. Another part of the preganglionic fibers passes through the bulbar cord, joins the lingual nerve, and then goes to the submandibular nerve ganglion, and the postganglionic fibers are distributed in the submandibular and sublingual glands.
   - The parasympathetic preganglionic fibers from the inferior salivary nucleus exit the skull with the glosso-

pharyngeal nerve, transfer to the auricular nerve ganglion below the foramen ovale via the bulbar nerve, and the postganglionic fibers are distributed to the parotid gland via the auriculotemporal nerve.

- The parasympathetic preganglionic fibers from the dorsal nucleus of the vagus nerve in the medulla oblongata follow the vagus nerve out of the cranium and branch to parasympathetic ganglion neurons near or in the walls of the thoracic and abdominal organs, and the postganglionic fibers are distributed in the cardiac muscle, smooth muscle, and glands. Among them, the preganglionic fibers to the heart are in the cardiac plexus or intramural nerve ganglia: the preganglionic fibers to the digestive canal are in the wall of the digestive canal and participate in forming the submucosal plexus (Meissner's plexus) and the intermuscular plexus (Auerbach's plexus), and send postganglionic fibers to innervate the corresponding organs in the intramural ganglia or interplexus nerve ganglia.

(b) Sacral parasympathetic nerve: The preganglionic fibers originate from the sacral parasympathetic nucleus in the S_{2-4} segment of the spinal cord, and then branch out from the sacral nerve to form the pelvic splanchnic nerve, which joins the inferior abdominal plexus, i.e., the pelvic plexus. The pelvic plexus branches to the digestive ducts and pelvic organs below the left curvature of the colon, and in the paramedian or intramural ganglia of these organs, postganglionic fibers are distributed to the smooth muscles and glands of these organs. Some of the parasympathetic fibers are distributed to the penis or clitoris, causing vasodilation of the cavernous body to make it erect, so the pelvic visceral nerve is also called the erectile nerve.

2.1.4 Main Differences Between Sympathetic and Parasympathetic Nerves

Both sympathetic and parasympathetic nerves are visceral motor nerves and often innervate an organ together, forming a dual innervation of the visceral organs. However, the sympathetic and parasympathetic nerves have their own characteristics in terms of origin, morphological structure, distribution range and function, as summarized in Table 2.2.

Table 2.2 Main differences between sympathetic and parasympathetic nerves

Differences	Sympathetic nerve	Parasympathetic nerve
Low-level nociceptors	Lateral nucleus of the intermediate band of gray matter in the thoracolumbar region of the spinal cord	Parasympathetic nucleus of the brainstem cerebral nerve and parasympathetic nucleus of the sacral part of the spinal cord
Location of peripheral ganglia	Both sides of the spine (paravertebral ganglia), anterior spine (anterior vertebral ganglia)	Near organs (paranodes), within the walls of organs (intra-organ nodes)
Ratio of preganglionic to postganglionic neurons	Axons of one preganglionic neuron can form synapses with many postganglionic neurons	Axons of one preganglionic neuron form synapses with fewer postganglionic nerves
Distribution	In addition to the head and neck, thoracic and abdominal organs, it also covers the blood vessels, glands, and trichomes of the body	The distribution is relatively limited, and most of the blood vessels, sweat glands, erector spinae, and adrenal medulla are not parasympathetically innervated
Effects on organs	The two act differently, antagonizing and unifying each other	

2.1.5 Visceral Plexus

Sympathetic, parasympathetic, and visceral sensory nerves are intertwined in the process of distribution in the viscera to form the visceral plexus (autonomic or vegetative plexus). These plexuses mainly climb around the head, neck and internal thoracic and abdominal arteries, or are distributed near organs and within organs. All visceral plexuses are composed of sympathetic and parasympathetic nerves, except for the internal carotid plexus, external carotid plexus, subclavian plexus, and vertebral artery plexus, in which no parasympathetic nerves participate. In addition, there are visceral sensory fibers passing through these plexuses. The important plexuses in the thoracic, abdominal, and pelvic-sacral regions are described below.

