

NEUROPHYSIOLOGY OF MICTURITION AND CONTINENCE

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The bladder and its outlet, the urethra, primarily serve two functions: (1) to store urine without leakage at low pressures and (2) to expel urine periodically through a relaxed outlet. These processes involve the coordination of neural events in the peripheral autonomic, somatic, and central nervous systems (CNS). A failure to coordinate these events leads to increased postvoid residual urine with high resting pressures in the bladder. Loss of renal function occurs when high intravesical pressures are transmitted to the upper urinary tract. Other manifestations of altered neural function include irritative voiding or urinary incontinence.

Because of the bladder's dual function in storage and elimination of urine, many of the neural circuits controlling micturition demonstrate phasic or switch-like patterns of activity unlike other viscera. The voluntary control over the function of the bladder and urethra requires participation of higher cortical center. These are unique characteristics distinguishing autonomic control of the lower urinary tract from other viscera.

Knowledge of the neuroanatomy and neurophysiology of the lower urinary tract has been derived from animal and human studies. Fortunately, the findings in animals often correlate with clinical observations. Because of the complex integration of neural events,

the innervation of the lower urinary tract is susceptible to metabolic disorders, neurologic disease, trauma, drugs, and aging. An understanding of the neurophysiology of the bladder and urethra is essential for clinicians treating patients with voiding dysfunction.

NEUROANATOMY

Efferent Parasympathetic Pathways

The preganglionic neurons in the parasympathetic division of the autonomic nervous system reside in the brain and sacral spinal cord. The parasympathetic outflow to the bladder, which provides the main excitatory input, originates in the sacral parasympathetic nucleus (SPN).^{70, 71} The SPN encompasses the interomediolateral cell column in lamina VII of the S2 to S4 spinal cord.¹¹⁴ Cholinergic preganglionic neurons exit the spinal cord in the ventral spinal nerves to form the pelvic nerve. These preganglionic fibers then synapse on cholinergic postganglionic neurons in the pelvic plexus, which reside in close proximity to the bladder. Preganglionic fibers may also synapse on the intramural ganglia within the bladder (Fig. 1).

The pelvic plexus is a network of neural fibers within the pelvic fascia lateral to the

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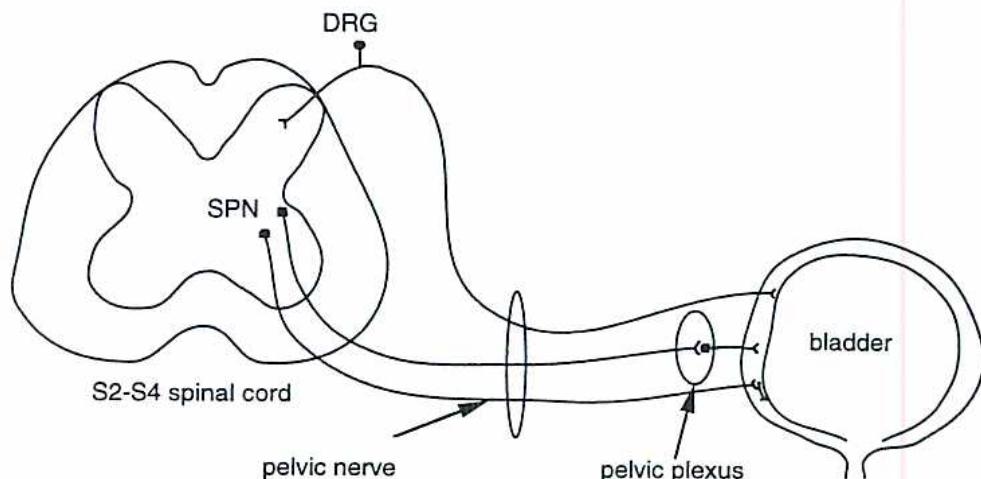


Figure 1. Parasympathetic afferent and efferent innervation of the bladder and urethra. The preganglionic efferents originate in the sacral parasympathetic nucleus (SPN) of the S2–S4 spinal cord. Preganglionics synapse in the pelvic plexus or within the bladder or urethra. Neurons conveying afferent signal to the spinal cord dorsal horn have the cell bodies located in the S2–S4 dorsal root ganglia (DRG). Both afferent and efferent pathways are necessary for micturition and pain travel in the pelvic nerve.

rectum.⁹⁰ The left and right pelvic plexuses interconnect posteriorly behind the rectum. The pelvic plexus contains a mix of parasympathetic and sympathetic fibers.

Efferent Sympathetic Pathways

Sympathetic nerves supplying the pelvic viscera arise from the thoracolumbar spinal cord. The preganglionic neurons supplying the bladder and urethra arise from T11 through L2 spinal cord in the interomedialateral cell column and nucleus intercalatus. These cholinergic preganglionics exit the spinal cord in the ventral roots and can either course through or synapse on postganglionic neurons in the sympathetic chain (paravertebral ganglia). The more rostral fibers of the sympathetic nervous system usually course through the sympathetic chain without synapsing. These preganglionics then can synapse on noradrenergic neurons at the pelvic plexus or within the bladder or urethra. The hypogastric nerve consists of sympathetic efferents and afferents. The pelvic nerve contains both sympathetic and parasympathetic components (Fig. 2).

Debate continues about the role that the sympathetic efferents play in the lower urinary tract in humans. In the cat, the sympathetic efferents modulate the function of the lower urinary tract through events, such as inhibition of the parasympathetic efferents.^{21, 23, 26} The human detrusor contains very few

sympathetic nerves.¹²³ The bladder base (trigonal area), bladder neck, and proximal urethra, however, receive substantial noradrenergic innervation especially in males.^{32, 34, 35, 47, 130} This arrangement occurs primarily to prevent retrograde ejaculation.

Efferent Somatic Pathways

The neurons innervating the external urethral sphincter or rhabdosphincter and the pelvic floor musculature originate from the anterior horn of the S2 to S4 spinal cord. These motoneurons arise from an area termed *Onuf's nucleus*.¹⁰¹ The axons of these neurons exit the spinal cord as the pudendal nerve to innervate the pelvic diaphragm muscles and the external urethral sphincter (Fig. 3). Evidence exists that the external urethral sphincter is innervated by the pelvic nerve as well.^{30, 46} Stimulation of sacral nerves (parasympathetic efferents) after sacral rhizotomy has been shown to increase bladder pressure as expected, but also reciprocally to decrease urethral pressures in both animals and humans, implying that there is innervation of the urethra through the parasympathetic nervous system.^{87, 129} On the basis of animal models, Elbadawi^{32, 34} proposes that the efferent outflow to the urethral sphincter consists of parasympathetic, sympathetic, and somatic nerves. Electrophysiologic data also show that fibers in the hypogastric nerves supply the striated muscle in the external urethral

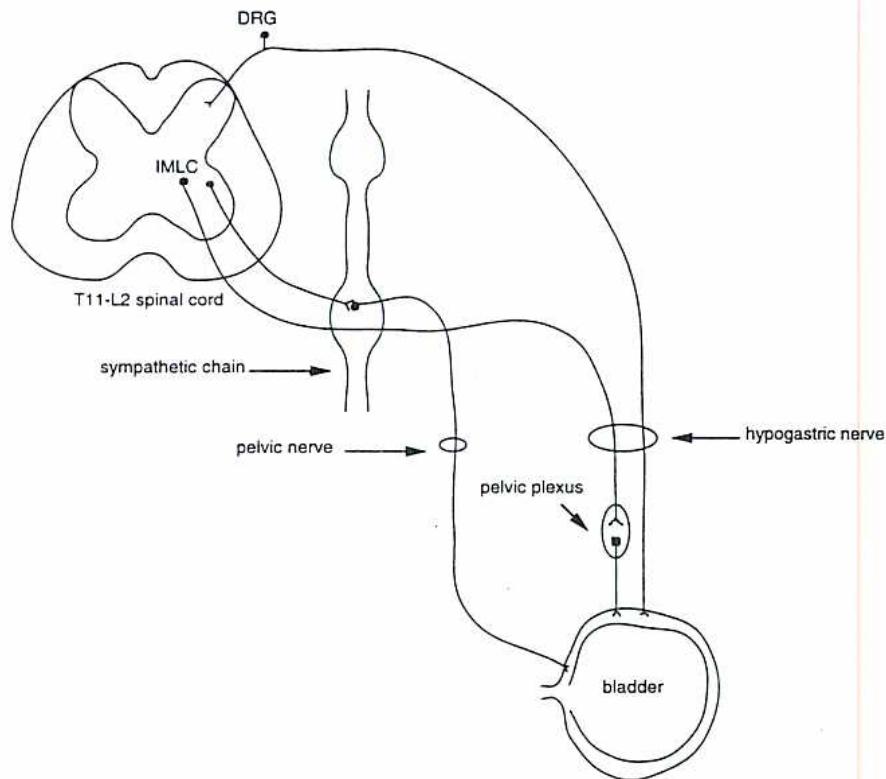


Figure 2. Sympathetic afferent and efferent innervation of the bladder and urethra. The preganglionic efferents originate in the interomedial cell column (IMLC) as well as in the nucleus intercalatus (not shown) of the T11–L2 spinal cord. Preganglionics can synapse on postganglionics in the sympathetic chain or pelvic plexus. Afferents have their cell bodies located in the T11–L2 DRG. The hypogastric nerve conveys sympathetic afferents and efferents. Note that the pelvic nerve also contains sympathetic fibers from the chain ganglia.

