

Chapter 2

The Neuroanatomy of Female Pelvic Pain

Frank H. Willard and Mark D. Schuenke

Introduction

The female pelvis is innervated through primary afferent fibers that course in nerves related to both the somatic and autonomic nervous systems. The somatic pelvis includes the bony pelvis, its ligaments, and its surrounding skeletal muscle of the urogenital and anal triangles, whereas the visceral pelvis includes the endopelvic fascial lining of the levator ani and the organ systems that it surrounds such as the rectum, reproductive organs, and urinary bladder. Uncovering the origin of pelvic pain patterns created by the convergence of these two separate primary afferent fiber systems – somatic and visceral – on common neuronal circuitry in the sacral and thoracolumbar spinal cord can be a very difficult process. Diagnosing these blended somatovisceral pelvic pain patterns in the female is further complicated by the strong descending signals from the cerebrum and brainstem to the dorsal horn neurons that can significantly modulate the perception of pain. These descending systems are themselves significantly influenced by both the physiological (such as hormonal) and psychological (such as emotional) states of the individual further distorting the intensity, quality, and localization of pain from the pelvis.

The interpretation of pelvic pain patterns requires a sound knowledge of the innervation of somatic and visceral pelvic structures coupled with an understanding of the interactions occurring in the dorsal horn of the lower spinal cord as well as in the brainstem and forebrain. This review will examine the somatic and visceral innervation of the major structures and organ systems in and around the female pelvis. It will then consider the properties of visceral afferent fibers, their interactions in the spinal cord, as well as their modulation by descending systems from the brainstem and cerebrum.

F.H. Willard, Ph.D. (✉) • M.D. Schuenke, Ph.D.
Department of Anatomy, College of Osteopathic Medicine,
University of New England, Biddeford, ME, USA

Somatic Structures of the Pelvis

Ligamentous Structure of the Pelvis

The pelvic basin is a funnel-shaped structure bound anteriorly by the pubic symphysis and posteriorly by a complex of ligaments and muscles related to the thoracolumbar fascia [1]. The ligaments of the posterior aspect of the pelvis are closely associated with muscles derived from the back, abdomen, and upper and lower extremities. The anterior ligaments of the pelvis surrounding the pubic symphysis are intimately associated with the abdominal muscles and the adductor muscles of the lower extremity.

Pubic Symphysis

The pubic symphysis is a fibrocartilaginous joint between the bodies of the two pubic bones (Figs. 2.1 and 2.2) [2]. Although the joint is generally considered to be



Fig. 2.1 The pubic symphysis. The *upper photograph* demonstrates an anterior view of the pubic symphysis in an 84-year-old female after removing the skin, subcutaneous fat and fascia, and thigh muscles. The *arrows* indicate the fibrocartilage disc in the joint. The *lower photograph* was taken following removal of the pubic symphysis to reveal the periosteum on the posterior aspect of the pubic rami. The *arrows* indicate where the fibrocartilaginous disc was located

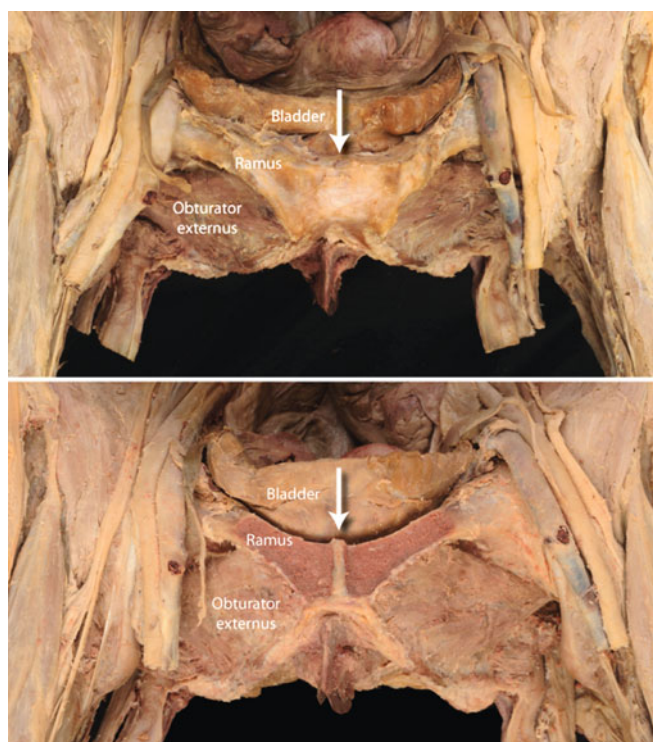


Fig. 2.2 The pubic symphysis. The *upper photograph* demonstrates an anterior view of the pubic symphysis in a 50-year-old female after removing the skin, subcutaneous fat and fascia, and thigh muscles. The *arrow* indicates the fibrocartilage disc in the joint. The *lower photograph* was taken following section of the pubic symphysis in the coronal plane to reveal the fibrocartilaginous located between the two pubic rami

restricted in motion, there is a slight displacement that can occur between the two articular surfaces. This displacement consists of a vertical shift of up to 2 mm and rotation of approximately 1° [3]. For most individuals, the two joint surfaces approximate each other symmetrically. However, a disparity in the heights of the two sides of the joint has been observed and is present mainly in females. The articular surface is covered with a thin layer of hyaline cartilage which appears to decrease with age. The joint is stabilized by superior and inferior ligaments, a multilayered anterior ligament, and a little-studied posterior ligament. Between the two articular surfaces is an interpubic disc composed of fibrocartilage (Fig. 2.3). A retropubic eminence can be present in multiparous females. An interpubic cleft is seen in the normal joint, which has been suggested to represent a possible joint space. However, the pubic symphysis generally is not considered a synovial joint by most accounts.

Muscle attachments surrounding the joint include the rectus abdominis superiorly and the adductor longus inferiorly, while an aponeurosis extends across the pubic symphysis to connect these two muscles. Rotational and extensional injuries

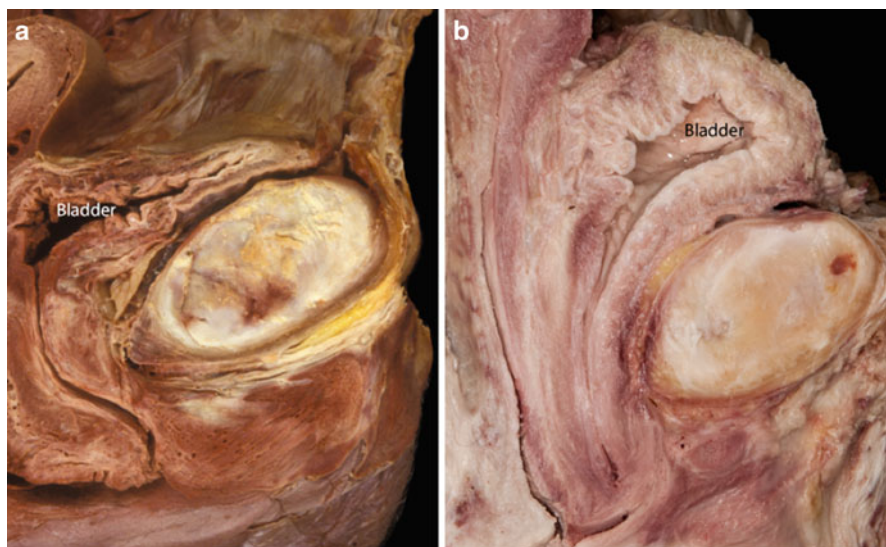


Fig. 2.3 The pubic symphysis. (a) A sagittal view of the pubic symphysis in a 54-year-old female. (b) A sagittal view of the pubic symphysis in an 84-year-old female. Both views reveal a dense connective tissue capsule surrounding the joint and a degree of fibrocartilage degeneration (discolored material) in the center of the joint. The bladder in (a) is relatively normal in size while the bladder wall in (b) is hypertrophied

can stress this aponeurosis resulting in radiographically demonstrable dysfunction about the joint [4]. A pubalgia, or sports hernia, has been demonstrated on MR imaging to involve damage to the attachments of one or both of these two muscles or to the joint itself, a condition termed osteitis pubis [4–6]. Suggested innervations of the pubic symphysis include the pudendal nerve, genitofemoral nerve, and iliohypogastric and ilioinguinal nerves [2].

SI Joint Capsule and Associated Ligaments

The sacroiliac joint capsule has a smooth anterior surface (Figs. 2.4 and 2.5) and an irregular, woven posterior surface (Fig. 2.5) [1, 7]. The anterior surface of the joint capsule is in contact with the piriformis muscle and lumbosacral plexus. The superior aspect of the capsule blends with the iliolumbar ligament, while the inferior aspect blends with the sacrospinous ligament anteriorly and the sacrotuberous ligament posteriorly. Bands of the iliolumbar ligament form tight hoods arching over the L4 and L5 ventral rami (Fig. 2.4) and are potentially a source of compression neuropathy [8].

Posterior muscles influencing the sacroiliac joint include the multifidus muscle on the midline and its fusion to the gluteus maximus through a connective tissue raphe [9] and the biceps femoris across the sacrotuberous ligament [10]. In addition,

Fig. 2.4 The anterior ligaments of the sacroiliac joint in a 54-year-old female. This is an anterior view into the pelvis following the removal of all organs and neurovascular structures. The iliolumbar ligament is seen blending into the superior portion of the anterior sacroiliac joint capsule. The *white arrow* indicates a ligament forming a hood that covered the L5 ventral ramus. The *black arrow* indicates a defect in the joint capsule. This defect formed an open conduit into the joint. If anesthetic had been injected into the joint capsule, it would have leaked out through this defect. The defect was positioned deep to the lumbosacral trunk (L4–L5) in the endopelvic fascia

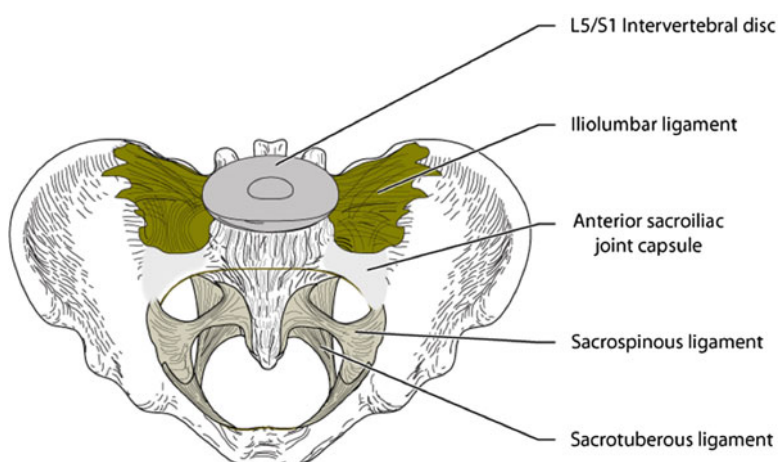
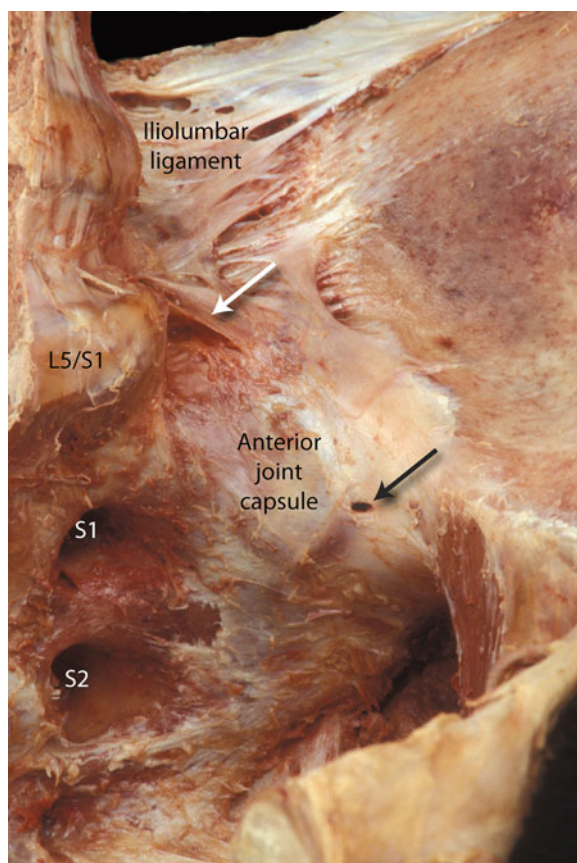


Fig. 2.5 The anterior ligaments of the sacroiliac joint. This drawing illustrates the position of the iliolumbar ligament superior to the sacroiliac joint capsule and the sacrospinous ligament inferior to the joint capsule. The sacrotuberous ligament is located posterior to the joint capsule

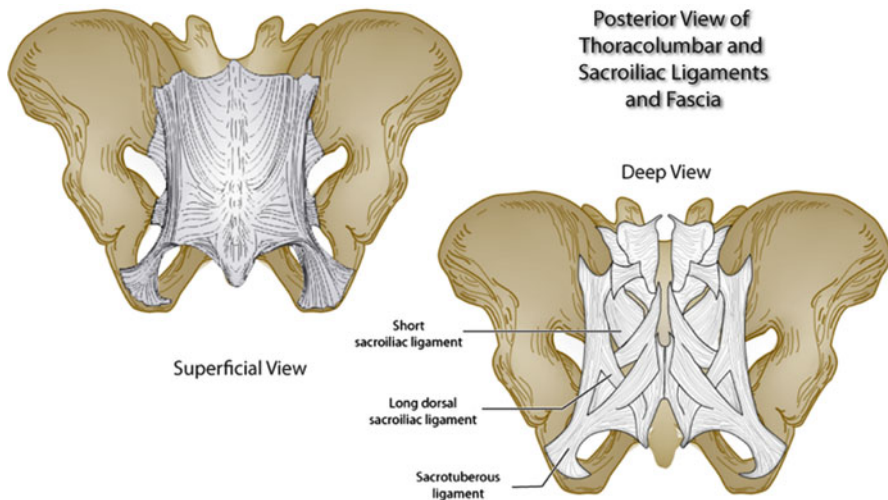


Fig. 2.6 The posterior ligaments of the sacroiliac joint. The drawing on the *left* illustrates the combined aponeuroses of the latissimus dorsi, posterior inferior serratus, and erector spinae muscles covering the multifidus muscle on the posterior aspect of the sacrum. The drawing on the *right* illustrates the short sacroiliac ligaments following the complete removal of the multifidus muscle. The short sacroiliac ligaments and the multifidus muscle lie in a trough or gutter formed by the medial sacral tubercles on the midline and the lateral sacral tubercles along the lateral border of the sacrum. Deep to the short sacroiliac ligaments are the dorsal sacral foramina and their dorsal sacral primary rami

the piriformis is positioned laterally on the sacrum. The latissimus dorsi through its attachment to the thoracolumbar fascia and the aponeurosis of the erector spinae muscles has also been postulated to influence the sacroiliac joint [10–12].

