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Review Article

Neurophysiology of Micturition and Continence in Women

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Abstract: Micturition and continence involve the coordination of complex neural events between the central and peripheral nervous systems. An understanding of these events provides a foundation for the treatment of voiding disorders in women such as stress urinary incontinence, urge incontinence and interstitial cystitis. The purpose of this paper is to comprehensively review the neuroanatomy, neurophysiology and neuropharmacology of micturition and continence. However, a brief section discussing clinical correlations will follow each of these topics to help integrate the basic science with clinical obervations.

Keywords: Continence; Females; Micturition; Neuroanatomy; Neuropharmacology; Neurophysiology

Introduction

The bladder and its outlet, the urethra, serve two functions: to store urine without leakage at low pressures, and 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). 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 the storage and elimination of urine, many of the neural circuits controlling micturition demonstrate a phasic or switch-like pattern of activity distinct from other viscera. The voluntary control of the function of the bladder and urethra requires the participation of higher cortical centers. 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 both 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 micturition reflexes has led to the development of electrical stimulation in the treatment of urge and stress urinary incontinence in women. Neuropharmacologic manipulations designed to reduce bladder instability have arisen from experimental findings.

Neuroanatomy

Efferent 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 S2–S4 sacral parasympathetic nucleus (SPN) [1,2]. These cholinergic preganglionic neurons exit the spinal cord in the ventral spinal nerves to form the pelvic nerve. They then synapse on to cholinergic postganglionic neurons in the pelvic plexus, which reside in close proximity to the bladder, or on the

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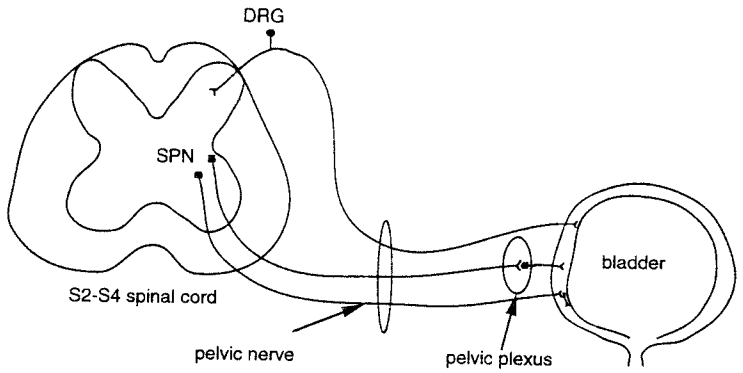

Fig. 1. Parasympathetic afferent and efferent innervation of the bladder and urethra. The preganglionic efferents originate in the sacral parasympathetic nucleus (SPN) of the S2–S4 spinal cord. Preganglionics synapse in the pelvic plexus or within the bladder or urethra. Neurons conveying afferent signal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

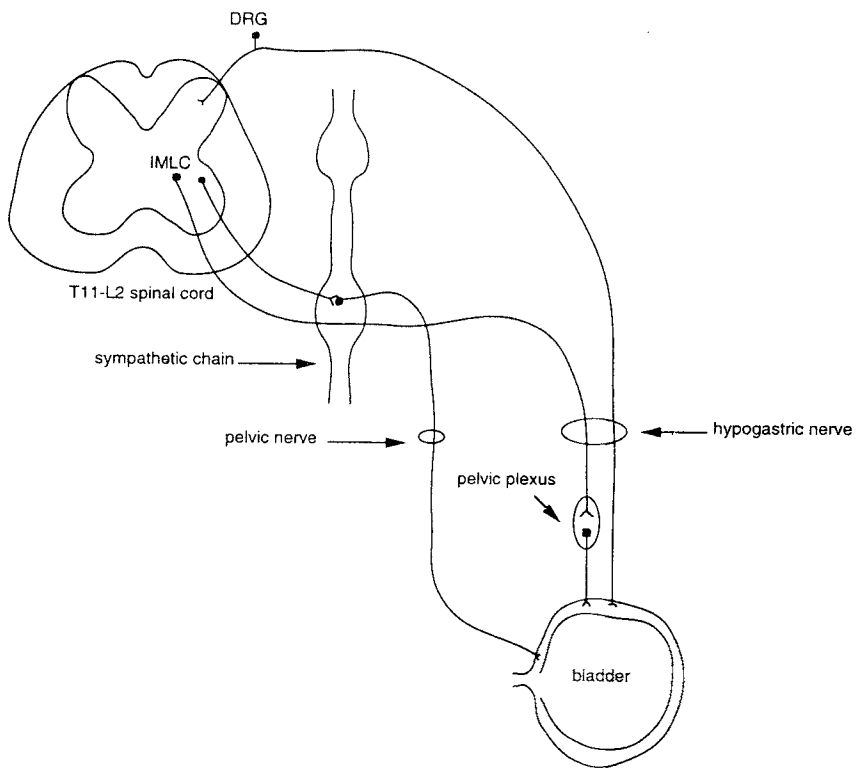

Fig. 2. Sympathetic afferent and efferent innervation of the bladder and urethra. The preganglionic efferents originate in the intermediolateral cell column (IMLC) as well as the nucleus intercalatus (not shown) of the T11–L2 spinal cord. Preganglionics can synapse on postganglionic in the sympathetic 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.

intramural ganglia within the bladder (Fig. 1). The pelvic plexus is a network of neural fibers within the pelvic fascia lateral to the rectum [3]. The left and right pelvic plexuses interconnect posteriorly behind the rectum. The pelvic plexus contains a mix of both parasympathetic and sympathetic fibers.