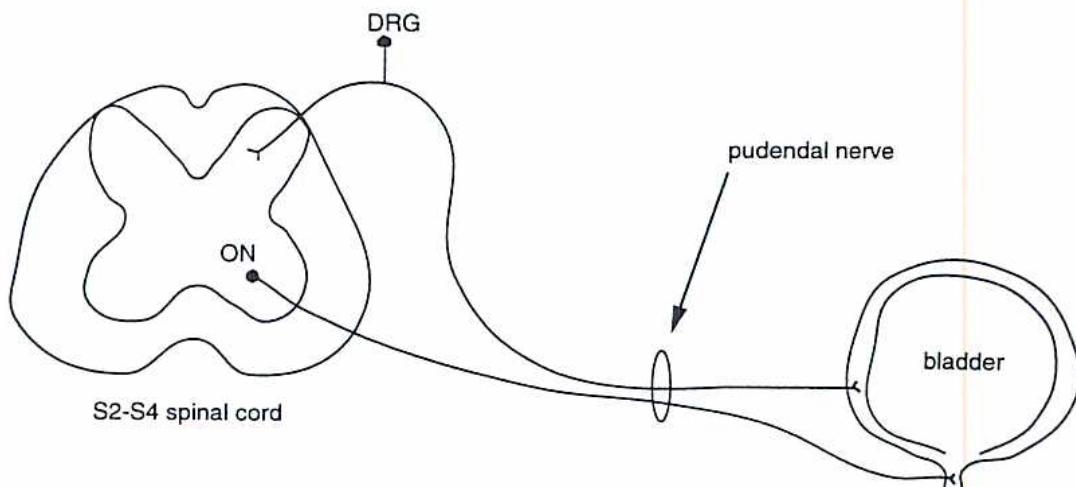


Figure 3. Somatic afferent and efferent innervation of the bladder and urethra. Efferents reside in Onuf's nucleus (ON) of the S2–S4 spinal cord. The efferents supply the innervation of the external urethral sphincter through the pudendal nerve. Data indicate that the external urethral sphincter is both autonomically and somatically innervated (see text). Somatic afferents are conveyed to the dorsal horn of the spinal cord with their cell bodies in S2–S4 DRG.

sphincter.⁵⁸ Branching sacral preganglionic parasympathetic neurons are closely linked physiologically and anatomically to these motoneurons providing potential feedback to Onuf's nucleus during voiding.^{22, 92}

Afferent Parasympathetic Pathways

The afferent limb of the parasympathetic pathway from the bladder originates in the S2 to S4 dorsal root ganglia (see Fig. 1) in humans.¹³⁸ These neurons are bipolar and send long processes to the urinary bladder smooth muscle and epithelium as well as to the urethra. Animal studies show that low threshold myelinated (A- δ) and unmyelinated (C-fibers) afferents convey mechanical or noxious stimuli via the pelvic nerve to the dorsal horn of the spinal cord.^{2, 3, 49, 55} The mechanoceptive afferents responsible for initiation of micturition travel in the pelvic nerve.^{19, 20, 28, 55, 80} The mechanism for central decoding of afferent signals from the bladder and urethra into different sensations (pain, distention, urgency, and so forth) is unknown. It may involve different subpopulations of afferent neurons encoding for different sensations (specificity theory); different intensities of discharges of the same primary afferent neurons (intensity theory); or may be owing to different patterns of discharge in the same population of afferent neurons (gate theory).⁵⁶

Using retrograde axonal labeling techniques in animals, investigators have examined the projections of bladder parasympathetic afferents onto the spinal cord. Bladder afferents enter the dorsal horn of the spinal cord at Lissauer's tract and lamina I. These afferents project laterally in the lateral-collateral pathway (lamina II to IV) toward the SPN in lamina VII providing feedback to the SPN (Fig. 4).^{91, 120} A medial-collateral pathway extends medially into the dorsal gray commissure (lamina X). Overlap of bladder and urethral afferents suggests that these regions coordinate vesicosphincteric function.^{7, 88} Second order neurons in Lissauer's tract of lamina I and the dorsal gray commissure in lamina X relay afferent input to supraspinal sites including the hypothalamus and the pons via the spinothalamic tract of the sacral spinal cord.^{11, 95, 130} The hypothalamus coordinates autonomic activity between multiple organ systems. On the other hand, the pons controls visceral functions including micturition.

Afferent Sympathetic and Somatic Pathways

The sympathetic afferent neurons reside in the T11 to L2 dorsal root ganglia (see Fig. 2). Similar to parasympathetic afferents entering the sacral spinal cord, retrograde axonal tracing studies show termination of sympathetic afferents in lateral lamina I through lamina V of the dorsal horn. High-threshold sympathetic afferents transmit nociceptive (pain) information from the lower urinary tract.^{2, 49} Somatic afferents from the external urethral sphincter travel in the pudendal nerve (see Fig. 3) and terminate in regions that overlap with parasympathetic afferents in the pelvic nerve from the bladder.^{88, 91, 108, 125}

Supraspinal Centers

The afferent and efferent innervation to the bladder and urethra ultimately are under control of higher centers in the CNS. The frontal cortex and septal areas of the brain exert voluntary inhibitory control of the detrusor in the human.^{1, 84} Lesions in these areas can produce detrusor hyperreflexia with a coordinated external urethral sphincter. Although there does not appear to be a distinct pontine micturition center, several discrete regions of the pons and medulla initiate and coordinate lower urinary tract function.^{5, 6, 19, 28, 68, 112, 126}

Electrophysiologic studies support a concept of a pontine micturition center. Stimulation of bladder afferents produces field potentials in the pontine micturition center.⁹⁹ Electrical and chemical activation of discrete areas of the pons induce bladder contractions and relaxation of the urethral sphincter.^{48, 54, 63, 141} Electrical stimulation of afferents in the pelvic nerve elicits a long latency (120 to 140 millisecond) discharge measured in the bladder nerves that corresponds to the combined ascending latency (80 milliseconds) and descending latency (40 milliseconds).^{80, 99} These findings are consistent with the notion that a supraspinal (spinobulbospinal) reflex relayed through the pons governs micturition.

Positron emission tomography scanning of the human brain during micturition has documented increased metabolic activity in the pontine area and provided compelling evidence for pontine regulation of urinary storage and release both in animal models and humans.⁹ Additional studies have shown that the locus coeruleus alpha, dorsolateral teg-

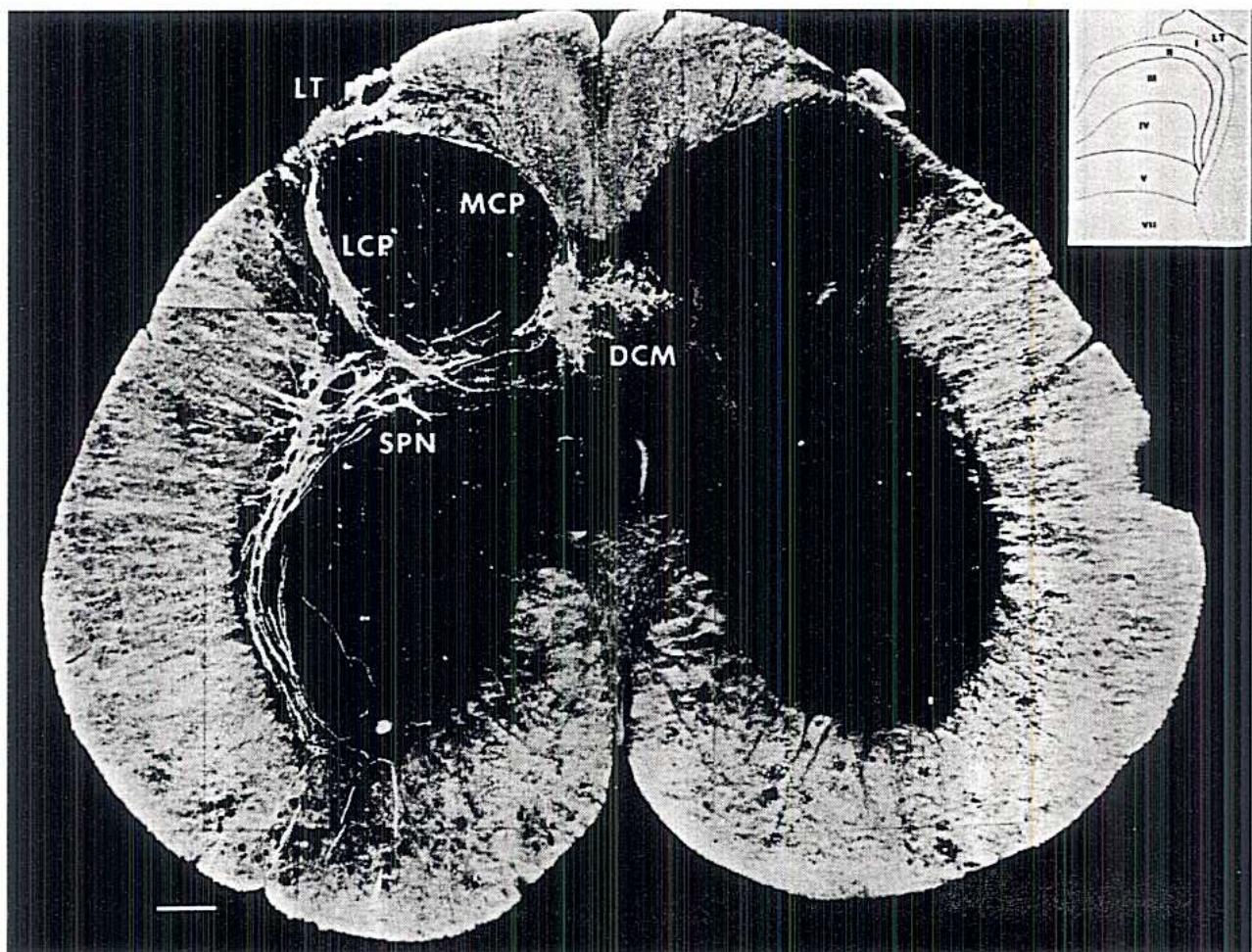


Figure 4. Section of S2 spinal cord after retrograde labeling of pelvic nerve with horseradish peroxidase. The afferents enter Lissauer's tract (LT). The afferents then project laterally in the lateral collateral pathway (LCP) toward the sacral parasympathetic nucleus (SPN). Fewer axons project to the medial collateral pathway (MCP). Afferents also terminate with the dorsal commission (DCM). (From Morgan C, Nadelhaft I, de Groat WC: The distribution of visceral primary afferents from the pelvic nerve within Lassauer's tract and the spinal gray matter and its relationship to sacral parasympathetic nucleus. *J Comp Neurol* 201:415-440, 1981; reprinted by permission of John Wiley & Sons, Inc.)

