Neurophysiology of Stress Urinary Incontinence

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Stress urinary incontinence (SUI) involves involuntary leakage of urine in response to abdominal pressure caused by activities such as sneezing and coughing. The condition affects millions of women worldwide, causing physical discomfort as well as social distress and even social isolation. Until recently, SUI was approached by clinicians as a purely anatomic problem requiring behavioral or surgical therapy. Over the past several years, extensive basic and clinical research in the field of neurourology has enhanced our understanding of the complex neural circuitry regulating normal function of the lower urinary tract. As a result, novel concepts have emerged regarding possible neurologic dysfunctions that might underlie the development of SUI, as well as potential novel strategies for pharmacologic therapy. This article reviews the normal neurophysiologic control of lower urinary tract function and considers potential pharmacologic approaches to correcting SUI.
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Key words: Lower urinary tract • Neurourology • Stress urinary incontinence

The lower urinary tract is composed of the bladder and the urethra—the 2 functional units for storage (the bladder body, or reservoir) and elimination (the bladder neck and urethra, or outlet) of urine. The wall of the bladder body is lined with bundles of intertwining smooth muscle fibers, which comprise the detrusor. The smooth muscles lining the bladder neck and the urethra form the internal sphincter, which is surrounded by striated muscle called the rhab-

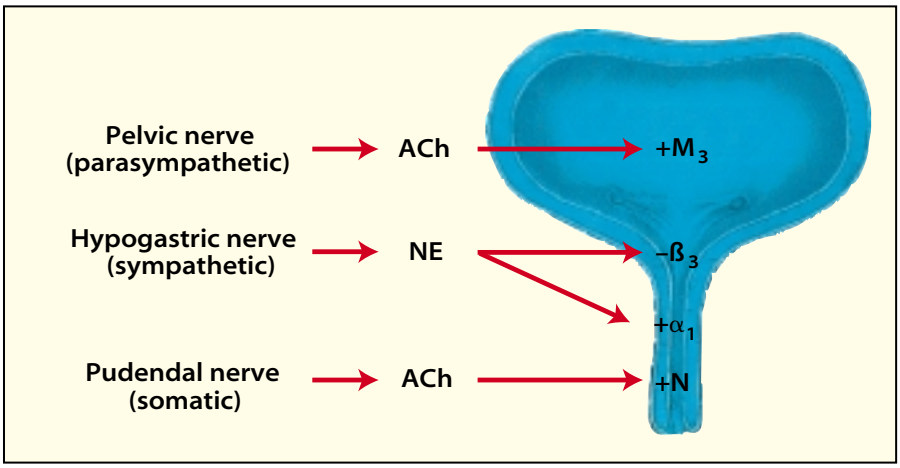

Figure 1. *Innervation of the lower urinary tract: The parasympathetic pelvic nerve stimulates the bladder detrusor muscle, mediated by muscarinic receptors (M_3) being activated by acetylcholine (ACh). The sympathetic hypogastric nerve stimulates urethral smooth muscle and inhibits bladder detrusor, mediated by α_1-adrenergic and $ß_3$-adrenergic receptors, respectively. The somatic pudendal nerve stimulates striated muscle of the external urethral sphincter, mediated by ACh activating nicotinic (N) receptors. NE, norepinephrine. Plus and minus signs indicate neural stimulation and inhibition, respectively.*

dosphincter. Together, the periurethral striated muscle—striated muscle fibers surrounding the urethra—and the rhabdosphincter constitute the external urethral sphincter (EUS).

The bladder and urethra function reciprocally. As the bladder fills during the urine storage phase, the detrusor remains quiescent, with little change in intravesical pressure, adapting to the increasing volume by increasing the length of its muscle cells. Furthermore, neural pathways that stimulate the bladder for micturition are quiescent during this phase, and inhibitory pathways are active.[1-4] The urethral outlet remains closed, with progressively increasing EUS contractions; this progressive increase in EUS activity in response to increasing bladder volume is known as the guarding reflex.

When the bladder volume reaches a critical threshold, the EUS relaxes, detrusor muscles engage in a series of contractions, the bladder neck opens, and elimination occurs. In the human infant, this 2-mode process, generally referred to as the micturition reflex, occurs involuntarily, without sensory awareness of bladder volume or the guarding reflex. As the individual learns that micturition can be controlled, he or she becomes conscious of the bladder as it reaches its critical threshold; initiation of detrusor contractions is postponed, and continence is maintained. Thus, micturition involves a unique combination and interaction of autonomic and voluntary functions.

The lower urinary tract is innervated by parasympathetic, sympathetic, and somatic peripheral nerves that are components of intricate efferent and afferent circuitry derived from the brain and spinal cord. The neural circuits act as an integrated complex of reflexes that regulates micturition, allowing the lower urinary tract to be in either a storage or elimination mode. In persons with urinary incontinence, some aspect of the system is dysfunctional and urine leakage occurs during the storage phase.[5,6] Stress urinary incontinence (SUI)—leakage in response to increased abdominal pressure caused by physical exertion, such as sneezing or coughing—is the most common type of urinary incontinence in women, estimated to affect approximately 25 million women in the United States.[7,8]

Over the past 2 decades, extensive research has helped to elucidate the anatomy and physiology of the neural circuitry regulating lower urinary tract function. As the nature of normal regulation becomes more clearly defined, new possibilities for successful therapeutic approaches to abnormal conditions become evident.