The posterior aspect of the sacroiliac joint is protected by the interosseous ligaments located in the narrow space or joint cleft between the sacrum and the ilium, as well as the long and short sacroiliac ligaments located on the external surface of the joint between the posterior superior iliac spine (PSIS) and the spinous processes of the sacrum (Figs. 2.6 and 2.7). The posterior portion of the joint capsule is woven into the superior and medial bands of the sacrotuberous ligament. The posterior aspect of the joint capsule is innervated by the small branches from the dorsal primary rami of L5, S1, and S2 [13, 14]. A description of small twigs from the ventral primary rami of the lumbosacral plexus has been published in abstract form but awaits further study [15]. The sacrotuberous ligament extends from the ischial tuberosity to the coccyx, sacrum, and ilium (Figs. 2.6 and 2.8). This ligament is arranged in a three-layered sandwich with several taut internal ligamentous bands that are covered with outer and inner layers of investing fascia derived from the sacroiliac joint. The outermost layer of the sacrotuberous ligament extends onto the conjoined portion of the thoracolumbar fascia composed of aponeurosis of the latissimus dorsi

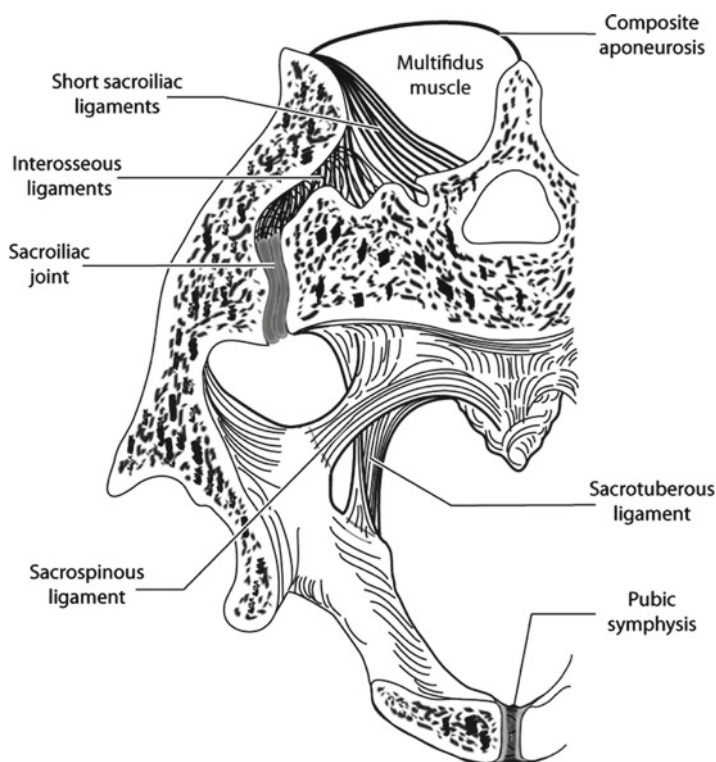


Fig. 2.7 An axial plane section through the sacroiliac joint. The sacroiliac joint is seen as two opposed cartilaginous surfaces between the ala of the sacrum and the internal surface of the ilium. The joint is located anteriorly. Posteriorly, the gap between the sacrum and ilium is filled with irregular bands of dense connective tissue termed the interosseous ligaments. Further posterior, the bed of the multifidus is composed of short sacroiliac ligaments (Figure modified from [1])

and the aponeurosis of the erector spinae muscles. The sacrotuberous ligament has been demonstrated to contain terminal ramifications, some appearing similar to naked nerve endings, while others resembling Ruffini endings [16].

At the superior margin of the SI joint capsule lies the iliolumbar ligament (Figs. 2.4 and 2.5). This ligament arises medially from the transverse process of the fifth, and in some cases fourth, lumbar vertebra and attaches laterally to the crest of the ilium as well as blends into the SI joint capsule [7]. In general, the ligament is composed of two broad anterior and posterior bands; however, complex interweaving can also occur throughout the ligament. Strains involving the ligament are described as iliolumbar syndrome and can involve a pain similar to sciatica [17]. This pain may arise from the internal innervations of the ligament or from the ligament's close relationship with the ventral rami of L4 and L5 [8].

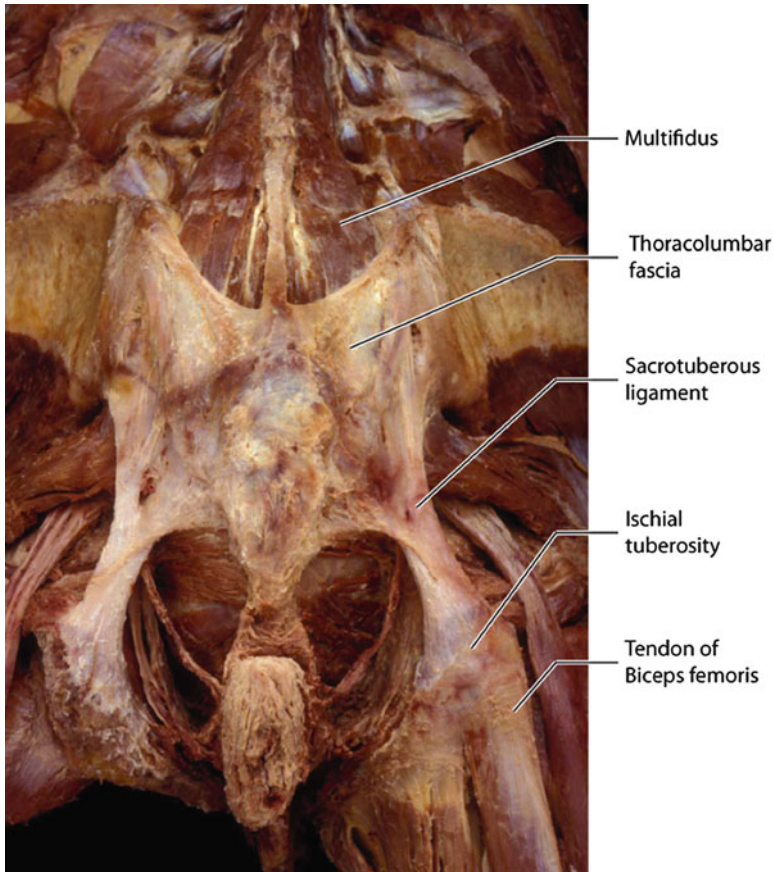


Fig. 2.8 The posterior ligaments of the sacrum. This is a posterior view of the sacrum after removing the gluteus maximus and medius as well as the iliocostalis and longissimus muscles. The multifidus muscle is seen entering a dense connective tissue covering composed of the combined aponeuroses of the latissimus dorsi, posterior inferior serratus, and erector spinae muscles. This composite structure (also termed posterior layer of the thoracolumbar fascia) is continuous with the sacrotuberous ligament and the tendon of the biceps femoris (as seen on the right side only in this illustration). Inferior and medial to the sacrotuberous ligament, the ischioanal (ischioanal) fossa has been opened and the levator ani and external rectal sphincter muscles exposed

Somatic Nerves Associated with the Pelvis

The Lumbar Plexus: Anterior Cutaneous Innervation in the Pelvic Region

The abdomen is banded by six thoracic spinal nerves that form dermatomes arranged in a superioposterior to inferoanterior orientation (Fig. 2.9) [1, 18]. Five of these nerves are termed thoracoabdominal (T7–T11) since they begin in the thorax and

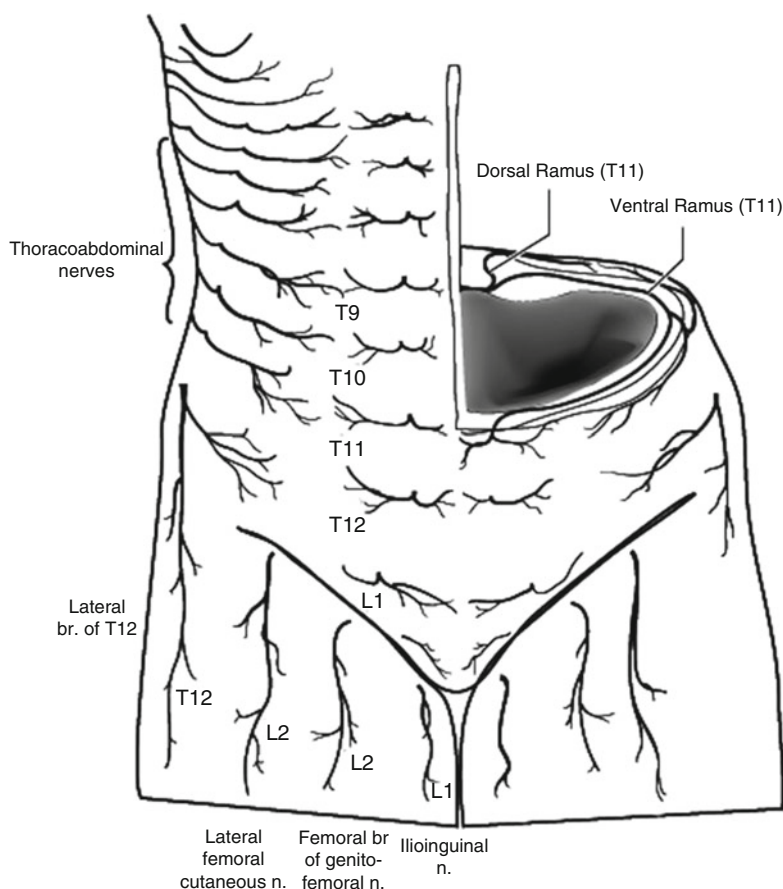


Fig. 2.9 The anterior peripheral nerves of the lower abdomen, pelvis, and thigh. The *lower* five thoracic spinal nerves, termed thoracoabdominal nerves, form bands circumscribing the torso. The first lumbar spinal nerve also follows this pattern, forming the iliohypogastric and ilioinguinal nerves. The terminal branches of the ilioinguinal nerve reach the anterior portion of the vulva and the medial aspect of the thigh (L1). The femoral branch of the genitofemoral nerve and the lateral femoral cutaneous nerve form medial and lateral bands, respectively, containing L2 on the anterior thigh. Finally, a lateral branch from the subcostal nerve brings T12 downward onto the lateral thigh (Figure modified from [95])

terminate in the abdomen. The sixth dermatome is the subcostal nerve (T12). Below the subcostal nerve is an additional dermatome band created by the iliohypogastric and ilioinguinal nerves (L1); twigs from the ilioinguinal nerve extend downward onto the anteromedial thigh as well as into the groin region. Distal twigs from the iliohypogastric nerve reach the mons pubis, while those from the ilioinguinal nerve provide cutaneous innervations to the anterior portions of the vestibule and labia. Spinal root L2 also contributes to the lateral femoral cutaneous nerve and the genitofemoral nerve