mentum, and periaqueductal gray areas in the pons are implicated in micturition.^{64, 65, 81, 93, 140, 141} Stimulation of a discrete area in the dorsomedial pons duplicates events that occur during micturition, such as bladder contraction and synchronous inhibition of the external urethral sphincter (Fig. 5).^{48, 54, 63, 66, 67, 100} It has been shown that destruction of an area in the dorsolateral pons leads to urinary incontinence in cats, suggesting that this area may be a supraspinal area for maintenance of urinary continence (Fig. 6); however, stimulation of the dorsolateral pons can lead to either relaxation or contraction of the external urethral sphincter.⁴⁸ Neurons in the dorsomedial pons send axons to preganglionic neurons and bladder afferents in lamina VII, the lateral collateral pathway, and the dorsal gray commissure.⁵³ Ascending input from the pons also projects to the anterior hypothalamic nu-

clei located rostral to the pons. Onuf's nucleus receives projections from the dorsolateral pons and the medial hypothalamus.⁵³

NEUROPHYSIOLOGY

Voiding Reflexes

The cystometrogram represents a urodynamic monitor of storage and voiding reflexes. At some point, as the bladder fills with urine, bladder afferent activity relayed through the mechanoceptive neurons triggers a micturition reflex. This reflex causes a bladder contraction with a reciprocal decrease in outlet or urethral resistance. The bladder afferents fire at threshold intravesical pressures of less than 15 to 20 cm water.³ The conduction velocities of the afferent signal range

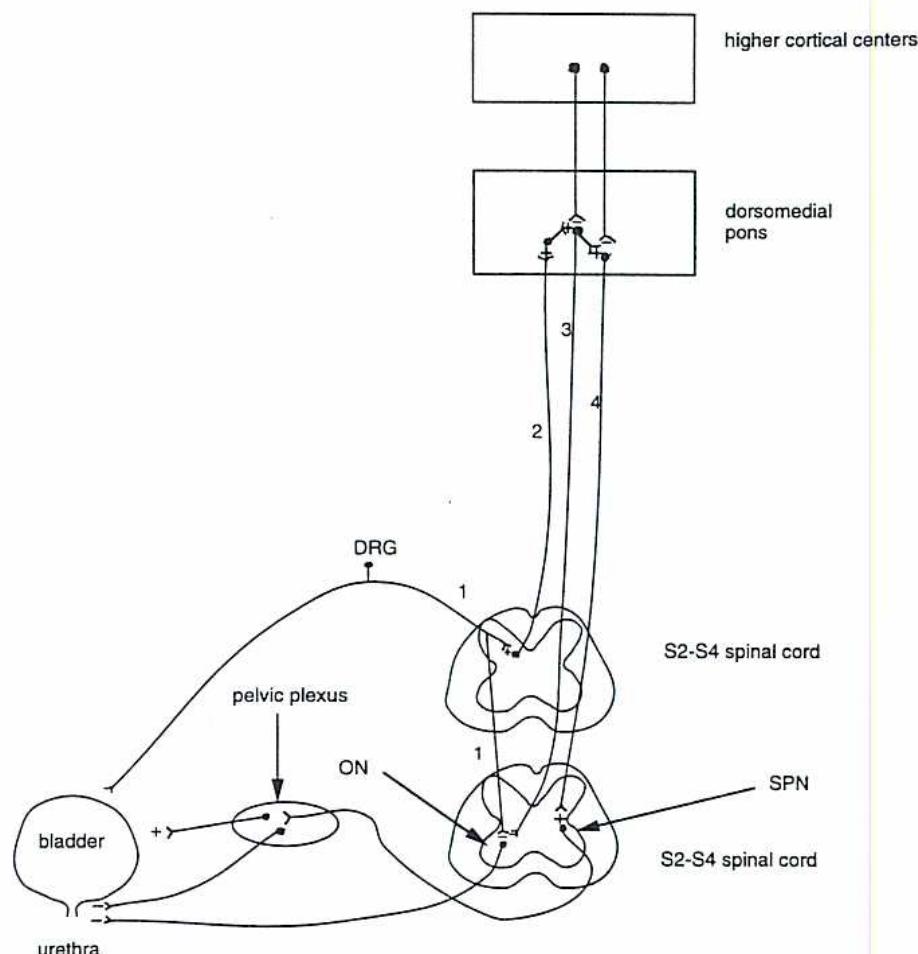


Figure 5. Voiding Reflexes. 1. Mechanoreceptor afferents on bladder fire at a threshold bladder pressure. These bladder afferents provide excitatory input onto second order neurons in the dorsal horn of the S2–S4 spinal cord. Additionally, afferent projections onto Onuf's nucleus (ON) inhibit these motoneurons. 2. Second order neurons project onto the dorsomedial pons providing excitatory input. 3. Descending projections from the dorsomedial pons provide excitatory input to the sacral parasympathetic nucleus (SPN) in the S2–S4 spinal cord thereby contracting the bladder and relaxing the outlet (urethra). 4. Descending projections from the dorsomedial pons also provide inhibitory input to ON in the sacral spinal cord to decrease outlet resistance. DRG = dorsal root ganglia.

from 1.2 to 30 m/s corresponding to the A- δ , lightly myelinated fibers.^{3, 19, 27, 80, 133} Bladder afferents in the pelvic nerve synapse on neurons in the sacral spinal cord. Second-order neurons project rostrally to the pons. The dorsomedial pons when stimulated evokes a bladder contraction and simultaneous inhibition of the external urethral sphincter (see Fig. 5).^{48, 54, 63, 66, 67, 100}

Interestingly, afferent input from the bladder is not essential for micturition. When ascending afferent input from the bladder is eliminated in experimental animals, stimulation of the dorsomedial pons still triggers a detrusor contraction.⁶⁶ Without ascending input from the bladder, however, the contraction of the detrusor is diminished and it appears that a normal contraction requires

continuous pontine stimulation via bladder afferents. Evidently, once a detrusor contraction begins, the tension-generated afferent discharge reinforces the micturition reflex. This process could partially explain why patients with sensory neuropathies, such as diabetes, sometimes fail fully to empty their bladders.

Afferent input from the urethra may also influence the voiding reflex. Urine flowing through the bladder outlet facilitates bladder emptying by means of a reflex mediated by urethral afferents.⁴ With stress urinary incontinence, urine entering the urethra may activate a urethrovesical reflex and trigger an involuntary detrusor contraction. This mechanism could explain the relatively common association of stress and urge (owing to in-

voluntary detrusor contractions) urinary incontinence. It could also explain why procedures to correct stress incontinence cure not only stress urinary incontinence but also urge incontinence.⁴¹

Voiding relies on a reciprocal relationship between the bladder and its outlet. Apart from a micturition reflex controlling bladder contraction, other reflexes promote emptying by reducing outlet resistance. Pudendal efferents from Onuf's nucleus become quiescent during voiding.^{67, 115} This corresponds to electromyographic quieting of the pelvic musculature and external urethral sphincter during voiding. Inputs from at least three sites in the neuraxis inhibit motoneurons in Onuf's nucleus during urination. The descending input from the dorsomedial pons inhibits these pudendal motoneurons (see Fig. 5).^{48, 54, 63, 66, 67, 100} Additionally, axon collaterals from sacral preganglionic neurons project to Onuf's nucleus.⁹² With firing of bladder preganglionics, inhibition of sphincter motoneurons occurs,

possibly by hyperpolarizing these cells.¹¹⁵ Lastly, certain pudendal afferents hyperpolarize and thereby inhibit pudendal motoneurons.³⁸ Descending pontine projections and preganglionic axons also may synapse on interneurons that regulate sphincter motoneurons.

In addition to the neural inhibition of the external urethral sphincter, the smooth muscle of the urethra relaxes prior to voiding. Ambulatory urodynamics demonstrate a fall in urethral pressure seconds before the increase in intravesical pressure.¹³² Parasympathetic pathways in the pelvic nerve appear to be involved in relaxation of the bladder outlet because electrical stimulation of sacral nerve roots lowers urethral pressure even with paralysis of the striated external urethral muscle.^{85, 87, 129} It is likely that the bladder afferents trigger a pelvic nerve-mediated urethral reflex. Relaxation of the urethra may occur by the release of nitric oxide (NO) from urethral nerves.^{8, 102, 103, 128} Alternatively, parasympa-