Efferent Pathways: Spinal Cord to Lower Urinary Tract

The smooth muscles of the bladder—the detrusor—are innervated primarily by parasympathetic nerves; those of the bladder neck and urethra—the internal sphincter—are innervated by sympathetic nerves. The striated muscles of the EUS receive their primary innervation from somatic nerves (Figures 1 and 2; Table 1).

Parasympathetic Nerves

The efferent parasympathetic pathway provides the major excitatory innervation of the bladder detrusor.[4,6] Preganglionic axons emerge, as the pelvic nerve, from the sacral parasympathetic nucleus in the intermediolateral column of sacral spinal segments S_2 to S_4 and synapse in the pelvic ganglia, as well as in small ganglia on the bladder wall, releasing acetylcholine (ACh). ACh excitation of postsynaptic neurons is mediated by nicotinic receptors. Postganglionic axons continue for a short distance in the pelvic nerve and terminate in

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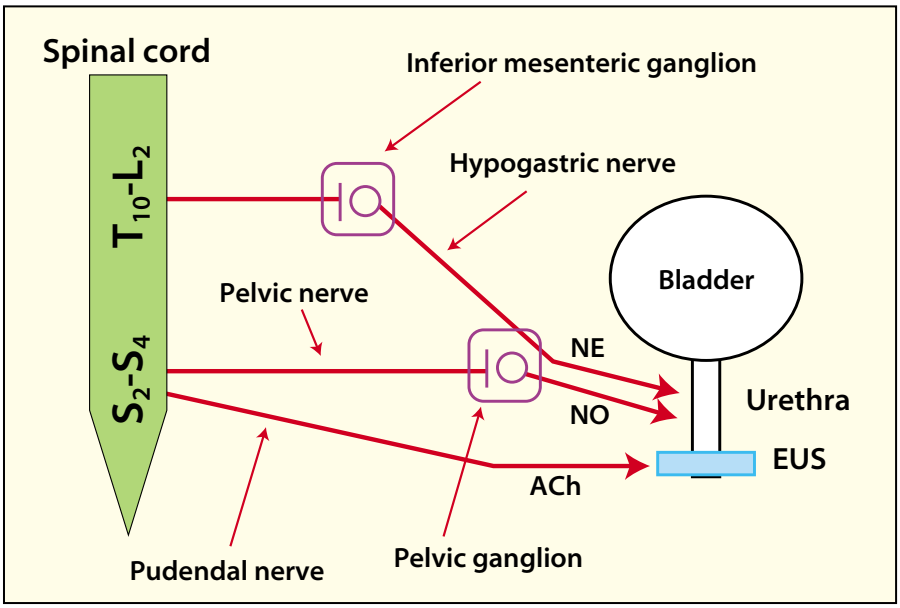


Figure 2. *Major preganglionic and postganglionic neural pathways from the spinal cord to the lower urinary tract: The sympathetic hypogastric nerve, emerging from the inferior mesenteric ganglion, stimulates urethral smooth muscle. The parasympathetic pelvic nerve, emerging from the pelvic ganglion, stimulates bladder detrusor muscle and inhibits urethral smooth muscle. The somatic pudendal nerve stimulates striated muscle of the external urethral sphincter (EUS). ACh, acetylcholine; NE, norepinephrine; NO, nitric oxide; S_2-S_4, sacral segments of the spinal cord; T_{10}-L_2, thoracolumbar segments of the spinal cord.*

the detrusor layer, where they transmit ACh to the smooth muscle fibers, with consequent contractions of the bladder. This stimulatory effect of ACh at the postganglionic axon terminal is mediated by muscarinic receptors in detrusor cells. Two muscarinic subtypes, M_2 and M_3, are known to be present in the bladder; although M_2 is most abundant in detrusor cells, the M_3 subtype is the major receptor mediating stimulation of detrusor contractions.[4,9,10]

Although ACh is the principal excitatory transmitter at the parasympathetic/detrusor cell synapse, it is not the only one: the anticholinergic drug atropine does not completely eliminate neurogenic bladder contractions. Adenosine triphosphate (ATP)-induced stimulation of bladder smooth muscle contractions has been demonstrated in numerous mammalian species, and this purine nucleotide is considered to be a parasympathetic cotransmitter responsible for atropine-resistant detrusor activity.[4,10] The ATP effect appears to be mediated by stimulation of one or more members of the P2X family of purinoceptors.

Although purinergic stimulation is considered only a minor contributor to normal bladder function in humans,[4] the presence of P2X purinoceptors—predominantly the $P2X_1$ subtype—has been demonstrated in biopsies of normal and abnormal human bladders.[11] In an analysis conducted by O'Reilly and colleagues,[11] the concentration of $P2X_1$ receptors was significantly higher in abnormal bladders compared with control bladders, prompting the investigators to suggest that upregulation of purinergic activity might contribute to development of the overactive bladder associated with pathologic conditions such as outlet obstruction.