1. Cardiac plexus

   The cardiac plexus is composed of the superior, middle, and inferior cervical segments of the sympathetic trunk and the cardiac branches emanating from $T_{1–4/5}$ segments and the cardiac branches of the vagus nerve. The superficial plexus is located below the aortic arch and the deep plexus is located between the aortic arch and the tracheal fork. The plexus contains the cardiac ganglion (parasympathetic ganglion), where the parasympathetic preganglionic fibers from the vagus nerve exchange neurons. The branches of the plexus in turn form the atrial plexus and the left and right coronary plexus, which are distributed to the myocardium along with the arterial branches.
2. Pulmonary plexus

   The pulmonary plexus is located anteriorly and posteriorly to the pulmonary roots, and there are also small ganglia within the plexus. The pulmonary plexus is composed of the bronchial branches of the vagus nerve and branches of the $T_{2–5}$ nodes of the sympathetic trunk, whose branches follow the branches of the bronchi and pulmonary vessels to the lungs.
3. Celiac plexus

   The celiac plexus is the largest visceral plexus and is located around the roots of the celiac artery and superior mesenteric artery. It is mainly composed of the celiac ganglion, superior mesenteric ganglion, aortic renal ganglion, etc., as well as branches of the major and minor visceral nerves from the thoracic sympathetic trunk and the ventral branches of the posterior vagus trunk and the upper lumbar sympathetic ganglion. The ventral plexus, along with the branches of the arteries, can be divided into many subplexuses, such as the hepatic plexus, gastric plexus, splenic plexus, renal plexus, and superior mesenteric plexus, and each subplexus reaches each organ along the eponymous vascular branches.
4. Abdominal aortic plexus

   The abdominal aortic plexus is located on both sides of the abdominal aorta and is a continuation of the abdominal plexus down the surface of the abdominal aorta, which also receives branches from the $L_{1–2}$ sympathetic ganglia. This plexus divides into the inferior mesenteric plexus, which distributes along the branches of the eponymous artery below the left curvature of the colon to the superior rectum. A portion of the fibers descends into the pelvis and participates in the composition of the infra-abdominal plexus, and another portion is distributed along the common iliac artery and external iliac artery to the vessels of the lower extremities, sweat glands, and the erector spinae.
5. Hypogastric plexus

   The hypogastric plexus is divided into the superior and inferior hypogastric plexus. The inferior hypogastric plexus is located in front of the Ls vertebrae, between the end of the abdominal aorta and the two common iliac arteries, and is the downward continuation of the abdominal aortic plexus. The pelvic plexus continues from the inferior hypogastric plexus to the sides of the rectum and also receives postganglionic fibers from the sacral sympathetic trunk and parasympathetic preganglionic fibers from the $S_{2–4}$ nerves. The hypogastric plexus is accompanied by branches of the internal iliac artery to form the rectal plexus, spermatic plexus, ureteral plexus, bladder plexus, prostatic plexus, and

vaginal plexus of the uterus, and is distributed with the arteries to the pelvic organs.

2.1.6 The Enteric Nervous System

The enteric nervous system is a reticular system composed of neurons, neurotransmitters, and proteins located in the wall of the gastrointestinal tract (including the pancreas and gallbladder) and its supporting cells, which has the function of regulating and controlling the function of the gastrointestinal tract. The enteric nervous system is structurally and functionally different from the sympathetic and parasympathetic nervous systems in that its neurons are interconnected to form an independent system with the ability to integrate and process information similar to the brain and spinal cord, but it is still a component of the autonomic nervous system, also known as the "second brain".