Sympathetic nerves supplying the pelvic viscera arise from T11 to L2 thoracolumbar spinal cord in the nucleus intercalcatus located in the intermediolateral cell column (Fig. 2). 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 usually course through the sympathetic chain without synapsing. These preganglionics can then synapse on noradrenergic neurons of the pelvic plexus or within the bladder or urethra.

There is debate as to the role that the sympathetic efferents play in the low 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 [4–7]. This observation suggests that increasing sympathetic outflow to the bladder can inhibit urge incontinence or detrusor overactivity.

The efferent neurons innervating the external urethral sphincter, or rhadosphincter, and the pelvic floor musculature originate from the anterior horn of the S2–S4 spinal cord. These motor neurons arise from an area termed Onuf's nucleus [8]. The axons of these neurons

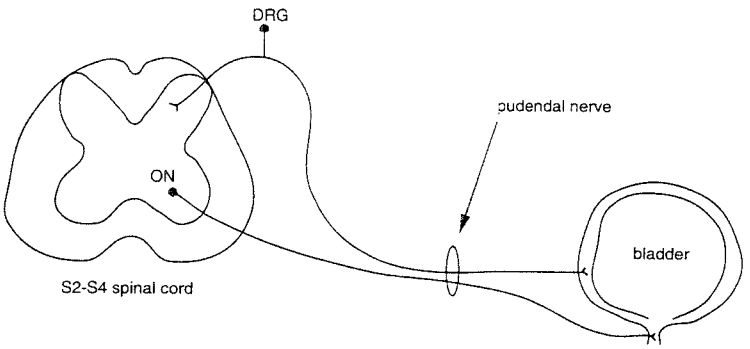

Fig. 3. Some afferent and efferent innervation of the bladder and urethra. Efferent neurons reside in Onuf's nucleus (ON) of the S2–S4 spinal cord. The efferents supply the innervation of the external urethral sphincter through the pudendal nerve. Data that indicate that the external urethral sphincter 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.

exit the spinal cord as the pudendal nerve to innervate muscles of the pelvic diaphragm and the external urethral sphincter (Fig. 3). Evidence exists that the external urethral sphincter is also innervated by the pelvic nerve [9,10]. Stimulation of the sacral nerves (parasympathetic efferents) after sacral rhizotomy has been shown to increase bladder pressure as expected, but also reciprocally to decrease urethral pressure in both animals and humans, implying that there is innervation of the urethra through the parasympathetic nervous system [11,12]. Based on animal models, Elbadawi proposes that the efferent outflow to the urethral sphincter consists of parasympathetic, sympathetic and somatic nerves [13,14]. Electrophysiological data also show that fibers in the hypogastric nerves supply the striated muscle in the external urethral sphincter [15]. Branching sacral preganglionic parasympathetic neurons are closely linked physiologically and anatomically to these motor neurons, providing potential feedback to Onuf's nucleus during voiding [16–17]. Thus, efferent pathways are well suited to serve as an activating and switching circuits.

Afferent Pathways

The afferent pathway from the bladder to the central nervous system, which is responsible for micturition and pain sensation, originates in the S2–S4 dorsal root ganglia (Fig. 1) [18]. These neurons are bipolar and send long processes to the urinary bladder smooth muscle and epithelium as well as the urethra. Based on animal studies, 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 [19,22]. The mechaniceptive afferents responsible for initiation of the micturition reflex travel in the pelvic nerve [22–26]. The mechanisms for central decoding of afferent signals from the bladder and urethra into different sensations (pain, distension, urgency etc.) are unknown, but 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 due to different patterns of discharge in the same population of afferent neurons (gate theory) [27].

High threshold afferents transmit nociceptive (pain) information from the lower urinary tract to T11–L2 DRG [19,21]. Somatic afferents from the external urethral sphincter travel in the pudendal nerve (Fig. 3) and terminate in regions that overlap with parasympathetic afferents from the pelvic nerve from the bladder [28–31].

Supraspinal Centers

Afferent and efferent innervation to the bladder and urethra is ultimately under the coordination 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 [32,33]. Lesions in these areas can produce detrusor hyperreflexia, yet preserve 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 [23,25,34–38].