In addition to the parasympathetic stimulation of bladder smooth muscle, some postsynaptic parasympathetic neurons exert a relaxation effect on urethral smooth muscle, most likely via transmission of nitric oxide (NO).[1,4,10,12] Thus, as the bladder contracts during the elimination phase, the internal urethral sphincter relaxes.

Sympathetic Nerves

Sympathetic nerves stimulate smooth muscle contraction in the urethra and bladder neck and cause relaxation of the detrusor. Preganglionic sympathetic neurons are located in the intermediolateral column of thoracolumbar cord segments T_{10} to L_2.[4,10] Most of the preganglionic fibers synapse with postganglionic neurons in the inferior mesenteric ganglia. The preganglionic neurotransmitter is ACh, which acts via nicotinic receptors in the postganglionic neurons. Postganglionic axons travel in the hypogastric nerve and transmit norepinephrine (NE) at their terminals. The major terminals are in the urethra and bladder neck, as well as in the bladder body. NE stimulates contraction of urethral and bladder neck smooth muscle via α_1-adrenoceptors and causes relaxation of detrusor via $ß_2$-adrenoceptors and $ß_3$-adrenoceptors, the latter being most predominant.[13]

Some preganglionic sympathetic fibers pass through (but do not terminate in) the inferior mesenteric ganglia and ultimately synapse with postganglionic neurons in the paravertebral ganglia. The postganglionic sympathetic axons that emerge from the paravertebral ganglia form synapses with postganglionic parasympathetic neurons in the pelvic ganglia, where, by acting on α_1- or α_2-adrenoceptors, they can exert facilitatory or inhibitory influence, respectively, on parasympathetic transmission.[4,14-16]

Somatic Nerves

Somatic nerves provide excitatory innervation to the striated muscles of the EUS and pelvic floor. The efferent

Table 1
Efferent Pathways: Spinal Cord to Lower Urinary Tract (LUT)

Peripheral Nervous System	Site of Exit From Spinal Cord	Peripheral Ganglia	Preganglionic Neurotransmitter	Postganglionic or Motor Neuron Pathway	Postganglionic or Motor Neuron Target in LUT	Postganglionic or Motor Neuron Neurotransmitter	Excitatory (+) or Inhibitory (–) Effect on Target	Target Receptors Mediating Effect
Parasympathetic	SPN (S_2-S_4)	Pelvic	ACh	Pelvic nerve	Detrusor	ACh	+	M_3
						ATP	+	P2X
					Urethral smooth muscle	NO	–	–
Sympathetic	Thoracolumbar (T_{10}-L_2)	Inferior mesenteric	ACh	Hypogastric nerve	Urethral smooth muscle	NE	+	α_1-adrenoceptor
					Detrusor	NE	–	$ß_2$- or $ß_3$-adrenoceptor
Somatic	Onuf's nucleus (S_2-S_4)	–	–	Pudendal nerve	Striated muscle of EUS	ACh	+	N

ACh, acetylcholine; ATP, adenosine triphosphate; EUS, external urethral sphincter; M_3, muscarinic receptor; N, nicotinic receptor; NE, norepinephrine; NO, nitric oxide; P2X, family of purinoceptors; S_2-S_4, sacral segments of spinal cord; SPN, sacral parasympathetic nucleus; T_{10}-L_2, thoracolumbar segments of spinal cord.

motoneurons are located in Onuf's nucleus, along the lateral border of the ventral horn in sacral spinal cord segments S_2 to S_4.[4,17] The motoneuron axons are carried in the pudendal nerve and release ACh at their terminals. The ACh acts on nicotinic receptors in the striated muscle, inducing muscle contraction to maintain closure of the EUS.[4,17,18]

Efferent Pathways: Supraspinal Components

Information accrued from decades of animal experiments and clinical studies has clearly shown that normal coordination of storage and voiding functions requires integration from supraspinal input.[2,4,15,18–21]

Investigations into the supraspinal circuitry that mediates lower urinary tract function have utilized numerous experimental approaches. One particularly valuable methodology involved the use of neurotropic viruses, such as the pseudorabies virus (PRV), to trace and identify specific brain regions involved in lower urinary tract function. The retrograde movement of PRVs injected into a target organ can be traced from periphery to brain as the viruses cross synapses and infect all central nervous system (CNS) neurons in the active pathway.[4,15] Alternatively, anterograde axonal tracing can follow the direct path of neurons in a selected brain region to their terminals.

Other experimental approaches have included tracing neurotransmitters histochemically, determining effects of electric stimulation or bilateral lesions in various brain regions, and conducting pharmacologic studies with numerous neurotransmitter agonists or antagonists. Ultimately, investigators have been able to identify—particularly in rats and cats—populations of central neurons that contribute to specific lower urinary tract functions, as well as the pathways and mediating neurotransmitters involved.

Following PRV injection into the bladder, several regions in the brainstem were found to be infected with the virus and were thus identified as components of the supraspinal-spinal-lower urinary tract pathway: the laterodorsal tegmental nucleus, known as the pontine micturition center (PMC); the locus coeruleus, in the rostral pons; the medullary raphe nucleus; the periaqueductal gray matter; and noradrenergic cell group A5. Virus-infected cells were also present in the hypothalamus and the cerebral cortex. Injection of PRV into the urethra resulted in similar patterns of infected brain areas, indicating that similar populations of supraspinal neurons influence urethral and bladder activity.