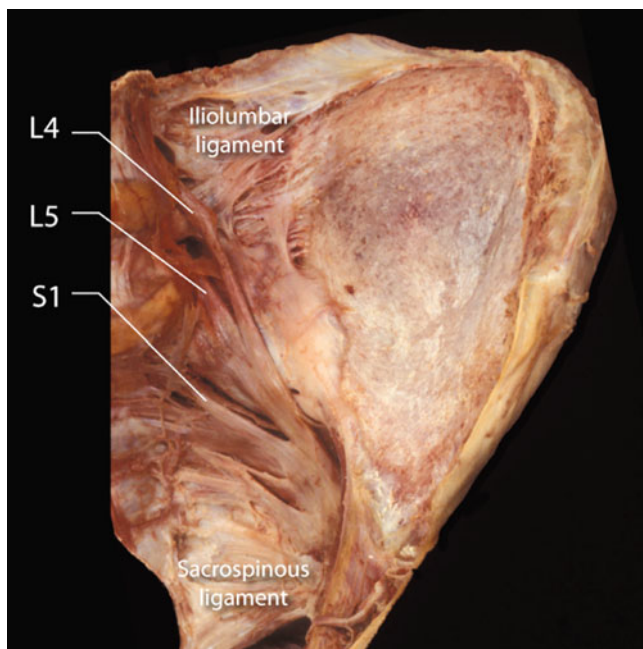


Fig. 2.10 The lumbosacral plexus. This is an anterior view of the lumbosacral plexus in a 54-year-old female. The organ system and surrounding visceral fascia have been removed from the pelvic basin. The lumbosacral trunk (L4 and L5) can be seen passing out from under bands of the iliolumbar ligament and joining the sacral ventral rami to form the sacral plexus. This plexus exits the pelvic basin by passing through the greater sciatic foramen

as well as the femoral nerve and the obturator nerve. Four cutaneous nerves – the lateral branches of T12, the lateral femoral cutaneous nerve, the femoral branches of the genitofemoral nerve, and the terminal branches of the ilioinguinal nerve – form successive dermatome bands from lateral to medial across the thigh (Fig. 2.9). These dermatomes are of special interest since much visceral nociceptive sensory information arrives in the T12–L2 spinal cord segments via the white rami at these levels (as described below). As such, this visceral input is commonly referred to the somatic body innervated by these segments and presents as body wall pain following the iliac crest, the groin region, and the thigh.

The Lumbosacral Plexus: Posterior Cutaneous Innervation in the Pelvic Region

The final two ventral rami of the lumbar nerves (L4 and L5) join together to form the lumbosacral trunk (Fig. 2.10). This combined nerve enters the pelvic basin by passing over the ala of the sacrum in close juxtaposition with the lateral margin of the L5/S1 disc. Once in the pelvic region, the lumbosacral trunk joins with the

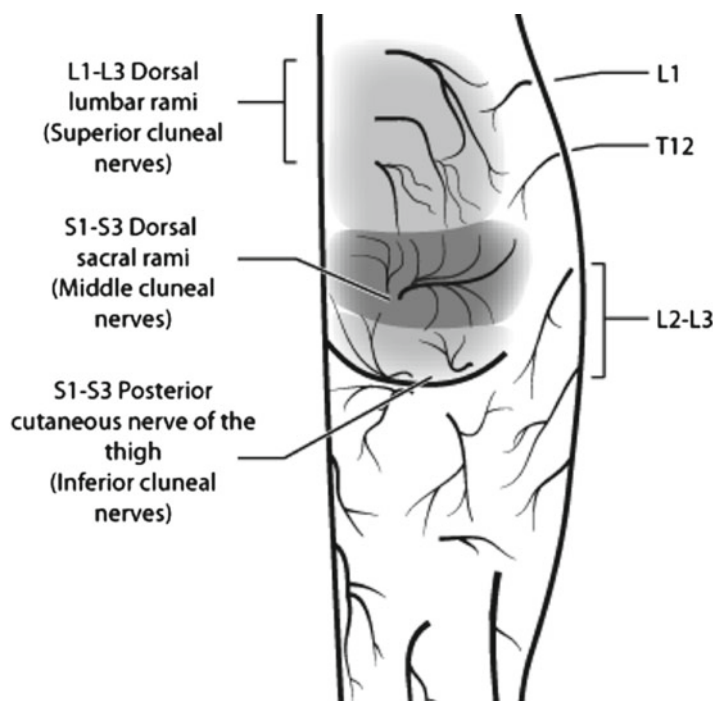


Fig. 2.11 The posterior peripheral nerves of the lower abdomen, pelvis, and thigh. Lateral branches of the upper three lumbar dorsal primary rami cover the posterior lumbar region forming the superior cluneal nerves; L4 and L5 typically lack lateral cutaneous branches. The dorsal primary rami of the sacral region (S1–S3) provide the middle cluneal nerves. Note that a contribution to the dorsal sacral rami has been noted from the L5 dorsal ramus as well. Finally, the ventral primary rami (S1–S3) provide the posterior cutaneous nerves of the thigh that curl around the gluteal fold to reach the territory of the middle cluneal nerves (figure modified from reference [18])

ventral rami of S1 through S3. These five roots give rise to the superior and inferior gluteal nerves and the sciatic nerve as well as the pudendal nerve and the nerves to the external rotators of the thigh such as the obturator internus. For the most part, the superior (L4, L5, and S1) and inferior (L5, S1, and S2) gluteal nerves are motor nerves; however, a few scattered branches continue through the muscle to reach the skin over the posterior buttocks (mostly from the S2 level). The posterior femoral cutaneous nerve receives contributions from ventral rami S2 and S3. This nerve also gives rise to the inferior cluneal nerves (or gluteal branches) to the inferior margin of the gluteal fold and twigs to the posterolateral perineal region (perineal branches) before extending downward along the posterior aspect of the thigh. The inferior cluneal nerves are three or four in number and curve upward from the gluteal fold to cover the inferior skin over the gluteal muscles (Fig. 2.11). Note that the skin over the gluteal muscles also receives cutaneous innervation from the first and second sacral dorsal primary rami as will be described below.

Course of the Pudendal Nerve

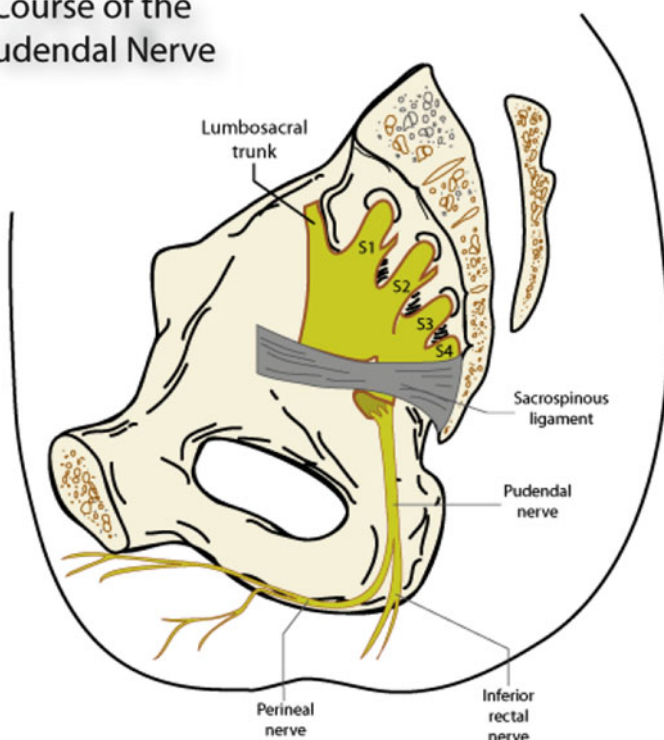


Fig. 2.12 The course of the pudendal nerve. This is a medial view of a sagittal section through the female pelvis to illustrate the course of the pudendal nerve (S2–S4) as it passes around the sacrospinous ligament, attaches to the medial aspect of the ischial tuberosity (pudendal canal), and terminates by passing through the urogenital diaphragm to reach the external genitalia

The pudendal nerve receives contributions from the ventral rami of S2–S4. It passes out of the pelvic basin through the greater sciatic foramen and immediately returns into the pelvis through the lesser sciatic foramen, following which it enters a narrow fascial (pudendal or Alcock's) canal on the inner aspect of the ischial tuberosity (Fig. 2.12). Terminal branches of the pudendal nerve reach the skin in the vestibule and over the posterior labia. It has been suggested that burning pain in the territory approximating the pudendal nerve could represent a form of neuralgia [19]. Although the etiology of pudendal neuralgia is not certain, it has been suggested that entrapment of the pudendal nerve in the fascial canal along the medial aspect of the ischial tuberosity is a strong possibility [20]. At least four entrapment sites have been described for the pudendal nerve: around the piriformis muscle/greater sciatic notch, at the ischial spine, in the pudendal canal on the side of the obturator muscle, and in the distal branches of the nerve [21].

The Lumbar and Sacral Dorsal Primary Rami: Posterior Cutaneous Innervation in the Pelvic Region

Each spinal nerve divides as it leaves the intervertebral foramen to form a ventral and dorsal primary ramus (Fig. 2.9) [1, 18]. The ventral ramus innervates structures that develop ventral to the transverse process of the vertebrae, while the dorsal ramus innervates those structures derived from tissue located dorsal to the transverse process. The ventral rami also innervate the upper and lower extremities. The innervation of the posterior aspect of the pelvis is complex, involving branches from both dorsal and ventral rami.

This posterior region shows the greatest variability of any region in the body when comparing the published dermatome and peripheral nerve maps. At all levels of the spine except C1 and C2 and possibly S3 and S4, the dorsal rami typically divide into medial and lateral branches shortly after their separation from the ventral rami [22]. One of these two branches will provide cutaneous innervation to a vertical band of skin extending from the vertex of the head to the anus and approximately as wide as a vertical line drawn down the back along the medial border of the scapulae. At most levels, this vertical band of skin is partitioned into horizontal segmentally oriented dermatomes by each of the dorsal rami. In the cervical and upper thoracic regions, the cutaneous innervation is provided by the medial branch of the dorsal ramus. However at T6, the cutaneous innervation shifts to the lateral branches of the dorsal rami.

In the lumbar region, L1–L3 dorsal primary rami typically have cutaneous branches that begin at spinous processes as a horizontal orientation but rapidly curve inferiorly to extend downward onto the buttocks to end as the superior cluneal nerves (Fig. 2.11). This downward movement extends the coverage of L1–L3 to make up for the lack of cutaneous branches from L4 and L5. The sacral dorsal rami emerge from their dorsal foramina, divide into medial and lateral branches, and course in the short sacroiliac ligaments deep to the multifidus muscle. Passing through and around the ligaments, the medial branches enter the multifidus, while the lateral branches of S1–S3 join with a contribution from L5 to form a complex arcade that ultimately passes under the long sacroiliac ligament to enter the sacrotuberous ligament [14, 23]. These cutaneous sacral branches then exit the posterior side of the ligament through small defects and pass outward through the gluteus maximus to gain access to the skin over the medial aspect of the buttocks, terminating as the middle cluneal nerves (Fig. 2.11). Irritation of these cutaneous nerves as they pass through the long posterior sacroiliac ligament may play a role in generating diffuse pain over the middle sacral region of the buttocks (J. Carreiro, personal observations). Small twigs from L5 through S2 can be found leaving the dorsal sacral plexus and entering the sacroiliac joint [13, 14]. Sacroiliac joint pain due to irritation of these nerves is estimated to affect 15–25% of patients with axial low back pain [24]. Finally, the lateral branches of S3 and below contribute to a delicate nerve plexus that extends inferiorly to surround the coccyx; this plexus is relatively unstudied but may play a role in coccygodynia (personal observations).

Visceral Nerves Associated with the Pelvis

Distinction Between Pain of Somatic and Visceral Origin

Based on the neuroanatomy of the visceral sensory system, six properties can be derived that help distinguish visceral pain from somatic pain [25, 26]:

1. Visceral pain is not evoked from all viscera; typically solid organs are only innervated in their capsule.
2. Visceral pain is not always linked to visceral organ injury.
3. When evoked, it is diffuse and poorly localized.
4. It is typically referred and not felt at the source.
5. It is produced by stimuli different from those adequate for activation of somatic nociceptors.
6. It is associated with strong motor, emotional, and autonomic responses.

In the following sections, the basis for these distinctions will be considered.

Each organ system in the pelvis is innervated by a dual set of fibers: sympathetic and parasympathetic. These nerves arise from the sympathetic trunk and the sacral spinal nerves, respectively, and form a massive abdominopelvic plexus extending from the thoracoabdominal diaphragm superiorly to the pelvic diaphragm inferiorly. This plexus and its associated connections were initially described as part of the autonomic nervous system by James Langley [27]. Although it was known that the plexus contained sensory fibers as well as efferent fibers, only the efferent fibers were included in the term autonomic nervous system. Since that time, it has become clear that each visceral nerve is mixed having an autonomic (efferent) component that extends outward from the spinal cord or brainstem to the organ system and a sensory (afferent) component that brings information back to the spinal cord or brainstem. The sensory fibers that course along with the sympathetic and parasympathetic fibers are termed visceral afferent (or sensory) fibers [28] and generally are not referred to as “sympathetic afferent” or “parasympathetic afferent” fibers.