Electrophysiological studies support the concept of a pontine micturition center. Stimulation of bladder afferents produces field potentials in the pontine micturition center [39]. Electrical and chemical activation of discrete areas of the pons induces bladder contractions and relaxation of the urethral sphincter [40–43]. Electrical stimulation of afferents in the pelvic nerve elicits a long latency (120–140 ms) discharge measured in the bladder nerves which corresponds to the combined ascending latency (80 ms) and descending latency (40 ms) [26,39]. These findings are consistent with the notion that a supraspinal (spinobulbospinal) reflex relayed through the pons governs micturition.

Neuroanatomic Clinical Correlation

The concept of a neuroanatomic cause for both pelvic floor prolapse and stress urinary incontinence has been proposed by several investigators [44–49]. Because the pudendal nerve is an efferent nerve to both the pelvic floor musculature and the external urethral sphincter, injury to it may cause both weakness of the pelvic floor, resulting in pelvic floor prolapse, and relaxation of the external urethral sphincter, resulting in stress urinary incontinence. A laxity in the pelvic floor also prevents adequate compensatory compression of the urethra during increases in intra-abdominal pressure. It has

been shown that pudendal nerve blockade in women resulted in a significant decrease in maximal urethral closure pressure [50], supporting the importance of this nerve in maintenance of the tone of the external urethral sphincter. The pudendal nerve may be damaged during childbirth, especially secondary to a prolonged second stage of labor [51]. Vaginal dissection during pelvic floor reconstruction resulted in a higher incidence of pudendal nerve injury compared to abdominal approaches [52]. This observation could explain the 50% long-term (>5 years) failure rate for transvaginal needle suspension for genuine stress urinary incontinence [53]. Therefore, the pudendal nerve plays an important role in the maintenance of continence and pelvic floor integrity.

However, the concept of neurogenic dysfunction in pelvic floor prolapse and stress urinary incontinence has recently been challenged. Investigators found that the majority of women with both stress urinary incontinence and cystocele were able to strongly contract their levator ani and thus reduce their cystocele [54]. These investigators inferred from these findings that neuromuscular damage of the levator ani muscle is not a common cause of pelvic organ prolapse.

Another area of clinical importance is iatrogenic trauma to the innervation of the lower urinary tract during extensive pelvic dissection, as in abdominoperineal resection (APR) for rectal carcinoma or radical pelvic lymphadenectomy. Since the pelvic plexus contains mixed sympathetic, parasympathetic and somatic components which innervate the bladder, urethra and external urethral sphincter, injury to this plexus may result in a variety of urinary symptoms, such as decreased bladder sensation, decreased ability of the bladder to empty, decreased bladder compliance, urgency and incontinence. The incidence of bladder dysfunction after extensive pelvic surgery has been estimated to be 10%–17% [55]. Clinicians need to be aware of these potential voiding complications related to disruption of the innervation of the bladder and urethra.

Neurophysiology

Voiding Reflexes

At some point as the bladder fills with urine, bladder afferent activity relayed by the mechanoceptive neurons will trigger a micturition reflex. This causes a bladder contraction, with a reciprocal decrease in outlet or urethral resistance. The bladder afferents fire at threshold intravesical pressures of less than 15–20 cmH_O [20]. The conduction velocities of the afferent signal will range from 1.2 to 30 m/s corresponding to the A-δ, lightly myelinated fibers [20,23,26,56,58]. First-order 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 (Fig. 4) [40–42,58–60].

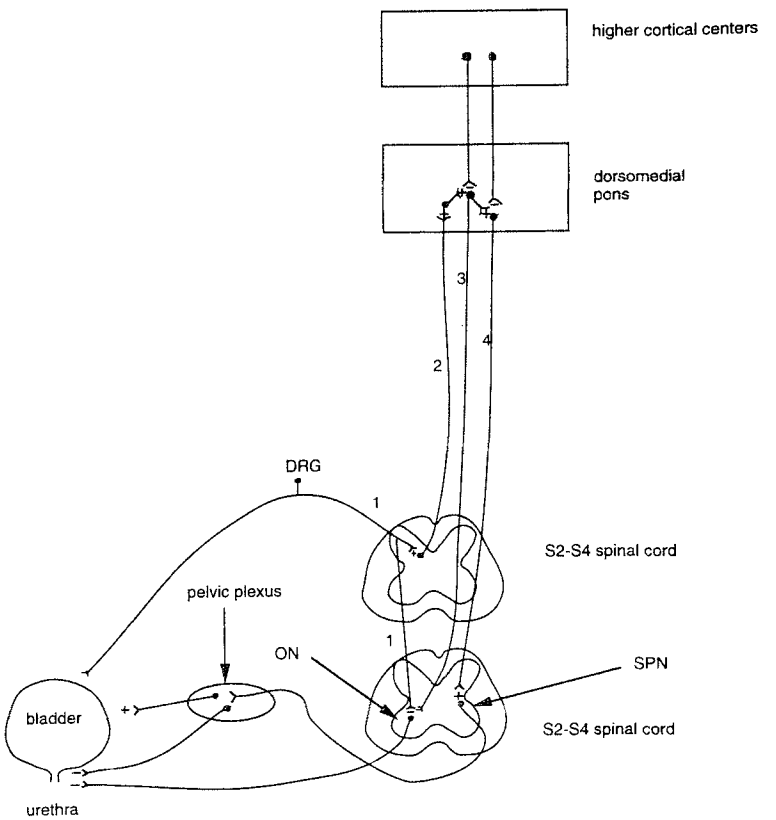

Fig. 4. Voiding reflexes. 1. Mechanoreceptor afferents on bladder fire at a threshold bladder pressure. The bladder afferents provide excitatory input on to second-order neurons in the dorsal horn of the S2–S4 spinal cord. Additionally, afferent projections into Onuf's nucelus (ON) inhibit these motor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