Ventrolateral to the PMC is a region referred to as the pontine storage center (PSC). The PMC and PSC are the final integrative centers, receiving and integrating input from afferent spinal cord nerves and more rostral brain regions and controlling an on/off switch for the lower urinary tract. Neurons in the PSC project directly to the motoneurons in Onuf's nucleus, and stimulation of PSC neurons causes EUS contractions. Neurons in the PMC project to the sacral parasympathetic nucleus, and stimulation of PMC neurons results in bladder contractions as well as relaxation of the internal urethral sphincter and EUS.

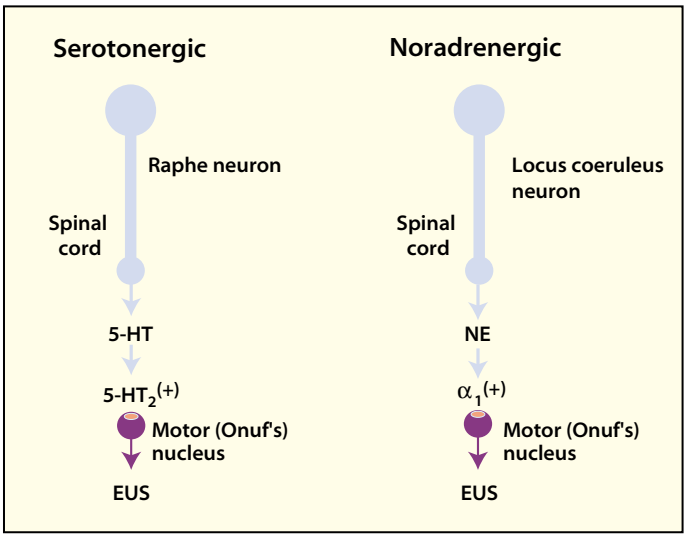


Figure 3. *Serotonergic and noradrenergic innervation of Onuf's nucleus in the sacral spinal cord: Serotonin (5-HT), derived from the raphe nucleus in the brainstem, and norepinephrine (NE), derived from the locus coeruleus, both provide excitatory innervation to motor neurons of Onuf's nucleus. This, in turn, is believed to facilitate excitation of the external urethral sphincter (EUS), contributing to maintenance of urethral closure during the urine storage phase.*

Glutamic acid, the major CNS excitatory neurotransmitter, appears to function as the on switch for the EUS; while the pudendal nerve is receiving excitatory glutamatergic transmission, EUS contractions continue and the lower urinary tract remains in the storage mode. Suppression of glutamatergic transmission serves as the final signal for EUS relaxation and bladder elimination.

Numerous other supraspinal neurotransmitters have modulatory roles in lower urinary tract function. Two that appear to have a positive neuromodulatory effect on EUS contractions are NE and serotonin.[4,10,15,19,20] Onuf's nucleus is densely innervated by serotonergic and noradrenergic terminals, largely derived from neurons in the raphe nucleus and locus coeruleus, respectively (Figure 3). Rajaofetra and colleagues[19] demonstrated that, in baboons with transected spinal cords, NE had disappeared from Onuf's nucleus; however, some serotonin remained, demonstrating a more local source for a portion of this neurotransmitter.

Results of experiments with receptor subtype–specific serotonin and NE agonists and antagonists indicate that both of these monoamines can have a stimulatory effect on EUS activity.[22-24] There is currently a considerable amount of experimental and clinical data supporting the theory that the supraspinal serotonergic and noradrenergic input to Onuf's nucleus facilitates glutamate-induced activation of the pudendal nerve and, thereby, helps to maintain the EUS in a storage mode (Figure 4).[4,10,15,20,25-28]

Other brain neurotransmitters that contribute to coordination of lower urinary tract function include dopamine and γ-aminobutyric acid, the latter being a principal inhibitory neurotransmitter in the brain.[4,10]

Afferent Pathways

The pelvic, hypogastric, and pudendal nerves carry sensory information in afferent fibers from the lower urinary tract to the lumbosacral spinal cord.[4,6,17] The somata of the pelvic and pudendal afferent nerves are located in dorsal root ganglia at sacral segments S_2 to S_4; the somata of the hypogastric nerve are located in dorsal root ganglia at thoracolumbar segments T_{10} to L_2. After entering the spinal cord, the primary afferent fibers of the pelvic and pudendal nerves travel rostrocaudally in Lissauer's tract. Sensory information is transmitted to second-order neurons in the spinal cord.

The pelvic nerve afferents monitor bladder volume during the storage phase and the amplitude of bladder contractions during urination. Thus, this sensory nerve serves to initiate the micturition reflex, as well as to reinforce the drive that maintains bladder contractions. Pelvic nerve afferents are composed of small, myelinated Aδ fibers and unmyelinated C fibers. Electrophysiologic

Figure 4. *Diagrammatic cross-section of the sacral spinal cord at the level of Onuf's nucleus: Norepinephrine and serotonin facilitate glutamate-induced activation of pudendal nerve motor neurons, which innervate the urethral external sphincter. DC, dorsal columns; DH, dorsal horn; LF, lateral funiculus; VH, ventral horn.*