Visceral afferent fibers that reach the dorsal horn of the spinal cord, regardless of the route traveled in the body, typically can evoke the sensation of pain. Pain patterns created by visceral afferent fibers are usually diffuse in nature and often are referred to a portion of the somatic body wall. Generally, a given organ will refer pain to a specific set of body somites related to the ontology of the organ system [29] and are referred to as a viscerotome [30]; however, this pattern can be altered if previous pain patterns have been experienced by the individual [31]. An understanding of the pattern of sympathetic and parasympathetic innervation in the pelvis is critical to the diagnosis of pelvic pain since the visceral afferent fibers tend to use the autonomic nerves as their route for gaining access to the spinal cord.



Fig. 2.13 The sympathetic trunk. This is a lateral view of the sympathetic trunk in a 74-year-old female. The three cervical ganglia are seen positioned on the longus cervicis muscles. The thoracic ganglia are seen attached to the intercostal nerves by rami communicantes. The distal thoracic ganglia give off splanchnic nerves that pass through the diaphragm to enter the abdominal cavity and innervate the celiac and superior mesenteric ganglia. Finally, the lumbar trunk is seen passing over the psoas muscle

The Sympathetic Trunk and the Lumbar and Sacral Splanchnic Nerves

The Sympathetic Trunk Extends from the Cranial Base to the Pelvic Basin

The sympathetic trunk begins in the cervical region where it lies on the longus cervicis (colli) muscles (Fig. 2.13). As the trunk enters the thorax, it shifts to a position located adjacent to the heads of the ribs. Under the diaphragm in the lumbar region, the trunk moves medially to pass in an arch around the attachment of the psoas muscle on the anterior longitudinal ligament. At the inferior border of the psoas attachment to the anterior longitudinal ligament, the trunk enters the pelvic basin by passing lateral to the sacral promontory and then coursing along the ventral aspect of the sacrum, positioned just medial to the ventral sacral foramina. Deep in the pelvic basin and directly over the coccygeal segments, the left and right sympathetic trunks unite at the ganglion impar reviewed in reference [1, 18, 32].

The Sympathetic Trunk Is Connected to the Spinal Nerves via Rami Communicantes

Each ganglion has a gray communicating ramus that passes between the adjacent spinal nerve and the trunk (Fig. 2.14). The gray rami are a conduit for efferent fibers arising from neurons in the ganglion to reach the spinal nerve. Once intercalated

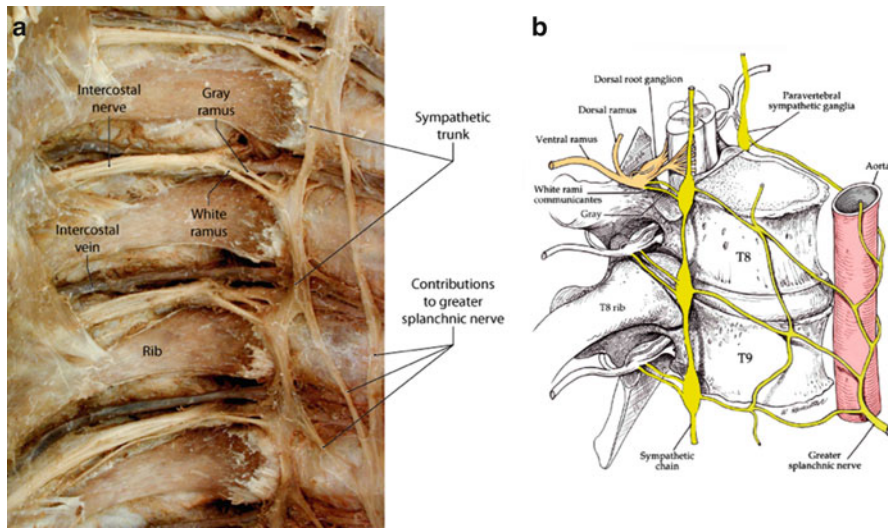


Fig. 2.14 The sympathetic trunk. (a) This is an anterior-oblique view of a dissection of the thoracic sympathetic trunk illustrating the white and gray rami. Figure (b) is a drawing of the thoracic spine demonstrating the relationship between the spinal nerve, sympathetic trunk, and splanchnic nerves. The spinal nerve is located posterior to the body of the vertebra, the sympathetic trunk is lateral to the body, and the splanchnic nerves progress anterior to the body ((b) is modified from [96])

into the spinal nerve, these efferent fibers are carried peripherally to eventually reach their target organs such as smooth muscle of blood vessels and hair follicles as well as the secretory cells in sweat glands. Since all spinal nerves need both vasomotor and secretomotor fibers, there are gray rami at all spinal nerve levels.

Conversely, white rami also pass from the spinal nerve to the sympathetic trunk (Fig. 2.14). These laterally positioned rami act as a passageway for preganglionic axons arising from neurons in the lateral horn of the spinal cord and terminating in either the sympathetic trunk or in a prevertebral ganglion such as the celiac, superior and inferior mesenteric, or hypogastric ganglia. Considering this relationship from the prospective of an individual neuron, a preganglionic motoneuron in the lateral horn of the spinal cord extends its axon through the ventral root to join the spinal nerve and course out of the intervertebral foramen. From the spinal nerve, the axon enters the white ramus to reach the sympathetic trunk. At the point of entry into the trunk, the axon has three options: (1) innervate ganglionic neurons at the level of entry, (2) ascend or descend several levels in the trunk to innervate ganglionic neurons, or (3) leave the trunk by entering a splanchnic nerve and eventually reach a neuron located in a prevertebral ganglion reviewed in reference [1, 18, 32].

The Ganglia in the Sympathetic Trunk Vary Considerably in Size and Function

The trunk has approximately one ganglion for each segment in the thoracic and lumbar regions but only two to three ganglia in the cervical region (Fig. 2.13) and a variable number in the sacral region. The ganglia above T5 tend to be large since they contain the cell bodies for neurons innervating the somatic territories (blood vessels, hair follicles, and sweat glands) and the cell bodies of those neurons innervating the upper thoracic viscera (heart and airways). Below T5, the cell bodies of neurons innervating the abdominal and pelvic viscera have migrated beyond the sympathetic trunk to reach a position surrounding the abdominal aorta. Here, these visceral ganglionic neurons cluster together to form the prevertebral or preaortic ganglia (celiac, superior mesenteric, inferior mesenteric, and hypogastric ganglia).

Communication between the sympathetic trunk and the abdominopelvic prevertebral ganglia occurs through a series of splanchnic (visceral) nerves. The thoracic sympathetic trunk also gives off a series of anteromedially directed thoracic splanchnic nerves (Fig. 2.14) that penetrate the diaphragm to enter the abdomen and reach the celiac and superior mesenteric ganglia. Contributions from thoracic ganglia T5–T9 join together to form the greater thoracic splanchnic nerve; it pierces the crus of the diaphragm and reaches the celiac and superior mesenteric ganglia. Additional small thoracic splanchnic nerves arise from T10 through T12 (often termed lesser and least thoracic splanchnics), but these nerves are inconsistent in nature. Below the diaphragm, the lumbar and sacral portions of the sympathetic trunk also contribute fibers to the abdominopelvic plexus (Fig. 2.15); these contributions are termed lumbar and sacral splanchnic nerves, respectively. As with the thoracic splanchnic nerves, the efferent fibers in the lumbar and sacral splanchnic nerves are preganglionic and terminate by synapsing on a ganglionic neuron located in the prevertebral ganglia such as the superior mesenteric, inferior mesenteric, or hypogastric ganglia. In the female, the hypogastric ganglia are clustered in the endopelvic fascia lying on the transverse cervical ligament and covered by the anterior and posterior sheets of the broad ligament reviewed in reference [1, 18, 32].

Two Routes for Sympathetic Fibers Entering the Pelvis

The sympathetic system for the pelvis has its origin at the thoracolumbar junction involving the lateral horn of spinal cord segments T12–L2. Notably, the ovaries receive sympathetic input from a slightly higher level, around T10–T12, due to their origin from the urogenital ridge. From T12 to L2 levels, fibers can pass through the lower sympathetic trunk and enter the superior hypogastric plexus via a lumbar splanchnic nerve (Fig. 2.15). Once in the plexus, these fibers can descend over the sacral promontory into the pelvic basin to join the inferior hypogastric plexus, ultimately targeting ganglia in the plexus. After leaving the ganglia, sympathetic fibers gain access to individual organs via small branches coursing with the vasculature.

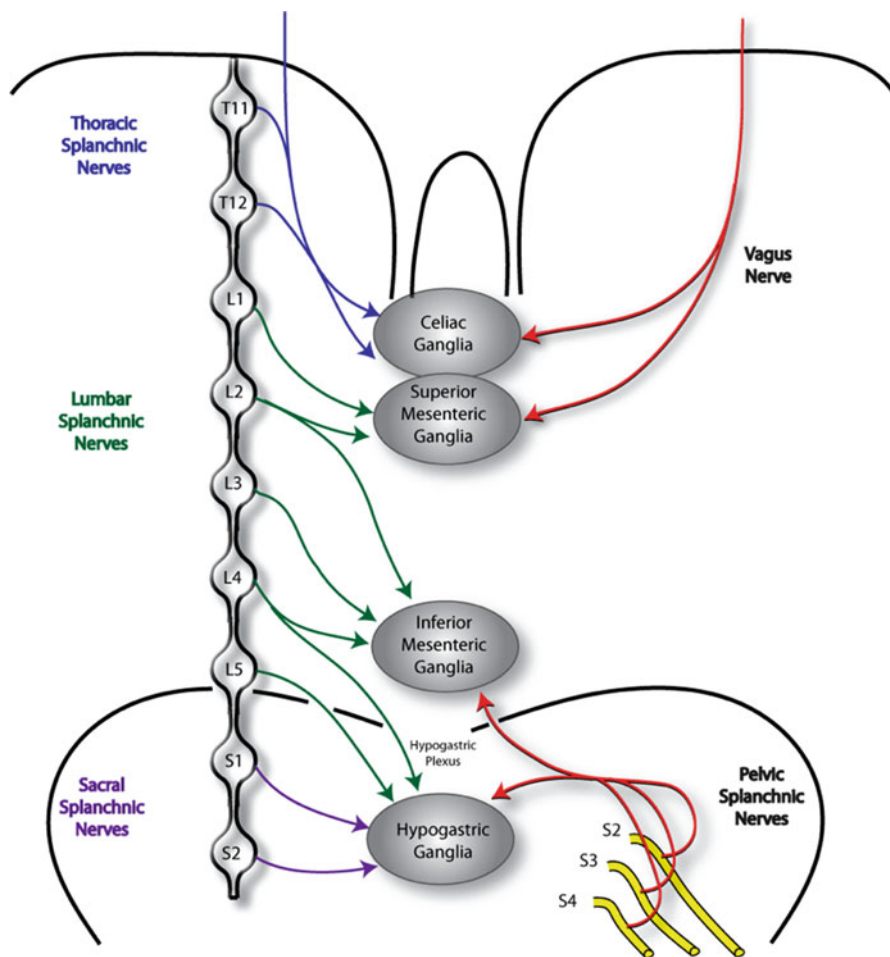


Fig. 2.15 The abdominopelvic autonomic nervous system. The abdominopelvic ganglia are positioned in the center of the diagram. The sympathetic trunk is represented on the *left* and the parasympathetic input on the *right*. The *blue arrows* are thoracic splanchnic nerves. The *green arrows* are lumbar splanchnic nerves, and the *purple arrows* are sacral splanchnic nerves. Even though the lower lumbar and sacral splanchnic nerves arise from the sympathetic trunk below L2, the cell bodies of origin for these nerves are located above L2 in the spinal cord, typically found between T12 and L2

Alternatively, sympathetic fibers from the T12 to L2 spinal levels can remain in the sympathetic trunk as it courses into the pelvic basin, exiting the trunk deep in the pelvis as sacral sympathetic nerves that target the sympathetic ganglia in the inferior hypogastric plexus (Figs. 2.15 and 2.16). In the female, these sacral sympathetic fibers are located in the endopelvic fascia, under the covering of the broad ligament. Importantly, the sacral sympathetic fibers would escape transection if the presacral nerve (hypogastric plexus) were divided in the procedure termed as “presacral neurectomy” typically used for intractable pelvic pain (reviewed in [1, 18, 32]).