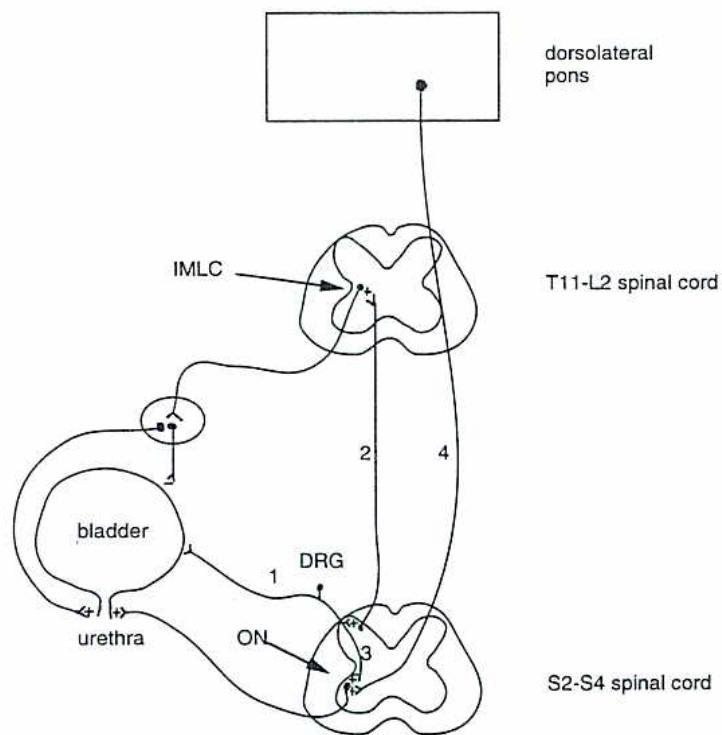


Figure 6. Storage Reflexes 1, In addition to viscoelastic properties of the bladder smooth muscle, afferents from the bladder excite second order neurons in the dorsal horn of S2–S4 spinal cord. 2, These interneurons project intraspinally to the thoracolumbar spinal cord onto preganglionic sympathetic neurons in the interomediolateral cell column (IMLC). The sympathetic outflow is increased, thereby inhibiting detrusor contraction as well as increasing urethral resistance. 3, Bladder afferents also project on Onuf's nucleus (ON) to increase motoneuron firing and thereby increase bladder outlet resistance. 4, Descending projections from the dorsolateral pons can also excite neurons in ON. DRG = dorsal root ganglia.

thetic neurons may merely block the sympathetic outflow responsible for maintaining the tone of urethral smooth muscle.⁸² Clinically, this urethral relaxation response is most noticeable in patients with acontractile bladders. Distention of the acontractile bladder with an intact afferent innervation causes relaxation of the urethra and urinary incontinence. This phenomenon has been termed *reflex urethral instability*.⁸⁶

Storage Reflexes

The filling portion of the cystometrogram represents the combined effects of passive properties of the bladder and its innervation. The maintenance of low detrusor pressure, absence of involuntary contractions, and maximal urethral pressures are the net result of storage reflexes. Viscoelastic properties of the bladder wall and the electromechanical properties of smooth muscle contribute to bladder compliance during filling; however, bladder compliance is also influenced by sacral neural input because intrathecal drugs dramatically alter compliance.^{94, 106, 121} Continence is further maintained by overall inhibition of the parasympathetic efferents and activation of the sympathetic and somatic efferents.

As the bladder fills, activity from mechanoreceptive input is relayed by the pelvic nerve to the dorsal horn of the sacral spinal cord.^{19, 20, 28, 55, 80} In the spinal cord, an intersegmental pathway from the sacral to the thoracolumbar cord stimulates sympathetic preganglionics. Activation of these preganglionics that travel in the hypogastric nerve provides excitatory outflow to the bladder base and urethra and results in an increase in outlet resistance (see Fig. 6).²⁶ In animals, the hypogastric outflow inhibits the detrusor smooth muscle.^{96, 98} Overactivity of the sympathetic efferents may contribute to the functional obstructive disorders seen in anxious young males. The importance of sympathetic innervation on bladder during filling is controversial, however, because (1) sympathectomy has no appreciable effect on urine storage; and (2) patients with deficiency of dopamine β -hydroxylase, the enzyme that converts dopamine to norepinephrine, void normally.^{11, 43}

Not much is known about supraspinal reflexes in maintenance of continence. A supraspinal center regulating urine storage may reside in the dorsolateral pons (see Fig. 6) because lesions of this center lead to urinary incontinence. Descending input from this re-

gion can excite the pudendal motoneurons to increase outlet resistance.⁴⁸

Other storage reflexes rely on afferents from pelvic organs, such as the vagina and uterine cervix, inhibiting the sacral preganglionics to the bladder as well as increasing urethral resistance (visceral-visceral reflex).^{18, 37} This concept explains why electrostimulation of the vagina is useful in treatment of detrusor instability.³⁶ Somatovisceral reflex occurs when cutaneous stimulation inhibits micturition. Inhibition of reflex micturition occurs with acupuncture.¹¹¹ Likewise, penile or clitoral stimulation can diminish detrusor hyperreflexia in suprasacral spinal cord-injured individuals.¹³⁵

A guarding reflex exists in which afferents from bladder filling and other pelvic structures provide positive feedback onto Onuf's nucleus thereby increasing outlet resistance as well (see Fig. 6).⁴² The external urethral sphincter neurons exhibit a tonic discharge that increases during bladder filling. The motor area of the cerebral cortex must project onto the external urethral sphincter as well, because voluntary interruption of micturition or an enhanced guarding reflex is possible. This pathway is the presumed cause of Hinman's syndrome or the nonneurogenic, voluntary dyssynergia syndrome observed in children.⁵¹ Differentiation of voluntary from involuntary external urethral sphincter contractions can be difficult. Correlation of sphincteric activity with the rise in intravesical pressure has been found to be clinically useful in distinguishing between the two.¹¹⁰ Quieting of electromyographic activity of the external urethral sphincter during the initial rise of intravesical pressure is associated with Hinman's syndrome, whereas increase in electromyographic activity during this initial period is associated with true detrusor sphincter dyssynergia.¹⁰⁹ This finding supports the principle of a central reflex that inhibits the pudendal motoneurons during micturition.

Peripheral mechanisms also can modulate excitatory parasympathetic input to the bladder. Noradrenergic sympathetic fibers synapse on parasympathetic postganglionic neurons or interneurons in the pelvic plexus. Heightened sympathetic activity stimulates α_2 -adrenoceptors on parasympathetic ganglion cells that block cholinergic ganglionic transmission.²¹ Purinergic adenosine triphosphate [ATP], enkephalinergic, tachykinin, gamma-aminobutyric acid (GABA) and serotonergic mechanisms also inhibit cholinergic transmission in bladder ganglia.^{24, 59, 60, 72, 113, 127}

These mechanisms allow the pelvic ganglia to function as high-pass filters. Prejunctional muscarinic-2 (M_2) receptors facilitate its release.¹¹⁸ Finally local factors, such as endothelin, can depress ganglionic transmission in the pelvic ganglia.⁹⁷

NEUROPHARMACOLOGY

Neuroeffector Junction and Ganglionic Transmission

The parasympathetic postganglionics release acetylcholine (ACh), which excites muscarinic receptors (M_2 and M_3) in the smooth muscle of the bladder and urethra. Nonadrenergic, noncholinergic (NANC) transmitters, most notably ATP, act with ACh to contract detrusor smooth muscle via the P2 (purinergic) receptors (Fig. 7).^{12, 75} Antimuscarinics in humans may fail to abolish bladder hyperactivity because of their inability to block NANC transmission to the bladder.¹¹⁷ Other candidates for NANC transmitters include neuropeptides colocalized in terminals with ACh. Vasoactive intestinal peptide (VIP)

and neuropeptide Y (NPY) are colocalized with ACh in some postganglionic nerves. These neuropeptides can influence release of classical transmitters, such as ACh and norepinephrine.^{25, 44, 61, 142}

In the pelvic plexus, preganglionic parasympathetic neurons release ACh, which activates nicotinic receptors on parasympathetic postganglionics. M_1 muscarinic receptors on axons of postganglionic neurons provide negative inhibition to ACh release when activated by ACh (Figs. 7 and 8). NANC transmitters modulate ganglionic transmission. Leucine enkephalin (ENK) released by pre-ganglionic neurons and endothelin, a substance produced by nonneuronal tissues, inhibit cholinergic transmission in pelvic ganglia.^{24, 97} In contrast, VIP and substance P (SP) facilitate ganglionic transmission in pelvic ganglia.^{59, 60} These observations suggest that neuropeptides gate, pattern, or adjust the frequency of neuronal firing. This capability allows the nervous system finely to adjust the degree of excitatory input to the bladder. A micturition reflex is difficult to initiate because of profound inhibitory mechanisms, once activated, excitatory systems ensure its maintenance.

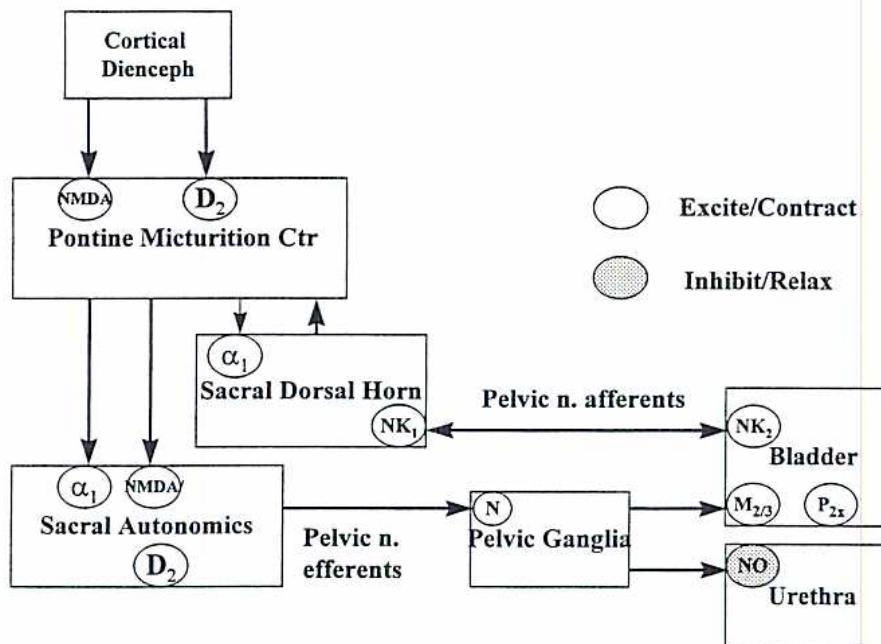


Figure 7. Neuropharmacology of Voiding; the pharmacology of micturition based on immunohistochemical and pharmacological investigations. Drugs or neurotransmitters (not depicted) that interact with its receptor (depicted with an oval) produce either an excitatory or inhibitory action and this is depicted at the pontine, sacral spinal cord, or peripheral levels. The receptor and its drug or neurotransmitter in parenthesis are: NMDA = glutamate receptor (glutamate); D₂ = dopamine receptor (dopamine); α₁ = adrenergic receptor (norepinephrine); NK1 and NK2 = neuropeptidergic receptor (substance P); N = nicotinic receptor (acetylcholine); M₂ or M₃ = muscarinic receptor (acetylcholine); NO = nitric oxide receptor (nitric oxide); P_{2x} = purinergic receptor (ATP).