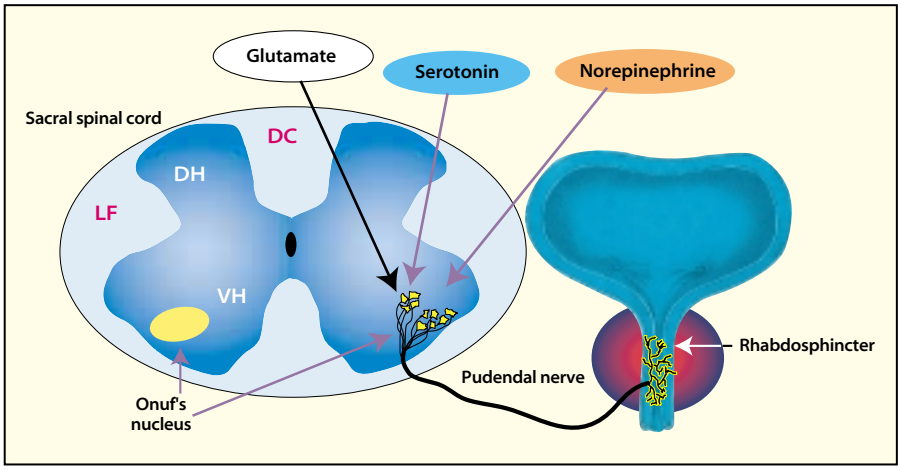


Table 2
Afferent Pathways From the Bladder to the Spinal Cord: Properties of Afferent Fibers in the Pelvic Nerve*

Fiber Type	Normal Function	Effect of Inflammation
Aδ (myelinated)	Function as mechanoreceptors responding to tension in bladder wall; transmit sensation of bladder fullness	Increase discharge at lower pressure threshold
C (unmyelinated)	Generally have high threshold for mechanical stimuli but function as nociceptors, responding to chemical irritants and overdistention	Become more mechanosensitive during inflammation; unmask new afferent pathway
	Small population of C fibers are mechanosensitive and respond to tension in bladder wall	Increase discharge at lower threshold

*Carry impulses responsible for initiating the micturition reflex from muscle layers in the bladder to the spinal cord.

studies in cats and rats determined that the normal micturition reflex is mediated by the Aδ fibers, which respond to bladder distention. The C fibers, having high thresholds, are unusually unresponsive to mechanical stimuli, such as bladder distention, and have been referred to as the "silent C fibers." However, these fibers respond to stimuli exerted by noxious chemicals or cold (Table 2).[4]

Immunohistochemical studies have identified various neuropeptides in the bladder afferent neurons, including substance P (SP), calcitonin gene-related peptide (CGRP), intestinal polypeptide, and enkephalin. Both SP and CGRP are widely present among C fiber afferent neurons (Figure 5).[4]

Overview: Interacting Reflexes

Multiple reflex pathways operate between the CNS and the lower urinary tract. At the simplest level of organization, the central pathways operate as on/off switching circuits that maintain a reciprocal relationship between the bladder and urethra (Figure 6).[29] These circuit switches are, of course, timed precisely: for example, when urethral smooth muscle is being stimulated by the hypogastric nerve to contract, the bladder detrusor is not receiving stimulatory input from the pelvic nerve. However, superimposed on the on/off switches from each neural center to its appropriate peripheral target, there are additional pathways directly from each center to the reciprocal target. Thus, while one pathway from the sympathetic hypogastric nerve transmits stimulatory information to urethral smooth muscle, another pathway from the same nerve transmits inhibitory information to the bladder.[4,10] Comparable dual pathway targets have been observed with the parasympathetic pelvic nerve, providing stimulatory input to the bladder and inhibitory input to the urethra. In this respect, the circuitry also involves on and off signals.

Circuits operating within the lower urinary tract further contribute to the complexity of reflex control. A primary example of this type of circuitry is the guarding reflex, which involves increasing contractions of the EUS in response to increasing bladder volume.[2,4,18]

The Storage Phase

Until the volume of urine in the bladder reaches a critical threshold for voiding, the detrusor is quiet, the bladder having a low and relatively constant level of internal pressure during filling.[4] This is, to some extent, achieved passively: 1) the intrinsic viscoelasticity of detrusor muscles

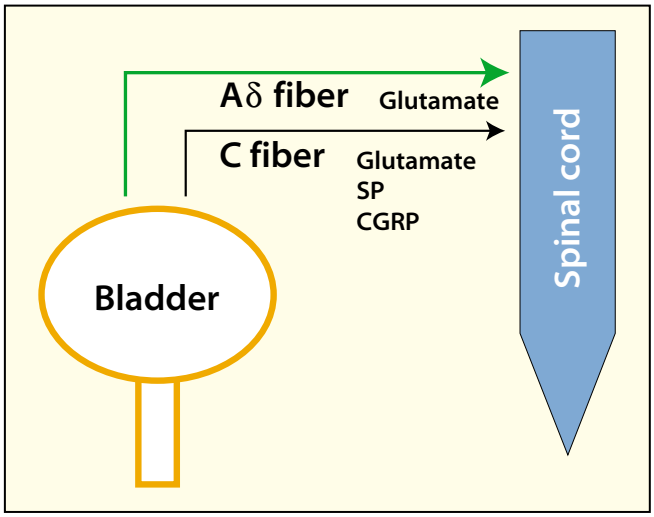


Figure 5. *Afferent fibers transmitting sensory information from the lower urinary tract to the spinal cord: Glutamate is a neurotransmitter present in both the Aδ and C fibers; additional neurotransmitters in the C fibers include substance P (SP) and calcitonin gene-related peptide (CGRP).*

permits the bladder wall to adjust to increasing volume by stretching, and 2) the stimulatory parasympathetic pathway is quiescent. However, there are also major neurogenic contributions toward maintaining an inactive bladder during the storage phase (Figure 7).[3,4]