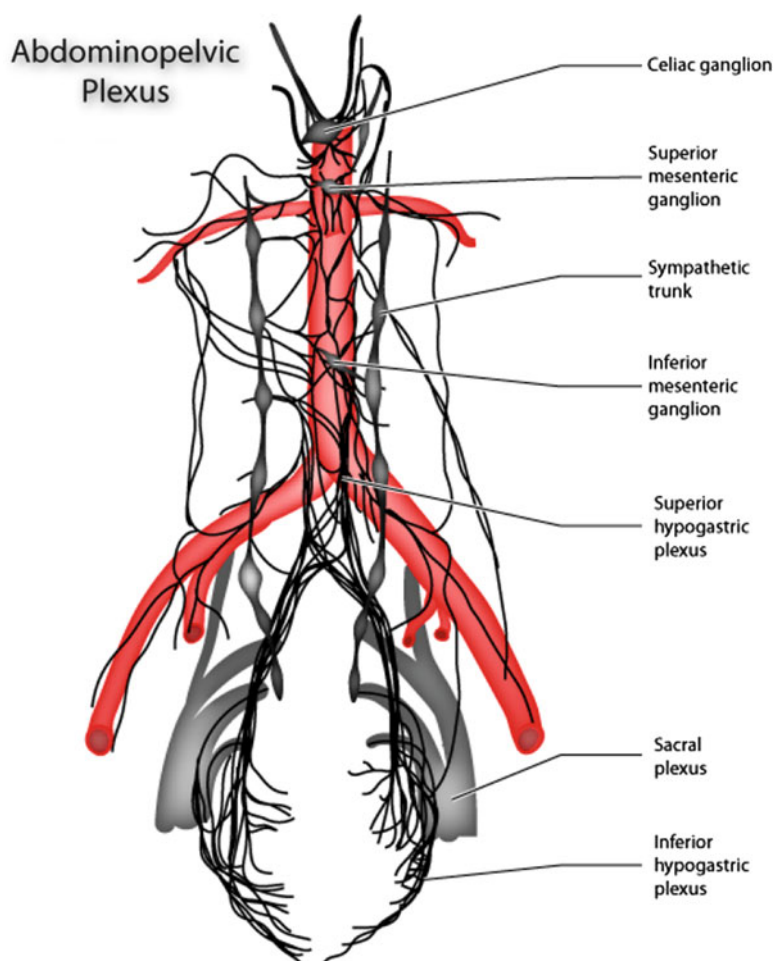


Fig. 2.16 The abdominopelvic autonomic nervous system. The abdominopelvic plexus can be seen as a complex network of fibers wrapped around the anterior and lateral aspects of the abdominal aorta and dividing just below the aorta to course in the endopelvic fascia of the pelvic basin (figure modified from reference [32])

The Pelvic Splanchnic Nerves

The pelvic splanchnic nerves (*nervi erigentes*) are commonly said to arise from the ventral rami of the S2–S4 nerves (Fig. 2.15) [1, 18]; however, these splanchnic nerves actually arise primarily from S3 with only small contributions from S2 or S4, but not both, and typically the secondary contribution comes from S4 only [32]. These parasympathetic nerves contribute fibers to the inferior hypogastric plexus (Figs. 2.16, 2.17, and 2.18), which is also regionally termed the pelvic plexus or Frankenhauser's plexus. It is located in the endopelvic fascia under the broad ligament and positioned on the transverse cervical ligament. The parasympathetic

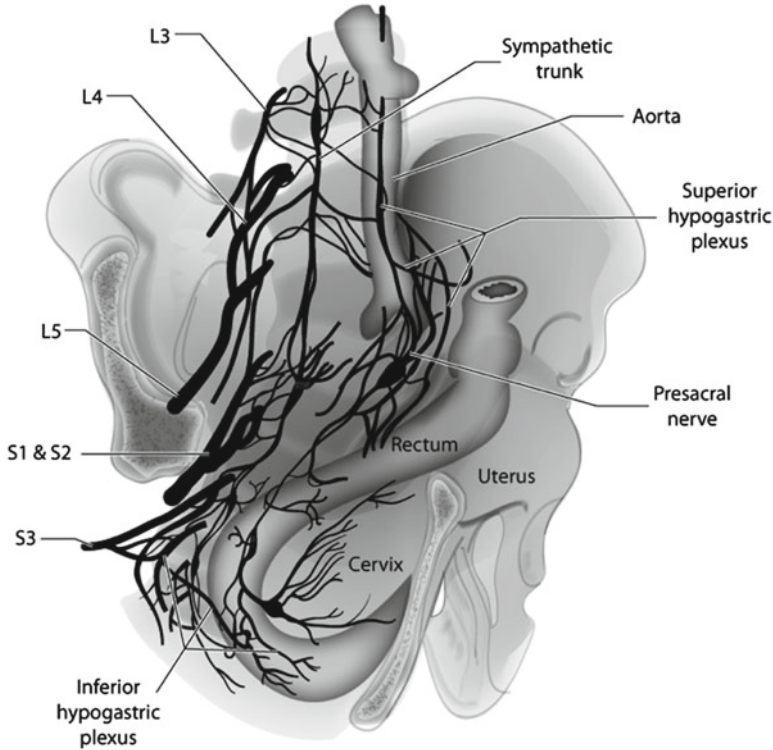


Fig. 2.17 The pelvic autonomic nervous system. This is a lateral oblique view of the female pelvis with the hypogastric plexus illustrated. The L3–S3 spinal nerves receive gray rami from the sympathetic trunk. The trunk also transmits small sacral splanchnic nerves into the hypogastric plexus. This plexus is seen along the walls of the pelvic organs (Figure modified from [32])

fibers pass through the plexus and target neurons located in ganglia on the walls of the rectum, uterus, or urinary bladder. The postganglionic fibers from these ganglia invade the layers of the target organ innervating smooth muscle and glands (reviewed in [1, 18, 32]).

The Great Abdominopelvic Plexus

The autonomic nerves and associated sensory fibers form a large plexus that extends from the thoracoabdominal diaphragm to pelvic diaphragm. This interwoven structure lies in the visceral fascia of the posterior body wall anterior to the aorta, in close juxtaposition with the aorta and its three unpaired visceral branches (Fig. 2.16): the celiac, superior mesenteric, and inferior mesenteric arteries. Clusters of prevertebral ganglia are embedded in the plexus, typically surrounding the three unpaired visceral arteries (reviewed in [1, 18, 32])

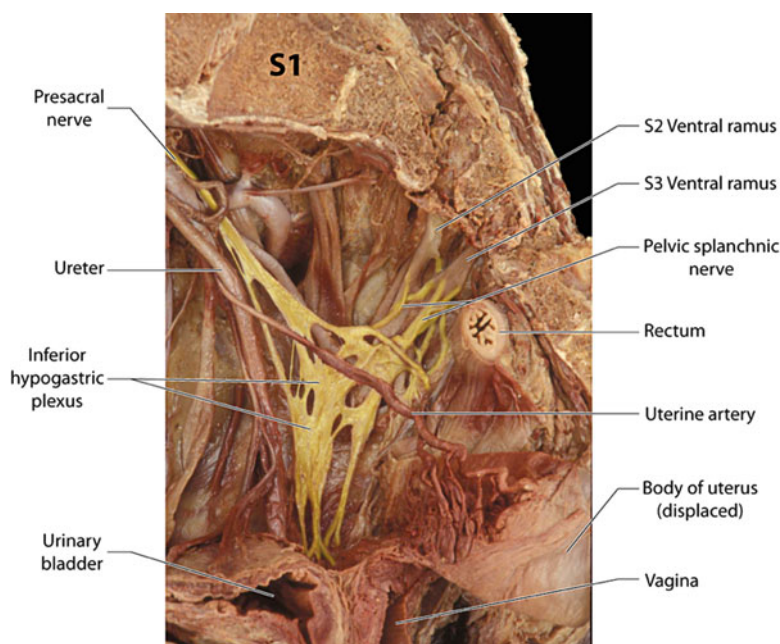


Fig. 2.18 The hypogastric plexus. This is a medial view of a sagittal section through the pelvis of a 54-year-old female. Her uterus has been displaced medially, and the broad ligament and underlying endopelvic fascia have been removed to reveal the inferior hypogastric plexus. Superiorly, the presacral nerve approaches the plexus, and inferiorly the plexus extends to the lateral wall of the bladder and the cervix by passing over the transverse cervical ligament. Posteriorly, the pelvic splanchnic nerves are seen approaching the plexus

The great abdominopelvic plexus is divided into four midline regions: celiac, superior and inferior mesenteric, and superior hypogastric plexuses located in the abdominal cavity and a fifth region in the pelvic basin, an inferior hypogastric plexus that is present laterally (Figs. 2.16 and 2.17). The distal end of the superior hypogastric plexus can taper to form a solitary band of fibers often termed the presacral nerve that passes over the sacral promontory. Opposite the body of S1, this structure divides into two laterally positioned regions [33] termed the inferior hypogastric plexus (Figs. 2.16 and 2.18). Rarely does the presacral nerve present as a well-defined structure. More typically, it is a broad tangled mass of multiple fiber bundles as seen in Fig. 2.17. The inferior hypogastric plexus lies in the endopelvic fascia on either side of the three midline pelvic organs – the rectum, the uterus, and the bladder. The plexus is covered by the broad ligament in the female. Posteriorly, the plexus receives sympathetic contributions through the tiny sacral splanchnic nerves derived from the sympathetic trunk as well as parasympathetic contributions from the larger pelvic splanchnic nerves, which branch directly from the S3 ventral ramus with additional small contributions from either S2 or S4 (Fig. 2.15; (reviewed in [1, 18, 32])).

Visceral Afferent Fibers in the Pelvic Basin

All of the various autonomic routes into the pelvic basin also serve as pathways for afferent or sensory fibers to return to the spinal cord. Typically, these visceral afferent fibers respond to noxious activity and convey the sense of pain.

Sensory fibers can often be identified in peripheral tissue by the presence of typical neurosecretory peptides such as substance P (SP), calcitonin gene-related peptide (CGRP), nitric oxide synthase (NOS), and vesicular acetylcholine transporter (VACHT). However, as of this writing, there are no specific neurochemical markers for visceral afferent fibers [35]. Most visceral afferent fibers are small unmyelinated fibers that end with a naked nerve ending [27] and are associated with A delta and C fibers [36].

Type of Stimuli Eliciting a Response from Visceral Fibers

Uniquely, visceral afferent fibers are generally unresponsive to most of the tissue-damaging stimuli that would occur in a surgical situation. Instead, these sensory fibers respond typically to pressure and distension as well as to changing tissue chemistry such as an increase in proinflammatory compounds [34]. Regardless of the type of stimulus, the predominant perception of visceral fiber activity appears to be pain and discomfort.

Both low- and high-threshold mechanoreceptors responding to pressure or distension are documented; the high-threshold fibers are most likely to be visceral nociceptors. The low-threshold fibers may not reach consciousness when activated by non-noxious stimuli; however, as the stimulus intensity rises into the noxious range, the discharge rate increases significantly, suggesting that when sufficiently activated the low-threshold fibers become nociceptors as well [35].

Chemical and thermal receptors are also present in pelvic organs but have not been studied as well as the mechanoreceptors. Chemoreceptive and mechanosensitive afferent fiber systems are present in the muscularis of the urinary bladder and involve sensory peptides derived from the urothelium [36]. Small-caliber, peptide-containing sensory fibers have been described in the myometrium and endometrium of the uterus [37], as well as in the mucosa, submucosa, muscularis, and serosa of the distal colon [38]. Visceral chemoreceptive fibers and some mechanoreceptive fibers respond to the typical proinflammatory substances or to common products of ischemia such as protons, histamine, bradykinins, prostaglandin E₂, serotonin, and potassium [35]. A category of visceral fibers has been described that will not respond to mechanostimulation unless they have been exposed to an inflammatory chemical soup. Following such exposure, the fibers sensitize and lower their thresholds of activation. These fibers have been termed silent or sleeping nociceptors [34].

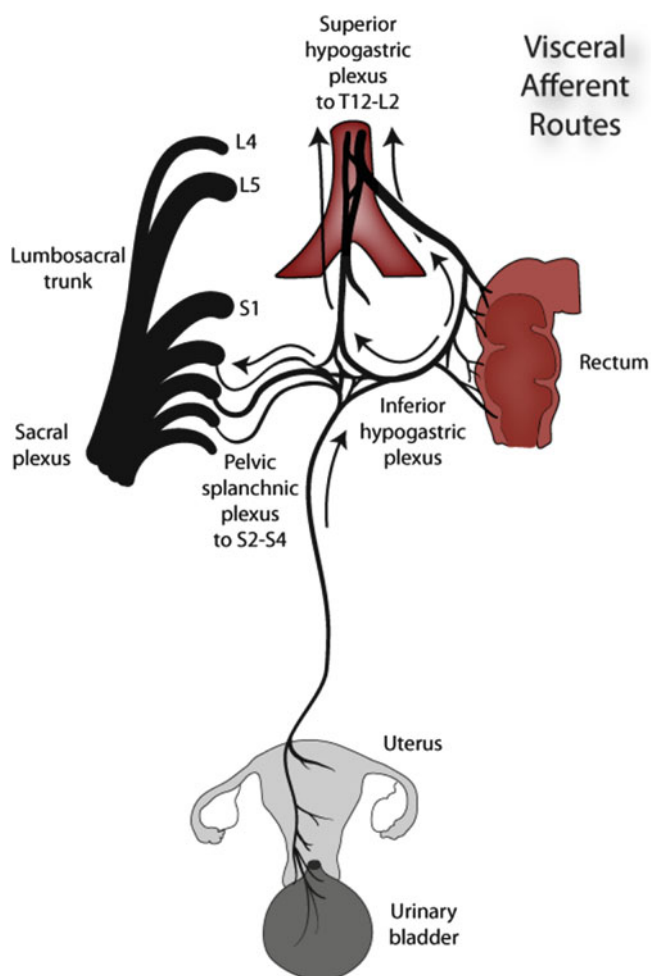


Fig. 2.19 The visceral afferent pathways of the hypogastric plexus. This diagram illustrates the flow of visceral afferent (sensory) information through the hypogastric plexus. Sensory fibers from the bladder, uterus, and colon project into the hypogastric plexus. From here, fibers can either approach the sacral spinal cord through the pelvic splanchnic nerves (*to the left*) or ascend in the hypogastric plexus to the T12–L2 level where they can use a white ramus to access the spinal nerves and the spinal cord (Figure modified from [95])

Pelvic Visceral Afferent Fibers Reach the Spinal Cord Through Several Routes

All visceral afferent fibers arising in the pelvic basin eventually reach the spinal cord by passing over a spinal nerve (Fig. 2.19). Those coursing in pelvic splanchnic nerves enter directly into the cord from spinal nerves S3 and S4. Visceral afferent

fibers in the sacral splanchnic nerves enter the sympathetic trunk and ascend to the L1–L2 level before passing through a white ramus to enter the spinal cord. Finally, visceral afferent fibers in the hypogastric plexus pass upward out of the pelvic basin, access a lumbar splanchnic nerve at L1–L2, and join the associated spinal nerves also by passage over a lumbar white ramus.