The enteric nervous system consists of two major internally interconnected plexuses that begin in the lower esophagus and extend to the level of the dentate line of the anal canal. The larger is the myenteric nerve plexus or Auerbach's plexus, which surrounds the entire alimentary canal and mainly innervates smooth muscle, transmits stimulus information such as pulling and distension of the intestinal wall, and regulates the relaxation and contraction of the longitudinal and circular muscles and peristalsis of the intestinal canal; the smaller is the submucous plexus or Meissner's plexus, which mainly innervates the intestinal mucosa, transmits impulses from various stimuli in the gastrointestinal lumen and regulates secretion of the intestinal epithelium, relaxation and contraction of the intestinal vasculature, and water-electrolyte metabolism. These two plexuses are interconnected and jointly regulate gastrointestinal function.

The enteric nervous system is structurally and functionally encapsulated by glia similar to astrocytes of the central nervous system [1]. In addition to the neurons and glia of the enteric nervous system, the intestinal wall also contains Cajal interstitial cells (interstitial cell of Cajal, ICC), which form synaptic-like contacts with the axon terminals of interstitial plexus neurons. The ICC is the pacemaker and conductor of gastrointestinal slow-wave activity and serves as a "bridge" and "link" between the enteric nervous system and the smooth muscle of the intestine. The ICC serves as a "bridge" and "link" between the enteric nervous system and intestinal smooth muscle. So far, it is believed that ICC has three functions: (1) pacemaker of the basic gastrointestinal electrical rhythm; (2) mediator of enteric neurotransmission; and (3) mechanoreceptor [2].

The total number of human enteric neurons has been found to reach about 10, which is equivalent to the total number of neurons contained in the entire spinal cord. There are three types of neurons: sensory neurons, interneurons, and motor neurons, which constitute the complete reflex pathway. The enteric nervous system contains intrinsic primary afferent neuron (IPAN). The projection targets of the IPAN in the interosseous and mucosal plexuses are the interneurons. Intermediate neurons modulate intestinal motility and secretory reflexes. It can be seen that IPAN, interneurons and effector neurons constitute the reflex microcircuit of the enteric nervous system, which allows the gastrointestinal tract to receive stimulus signals and generate reflexes in the absence of external innervation. However, the modulatory action of the enteric nervous system on the gastrointestinal tract requires its perception of pressure and chemical stimuli in the intestinal lumen without intrinsic or extrinsic nerve fibers reaching the mucosal epithelium. This process is mediated by intestinal chromophores, which release large amounts of 5-hydroxytryptamine after sensing intestinal luminal stimuli, which activates submucosal primary afferent nerve fibers [3]. 5-Hydroxytryptamine stimulates intrinsic primary afferent neurons, which form synapses with upstream and downstream interneurons in the intermuscular plexus, thereby regulating local excitation and inhibition. In addition, a large number of enteric glial cells are distributed in the enteric nervous system. Previously, it was thought that enteric glial cells were only support cells for enteric neurons, but recent studies have revealed that enteric glial cells in

the gastrointestinal tract are a unique class of peripheral glial cells distributed throughout the intestinal tract, with different subpopulations representing their unique functions in digestive and non-digestive diseases, especially in the epithelial barrier, neuroprotection, and mediation of intestinal inflammatory immunity important role [4, 5].

2.2 Visceral Sensory Nerves

The visceral organs of the human body are innervated by visceral motor nerves as well as sensory nerves. The visceral sensory nerve receives stimuli from the viscera and converts them into nerve impulses for transmission to the center. The center can regulate visceral activity by completing visceral-visceral or visceral-somatic reflexes directly through visceral motor nerves or somatic motor nerves. Visceral sensory nerves can also undergo complex conduction pathways to transmit impulses to the cerebral cortex, eliciting conscious responses and producing visceral sensations.

2.2.1 Characteristics of Visceral Sensory Nerves

Although visceral sensory nerves are morphologically and structurally similar to somatic sensory nerves, they still have some unique features.