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 [59]. However, without ascending input from the bladder the contraction of the detrusor is diminished, and it appears that a normal contraction requires continuous pontine stimulation via bladder afferents. It appears that once a detrusor contraction begins, the tension-generated afferent discharge reinforces the micturition reflex. This observation could partially explain why patients with sensory neuropathies, such as diabetes, sometimes fail to empty their bladders completely.

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 [61]. 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 (due to involuntary detrusor contractions) urinary incontinence. It could also explain why procedures to correct stress incontinence also cure urge incontinence [62].

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 [58,63]. 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 motor neurons in Onuf's nucleus during urination. The descending input from the dorsomedial pons inhibits these pudendal motor neurons (Fig. 4) [40–42,58–60]. In additional, axon collaterals from sacral preganglionic neurons project to Onuf's nucleus [17]. With firing of bladder preganglionics, inhibition of sphincter motor neurons occurs, possibly by hyperpolarizing these cells [63]. Lastly, certain pudendal afferents hyperpolarize and thereby inhibit pudendal motor neurons [64]. Descending pontine projections and preganglionic axons also may synapse on interneurons that regulate sphincter motor neurons.

In addition to the inhibition of the external urethral sphincter, the smooth muscle of the urethra relaxes during voiding. Ambulatory urodynamics demonstrate a fall in urethral pressure seconds before the rise in intravesical pressure [65]. However, this response may be due to a decrease in activity of the external urethral sphincter. Parasympathetic pathways in the pelvic nerve relax the bladder outlet, since electrical stimulation of sacral nerve roots lowers urethral pressure even with paralysis of the striated external urethral muscle [11,12,66]. 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 [67–70]. Alternatively, parasympathetic neurons may merely block the sympathetic outflow responsible for maintaining the tone of urethral smooth muscle [71]. Clinically, this urethral relaxation response is most noticeable in patients with acontractile bladders. Distension 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 [72,73] and is a rare cause of stress incontinence.

Storage Reflexes

A quiescent bladder during filling 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. The 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 and sacral dorsal rhizotomies dramatically alter compliance [74–76]. If, however, substantial changes in the extracellular matrix have occurred in response to injury, obstruction or inflammation, the neural contribution may be insignificant. Continence is further maintained by inhibition of the parasympathetic efferents and activation of the sympathetic and somatic efferents.

As the bladder fills, mechanoceptive input is relayed by the pelvic nerve to the dorsal horn of the sacral spinal cord [22–26]. In the spinal cord an intersegmental pathway from the sacral to the thoracolumbar cord stimulates sympathetic preganglionics. Activation of these preganglionics, which travel in the hypogastric nerve, provides excitatory outflow to the bladder base and urethral, resulting in an increase in outlet resistance (Fig. 5) [6]. In animals the hypogastric outflow inhibits the detrusor smooth muscle and the micturition reflex [7,77,78]. However, the importance of sympathetic innervation on the bladder during filling is controversial because sympathectomy has no appreciable effect on urine storage, and patients with a deficiency of dopamine β-hydroxylase, the enzyme that converts dopamine to norepinephrine, void normally [79,80]. Despite these observations, this reflex may be important in humans only when the bladder increases in capacity or after neural injury.

The supraspinal center regulating urine storage resides in the dorsolateral pons (Fig. 5). Descending input from this region restricts sacral preganglionic outflow to the bladder as well as exciting the pudendal motor neurons to increase outlet resistance [40,81]. This inhibition may be due to the release of transmitters that depress neural activity at several key sites, including afferent receiving areas in the dorsal horn and preganglionic neurons in the intermediolateral cell column.