There appears to be a distinction between the input accessing the spinal cord at the thoracolumbar junction and that entering in the midsacral region. In experimental situations focused on the gastrointestinal tract, acute hollow-organ distention will strongly activate neurons in the sacral region (and brainstem vagal nuclei), whereas inflammation in the viscera activates dorsal horn neurons in both thoracolumbar and sacral regions, as well as vagal nuclei [39, 40].

Studies on the reproductive system in the rat have also documented a distinction between visceral input to the thoracolumbar and lumbosacral spinal cord [41]. Sensory fibers from the uterus and adnexal tissue typically course upward out of the pelvic basin in the hypogastric plexus to reach the thoracolumbar spinal cord, while sensory fibers from the vaginal canal gain access to the sacral spinal cord through the pelvic splanchnic nerves. The cervix is the watershed zone; from here, afferent fibers can pass to the spinal cord through both routes.

Evidence suggests that uterine nociception will pass through the hypogastric plexus in acute situations in otherwise normal rats or humans. However, in the setting of existing pathology, afferent signals from the uterus may utilize both the hypogastric plexus and the pelvic splanchnic nerves to access the spinal cord (Fig. 2.20) [42]. In behavioral studies, sensory experiences related to mating and conception were more likely to activate primary afferent fibers in the sacral nerve roots, while those involved in pregnancy and nociceptive events were more likely to activate primary afferent fibers in the hypogastric plexus traveling to the thoracolumbar spinal cord. This pattern of neural activation is in agreement with the neuroanatomy of the rat reproductive organs: the tissue below the cervix projects heavily through the pelvic splanchnic nerves, the tissue above the cervix projects sensory fibers through the hypogastric plexus, and the cervical tissue sends afferent fibers through both routes.

Pelvic Visceral Afferent Fibers Terminate in the Spinal Cord

Three observations characterize the central termination of visceral afferent fibers [34]:

1. Although few in number compared to somatic afferent fibers, visceral fibers are more divergent upon entering the spinal cord, thereby contacting multiple dorsal horn neurons.
2. Visceral afferent fibers ascend and descend many more levels than typical somatosensory afferent fibers.
3. Almost all visceral afferent fibers are convergent on dorsal horn neurons that also receive somatic primary afferent fibers.

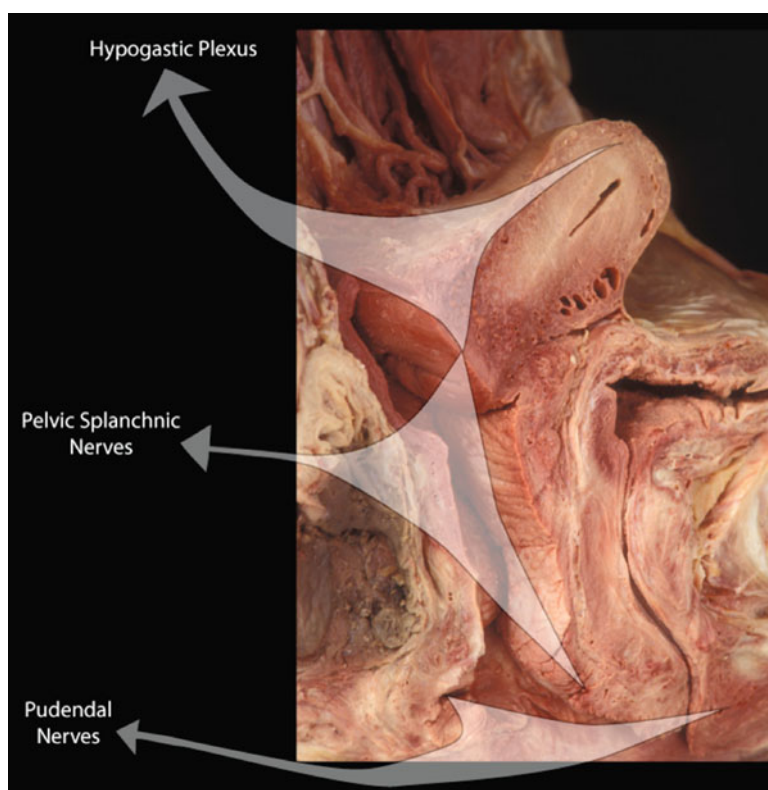


Fig. 2.20 Visceral pain pathways about the reproductive organs of the pelvis. This is a posterior-oblique view of a sagittal section of the uterus, cervix, and vagina in a 54-year-old female. The *arrows* indicate the differential flow of sensory information from these reproductive organs as described by Ruch [29]

All visceral primary afferent fibers from the pelvic basin have their cell bodies located in the dorsal root ganglia of either the thoracolumbar segments or the middle sacral segments; their central processes terminate in the dorsal and intermediate (lateral) horns of the spinal cord. As a given dorsal root approaches the spinal cord, its fibers segregate into a medial division of large fibers and a lateral division of small fibers (Fig. 2.21). The medial division fibers are well myelinated and enter into the dorsal columns, while the lateral division consists of lightly myelinated and unmyelinated fibers that enter the apex of the dorsal horn. The visceral afferent fibers are contained in the lateral division; thus, they enter the dorsal horn directly. Some of these fibers terminate in laminae I and II. However, most pass deep into the dorsal horn to terminate in lamina V, as well as in the base of the lateral horn. Finally, a few fibers extend medially to reach the area around the central canal in lamina X [43]. Visceral fibers appear to avoid much of the inner portion of lamina II and all of lamina III.

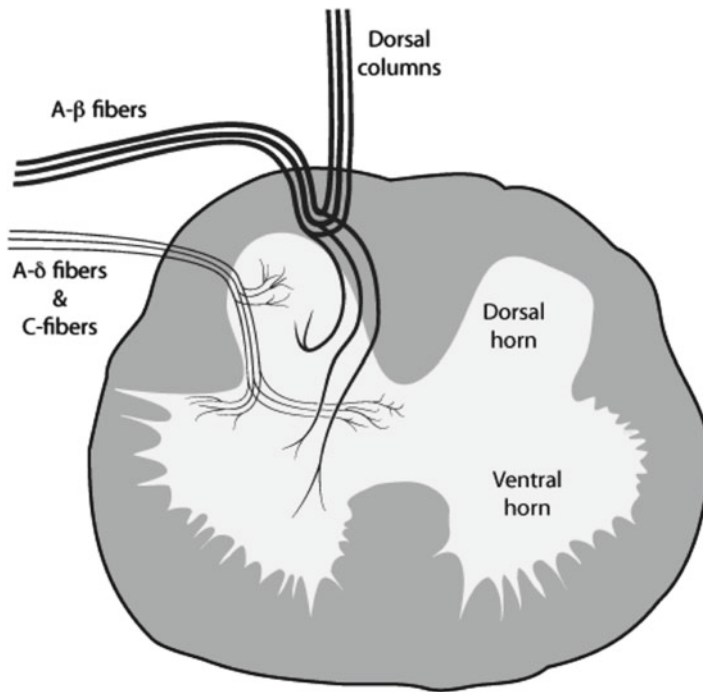


Fig. 2.21 The spinal terminations of primary afferent fibers. This is a schematic drawing of a lumbosacral spinal cord section illustrating the termination of collateral branches from large myelinated fibers and small lightly myelinated and unmyelinated fibers in the dorsal horn

Although visceral fibers in the dorsal roots are few in number (5–15%), a large percentage of spinal cord neurons respond to visceral afferent stimuli, suggesting wide-ranging distribution of visceral primary fibers in the spinal gray matter [44]. The primary afferent endings in the deep portion of the dorsal horn and the lateral horn are of much interest since it is here where visceral fibers converge with those of the somatosensory system. The distribution of visceral afferent fibers is similar to the distribution of small-caliber fibers from the deep somatic tissues such as bone, joint, and muscle [45]. However, somatic input is generally restricted to a narrow range of segments, while visceral fibers typically distribute over a wide range of segments [25]. Extensive convergence occurs between most visceral afferent systems and the deep somatic afferent systems, but there is ample evidence for viscerovisceral convergence in the dorsal horn as well [34].

A Viscerotropic Map Is Present in the Spinal Cord

A general relationship exists between the organ position in the body cavity and its innervation level in the spinal cord; this relationship forms the basis for a viscerotome. Viscerotomes are embryologically determined as detailed by Ness and Gebhart

[46]. Since significant movement of organ systems occurs during development, the arrangement of viscerotomes is not in register with the surrounding somatotomes.

In the human, the viscerotomes are initially studied by fine anatomical dissection and confirmed by examining patterns of evoked or pathological referred pain from the organ of concern. Considerable overlap exists between viscerotomes for anatomically related organs; thus, the viscerotropic maps are not precise and much viscerovisceral convergence in the spinal cord occurs. Dorsal horn neurons in each viscerotome also receive input from primary afferent fibers of somatic origin; this somatovisceral convergence is thought to underlie the existence of numerous referred pain patterns [28].

Spinal Cord Processing of Nociception from Pelvic Afferent Fibers

The patterns of neuronal activity in the dorsal horn following noxious stimulation of some visceral organs have been studied and found to share some common features with those involving somatic input [40]. The organs studied are mainly found in the gastrointestinal system and in the urinary tract. Three fundamental response patterns are seen: abrupt-onset neurons, sustained neurons, and inhibited neurons. The abrupt-onset neurons appear to be stimulus-bound, activating with the onset of the stimulus and ceasing with the stimulus offset.

Sustained neurons take longer to build to a crescendo (seconds) but will continue to discharge after cessations of the stimulus. Inhibited neurons typically cease their spontaneous activity in response to a noxious stimulus.

The activity of both abrupt and sustained neurons can be affected by modulation of the NMDA (N-methyl-D-aspartate) and AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) receptors, two receptor types known to be involved in the process of sensitizing dorsal horn neurons to noxious somatic stimuli [40]. The involvement of NMDA and AMPA chemistry with visceral spinal systems has prompted the suggestion that visceral hypersensitivity may utilize pathways similar to those of the well-documented central sensitization and hypersensitivity seen following repeated noxious somatic stimuli [43].

Sensitization of Primary Afferent Fibers and Their Central Pathways

When primary afferent fibers receive excessive stimuli such as in inflammation or extreme mechanical stimulation, they can undergo a process of sensitization in which their thresholds for activation drop and their response to a given stimulus increases [47, 48]. It is now clear that sensitization can occur, not only at the dorsal horn, but also at multiple levels in the nervous system [49]. Peripheral sensitization can produce an expanded local area of increased sensitivity, a process termed peripheral sensitization.

Spinal cord neurons receiving excessive input from a given peripheral fiber or convergent inputs from multiple peripheral fibers can undergo a process of central sensitization, which can produce hypersensitivity in a whole region of a body such as in a portion of a limb or a complete limb [50]. Evidence is accumulating to support the concept that sensitization may also occur at a higher level in the central nervous system such as in the anterior cingulate cortex [51] and the amygdala [52]. Such forebrain sensitization can result in hyperresponsiveness expressed throughout the entire system, a process that may be involved in such diffuse pain disorders as fibromyalgia.

That sensitization can occur involving the visceral sensory system has been suggested in numerous studies. In one such example, repeated stimuli delivered to a healthy organ can lead to increasing intensity of perceived pain [44]. The existence of sensitization at multiple levels in the somatic and visceral sensory systems can explain some of the progressively worsening patterns of chronic pain that can accompany dysfunction in the somatic and visceral pelvis.

Influence of Visceral Afferent Fibers on the Dorsal Horn of the Spinal Cord

A strong interaction exists between the visceral and somatic sensory systems in the dorsal horn of the spinal cord. Most dorsal horn neurons with receptive fields in the viscera can also be activated by somatic stimuli; thus, the visceral sensory system of the spinal cord is almost completely convergent with somatic systems. The combination of the two or more differing forms of input – one of visceral and one of somatic origin – to a population of dorsal horn neurons could contribute to enhanced sensitization and facilitation through a mechanism such as that described for somato-somatic convergence by Zimmermann [53]. Furthermore, cross-reaction between visceral organs can occur; repetitive stimuli delivered to one organ can lead to sensitization of surrounding organs such as repetitive noxious stimuli applied to the sigmoid colon sensitizing the rectum to innocuous stimuli [54].