1. The number of visceral sensory fibers is small, and the majority of fine fibers, and the pain threshold is high. For normal visceral activities, they generally do not cause subjective sensation, but stronger visceral activities can cause certain sensations, such as hunger sensation when the stomach undergoes strong hunger contraction, and rectal and bladder filling to a certain extent can cause bowel movement and urination.
2. The viscera are not sensitive to stimuli such as cutting, but they are sensitive to stimuli such as chemical inflammation, pulling, distension, and ischemia.
3. The afferent pathways of visceral sensation are diffuse, with sensory fibers from one organ entering the center through multiple segments of the spinal nerve, and one spinal nerve containing sensory fibers from several organs, e.g., segment $T_{1–5}$ can receive sensory afferents from several organs such as the heart, lung, trachea, bronchus, and esophagus. Therefore, the visceral sensation is often diffuse and difficult to locate accurately.

2.2.2 Endoreceptors

Endoreceptors (interoceptors) are distributed in various layers within the organ wall and in the walls of blood vessels, etc. They receive physical and chemical stimuli such as osmotic pressure, pressure, temperature, ion, and compound concentrations. The thick medullary visceral afferent fibers terminate in the annulus: the small medullary or non-medullary visceral afferent fibers terminate in the diffuse endoreceptors. There are three main types of endoreceptor morphological structures: (1) Free sensory nerve endings are formed by repeated branching of sensory fiber endings, usually found in the epithelial and plasma membrane layers of mucous membranes, the endomysium of organ muscle layers, and organ connective tissue. These end receptors sense nociceptive and other stimuli, while the free endings distributed in the mucosa are chemoreceptors and those located in the muscular layer are mechanoreceptors, and the mechanoreceptors in the gastrointestinal tract are similar to “tensor receptors”. (2) Nerve fiber endings form a complex network that is visible on the surface of the plasma membrane and within the muscular layer of the organ. (3) Circumferential vesicles, mostly round or oval in shape, are composed of flattened connective tissue cells and fibers forming concentric lamellae, and the interlamellae are filled with gel-like material, which are found in the mesentery, visceral layer of mesentery, supporting tissues of organs, extravascular membrane and pancreas.

Depending on their functions, the receptors can be classified as follows:

1. Chemoreceptors
   The main ones are aortic sinus and carotid sinus, which are oxygen and carbon dioxide concentration receptors; gastric mucosa has pH-sensitive receptors; chemoreceptors in the small intestine are sensitive to different solutions and osmotic pressure and are involved in food absorption: taste buds have the function of sensing acid, sweet, bitter, and salty; olfactory receptors are sensitive to gases, volatile oils, and acids.
2. Mechanoreceptors
   Circumferential vesicles belong to pressure receptors, mesenteric circumferential vesicles are sensitive to mechanical stimuli; aortic arch and carotid sinus have traction receptors, which sense blood pressure changes.
3. Injury receptors
   They sense injurious stimuli and produce nociception.
4. Temperature receptors
   Animal studies have confirmed that raising the temperature of abdominal organs, respiratory rate is accelerated, this is not related to the temperature regulation of the skin, spinal cord, and hypothalamus, but this response disappears after removal of visceral nerves, which may be located in the venous canal wall of the small intestine and mesentery, connected to the afferent fibers of visceral nerves.

2.2.3 Visceral Sensory Nerve Conduction Pathway

Visceral sensory conduction pathways are divided into general visceral sensory conduction pathways and special visceral sensory conduction pathways. The former refers to all cardiac, vascular, glandular, and visceral sensory conduction pathways other than olfaction and gustation; the latter refers to olfaction and gustation conduction pathways.