Afferents from pelvic organs such as the vagina, uterine cervix and rectum can inhibit the sacral pre-

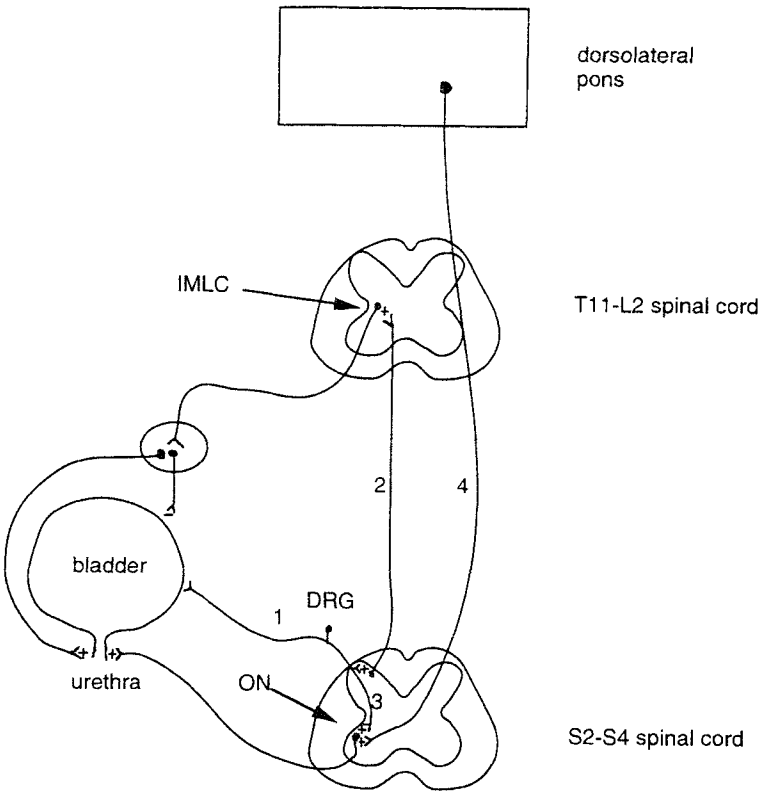

Fig. 5. Storage reflexes. 1. In addition to viscoelastic properties of the bladder smooth muscle, afferents from the bladder excite second-order neurons in the dorsal horn of S2–S4 spinal cord. Afferents from the vagina or rectum can also excite these second-order neurons to increase sympathetic outflow (see #2). This explains the neurophysiologic basis for intravaginal stimulation in treatment of urge incontinence. DRG = dorsal root ganglia. 2. These interneurons project intraspinally to the thoracolumbar spinal cord on to preganglionic sympathetic neurons in the intermediolateral cell column (IMLC). The sympathetic outflow is increased, thereby inhibiting detrusor contraction as well as increasing urethral resistance. 3. Bladder afferents also project on to Onuf's nucleus (ON) to increase motor neuron firing and thereby increase bladder outlet resistance. 4. Descending projections from the dorsolateral pons also excite neurons ON.

ganglionics to the bladder as well as increase urethral resistance (visceral–visceral reflex) [82,83]. This concept explains why electrostimulation of the vagina or rectum is useful in the treatment of detrusor instability [84]. Somatovisceral reflex occurs when cutaneous stimulation inhibits micturition. Inhibition of reflex micturition occurs with acupuncture [85] and with stimulation of muscle afferents from limbs [86]. Likewise, penile or clitoral stimulation can diminish detrusor hyperreflexia in suprasacral spinal cord-injured individuals [87] via pudendal afferents.

A guarding reflex exists in which afferents from bladder filling and other pelvic structures provide positive feedback to Onuf's nucleus, thereby increasing outlet resistance (Fig. 5) [88]. The external urethral sphincter neurons exhibit a tonic discharge that increase during bladder filling. As we can voluntarily contract the external urethral sphincter and pelvic floor muscles, the motor area of the cerebral cortex must also project on to these areas.

Peripheral mechanisms can also 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 [4]. Purinergic (ATP), enkephalinergic, tachykinin, β-aminobutyric acid (GABA) and serotonergic mechanisms also inhibit cholinergic transmission in bladder ganglia [89–94]. These mechanisms allow the pelvic ganglia to function as a filter of inhibitory and excitatory input into the bladder. Excitation of prejunctional muscarinic-2 (M_2) receptors with an agonist decreased acetycholine release by the nerve terminals in the bladder [95]. Finally, local factors such as endothelin can depress preganglionic transmission in the pelvic ganglia [96]. Taken together, these mechanisms help ensure that only high-output efferent activity of the proper frequency reaches the bladder, making it somewhat difficult for random activity to cause a detrusor contraction.

Neurophysiologic Clinical Correlation

The successful use of intravaginal stimulation (IVS) to control detrusor overactivity in urge incontinence in women can be explained by our current understanding of the neurophysiology of continence and micturition. Because of the bladder's dual role in storage and elimination of urine, many of the neural circuits controlling micturition demonstrate a phasic or switch-like pattern of activity. An imbalance of these functions may be manifested clinically as urge incontinence or detrusor instability. Therefore, accentuation of storage reflexes may be utilized to treat a patient with urge incontinence and detrusor instability.

IVS induces a long-lasting reflex discharge in the hypogastric nerve which supplies sympathetic input into the bladder [97] (Fig. 5). This sympathetic reflex inhibits the parasympathetic activity in the pelvic nerve elicited

by bladder filling [97]. The optimum frequency (Hz) and amplitude (V) of IVS to maximally inhibit parasympathetic efferent activity have been determined in experimental animals [97]. In addition, there is direct inhibition of the detrusor muscle by sympathetic activity [7]. The enhancement of storage reflexes explain the clinical usefulness of IVS in the treatment of detrusor instability or urge incontinence, which has been borne out in many clinical series. This therapy is especially useful for those patients who are refractory to maximal pharmacologic intervention.