Convergence of somatic (skin and muscle) and visceral information on visceroreceptive neurons in the dorsal horn is a key characteristic of referred pain [28] and of viscerosomatic reflexes [35] such as the paraspinal muscle spasms seen associated with strong input from experimentally induced inflammatory events in the rat uterus [55, 56]. Observations in humans document the presence of somatic hyperalgesia and trophic changes secondary to intense visceral noxious stimuli from the urinary bladder suggesting the presence of viscerosomatic reflexes [25, 57]. In fact, the degree and location of somatic response appear to be strongly related to the underlying visceral dysfunction. The longer the chronic pain patterns exist, the greater the degree of change in the associated somatic tissue, and the location of the somatic change appears to map closely to the appropriate viscerotomes [58]. Some of the somatotrophic and vasodynamic changes reported following both acute and chronic uterine or bladder pain patterns may have their origin in a series of dorsal root reflexes such as those described by Sluka and Willis [59, 60].

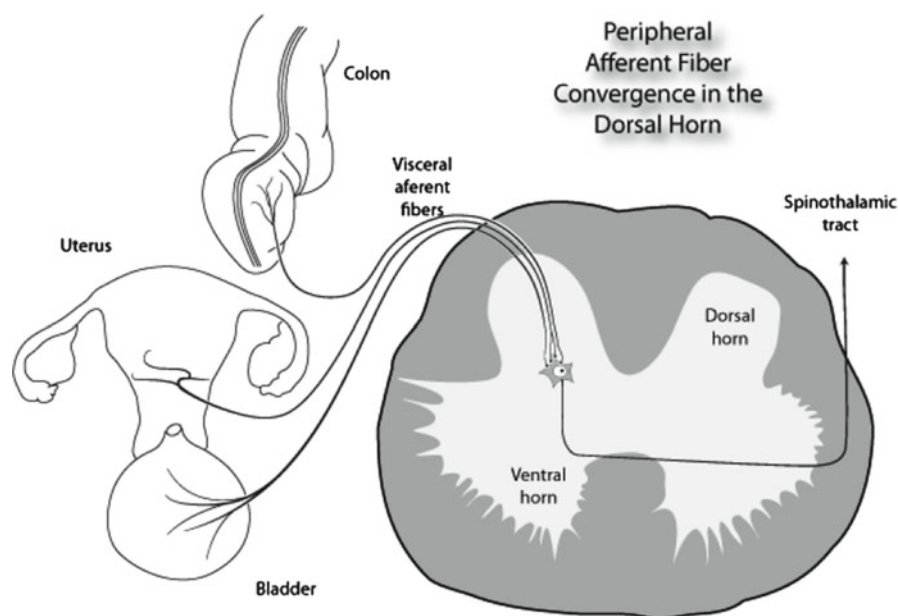


Fig. 2.22 The convergence of visceral afferent pathways in the dorsal horn of the spinal cord. This is a schematic diagram of the lumbosacral spinal cord illustrating the convergence of multiple small-caliber fiber systems on neurons in the deep portions of the dorsal horn. This convergence is thought to underlie the cross-organ interactions seen in specific pain patterns [63]

Along with cross talk between visceral and somatic systems, there appears to be ample evidence for viscerovisceral interaction (Fig. 2.22). The clinical observation that dysfunction in one internal organ can enhance the pain and hyperalgesia generated by a second organ has long been known [61]. The transient increase in pain perception associated with specific stages of the menstrual cycle is well documented [56]; specific examples include the exacerbation of discomfort in associations between irritable bowel syndrome and dysmenorrhea or between dysmenorrhea and urinary calculus. Suggested mechanisms for viscerovisceral cross-talk include such processes as the spread of neurogenic inflammation between organs of close juxtaposition, the sensitization of peripheral afferent fibers and their convergence onto common neurons in the dorsal horn, the sensitization of visceroreceptive neurons in the spinal cord, and the development of sensitized convergent neurons in brainstem, thalamus, or forebrain structures such as the amygdala [62].

In the reproductive organs, experimentally induced inflammation of the uterus in a rat resulted in signs of enhanced inflammation in surrounding non-treated organs such as the urinary bladder; this response was abolished by section of the hypogastric plexus [63]. Based on these results, it would appear that at least a portion of the cross talk between organ systems in the pelvis involves a neural reflex through the hypogastric plexus and the release of proinflammatory substances in the non-treated organ supports a mechanism utilizing dorsal root reflexes.

Ascending Pathways Involved in Pelvic Pain

Anterolateral System

The classical ascending pathway for somatic nociception involves the synaptic termination of the primary afferent fiber in the dorsal horn (Fig. 2.23). The postsynaptic neuron sends its axon through the anterior white commissure to the contralateral

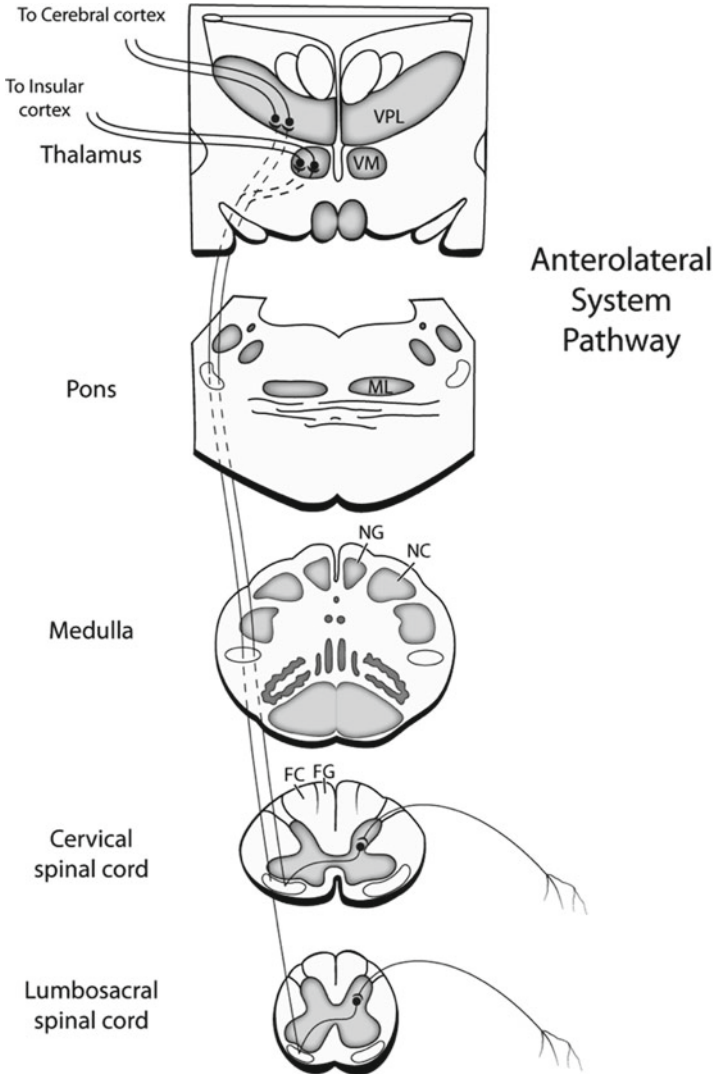


Fig. 2.23 The anterolateral system. This is the classic system of ascending information in the small-fiber systems of the spinal cord such as that derived from A delta and C fibers (Figure modified from [97])

anterolateral system at or slightly above the level of the dorsal horn neuron. Axons in the anterolateral system ascend to terminate in the medulla, pons, midbrain, hypothalamus, and thalamus. In the medulla, a major target of ascending somatic and visceral sensory information is the solitary nucleus of the vagal complex [64]; however, much of this input is related to reflex actions as opposed to nociception and pain perception.

Although some visceral nociceptive information ascends in this classic spinothalamic system to the thalamus, it does not appear to be the major route for this information from the pelvis. Instead, a significant portion of the pelvic nociceptive input ascends the spinal cord close to the midline in a postsynaptic dorsal column pathway [65–67].

Postsynaptic Dorsal Column System

The dorsal columns of the spinal cord have long been described as carrying the axons of well-myelinated cutaneous touch receptors whose cell bodies are found in the ipsilateral dorsal root ganglia (Fig. 2.24) [68]. However, a postsynaptic system present in the dorsal columns has also been well documented in the literature [69]. For example, many fibers of sacral origin in the dorsal columns appear to arise not from dorsal root ganglion cells but from ipsilateral dorsal horn neurons and to be involved with nociceptive visceral sensory information. Since the visceral pathway has a synapse present in the dorsal horn, it is termed a postsynaptic pathway.

The postsynaptic pathway appears to be topographically organized similar to the myelinated fibers of the dorsal columns; that is, thoracic fibers near the dorsal intermediate septum and the sacral fibers project medially in the fasciculus gracilis to the nucleus gracilis (Fig. 2.25) [70]. Pelvic splanchnic nerve input to the sacral spinal cord is relayed through dorsal horn neurons that project axons upward to reach the nucleus gracilis; from here, a second synaptic relay occurs to the ventroposterior lateral thalamic nucleus (VPL) [71]. Neurons in and around the VPL were responsive to both colorectal distention and cutaneous touch suggesting convergence of visceral and somatic input into these forebrain neurons [65, 72].

Experimental inflammation of the colon resulted in facilitation of the VPL neurons to noxious colorectal distension but did not significantly change the response of these neurons to cutaneous stimuli [73]. The presence of the postsynaptic dorsal column pathway for visceral pelvic pain helps explain the amelioration of intractable pelvic pain patterns following midline myelotomies in the lower thoracic region that damaged the medial aspect of the fasciculus gracilis [70].

Hormonal Associations

A growing body of evidence supports the concept that a sexual dimorphism exists in the perception of pain and that females, as a group, are more sensitive to pain and more prone to developing various chronic pain syndromes [40, 74, 75].

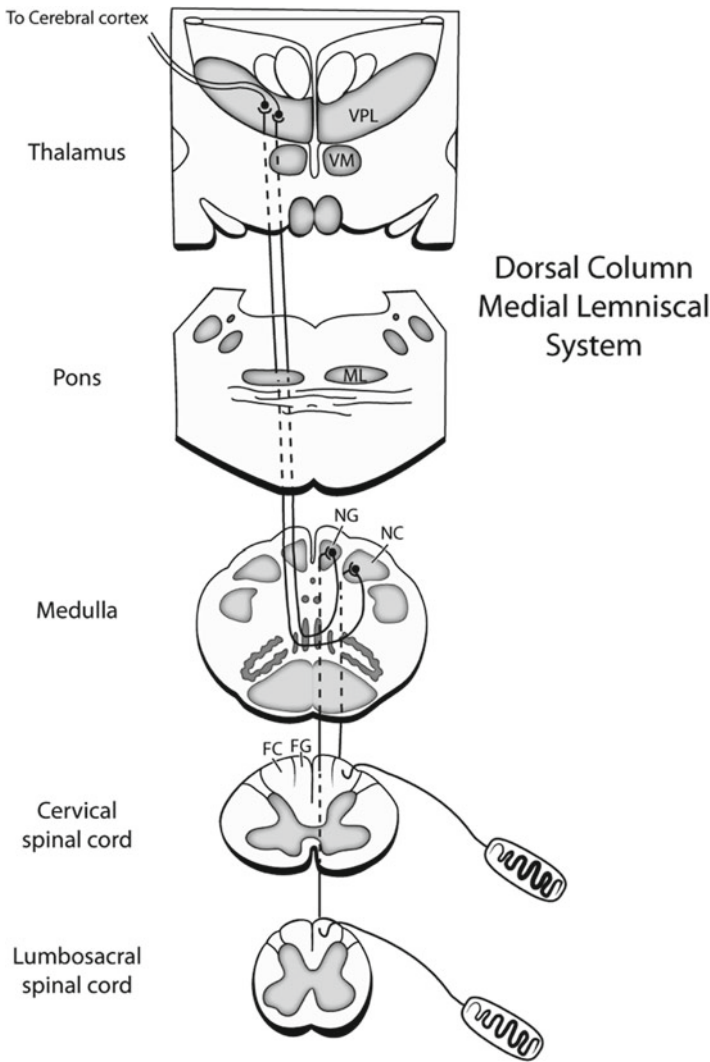


Fig. 2.24 The dorsal column-medial lemniscal pathway. This is the classic system of ascending information in the large-fiber systems of the spinal cord such as that derived from the A beta cutaneous touch corpuscles (Figure modified from [97])

The pathophysiology for this sexual dimorphism is yet to be clearly defined. Along with the influence of sex steroids, consideration must also be given to other factors such as age, environment, history of physical or emotional abuse, and comorbid conditions like sleep disorders. To date, however, there exists strong evidence pointing to a significant role of the estrogens in increasing the sensitivity of primary afferent nociceptors as well as dorsal horn neurons in the spinal cord (see Chap. 1).