1. General visceral sensory conduction
   (a) Conduction pathway via cerebral nerves: Visceral sensation is transmitted via facial nerve, glossopharyngeal nerve, vagus nerve to primary neurons such as geniculate ganglion, glossopharynx, and inferior vagus nerve. Its secondary neurons are located in the solitary bundle nucleus of the brainstem, from which crossed solitary spinal tracts emanate, follow the reticulospinal tract or intrinsic tract, and terminate in the gray matter of the spinal cord. In addition to constituting the visceral-visceral and visceral-somatic reflexes, the nucleus of the solitary fasciculus emits superior fibers that, after possibly exchanging neurons in the reticular formation, travel up through the midbrain perineurium and terminate in the ventral posterior medial nucleus of the thalamus, the midline nucleus, the inner platysmal nucleus, and the hypothalamus. Fibers emanate from the thalamus to the frontal and parietal cortices, and from the hypothalamus project to the cortical structures of the limbic system.
   (b) Trans-spinal conduction pathways: Visceral sensation is transmitted to the center via sympathetic nerves and pelvic-sacral parasympathetic nerves. The cytomes of primary neurons are located in T_1–L_3 and $S_{2–4}$ spinal ganglia, respectively, and are pseudo-unipolar neurons, as are the somatosensory ganglion elements. Their peripheral protrusions are distributed to visceral organs and cardiovascular via spinal nerves, anterior spinal nerve branches, traffic branches, sympathetic trunks and their branches, and secondary neurons in the middle frame protrusions into the posterior horn of the spinal cord or the posterior commissure nucleus. It is believed that there are three routes of transmission: (1) The neurons are replaced in the posterior commissure nucleus in the dorsolateral part of the central canal of the spinal cord, then in the

parabrachial nucleus, then up to the thalamus, and then to the cerebral cortex. (2) Neurons are replaced in the gray matter of the spinal cord, ascending in the ipsilateral or contralateral anterolateral spinal cord, accompanying the spinal thalamic tract up to the ventral posterior lateral nucleus of the thalamus, and then projecting to the postcentral gyrus and upper lateral sulcus of the cerebral cortex. (3) Ascending along the intrinsic tract of the spinal cord, it changes neurons multiple times within the spinal cord and brainstem reticular formation, ascending to the dorsal medial nucleus of the thalamus and then projecting to the limbic lobe of the brain.

It is now believed that nociception in the general organs is mainly transmitted to the center with sympathetic nerves. Nerve impulses via parasympathetic afferents are mainly associated with visceral reflexes, such as respiration, vomiting, and pressure reflexes. There are also some nociceptive sensations of some organs that are transmitted to the center with parasympathetic nerves, such as the nociceptive sensations of trachea and esophagus that are partially transmitted to the center via the vagus nerve, and the nociceptive sensations of bladder, prostate, urethra, cervix, and lower rectum that are mainly transmitted to the center via pelvic visceral nerves.

2. Special visceral sensory transmission
   (a) Taste receptors and taste conduction pathways: Taste receptors, namely taste buds, are distributed in the contour papillae, fungiform papillae, lobe papillae and epithelium of the soft palate and epiglottis of the tongue mucosa, and have the function of feeling sour, sweet, bitter, and salty taste. The taste buds are oval in shape and reach the substrate at the bottom, which can convert taste sensations into nerve impulses and then transmit them to the center through specific conduction pathways [6, 7].

The taste conduction pathway is composed of three levels of neurons. The first level neurons are located in the geniculate ganglion of the facial nerve, the inferior ganglion of the glossopharyngeal nerve, and the inferior ganglion of the vagus nerve. The central synapses of these ganglion cells enter the human medulla with their respective cerebral nerves to join the solitary tract and form synapses with secondary neurons in the nucleus of the solitary tract, where taste impulses are relayed superiorly. The nucleus of the solitary tract sends out secondary taste fibers, most of which cross left and right, and then travel upward with the medial thalamic tract, terminating in the medial apical part (parabasal nucleus) of the ventral posterior medial nucleus of the thalamus (arcuate nucleus) of tertiary neurons, which send out taste fibers that finally project to the central posterior gyrus 43 area of the cerebral cortex and insula cortex.