The guarding reflex is initiated by distention of the bladder during filling, which activates stretch-sensitive mechanoreceptors in the bladder wall. These mechanoreceptors, in turn, generate afferent signals to the sacral spinal cord, where pudendal motoneuron efferents are activated. The pudendal efferents stimulate EUS contractions, thereby maintaining outlet resistance and urinary continence. The guarding reflex rises in intensity as bladder volume increases. Park and colleagues[2] consider the EUS guarding reflex—"this beautiful piece of bioengineering . . ."—as the possible key to bladder control, serving as the essential on/off switch for voiding.

The bladder-to-sympathetic pathway reflex is also triggered by bladder distention: stimulated bladder afferents activate an intersegmental pathway from sacral cord to thoracolumbar sympathetic nerves. The activated sympathetic nerves stimulate contraction of the internal urethral sphincter and inhibit bladder activity. (The inhibition is achieved via direct restraint of detrusor contractions, as well as inhibition of the parasympathetic pathway.[14])

An additional possible reflex might be considered an extension of the guarding reflex: it has been suggested that contracting EUS muscles could activate pudendal afferents, which could lead—via spinal interneurons—to direct inhibition of parasympathetic motoneurons.[2] Finally, pudendal motoneurons to the EUS can also be activated by stimulation of urethral/perineal afferents[30]; this reflex may represent a mechanism that is

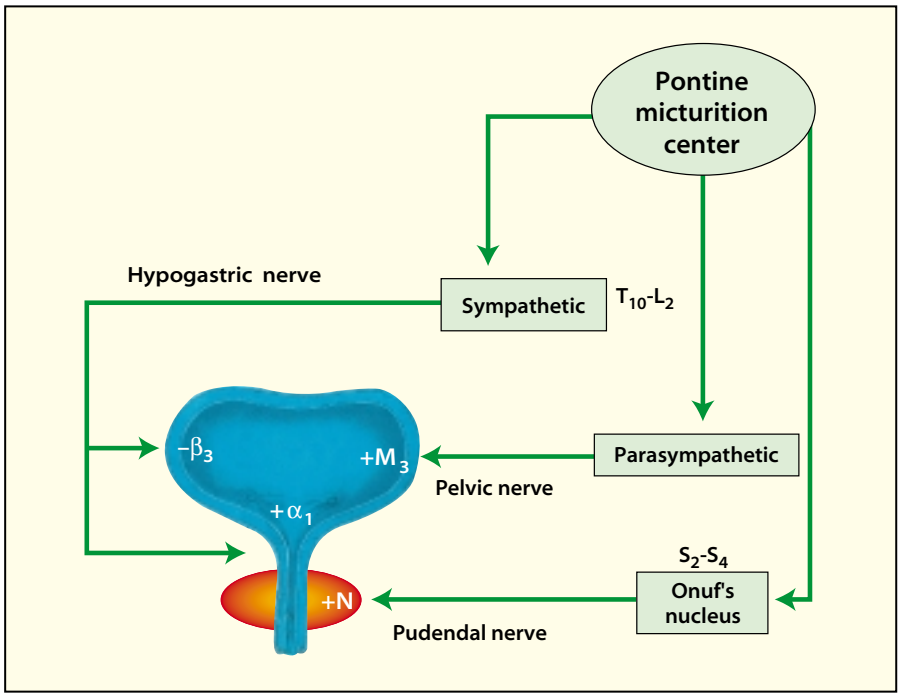
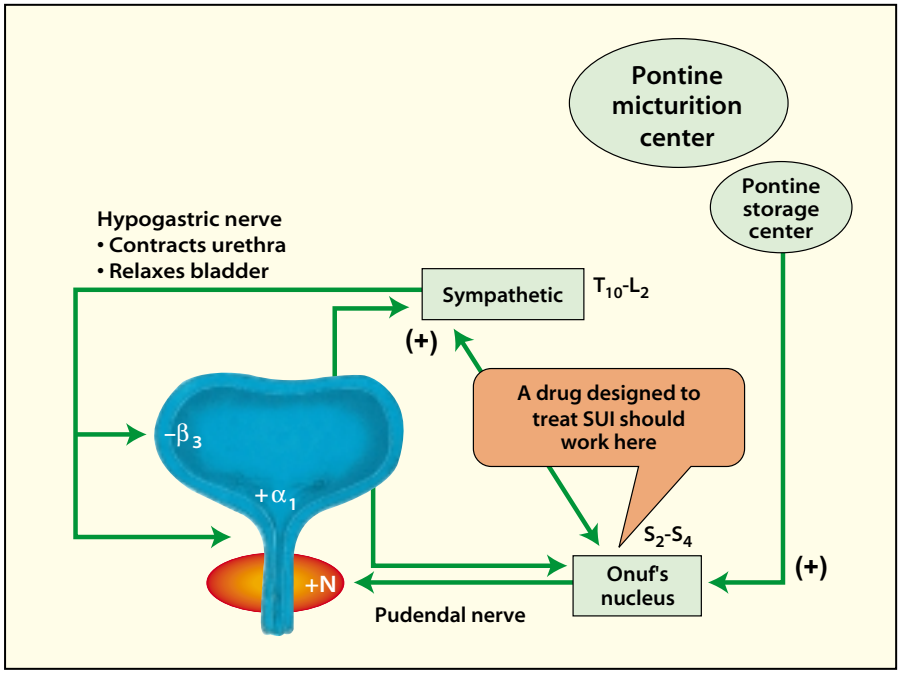