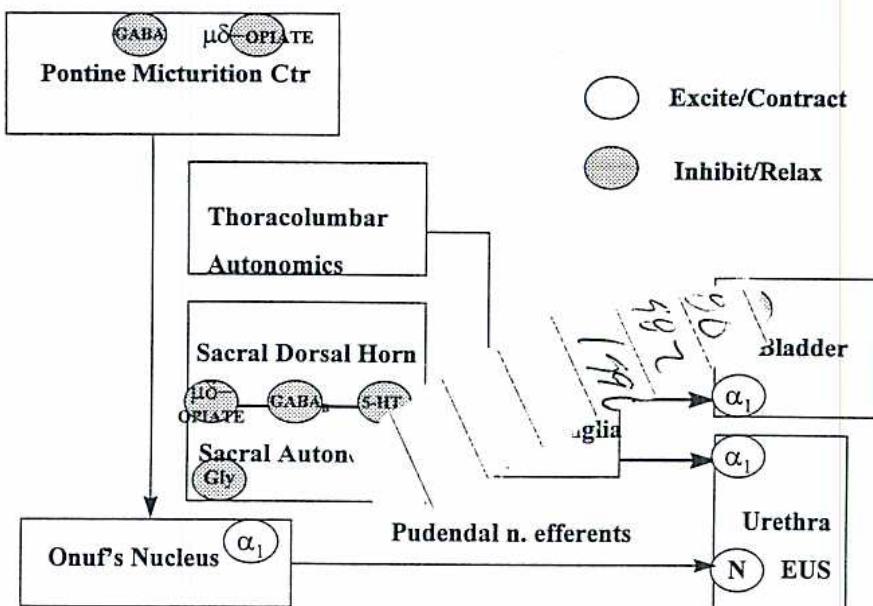


Figure 8. Neuropharmacology of Continence; the pharmacology of urinary storage based on immunohistochemical and pharmacological investigations. Drugs or neurotransmitters (not depicted) that interact with its receptor (depicted with an oval) produce either an excitatory or inhibitory action and this is depicted at the pontine, sacral spinal cord, or peripheral levels. The receptor and its drug or neurotransmitter in parenthesis are: GABA = gamma-aminobutyric acid receptor (gamma-aminobutyric acid); μ - or δ -opiate = opiate receptor (opiates); α_1 β_2 = adrenergic receptors (norepinephrine); 5-HT = 5-hydroxytryptamine receptor (serotonin); Gly = glycine receptor (glycine); N = nicotinic receptor (acetylcholine); M1 = muscarinic receptor (acetylcholine).

Thus, drugs that completely abolish voiding are rare or non-existent.

The role of cholinergic input to the urethra is less understood. Cholinergic agonist can contract urethral smooth muscle through the action of muscarinic receptors. Activation of muscarinic receptors on adrenergic terminals in lower urinary tract inhibits norepinephrine release.⁸³ This presynaptic inhibition of norepinephrine release may be regulated by cholinergic nerves in the urethra. This scheme was used to explain parasympathetic-induced urethral relaxation.^{82, 87, 129} Because cholinergic agonists contract urethral smooth muscle, however, relaxation may depend on noncholinergic parasympathetic transmitters, such as NO (see Fig. 7).^{8, 102, 103, 128} NO synthase (neuronal isoform), which catalyzes the production of NO from L-arginine, is expressed by nerves innervating the bladder and urethra.¹³⁴ Furthermore, inhibition of NO production reduces electrically induced relaxation of the urethra.^{8, 102, 103}

Sympathetic postganglionics release norepinephrine, which contracts urethral and bladder base smooth muscle. This contraction is mediated through the α_1 -adrenocep-

tor.^{96, 98, 139} In contrast, the action of norepinephrine at β_2 -adrenoceptors relaxes smooth muscle in the bladder body.¹³⁹ As in parasympathetics, preganglionic sympathetic neurons release ACh, which also activates nicotinic receptors on the postganglionic sympathetic neurons (see Fig. 8). Stimulation of α_1 and β receptors on preganglionic parasympathetic neurons facilitates transmission in the pelvic ganglia, whereas α_2 stimulation inhibits transmission in cats, suggesting that adrenergic nerves influence cholinergic transmission in the pelvic ganglia (see Fig. 8).²¹

The noradrenergic innervation of the human female urethra is sparse relative to other species. The proximal urethra of the male, however, receives a dense noradrenergic innervation.^{32, 34, 35, 46, 123} This arrangement prevents retrograde ejaculation. Because stimulation of the hypogastric nerves has a variable effect on urethral pressure, the importance of adrenergic nerves in relaxation of the bladder body is debated.¹³⁹

Innervation of the lower urinary tract is not static, but changes in response to disease. For example, an increase in noradrenergic innervation and clinical response to adrenergic-

blocking drugs occurs in several pathologic conditions including bladder outlet obstruction, bladder denervation, and possibly spinal cord injury.^{23, 57, 105, 124} These pharmacologic changes may explain why α_1 -adrenergic blockers improve voiding symptoms owing to obstructive voiding and decrease detrusor hyperreflexia secondary to spinal cord injury, but demonstrate minimal effect in normal individuals.¹⁵ It has also been shown that perhaps α_1 -adrenergic blockers work in the sacral spinal cord, and not peripherally, by inhibiting motoneurons to the external urethral sphincter.^{16, 35, 40} Thus, through central and peripheral actions α_1 -blockers reduce maximal urethral pressure.

Many adrenergic nerves contain NPY. The density of NPY fibers is greatest in the bladder base, as in noradrenergic innervation.¹⁰⁴ In the lower urinary tract, NPY suppresses the release of norepinephrine mimicking the action of norepinephrine at α_2 -adrenergic receptors.^{76, 131, 142}

The striated muscles of the lower urinary tract and pelvis are innervated by cholinergic fibers in the pudendal nerve.^{34, 47} ACh acts on nicotinic receptors located at the motor end plate and elicits a muscle contraction (see Fig. 8). Botulinum toxin and pancuronium both paralyze the external urethral sphincter^{31, 69}; however, neither drug produces urinary incontinence. Muscle fibers of the external urethral sphincter also receive noradrenergic input.^{32, 34, 47, 58, 139} Therefore, the striated urethral sphincter is unique in that it receives autonomic and somatic inputs.

Sensory Neurotransmitters

Afferents projecting to the sacral dorsal root ganglia contain VIP, SP, calcitonin gene related peptide, ENK, cholecystokinin (CCK), and NO.^{20, 25, 61, 62, 78, 89, 122} Therefore, it is not surprising that anticholinergic drugs have little or no effect on sensory disorders of the lower urinary tract. Depletion of SP and related peptides with the neurotoxin capsaicin depresses but fails to abolish the micturition reflex evoked by bladder distention in anesthetized animals.^{13, 20, 77, 78} In humans, intravesical administration of capsaicin transiently reduces bladder sensation and irritable voiding.^{39, 77} These responses imply that SP or related peptides play a role in micturition and encoding for bladder pain. SP and related neuropeptides act via NK-1 and NK-2 receptors

(see Fig. 7). Selective NK-2 receptor antagonists inhibit bladder contraction evoked by capsaicin or exogenous SP.⁴⁵ In the dorsal horn, NK-1 receptor antagonists inhibit micturition; however, neither NK-1 nor NK-2 antagonists abolish distention-evoked micturition.⁷⁴ Nevertheless, these findings indicate that neuropeptides play an important role in afferent transmission from the bladder (see Fig. 7).⁷³

The thoracolumbar dorsal root ganglia and dorsal horn contain neuropeptides identified in parasympathetic afferents, although their distribution is somewhat different.⁶² Some investigators have postulated that each afferent neuropeptide possesses a distinct functional role.²⁹ For example, SP usually is associated with transmission of pain signals to the spinal cord, whereas VIP may mediate thermoreceptive input; however, a unique functional encoding for any specific neuropeptide has yet to be proved.⁵⁶

Neurotransmitters in Supraspinal Centers and Spinal Cord

A variety of excitatory and inhibitory inputs regulate pontine function. ENK varicosities are found in the pons as well as the SPN and Onuf's nucleus.^{24, 25} The pontine micturition center is under tonic inhibition by ENK neurons (see Fig. 8). In the cat, intracerebroventricular injections of ENK analogs, μ - and δ -opiate agonists, increase the micturition threshold.⁵² Administration of naloxone, an opioid antagonist, decreases the volume at which a micturition reflex occurs and further supports a storage role for ENK or opiate pathways.¹⁰ In spinal cord-injured patients, intrathecal opiates depress the micturition reflex, but the development of tolerance with continuous intrathecal morphine prevents this from being clinically effective for the treatment of detrusor hyperreflexia.⁵⁰

Activation of N-methyl-D-aspartate (NMDA or glutamate) and dopamine receptors facilitates neurotransmission in the pons and spinal cord. Glutamate is released from (1) visceral afferents in the dorsal horn of the spinal cord, (2) spinal interneurons, (3) descending projections from the pontine micturition center, and (4) neurons within the pons. Glutamate appears to facilitate bladder function at all of these sites under certain conditions. Intracerebroventricular administration of glutamate in rats or within the pontine micturi-

tion center in cats increases bladder activity.^{79, 107, 116} Apomorphine, a dopamine agonist, facilitates bladder emptying in humans.¹⁴