   (b) Olfactory receptors and olfactory conduction pathways: Olfactory receptors (olfactory organ) are located in the upper part of the nasal cavity, i.e., the superior turbinate and the relative septum, and are composed of olfactory cells, supporting cells, and basal cells. The olfactory cells are nerve cells that receive stimuli and generate nerve impulses to the olfactory brain. The mammalian olfactory organ is very sensitive and is an important tool for foraging, courtship, and escape from the attack [8–10].

The olfactory conduction pathway consists of two levels of neurons: primary neurons are located in the olfactory cells and the central synapses form olfactory filaments (about 20) that cross the sieve plate of the sieve bone into the olfactory bulb: secondary neurons are cells within the olfactory bulb and form the olfactory bundle, which conducts to the telencephalon via the olfactory bundle. The olfactory bundle divides into three bundles of fibers in the dorsolateral part of the ante-

rior perineurium: the lateral olfactory stripe, the medial olfactory stripe, and the middle olfactory stripe. Most of the olfactory impulses are transmitted to the hook gyrus, insula, part of the amygdala, and the internal olfactory area via the lateral olfactory stripe, mainly transmitting conscious olfactory perception; some of the olfactory impulses are transmitted to the septal area via the medial olfactory stripe, which then sends nerve fibers to communicate with the limbic system and hypothalamus, mainly transmitting instinctive emotional olfactory experience; some of the olfactory impulses are transmitted to the olfactory node via the middle olfactory stripe, which then sends nerve fibers back to the olfactory bundle. The olfactory nerve is regulated internally by the olfactory bulb.

It should be noted that, so far, the understanding of the afferent pathways of the visceral nerves is still in the "dark", and it will take time to fully understand their conduction pathways.

2.2.4 Referred Pain

1. Overview of referred pain

   When lesions occur in certain internal organs, they often produce sensory allergy or nociception in certain areas of the body surface, which is called referred pain. Sometimes referred pain occurs in the skin adjacent to the diseased viscus, and sometimes it occurs in the skin distant from the diseased viscus. For example, in the early stage of appendicitis, pain often occurs in the upper abdomen or around the umbilicus; in angina pectoris, pain is often felt in the anterior chest area, the left shoulder, and the inner body surface of the left arm; in hepatobiliary disease, pain often occurs in the body surface of the right shoulder, etc.
2. Anatomical bases of referred pain

   Referred pain is an important physiological characteristic of visceral sensation, and the structural bases that cause involvement pain may be the following [11].

   (a) The primary sensory fibers of the diseased organ enter the spinal cord and terminate in the unique secondary neurons on the one hand, and in the neurons related to the sensory transmission of the somatic structures by lateral branches on the other hand.
   (b) The primary sensory fibers of the diseased organ and the corresponding somatic structure terminate in the same secondary neuron.
   (c) The peripheral synapses of primary sensory neurons have different lateral branches distributed in visceral and corresponding somatic structures.
3. Mechanistic hypothesis of referred pain

   There are several hypotheses about the mechanism of referred pain, but it has not been possible to confirm which hypothesis is correct.

   (a) Convergent projection theory: One of the earliest hypotheses about the mechanism of involved pain was proposed based on the research results of W. A. Sturge and J. Ross in 1888, and T. C. Ruch in 1961. This theory suggests that nociceptive afferent fibers from the visceral and somatic surfaces converge at the same neuron at the same level of the spinal cord before being uploaded to the cerebral cortex, and since most painful stimuli normally originate from the somatic surface, the brain continues to habitually mistake visceral pain for somatic pain, and implicated pain occurs. There is research evidence that when local pain increases, so does the referred pain. However, the doctrine has encountered some challenges in that it does not explain the presence of a delay between involvement pain and local pain stimulation [12].
   (b) Convergent facilitation theory: This theory suggests that the lateral branches of visceral afferent fibers form synaptic connections in the spinal cord with the same dorsal horn neurons that receive somatic nociceptive afferents. The impulses from the visceral lesion can increase the excitability of this neuron and thus produce a

facilitatory effect on the surface afferent impulses, making a weak surface stimulus a nociceptive stimulus and thus producing involvement pain. In recent years, the term "central sensitization" can be used to summarize this theory. The repeated nerve afferents from peripheral neurons increase the excitability of neurons in the dorsal horn of the spinal cord or brainstem, resulting in central sensitization, when even a weak stimulus can cause pain sensation.