Figure 6. *Major reflex pathways from the pontine micturition center in the brainstem to the lower urinary tract via the spinal cord regulating both micturition and urine storage. α_1, α-adrenergic receptors; β_3, ß-adrenergic receptors; M_3, muscarinic receptors; S_2-S_4, sacral segments of the spinal cord; T_{10}-L_2, thoracolumbar segments of the spinal cord. Plus and minus signs indicate neural stimulation and inhibition, respectively.*

Figure 7. *Major reflex pathways to the lower urinary tract initiating and maintaining urine storage. α_1, α-adrenergic receptors; β_3, ß-adrenergic receptors; N, nicotinic receptors; S_2-S_4, sacral segments of the spinal cord; T_{10}-L_2, thoracolumbar segments of the spinal cord; SUI, stress urinary incontinence. Plus and minus signs indicate neural stimulation and inhibition, respectively.*



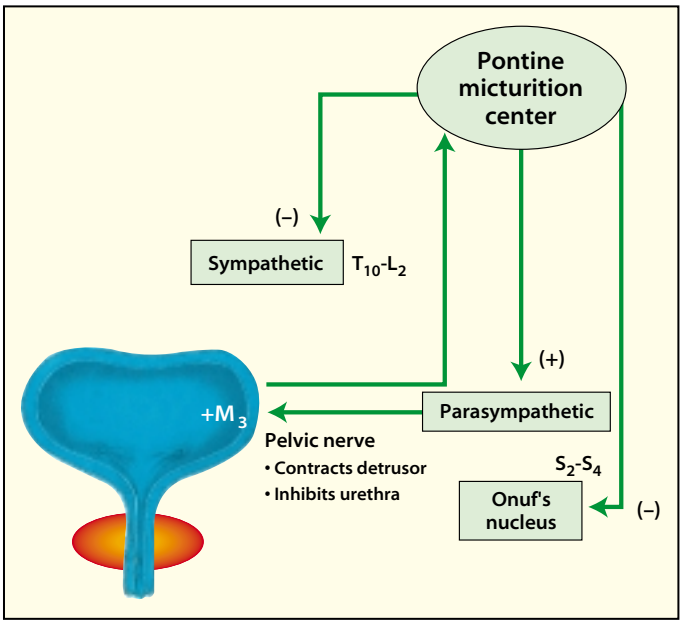


Figure 8. *Major reflex pathways from the pontine micturition center to the lower urinary tract stimulating initiation and completion of micturition. M_3, muscarinic receptors; S_2-S_4, sacral segments of the spinal cord; T_{10}-L_2, thoracolumbar segments of the spinal cord. Plus and minus signs indicate neural stimulation and inhibition, respectively.*

generated by proprioceptive input from the urethral/pelvic floor.

Alterations in any one of these reflex cycles might well contribute to lower urinary tract dysfunction; the therapeutic effects achieved with sacral nerve root neuromodulation most likely reflect activation of one or more of the reflexes by electric stimulation of the sacral spinal root.[7]

The reflexes involved in urine storage are integrated in the spinal cord and appear to function normally in animals with supraspinal transections. However, many patients with lesions that interrupt brainstem pathways have impaired voluntary control of micturition. Thus, although initiation of the storage phase seems to be established within the spinal cord, maintaining a stable urethral resistance apparently requires supraspinal input.[4,18] It is known that the PSC, the center in the dorsolateral pons, provides descending inputs that activate pudendal motoneurons and thus increase urethral resistance.

Elimination

The essential first step in micturition is relaxation of the EUS muscles. In human infants, the initiating stimulus occurs when the bladder volume reaches a critical threshold. In adult humans with normal lower urinary tract function, the individual has sensory awareness of a full bladder and the guarding reflex is intensified until voluntary elimination is possible. Both initiation and normal completion of the elimination process—whether voluntary or autonomous—unequivocally depend on input from the brain (Figure 8).[4,18]

In order for the guarding reflex to be reversed and the EUS relaxed, a final inhibitory signal must be generated from the PMC. Bladder afferent fibers in the pelvic nerve form synapses in the spinal cord, and axons from the second-order neurons travel rostrally to the micturition center. The micturition center integrates this sensory information with signals from more rostral brain regions and ultimately generates inhibitory input to the sympathetic and somatic centers in the spinal cord and stimulatory input to the parasympathetic center. This spino-bulbo-spinal reflex results in relaxation of the EUS and internal urethral sphincter, followed by contraction of detrusor muscles, increase in bladder pressure, and flow of urine. Secondary reflexes elicited by the flow of urine through the urethra facilitate bladder emptying.[3,31]

Potential Targets for Therapy

Extensive research in neurourology over the past several years has greatly increased our understanding of the neural mechanisms controlling normal lower urinary tract function and has pointed to potential causes of dysfunction. This enhanced understanding provides a rational basis for new therapeutic approaches to disorders of the lower urinary tract.