IVS has also been shown to be effective for stress urinary incontinence. It induces an increase in urethral pressure attributable to direct stimulation of efferent nerves to the urethra [98]. Secondly, it is theorized that IVS reinforces a reflex similar to the bulbocavernosus reflex, which increases the tone of the pelvic muscles [97]. Finally, IVS may cause sprouting of nerve terminals innervating the pelvic floor muscles and urethra, which could increase the overall tone [97].

The combination of stress urinary incontinence and urge incontinence is not uncommon in many patients. Because both of these conditions are treatable by IVS with minimal side effects, initial management with IVS can be considered. Biofeedback methods, which combine patient-initiated voluntary contractions of the pelvic muscles with an intravaginal device to provide feedback to the patient, have also been shown effective in combination with IVS in the treatment of urge and/or stress urinary incontinence [99].

Neuropharmacology

Neuroeffector Junction and Ganglionic Transmission

Parasympathetic postganglionics release acetylcholine (ACh), which excites muscarinic receptors (M_2 and M_3) in the smooth muscle of the bladder and urethra. However, non-adrenergic non-cholinergic (NANC) transmitters, most notably adenosine triphosphate (ATP), also contract detrusor smooth muscle via the P2 (purinergic) receptors (Fig. 6) [100,101]. Other candidates for NANC transmitters include neuropeptides colocalized in terminals with ACh, such as vasoactive intestinal peptide (VIP) and neuropeptide Y (NPY). These neuropeptides can influence the release of classical transmitters such as ACh and norepinephrine [102–105]. Once activated, postganglionics are influenced by both positive and negative feedback mechanisms to help maintain a detrusor contraction.

During micturition, at the pelvic plexus preganglionic parasympathetic neurons release ACh, which activates nicotinic receptors on parasympathetic postganglionics (Fig. 6). However, other compounds may modulate ganglionic transmission, such as NANC, leucine, enkephalin (ENK), endothelin, VIP and substance P (SP) [89–91,96]. This capability allows the nervous system to finely adjust the degree of excitatory input to the bladder. Thus at the central, ganglionic and neuroeffector levels, detrusor activity is tightly controlled.

The role of cholinergic input to the urethra is less well understood. Cholinergic agonists contract urethral smooth muscle through the action of muscarinic receptors. However, activation of muscarinic receptor on adrenergic terminal varicosities within the urethra inhibits norepinephrine release [106]. This scheme has been used to explain parasympathetic-induced urethral relaxation [11,27,71]. As cholinergic agonists also contract urethral smooth muscle, relaxation may depend on non-cholinergic parasympathetic transmitters such as nitric oxide (NO) (Fig. 6) [67–70]. Nitric oxide synthase (NOS), which catalyses the production of NO from L-arginine, is expressed by nerves innervating the bladder and urethra [107]. Furthermore, inhibition of NO pro-

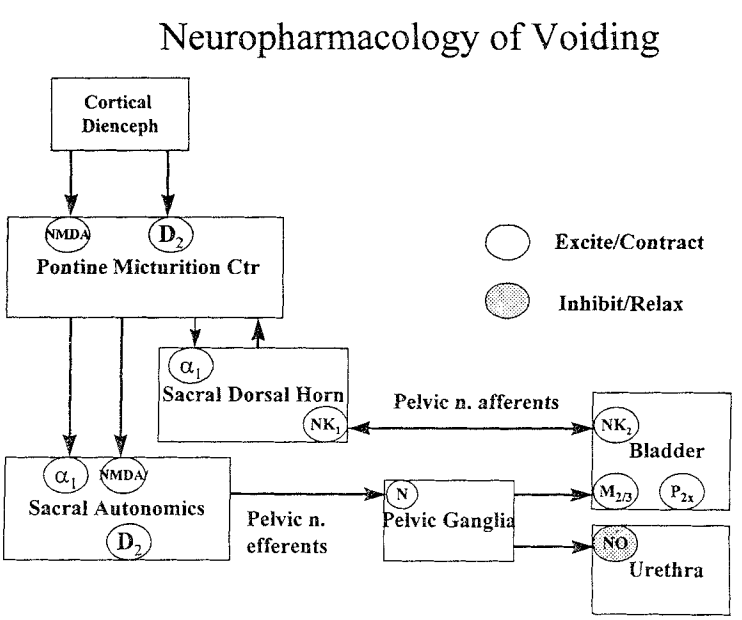

Fig. 6. Neuropharmacology of voiding. Diagrammatic representation of the pharamacology of micturition based on immunohistochemical and pharmacological investigations. Drugs or neurotransmitters (not depicted) which interact with its receptor (depicted with an oval) produce either an excitatory or inhibitory action, and this is depicted at the pontine, sacral spinal cord or peripheral levels. The receptor and its drug or neurotransmitter in parentheses are: NMDA = glutamate receptor (glutamate), D2 = dopamine receptor (dopamine), α_1 = adrenergic receptor (norepinephrine), NK1 and NK2 = neurokinin receptor (substance P), N = nicotinic receptor (acetylcholine), M_2 or M_3 = muscarinic receptor (acetylcholine), NO = nitric oxide receptor (nitric oxide), P2 = purinergic receptor (ATP).