Other potential neurotransmitters that may be involved in urinary storage include glycine, GABA, and 5-hydroxytryptamine (5-HT or serotonin) (see Fig. 8). In general, these substances inhibit bladder activity by interaction with afferent terminals, interneurons, or parasympathetic preganglionics in the sacral spinal cord.¹⁷ Intrathecal baclofen, a GABA agonist, raises the threshold for micturition in patients with spinal pathology probably by inhibiting afferent input.^{94, 121} Similarly, administration of 5-HT to thoracolumbar preganglionic neurons facilitates vesicosympathetic storage reflexes. Many 5-HT agonists when administered systemically inhibit micturition.¹¹⁹ Consistent with these observations, drugs that inhibit 5-HT uptake, such as tricyclic antidepressants, are useful for treating urinary incontinence and enuresis.¹³⁶

The neurons that project from the brainstem to the preganglionic neurons thoracolumbar, and sacral spinal cord contain norepinephrine (see Figs. 7 and 8).¹³⁷ Intrathecal norepinephrine, however, excites sacral preganglionic neurons and thus facilitates micturition overall.^{140, 141} Similarly, it has been shown that α_1 -adrenergic receptor antagonists (prazosin) inhibit bladder contractions elicited by pontine stimulation.^{140, 141}

These findings raise several important caveats in reaching conclusions about centrally acting drugs and mechanisms. First, anesthesia activates or inhibits certain pathways responsible for micturition. Second, a receptor-specific drug acts at multiple sites that may have opposing effects on visceral function. Lastly, transmitter mechanisms evolve during growth and differentiation and are profoundly altered following injury, disease, and aging.

CONCLUSION

Micturition and continence require switching from activation of a micturition reflex with inhibition of storage reflexes to inhibition of the micturition reflex with activation of storage reflexes. Complex excitatory and inhibitory mechanisms throughout the neuraxis provide this switching network. Drugs used to treat voiding disorders work by affecting these pathways. Because neurotransmitters and drugs may have an excitatory

effect on one portion of the neuraxis, but an inhibitory effect on another, it can be difficult to predict an overall net effect. Many disorders affect the intricate pathways involved in coordination between the neural networks and can lead to voiding dysfunction, incontinence, or even renal damage. Precise delineation of these networks will produce refinements in the treatment of many types of lower urinary tract dysfunction.

References

1. Andrew J, Nathan PW: Lesions of the anterior frontal lobe and disturbances of micturition and defaecation. *Brain* 87:233-261, 1964
2. Bahns E, Ernsberger U, Janig W, Nelke A: Functional characteristics of lumbar visceral afferent fibers from the urinary bladder and urethra in the cat. *Pflugers Arch* 407:510-518, 1986
3. Bahns E, Halsband U, Janig W: Responses of sacral visceral afferents from the lower urinary tract, colon, and anus to mechanical stimulation. *Pflugers Arch* 410:296-303, 1987
4. Barrington FJF: The component reflexes of micturition in the cat. *Brain* 54:177-188, 1931
5. Barrington FJF: The effect of lesions of the hind and midbrain on micturition in the cat. *Q J Exp Physiol* 15:181-202, 1925
6. Barrington FJF: The relation of the hind brain to micturition. *Brain* 44:23-53, 1921
7. Beattie MS, Li Q, Leedy MG, Bresnahan JC: Motoneurons innervating the external anal and urethral sphincters of the female cat have different dendritic arborization. *Neurosci Lett* 111:69-74, 1990
8. Bennett BC, Vizzard MA, Booth AM, de Groat WC: Role of nitric oxide in reflex urethral sphincter relaxation during micturition. *Society for Neuroscience Abstracts* 19:511, 1993
9. Blok BFM, Willemse ATM, Holstege G: Mapping micturition control areas in the central nervous system with positron emission tomography (PET). *Society for Neuroscience Abstracts* 21:1872, 1995
10. Booth AM, Hisamitsu T, Kawatani M, de Groat WC: Regulation of urinary bladder capacity by endogenous opioid peptides. *J Urol* 133:339-342, 1985
11. Bors E, Comarr AE: *Neurological Urology*. Baltimore, University Park Press, 1971
12. Burnstock G, Satchell DG, Smythe A: A comparison of the excitatory and inhibitory effects of non-adrenergic, non-cholinergic nerve stimulation and exogenously applied ATP on a variety of smooth muscle preparations from different vertebrate species. *Br J Pharmacol* 46:234-242, 1972
13. Cheng CL, Ma CP, de Groat WC: Effects of capsaicin on micturition and associated reflexes in rats. *Am J Physiol* 265:R132-R138, 1993
14. Christmas TJ, Chapple CR, Kempster PA, et al: The role of subcutaneous apomorphine in the treatment of Parkinsonian voiding dysfunction [abstract]. *J Urol* 141:327A, 1989
15. Christmas TJ, Kirby RS: Alpha-adrenoceptor blockers in the treatment of benign prostatic hyperplasia. *World J Urol* 9:36-40, 1991
16. Danuser H, Thor KB: Inhibition of central sympa-

- thetic somatic outflow to the lower urinary tract of the cat by the alpha-1 adrenergic receptor antagonist prazosin. *J Urol* 153:1308-1312, 1995
17. de Groat WC: The effects of glycine, GABA, and strychnine on sacral parasympathetic preganglionic neurons. *Brain Res* 18:542-544, 1970
 18. de Groat WC: Inhibition and excitation of sacral parasympathetic neurons by visceral and cutaneous stimuli in the cat. *Brain Res* 33:499-503, 1971
 19. de Groat WC: Nervous control of the urinary bladder in the cat. *Brain Res* 87:201-211, 1975
 20. de Groat WC: Neuropeptides in pelvic afferent pathways. *Experientia* 43:801-813, 1987
 21. de Groat WC, Booth AM: Inhibition and facilitation in parasympathetic ganglia of the urinary bladder. *Federation Proceedings* 39:2990-2996, 1980
 22. de Groat WC, Kawatani M: Neural control of the urinary bladder: Possible relationship between peptidergic inhibitory mechanisms and detrusor instability. *Neurourol Urodyn* 4:285-300, 1985
 23. de Groat WC, Kawatani M: Reorganization of sympathetic preganglionic connections in the cat bladder ganglia following parasympathetic denervation. *J Physiol (Lond)* 409:431-449, 1989
 24. de Groat WC, Kawatani M, Booth AM: Enkephalinergic modulation of cholinergic transmission in parasympathetic ganglia of the cat urinary bladder. In Hanin I (ed): *Dynamics of Cholinergic Function*. New York, Plenum Press, 1986, pp 1007-1017
 25. de Groat WC, Kawatani M, Hisamitsu T, et al: Role of neuropeptides in the sacral autonomic reflex pathways of the cat. *J Auton Nerv Sys* 7:339-350, 1983
 26. de Groat WC, Lalley PM: Reflex firing in lumbar sympathetic outflow to activation of visceral afferent fibers. *J Physiol (Lond)* 226:289-309, 1972
 27. de Groat WC, Nadelhaft I, Milne RJ, et al: Organization of the sacral parasympathetic reflex pathways to the urinary bladder and large intestine. *J Auton Nerv Sys* 3:135-165, 1981
 28. de Groat WC, Ryall RW: Reflexes to sacral parasympathetic neurones concerned with micturition in the cat. *J Physiol (Lond)* 200:87-108, 1969
 29. Dockray GJ, Sharkey KA: Neurochemistry of visceral afferent neurons. In Cervero G, Morrison JFB (eds): *Visceral Sensation. Progress in Brain Research*, vol 67. Amsterdam, Elsevier, 1986, pp 133-148
 30. Donker PJ, Dros JThPM, Ulden BM: Anatomy of the musculature and innervation of the bladder and the urethra. In Williams DI, Chisholm GD (eds): *Scientific Foundations of Urology*, vol 2. London, Heinemann, 1978, pp 32-39
 31. Dykstra DD, Sidi AA, Scott AB, et al: Effects of botulinum A toxin on detrusor sphincter dyssnergia in spinal cord patients. *J Urol* 139:919-922, 1988
 32. Elbadawi A: Neuromorphologic basis of vesicourethral function. I. Histochemistry, ultrastructure and function of intrinsic nerves of the bladder and urethra. *Neurourol Urodyn* 1:3-50, 1982
 33. Elbadawi A, Atta MA: Intrinsic neuromuscular defects in the neurogenic bladder. V. Autonomic reinnervation of the male feline rhabdosphincter following somatic denervation by bilateral sacral ventral rhizotomy. *Neurourol Urodyn* 5:65-86, 1986
 34. Elbadawi A, Atta MA: Ultrastructural analysis of vesicourethral innervation: Evidence for somatomotor plus autonomic innervation of the feline rhabdosphincter. *Neurourol Urodyn* 4:23-36, 1985
 35. Espey MJ, Downie JW, Fine A: Effect of 5-HT receptor and adrenoceptor antagonists on micturition in conscious cats. *Eur J Pharmacol* 221:167-170, 1992
 36. Fall M: Does electrostimulation cure urinary incontinence. *J Urol* 131:664-667, 1984
 37. Fall M, Erlandson BE, Carlsson CA, Lindstrom S: The effect of intravaginal electrical stimulation on the feline urethra and urinary bladder. *Scand J Urol Nephrol (suppl part II)*:19, 1978
 38. Fedirchuk B, Downie J, Shefchyk SJ: Reduction of perineal evoked excitatory postsynaptic potentials in cat lumbar and sacral motoneurons during micturition. *J Neurosci* 14:6153-6159, 1994
 39. Fowler CJ, Jewkes D, McDonald WI: Intravesical capsaicin for neurogenic bladder dysfunction. *Lancet* 339:1239-1240, 1992
 40. Gajewski J, Downie JW, Awad SA: Experimental evidence for a central nervous system site of action in the effect of alpha-adrenergic blockers on the external urethral sphincter. *J Urol* 132:403-409, 1984
 41. Gardy M, Kozminski M, DeLancey J, et al: Stress incontinence and cystoceles. *J Urol* 145:1211-1213, 1991
 42. Garry RC, Roberts TDM, Todd JK: Reflexes involving the external urethral sphincter in the cat. *J Physiol* 149:653-665, 1959
 43. Gary T, Robertson D: Lessons learned from dopamine β -hydroxylase deficiency in humans. *News in Physiological Sciences* 9:35-39, 1994
 44. Gibson SJ, Polak JM, Arand P, et al: A VIP/PHI pathway links urinary bladder and sacral spinal cord. *Peptides (suppl)* 7:205-219, 1986
 45. Giuliani R, Patacchi R, Brabanti G, et al: Characterization of tachykinin neurokinin-2 receptor in the human urinary bladder by means of selective receptor antagonists and peptidase inhibitors. *J Pharmacol Exp Ther* 267:590-595, 1993
 46. Gosling JA: The structure of the bladder and urethra in relation to function. *Urol Clin North Am* 6:31-38, 1979
 47. Gosling JA, Dixon JS, Lendon RG: The autonomic innervation of the human male and female bladder neck and proximal urethra. *J Urol* 118:302-305, 1977
 48. Griffiths D, Holstege G, Dalm E, de Wall H: Control and coordination of bladder and urethral function in the brainstem of the cat. *Neurourol Urodyn* 9:63-82, 1990
 49. Habler HJ, Janig W, Koltzenburg M: Activation of unmyelinated afferent fibers by mechanical stimuli and inflammation of the urinary bladder in the cat. *J Physiol (Lond)* 425:545-562, 1990
 50. Herman RM, Wainberg MC, del Guidice P, Wellscher MD: The effect of low dose intrathecal morphine on impaired micturition reflexes in human subjects with spinal cord lesions. *Anesthesiology* 69:313-318, 1988
 51. Hinman F: Urinary tract damage in children who wet. *Ped* 54:143-150, 1974
 52. Hisamitsu T, de Groat WC: Inhibitory effect of opioid peptides and morphine applied intrathecally and intracerebroventricularly on the micturition reflex in the cat. *Brain Res* 298:51-65, 1984
 53. Holstege G: Some anatomical observations on the projections from the hypothalamus to brainstem and spinal cord: An HRP and autoradiographic tracing study in the cat. *J Comp Neurol* 260:98-126, 1987
 54. Holstege G, Griffiths D, de Wall H, Dalm E: Anatomical and physiological observations on supraspinal control of bladder and urethral sphincter muscles in cat. *J Comp Neurol* 250:449-461, 1986