No therapy currently in use has had widespread success for patients with SUI.[25] Until recently, SUI was considered primarily in terms of local anatomic damage, and patients were, and still are, treated primarily with physical measures. These physical approaches include conservative techniques, such as pelvic floor muscle training, biofeedback, and intravaginal urethral compression devices. Periurethral bulking agents and retropubic suspension procedures are among the more invasive physical approaches to correcting conditions of SUI. There has been a dearth of novel pharmacologic strategies for increasing urethral resistance.

Drugs traditionally used to treat SUI tend to target the smooth muscle or postjunctional muscarinic or adrenergic receptors.[10] However, our increased understanding of the complex neural circuitry regulating lower urinary tract function and the neurotransmitters involved has identified afferent neurons, efferent nerve terminals, urothelial cells, and the CNS as additional potential targets for pharmacologic intervention. Numerous specific possibilities have been proposed.

Lepor and colleagues[32] compared neuroreceptor densities in biopsies of

normal and hyperreflexic human bladders and reported a lower-than-normal density of muscarinic receptors and a high density of α-adrenoceptors in the abnormal bladders. The normal detrusor response to noradrenergic innervation is one of relaxation, mediated by ß-adrenoceptors. It was therefore hypothesized that the high concentration of α-adrenoceptors in the hyperreflexic bladder might contribute to the condition of hyperactivity. Another suggested approach to ameliorating overactivity of the bladder is to activate the detrusor-relaxing $ß_3$-adrenoceptor that is normally acted on by NE from the hypogastric nerve.[13]

It has been speculated that, in women with mixed urge and stress incontinence, leakage of urine into the urethra can stimulate urethral afferents and thereby induce or increase detrusor instability.[31] Can SUI induce urge incontinence? If so, it may be logical to treat SUI first in women with mixed incontinence. Results of a recent study with rats by Jung and colleagues[31] indicate that SUI can indeed induce and/or increase detrusor instability.

NO is an important inhibitory neurotransmitter, transmitted to the urethra by the pelvic nerve to inhibit contraction of the internal urethral sphincter. NO may also be involved in controlling afferent nerve activity.[10] Results of studies with rats have indicated that intravesical application of NO can suppress hyperactivity induced by some irritants.[33]

Two potential targets for SUI therapy that have recently drawn considerable attention are serotonin and NE, which are transmitted to Onuf's nucleus from the raphe nucleus and locus coeruleus, respectively. These monoamines are believed to facilitate activation of the pudendal nerve that stimulates EUS contraction. Duloxetine, a drug that inhibits reuptake of both serotonin and NE and thereby enhances their potency at the site of action, is currently undergoing clinical trials for the treatment of SUI.[27]

Given the complexity of central and peripheral neural mechanisms controlling lower urinary tract function and the variety of neurotransmitters involved, it is likely that SUI can be caused by dysfunction at numerous sites. It is therefore also likely that many types of drugs will eventually be used to treat SUI, reflecting individual patients' needs.[5,10] An important goal that has been emphasized is the identification of drugs with "uroselectivity," that is, efficacy in correcting lower urinary tract problems with a minimum of side effects at other sites.[10]

Lastly, an additional research focus has been the development of advanced drug delivery systems, such as intravesical therapy, that can provide significant treatment advantages, including long-term efficacy and fewer side effects.[34] ■

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Main Points

- Stress urinary incontinence (SUI) affects millions of women worldwide, causing physical discomfort as well as severe social distress. Until recently, SUI was approached by physicians as a purely anatomic problem requiring behavioral or surgical therapy.
- The smooth muscles of the bladder—the detrusor—are innervated primarily by parasympathetic nerves; those of the bladder neck and urethra—the internal sphincter—are innervated by sympathetic nerves. The striated muscles of the external urethral sphincter (EUS) receive their primary innervation from somatic nerves.
- Results of experiments with receptor subtype–specific serotonin and norepinephrine (NE) agonists and antagonists indicate that both of these monoamines can have a stimulatory effect on EUS activity. There is currently a considerable amount of experimental and clinical data supporting the theory that the supraspinal serotonergic and noradrenergic input to Onuf's nucleus facilitates glutamate-induced activation of the pudendal nerve and, thereby, helps to maintain the EUS in a storage mode.
- Multiple reflex pathways operate between the central nervous system (CNS) and the lower urinary tract. At the simplest level of organization, the central pathways operate as on/off switching circuits that maintain a reciprocal relationship between the bladder and urethra.
- Our increased understanding of the complex neural circuitry regulating lower urinary tract function and the neurotransmitters involved has identified afferent neurons, efferent nerve terminals, urothelial cells, and the CNS as potential targets for pharmacologic intervention. Two targets for SUI therapy that have recently drawn considerable attention are serotonin and NE.

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