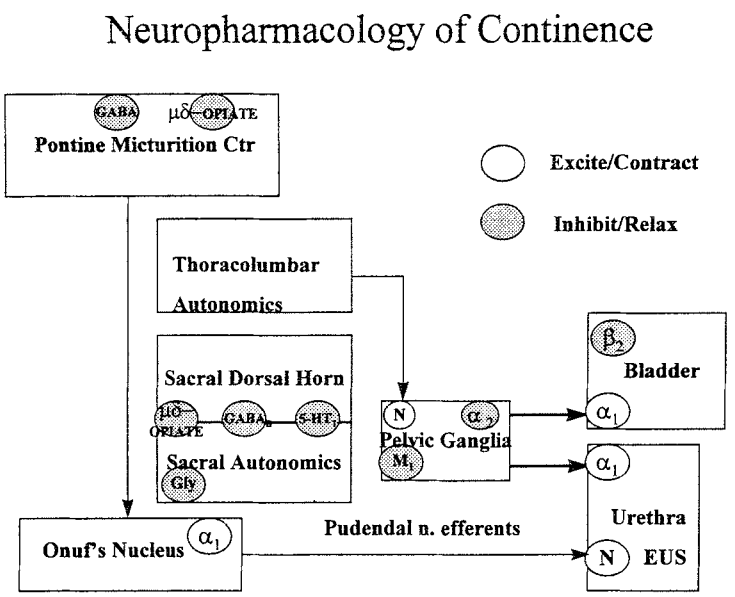

Fig. 7. Neopharmacology of continence. Diagramatic representation of the pharmacology of urinary storage based on immunohistochemical and pharmacological investigations. Drugs or neurotransmitters (not depicted) which interact with its receptor (depicted with an oval) produce either an excitatory or inhibitory action and this is depicted at the pontine, sacral spinal cord or peripheral levels. The receptor and its drug or neurotransmitter in parentheses are: GABA = α-aminobutyric acid receptor (α-aminobutyric acid), μ- or δ-opiate = opiate receptor (opiates), α_1, α_2, or β_2 = adrenergic receptors (norepinephrine), 5-HT_1 = 5-hydroxytryptamine receptor (serotonin), Gly = glycine receptor (glycine), N = nicotinic receptor (acetylcholine), M_1 = muscarinic receptor (acetylcholine).

duction reduces electrically induced relaxation of the urethra [67–69].

Sympathetic postganglionics release norepinephrine, which contracts urethral and bladder base smooth muscle, which may be important in continence (Fig. 7). This contraction is mediated through the α_1-adrenoceptor [77,78,108]. In contrast, the action of norepinephrine at β_2-adrenoceptors relaxes smooth muscle in the bladder body (Fig. 7) [108]. As in parasympathetics, preganglionic sympathetic neurons release ACh, which also activates nicotinic receptors on the postganglionic sympathetic neurons (Fig. 7). Stimulation of α_1- and β-receptors on preganglionic parasympathetic neurons facilitates transmission in the pelvic ganglia, whereas in cats, α_2 stimulation inhibits transmission, suggesting that adrenergic nerves influence cholinergic transmissions in the pelvic ganglia (Fig. 7) [4].

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 pathological conditions, including bladder outlet obstruction, bladder denervation, and possibly spinal cord injury [5,109–111]. These pharmacological changes may explain why α-$_1$-adrenergic blockers improve voiding symptoms caused by obstructive voiding and decrease detrusor hyperreflexia secondary to spinal cord injury, but demonstrate minimal effect in normal individuals [112].

The striated muscles of the lower urinary tract and pelvis are innervated by cholinergic fibers in the pudendal nerve [14,113]. Acetylcholine acts on nicotinic receptors located at the motor end plate, which elicits a muscle contraction (Fig. 7). Botulinum toxin and pancuronium both paralyse the external urethral sphincter [114,115]. However, neither drug produces urinary incontinence. Muscle fibers of the external urethral sphincter also receive noradrenergic input [13–15,108,113]. Therefore, the striated urethral sphincter appears to be unique in that it receives both autonomic and somatic inputs.