55. Iggo A: Tension receptors in the stomach and urinary bladder. *J Physiol (Lond)* 128:593–607, 1955
56. Janig W, Morrison JFB: Functional properties of spinal visceral afferents supplying abdominal and pelvic organs, with special emphasis on visceral nociception. In Cervero F, Morrison JFB (eds): *Visceral Sensation. Progress in Brain Research*, vol 67. Amsterdam, Elsevier, 1986, pp 87–114
57. Jensen D: Pharmacological studies of uninhibited neurogenic bladder: The influence of adrenergic excitatory and inhibitory drugs on the cystometograms of neurological patients with normal and uninhibited bladder. *Acta Neurol Scand* 64:401–426, 1981
58. Kakizaki H, Koyanagi T, Shinno Y, et al: An electromyographic study on the urethral rhabdosphincter in normal and chronically rhizotomized cats. Analysis of electrical potentials evoked by sympathetic nerve stimulation. *J Urol* 151:238–243, 1994
59. Kawatani M, Rutigliano M, de Groat WC: Selective facilitatory effects of vasoactive intestinal polypeptide on muscarinic mechanisms in sympathetic and parasympathetic ganglia of the cat. In Hanin I (ed): *Dynamics of Cholinergic Function*. New York, Plenum Press, 1986, pp 1057–1066
60. Kawatani M, Whitney T, Booth AM, de Groat WC: Excitatory effect of substance P in parasympathetic ganglia of cat urinary bladder. *Am J Physiol* 257:R1450–R1456, 1989
61. Keast J, de Groat WC: Immunocytochemical characterization of pelvic neurons which project to the bladder, colon, and penis in rats. *J Comp Neurol* 288:387–400, 1989
62. Keast J, de Groat WC: Segmental distribution and peptide content of primary afferent neurons innervating the urogenital organs and colon of male rats. *J Comp Neurol* 319:615–623, 1992
63. Kruse MN, de Groat WC: Micturition reflexes in decerebrate and spinalized neonatal rats. *Am J Physiol* 258:R1508–R1511, 1990
64. Kruse MN, de Groat WC: Spinal pathways mediate coordinate bladder/urethra sphincter activity during reflex micturition in decerebrate and spinalized neonatal rats. *Neurosci Lett* 152:141–144, 1993
65. Kruse MN, Mallory BS, Noto H, et al: Modulation of the spinobulbospinal micturition reflex pathways in cats. *Am J Physiol* 262:R478–R484, 1992
66. Kruse MN, Mallory BS, Noto H, et al: Properties of the descending limb of the spinobulbospinal micturition reflex pathway in the cat. *Brain Res* 556:6–12, 1991
67. Kruse MN, Noto H, Ropollo JR, de Groat WC: Pontine control of urinary bladder and external urethral sphincter in the rat. *Brain Res* 532:182–190, 1990
68. Kuru M: Nervous control of micturition. *Physiol Rev* 45:424–494, 1965
69. Lapidés J, Sweet RB, Lewis LW: Function of striated muscle in control of urination: II. Effect of complete skeletal muscle paralysis. *Surgical Forum* 6:613–615, 1955
70. Laruelle L: Etude d'anatomie microscopique du nerf vésical sur coupes longitudinales. *Acta Neurol Belg* 48:138–280, 1948
71. Laruelle L: La structure de la moelle épinière en coupes longitudinales. *Rev Neurol* 67:695–725, 1937
72. Learmonth JR: A contribution to the neurophysiology of the urinary bladder in man. *Brain* 54:147–176, 1931
73. Lecci A, Giuliani S, Maggi CA: Effect of the NK-1 receptor antagonist GR 82,334 on reflexly-induced bladder contractions. *Life Sci* 51:PL277–PL280, 1992
74. Lecci A, Giuliani S, Patacchini R, Maggi C: Evidence against a peripheral role of tachykinins in the initiation of micturition reflexes in the anesthetized rat. *J Pharmacol Exp Ther* 264:1327–1332, 1993
75. Levin RM, Ruggieri MR, Wein AJ: Functional effects of the purinergic innervation of the rabbit urinary bladder. *J Pharmacol Exp Ther* 236:452–457, 1986
76. Lundberg JM, Hua X, Cereceda AF: Effects of neuropeptide Y (NPY) on mechanical activity and neurotransmission in the heart, vas deferens, and urinary bladder of guinea pig. *Acta Physiol Scand* 121:325–332, 1984
77. Maggi CA, Barbanti G, Santicioli P, et al: Cystometric evidence that capsaicin-sensitive nerves modulate the afferent branch of micturition reflex in humans. *J Urol* 142:150–154, 1989
78. Maggi CA, Meli A: The role of neuropeptides in the regulation of the micturition reflex. *J Auton Pharmacol* 6:133–162, 1986
79. Mallory BS, Ropollo JR, de Groat WC: Pharmacological modulation of the pontine micturition center. *Brain Res* 546:310–320, 1991
80. Mallory B, Steers WD, de Groat WC: Electrophysiological study of micturition reflexes in the rat. *Am J Physiol* 257:R410–R421, 1989
81. Marston L: Brain and spinal neurons identified in the female rat after injection of pseudorabies into the bladder body, base and external urethral sphincter. *Society for Neuroscience Abstracts* 21:1872, 1995
82. Mattiasson A, Andersson KE, Sjogren C: Adrenoceptors and cholinoreceptors controlling noradrenaline release from adrenergic nerves in the urethra of rabbit and man. *J Urol* 131:1190–1195, 1984
83. Mattiasson A, Ekstrom B, Andersson KE: Interaction between adrenergic and cholinergic nerve terminals in the urinary bladder of rabbit, cat and man. *J Urol* 137:1017–1019, 1987
84. Maurice-Williams RS: Micturition symptoms in frontal tumours. *J Neurol Neurosurg Psychiatry* 37:431–436, 1974
85. McGuire EJ: Experimental observations on the integration of bladder and urethral function. *Transactions of the American Association of Genitourinary Surgeons* 68:38, 1977
86. McGuire EJ: Reflex urethral instability. *Br J Urol* 50:200–204, 1978
87. McGuire EJ, Herlihy E: Bladder and urethral responses to isolated sacral motor root stimulation. *Investigational Urology* 16:219–223, 1978
88. McKenna KD, Nadelhaft I: The organization of the pudendal nerve in the male and female cat. *J Comp Neurol* 248:532–549, 1985
89. McNeill DL, Traugh NE, Vaidya AM, et al: Origin and distribution of NADPH-diaphorase positive neurons and fibers innervating the urinary bladder of the rat. *Neurosci Lett* 147:33–36, 1992
90. Mitchell GAG: Anatomy of the Autonomic Nervous System. Edinburgh, Livingstone, 1953, pp 257–310
91. Morgan C, Nadelhaft I, de Groat WC: The distribution of visceral primary afferents from the pelvic nerve within Lissauer's tract and the spinal gray matter and its relationship to sacral parasympathetic nucleus. *J Comp Neurol* 201:415–440, 1981
92. Morgan CW, de Groat WC, Flekins LA: Axon collaterals indicate broad intraspinal role for sacral pre-ganglionic neurons. *Proc Natl Acad Sci U S A* 88:6888–6892, 1991