(c) Visceral hypersensitivity theory: This theory suggests that there is no central mechanism involved in the formation of referred pain, but it has central characteristics. Due to the opening of potential convergent afferent fibers in the dorsal horn of the spinal cord, a new receptive field appears in the distal part of the primary stimulus, and the signal afferent from the new receptive field is then considered as referred pain.

(d) Axonal reflex theory: The afferent fibers contain two parts before entering the dorsal horn of the spinal cord, one part is distributed in visceral organs and the other part is distributed in muscles, skin and intervertebral discs, and other tissues. This theory also cannot explain the delayed appearance of referred pain, the difference in threshold between local pain and referred pain, and the change in somatosensory sensitivity at the site of referred pain.

(e) Thalamic convergence theory: This theory suggests that nerve impulses from the affected visceral and involved pain sites overlap in the brain rather than the dorsal horn of the spinal cord. There is a lack of evidence from relevant studies to support this theory. However, in pain studies in monkeys, some neural pathway convergence was found in cortical and subcortical neurons.

References

1. Farrell KE, Keely S, Graham BA, Callister R, Callister RJ. A systematic review of the evidence for central nervous system plasticity in animal models of inflammatory-mediated gastrointestinal pain. Inflamm Bowel Dis. 2014;20(1):176–95.
2. Martinucci I, Blandizzi C, de Bortoli N, Bellini M, Antonioli L, Tuccori M, et al. Genetics and pharmacogenetics of aminergic transmitter pathways in functional gastrointestinal disorders. Pharmacogenomics. 2015;16(5):523–39.
3. Spencer NJ, Zagorodnyuk V, Brookes SJ, Hibberd T. Spinal afferent nerve endings in visceral organs: recent advances. Am J Physiol Gastrointest Liver Physiol. 2016;311(6):G1056.
4. Yoo BB, Mazmanian SK. The enteric network: interactions between the immune and nervous systems of the gut. Immunity. 2017;46(6):910–26.
5. Smith TK, Koh SD. A model of the enteric neural circuitry underlying the generation of rhythmic motor patterns in the colon: the role of serotonin. Am J Physiol Gastrointest Liver Physiol. 2017;312(1):G1.
6. Matsumoto I. Gustatory neural pathways revealed by genetic tracing from taste receptor cells. Biosci Biotechnol Biochem. 2013;77(7):1359–62.
7. Li C-S, Lu D-P, Cho YK. Descending projections from the nucleus accumbens shell excite activity of taste-responsive neurons in the nucleus of the solitary tract in the hamster. J Neurophysiol. 2015;113(10):3778–86.
8. Courtiol E, Wilson DA. Neural representation of odor-guided behavior in the rat olfactory thalamus. J Neurosci. 2016;36(22):5946–60.
9. Courtiol E, Wilson DA. The olfactory thalamus: unanswered questions about the role of the mediodorsal thalamic nucleus in olfaction. Front Neural Circuits. 2015;9:49.
10. Sanda P, Kee T, Gupta N, Stopfer M, Bazhenov M. Classification of odorants across layers in locust olfactory pathway. J Neurophysiol. 2016;115(5):2303–16.
11. Arendt-Nielsen L, Svensson P. Referred muscle pain: basic and clinical findings. Clin J Pain. 2001;17(1):11–9.
12. Roman CW, Sloat SR, Palmiter RD. A tale of two circuits: CCK NTS neuron stimulation controls appetite and induces opposing motivational states by projections to distinct brain regions. Neuroscience. 2017;358:316–24.