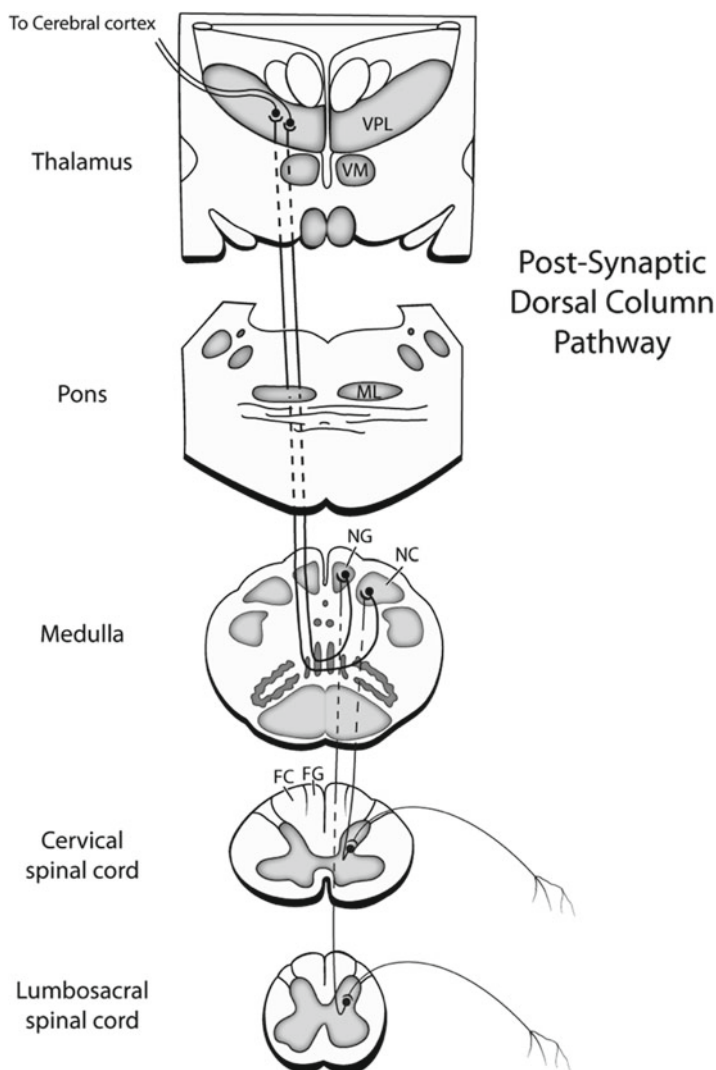


Fig. 2.25 The postsynaptic dorsal column pathway. Compare this diagram to that of Fig. 2.24; in the postsynaptic pathway, dorsal horn neurons receive information from small-caliber visceral afferent fibers and project their axons upward in the dorsal columns to reach the dorsal column nuclei in the medulla. Although the dorsal columns were traditionally thought of as carrying discriminative sensory information and proprioception, it is now apparent that they also carry visceral noxious sensations in the postsynaptic pathway as well (Figure modified from [97])

Estrogen receptors are present on cells that are involved in the peripheral as well as spinal and forebrain mechanisms for processing nociceptive information. Although much of the experimental work was done using colorectal distension as a model, several studies have addressed the suppressive influence of estrogen on the

ability of morphine to attenuate the reflex responses generated by uterine-cervical distention [76].

A strong argument supporting the role of sex steroids in increased sensitivity to noxious stimuli is found in the fluctuation of sensitivity with the phase of the menstrual cycle [63, 75]. Interestingly, in the study by Winnard and coworkers, the experimentally induced inflammation in one pelvic organ induced inflammation in other pelvic organs. This reflex response was dependent on the intact condition of the hypogastric plexus and varied in potency with the phase of the estrous cycle in the rat. This neuronally dependent, cross-organ spread of inflammation supports a possible role for dorsal root reflexes and suggests that the neurogenic inflammatory process may be strongly modulated by sex steroids.

It is known that estrogens have a diverse influence on many of the biological pathways leading to inflammation and nociception [74]. Although there is a large body of information supporting the concept that estrogen can enhance sensitization to a noxious stimulus [40], it is not certain where this enhancement occurs: in the periphery of the nervous system, in the spinal cord, at supraspinal levels, or in some combination of all levels. However, it is becoming apparent that the mechanism behind this relationship between sex steroids and pain perception is intimately tied to how the brain processes pain, and our knowledge of that field is just beginning to crystallize.

Forebrain Areas Involved in Pelvic Pain

Nociceptive input from various tracts in the spinal cord relays through the thalamus, eventually to be mapped on the cerebral cortex. The distribution of forebrain areas that demonstrate altered neural activity to a painful stimulus has been termed a body-self neuromatrix for the integration of the multiple inputs resulting in the perception of pain [77] or simply “central pain matrix” [78, 79].

The processing of nociceptive information and the generation of the feelings of pain can be thought of as involving three separate but interconnected aspects of the forebrain pain matrix:

Sensory/discriminative
Cognitive/behavioral
Affective/motivational

While the first component (sensory/discriminative) allows for the localization and description of the pain, the second component (cognitive/behavioral) allows for the understanding of the pain. The third component (affective/motivational) brings in the emotional aspect of the pain, relating the current pain to past experiences and feelings.

Significant numbers of studies have examined the pain matrix created by noxious stimuli expressed on somatic tissue [48, 80]. The forebrain regions responding most reliably to noxious somatic stimuli include primary and secondary somatic

sensory cortex, motor cortex, supplementary motor cortex, insular cortex, anterior portions of the cingulate cortex, posterior parietal cortex, prefrontal cortex, thalamus, as well as regions involving the amygdala and less often the basal ganglia and cerebellum [79]. To date, the few studies examining visceral pain representation in the forebrain show a fundamental pain matrix of cortical activity that is essentially the same for either somatic or visceral stimuli with certain differences [81].

The distinctions between evoked neural patterns from somatic and visceral noxious stimuli of matched perceived intensity are focused on intensity of neural response rather than its forebrain location. Thus, visceral noxious stimuli tend to produce more activity in such areas as the insular cortex and the anterior cingulate cortex, both regions known to be involved in the autonomic response and the emotive response, respectively, to harmful or potentially harmful stimuli [34].

It is apparent that visceral pain is more adept at activating the affective/motivational component of the pain matrix. This is in line with the observations that visceral stimuli are better at evoking an emotional response than equivalent somatic stimuli [56]. A significant structure of the affective/motivational component is the amygdala [82], a region of the brain associated with negative feelings, fear memories, and a strong drive on numerous brainstem regions including the arousal system.

Amygdala

The amygdala is located in the medial portion of the temporal lobe, rostral to the hippocampus, and is composed of multiple nuclei whose precise borders are still in dispute [83]. The role of the amygdala in receiving adverse stimuli and generating a fear response is becoming reasonably well known [84, 85]. Of particular interest is the spinal input to the amygdala related to nociception [82, 86].

Spinal input to portions of the amygdala can facilitate neurons, resulting in a change of activity that is essentially a form of central sensitization. This response is similar to the central sensitization that occurs in the dorsal horn of the spinal cord to an intense nociceptive stimulus and has been described as sensitization at a supraspinal level. Importantly, the sensitization in the amygdala has been seen to accompany visceral pain paradigms [87] as well as arthritic pain [88] and neuropathic pain [89]. The anatomy, connectivity, and response properties of the amygdala strongly support a role for this region of the forebrain in the emotional-affective dimension of pain.

Descending Pathways Regulating Pelvic Pain

The transmission of nociceptive information through the spinal cord and into forebrain structures is modulated by a complex array of descending systems capable of

significantly controlling the amount of pain experienced by the individual [90–93]. One of these descending systems involves the midbrain (periaqueductal gray) and the rostral ventromedial medulla, while a second descending system arises dorsolaterally at the pontomedullary junction and includes such structures as the locus coeruleus (adrenergic fibers). Both of these pathways contain axons that terminate in the dorsal horn of the spinal cord and can influence the transmission between primary afferent fibers and second-order ascending tract neurons. Interestingly, in the descending system from the rostral ventromedial medulla, there are neurons present that can either suppress nociceptive transmission in the dorsal horn (OFF-cells) or facilitate nociceptive transmission (ON-cells).

Thus, the so-called endogenous pain control systems can function to either suppress the processing of nociceptive information at the spinal cord level reducing the pain experience or to enhance this transmission, thereby making the patient experience more pain [90–93]. Recent experimental studies suggest that the brainstem nuclei controlling the descending systems can become facilitated consequent to prolonged stimulation in a manner similar to that seen in the sensitization of dorsal horn neurons. In such a case, it has been suggested that facilitation of that portion of the system that enhances the perception of pain could be an important step in the development of persistent or chronic (maldynic) pelvic pain patterns [92].

Finally, what controls the pain control systems? From numerous studies, it appears that the brainstem nuclei involved in the modulation of pain receive their input in part from such regions as the hypothalamus, amygdala, and anterior cingulate cortex. Through this organization, the emotional portion of the brain can exert a direct influence over our perception of pain [82].

Since the activity of such regions as the amygdala and cingulate cortex is a summation of a lifetime of experiences, it allows the past to strongly color our perception of current events. Painful stimuli are known to activate the amygdala and contribute to its facilitation. In this fashion, a mildly painful event – which would otherwise pass with little attention or concern – when imposed on sensitized neurons in the amygdala could become grossly magnified through enhanced processing of nociceptive information in the spinal cord. The resultant enhanced ascending input to the amygdala further increases anxiety as well as facilitates obsession with the pain. This represents a feed-forward situation, increasing the facilitation in the forebrain and exacerbating and prolonging the pain pattern (Fig. 2.26).

Thus, past emotional events such as trauma or abuse could, through a process of facilitation at multiple levels in the nervous system, drive, in part, both the initiation of pain patterns as well as the development of persistent pain from pelvic dysfunctions (see Chap. 11). Finally, through the close connections between the amygdala and the prefrontal cortex, especially the ventromedial and orbital portions, emotional activity can influence cognitive decisions and alter patterns of behavior [94].

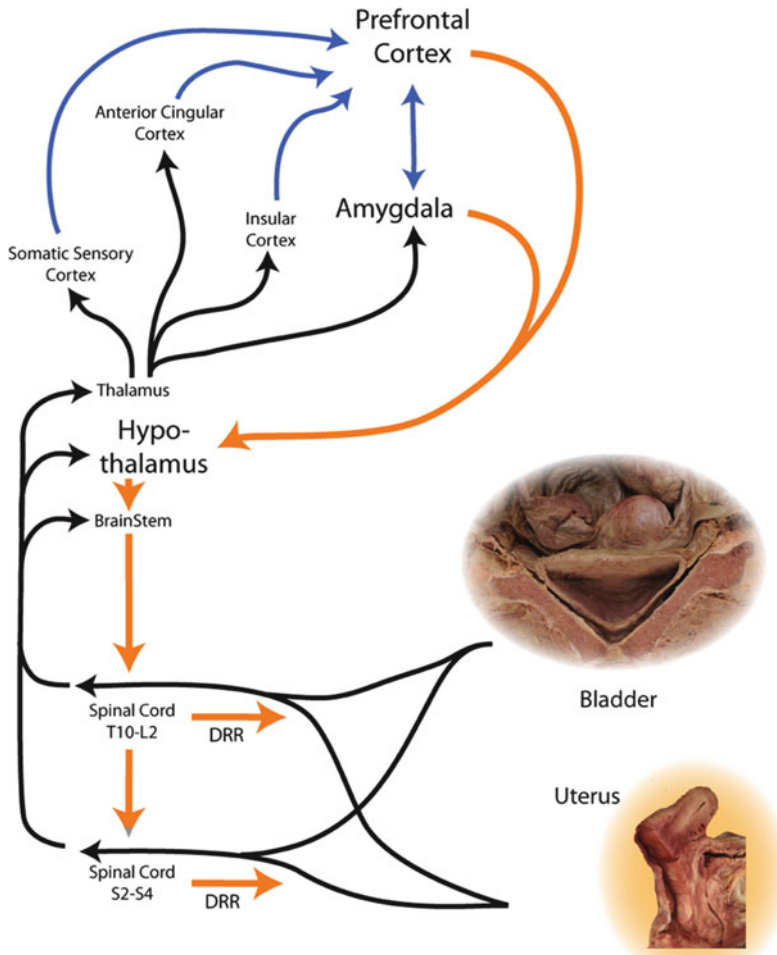


Fig. 2.26 Forebrain modulation of visceral pain. The *black arrows* indicate the ascending flow of sensory information from the pelvic visceral structures. The *blue arrows* indicate forebrain pathways for processing the visceral sensory information. The *orange arrows* indicate the pathways through which the forebrain structures modify the processing of pain in the brainstem and spinal cord structures. Finally, the orange arrows marked DRR (dorsal root reflexes) suggest that fore-brain structures may be able to influence the activity of pathological situations in the peripheral tissues through the release of proinflammatory peptides from the visceral primary afferent fibers

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