93. Nadelhaft I, Vera PL, Card JP, Miselis RR: Central nervous system neurons labelled following the injection of pseudorabies virus into the rat urinary bladder. *Neurosci Lett* 143:271-274, 1992
94. Nanninga J, Frost F, Penn R: Effect of intrathecal baclofen on bladder and sphincter function. *J Urol* 142:101-105, 1989
95. Nathan PW, Smith MC: The centrifugal pathway for micturition within the spinal cord. *J Neurol Neurosurg Psychiatr* 21:177-189, 1958
96. Nergardh A, Boreus LO: Autonomic receptor function in the lower urinary tract of man and cat. *Scand J Urol Nephrol* 6:32-36, 1972
97. Nishimura T, Akasu T, Krier J: Endothelin causes prolonged inhibition of nicotinic transmission in feline colonic parasympathetic ganglia. *Am J Physiol* 261:G628-G633, 1991
98. Nordling L: Influence of the sympathetic nervous system on lower urinary tract in man. *Neurourol Urodyn* 2:3-45, 1983
99. Noto H, Roppolo JR, Steers WD, de Groat WC: Electrophysiological analysis of ascending and descending pathways of the micturition reflex in the rat. *Brain Res* 549:95-105, 1991
100. Noto H, Roppolo JR, Steers WD, de Groat WC: Excitatory and inhibitory influences on bladder activity elicited by electrical stimulation of the pontine micturition center in the rat. *Brain Res* 492:99-115, 1989
101. Onuf (Onufrowicz) B: Notes on the arrangement and function of the cell groups in the sacral region of the spinal cord. *J Nerv Ment Dis* 26:498-504, 1899
102. Persson K, Alm P, Johansson K, et al: Nitric oxide synthase in pig lower urinary tract: immunohistochemistry, NADPH diaphorase histochemistry and functional effects. *Br J Pharmacol* 110:521-530, 1993
103. Persson K, Igawa Y, Mattiasson A, Andersson KE: Effects of inhibition of the L-arginine/nitric oxide pathway in the rat lower urinary tract *in vivo* and *in vitro*. *Br J Pharmacol* 107:178-184, 1992
104. Prieto D, Benedito S, Rodrigo J, et al: Distribution and density of neuropeptide Y immunoreactive nerve fibers and cells in the horse urinary bladder. *J Auton Nerv Syst* 27:173-180, 1989
105. Rohner T, Hannigan J, Sanford E: Altered *in vitro* adrenergic response of dog detrusor muscle after chronic bladder outlet obstruction. *Urology* 11:357-361, 1978
106. Roppolo JR, Booth AM, de Groat WC: The effects of naloxone on the neural control of the urinary bladder of the cat. *Brain Res* 264:355-358, 1983
107. Roppolo JR, Mallory BS, Ragoowansi A, de Groat WC: Modulation of bladder function in the cat by application of pharmacological agents to the pontine micturition center [abstract]. Abstract of Society for Neuroscience 12:645, 1986
108. Roppolo JR, Nadelhaft I, de Groat WC: The organization of pudendal motoneurons and primary afferent projections in the spinal cord of the rhesus monkey revealed by horseradish peroxidase. *J Comp Neurol* 234:475-487, 1985
109. Rudy DC, Awad SA, Downie JW: External sphincter dyssynergia: An abnormal continence reflex. *J Urol* 140:105-110, 1988
110. Rudy DC, Woodside JR: Non-neurogenic neurogenic bladder: The relationship between intravesical pressure and the external sphincter electromyogram. *Neurourol Urodyn* 10:169-176, 1991
111. Sato A, Sato Y, Suzuki A: Mechanism of the reflex inhibition of micturition contractions of the urinary bladder elicited by acupuncture-like stimulation in anesthetized rats. *Neurosci Res* 15:189-198, 1992
112. Satoh K, Shimizu N, Tohyama M, Maeda T: Localization of the micturition reflex at dorsolateral pontine tegmentum of the rat. *Neurosci Lett* 8:27-33, 1978
113. Saum WR, de Groat WC: The actions of 5-hydroxytryptamine on the urinary bladder and on the vesical autonomic ganglia in the cat. *J Pharmacol Exp Ther* 185:70-83, 1973
114. Sheehan D: Spinal autonomic outflows in man and monkey. *J Comp Neurol* 45:341-370, 1941
115. Shimoda N, Takakusaki K, Nishizawa O, et al: The changes in the activity of pudendal motoneurons in relation to reflex micturition evoked in decerebrate cats. *Neurosci Lett* 135:175-178, 1992
116. Sillen U, Rubenson A, Hjalmas K: Central cholinergic mechanisms in L-dopa induced hyperactive urinary bladder of the rat. *Urol Res* 10:239, 1982
117. Sjogren C, Andersson KE, Husted S, et al: Atropine resistance of transmurally stimulated human bladder muscle. *J Urol* 128:1368-1371, 1982
118. Somogyi GT, de Groat WC: Evidence for inhibitory nicotinic and facilitatory muscarinic receptors in cholinergic nerve terminals of the rat urinary bladder. *J Autonom Nerv Syst* 37:89-98, 1992
119. Steers WD, Albo M, van Asselt E: Effects of serotonergic agonists on micturition and sexual function in the rat. *Journal of Drug Development and Research* 27:361-375, 1992
120. Steers WD, Ciambotti J, Etzel B, et al: Alterations in afferent pathways from the urinary bladder in response to partial urethral obstruction. *J Comp Neurol* 310:401-410, 1991
121. Steers WD, Meythaler JM, Herrell D, et al: The effects of acute bolus and continuous intrathecal baclofen on genitourinary dysfunction in patients with disorders of the spinal cord. *J Urol* 148:1849-1855, 1992
122. Su HC, Wharton J, Polak JM, et al: Calcitonin gene-related peptide immunoreactivity in afferent neurons supplying the urinary tract: Combined retrograde tracing and immunohistochemistry. *Neuroscience* 18:737-747, 1986
123. Sundin T, Dhalstrom A, Norlen L, Svedmyr N: The sympathetic innervation and adrenoreceptor function of the human lower urinary tract in the normal state and after parasympathetic denervation. *Investigation Urology* 14:322-328, 1977
124. Swierzezski S, III, Gormley EA, Belville W, et al: The effect of terazosin on bladder function in the spinal cord injured patient. *J Urol* 151:951-954, 1994
125. Tanagho EA, Schmid RA, Gomes de Araujo C: Urinary striated sphincter: What is its nerve supply? *Urology* 20:415-417, 1982
126. Tang PC, Ruch TC: Localization of brainstem and diencephalic areas controlling the micturition reflex. *J Comp Neurol* 106:213-245, 1956
127. Theobald RJ, de Groat WC: The effects of purine nucleotides on transmission in vesical parasympathetic ganglia of the cat. *J Auton Pharmacol* 9:167-182, 1989
128. Thornbury KD, Hollywood MA, McHale NG: Mediation by nitric oxide of neurogenic relaxation of the urinary bladder neck muscle in sheep. *J Physiol (Lond)* 451:133-144, 1992
129. Torrens MJ: Urethral sphincteric responses to stimulation of the sacral nerves in the human female. *Urol Int* 33:22-26, 1978

130. Torrens M, Morrison JFB (eds): *The Physiology of the Lower Urinary Tract*. Berlin, Springer-Verlag, 1987
131. Tran LV, Somogi GT, de Groat WC: Inhibitory effect of neuropeptide Y on adrenergic and cholinergic transmission in the rat urinary bladder and urethra. *Am J Physiol* 266:R1411-R1417, 1994
132. van Waalwijk van Doorn ESC, Remmers A, Janknegt RA: Extramural ambulatory urodynamic monitoring during natural filling and normal daily activities: Evaluation of 100 patients. *J Urol* 146:124-131, 1991
133. Vera PL, Nadelhaft I: Conduction velocity distribution of afferent fibers innervating the rat urinary bladder. *Brain Res* 520:83-89, 1990
134. Vizzard MA, Erdman S, Forstermann U, de Groat WC: Differential expression of nitric oxide synthase in neural pathways to the urogenital organs (urethra, penis, urinary bladder) of the rat. *Brain Res* 646:279-291, 1994
135. Vodusek DB, Light JK, Libby JM: Detrusor inhibition induced by stimulation of pudendal nerve afferents. *Neurourol Urodyn* 5:381-389, 1986
136. Wein AJ: Pharmacologic therapy for incontinence. *Urology* 36:36-43, 1990
137. Westlund KN, Coulter JD: Descending projections of the locus coeruleus and subcoeruleus/medial parabrachial nuclei in monkey: Axonal transport studies and dopamine beta hydroxylase immunocytochemistry. *Brain Res Rev* 2:235-264, 1980
138. White JC: Sensory innervation of the viscera: Studies on visceral afferent neurons in man based on neurosurgical procedures for the relief of intractable pain. *Res Publ Assoc Res Nerv Ment Dis* 23:373-390, 1943
139. Williams JH, Brading A: Urethral sphincter: normal function and changes in disease. In Daniel EE, Tomira T, Tschida S, Watanabe M (eds): *Sphincters*. Boca Raton, CRC Press, 1992, pp 315-338
140. Yoshimura N, Sasa M, Yoshida O, Takaori S: Alpha-1 adrenergic receptor-mediated excitation from the locus coeruleus of the sacral parasympathetic pre-ganglionic neuron. *Life Sci* 47:789-797, 1990
141. Yoshimura N, Sasa M, Yoshida O, Takaori S: Mediation of the micturition reflex by central norepinephrine from the locus coeruleus in the cat. *J Urol* 143:840-843, 1990
142. Zoubek J, Somogyi GT, de Groat WC: A comparison of inhibitory effects of neuropeptide Y on rat urinary bladder, urethra, and vas deferens. *Am J Physiol* 265:R537-R543, 1993

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