Sensory Neurotransmitters

Afferents projecting to the sacral dorsal root ganglia contain VIP, SP, calcitonin gene-related peptide (CGRP), ENK, cholecystokinin (CCK), glutamate, pituitary adenylate cyclase and NO [24,102,104,116–119]. Therefore, it is no 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 distension in anesthetized animals [24,117,120,121]. In humans, intravesical administration of capsaicin transiently reduces bladder sensation and irritable voiding [121,122]. These observations imply that SP or related peptides play a role in micturition, especially encoding for bladder pain. SP and related neurokinins act via NK-1 and NK-2 receptors (Fig. 6). Selective NK-2 receptor antagonists inhibit bladder contraction evoked by capsaicin or exogenous SP [123]. In the dorsal horn, NK-1 receptor antagonists inhibit micturition. However, neither NK1 nor NK2 antagonists abolish distensions-evoked micturition [124]. Nevertheless, these findings indicate that neurokinins play an important modulatory role in afferent transmission from the bladder (Fig. 6) [125].

The thoracolumbar dorsal root ganglia and dorsal horn contain neuropeptides identified in parasympathetic afferents, although their distribution is somewhat different [116]. Some investigators have postulated that each afferent neuropeptide possesses a distinct functional role [126]. For example, SP is usually 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 proven [27].

Neurotransmitters in Supraspinal Centers and Spinal Cord

A variety of excitatory and inhibitory inputs regulate pontine function. Enkephalinergic varicosities are found in the pons as well as the SPN and Onuf's nucleus [89,102]. The pontine micturition center is under tonic inhibition by enkephalinergic neurons (Fig. 7). In the cat, intracerebroventricular injections of ENK analogos, μ- and δ-opiate agonists, increase the micturition threshold [127]. Administration of naloxone, an opioid antagonist, decreases the volume at which a micturition reflex occurs, which further supports a storage role for enkephalinergic or opiate pathways [128]. 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 [129].

Activation of *n*-methyl diaminoaspartate (NMDA or glutamate) and dopamine receptors facilitates neurotransmission in the pons and spinal cord. Glutamate is released from visceral afferents in the dorsal horn of the spinal cord, spinal interneurons, descending projections from the pontine micturition center, and 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 micturition center in cats increases bladder activity [130–132]. Apomorphine, a dopamine agonist, facilitates bladder emptying in humans [133].

Other potential neurotransmitters which may be involved in urinary storage include glycine, GABA and 5-hydroxytryptamine (5-HT or serotonin) (Fig. 7). In general, these substances inhibit bladder activity by interaction with afferent terminals, interneurons or parasympathetic preganglionics in the sacral spinal cord [134]. Intrathecal baclofen, a GABA agonist, raises the threshold for micturition in patients with spinal pathology, probably by inhibiting afferent input [74,76]. Similarly, administration of 5-HT to thoracolumbar preganglionic neurons facilitates vesicosympathetic storage reflexes. Many 5-HT agonists, when administered systemically, inhibit micturition [135]. 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 contains norepinephrine (Figs 6 and 7) [137]. However, intrathecal norepinephrine excites sacral preganglionic neurons, thereby facilitating micturition overall [43,138]. Similarly, it has been shown that α_1-adrenergic receptor antagonists (e.g. prazosin) inhibit bladder contractions elicited by pontine stimulation [43,138].

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. Secondly, a receptor-specific drug acts at multiple sites, which may have opposing effects on bladder function. Lastly, transmitter mechanisms evolve during growth and differentiation and are profoundly altered following injury, disease and aging.

Neuropharmacologic Clinical Correlations

Different pharmacological agents are used to treat both urge and stress incontinence based on our understanding of neuropharmacology. The prototypical medication in controlling detrusor instability is the anticholinergic oxybutynin. Its anticholinergic action theoretically prevents or delays an uninhibited bladder contraction. By reducing cholinergic excitation and/or reducing intravesical pressure, oxybutynin may allow an increase in volume before an afferent volley in triggered. However, its overall usefulness is limited by systemic side effects such as dry mouth, constipation and drowsiness. In addition, it is contraindicated in patients with narrow-angle glaucoma and a history of seizures, since oxybutynin lowers the seizure threshold. These systemic side effects may be circumvented by intravesical instillation of oxybutynin. Finally, oxybutynin would not be expected to prevent bladder contractions mediated by non-cholinergic mechanisms. Terodiline has been shown clinically to be effective in controlling detrusor hyperactivity [139,140], presumably through its calcium and cholinergic antagonism. Imipramine, a tricyclic antidepressant, has also been used extensively for urge incontinence. Part of its action may be anticholinergic effects, but its central effect in inhibiting 5-HT reuptake probably facilitates vesicosympathetic storage reflexes.

α_1-Adrenergic receptor blockers may also have therapeutic efficacy in the treatment of bladder instability in women. The clinical efficacy of α_1-blockers in relieving irritative voiding symptoms in men secondary to benign prostatic hypertrophy has been well documented [141,142]. Experimentally, there is evidence for a central action of α_1-blockers in reducing detrusor hyperactivity. Systemic and intrathecal α_1-adrenergic receptor blockade abolishes centrally induced bladder hyperactivity in experimental animals [43,138,143]. α_1-Receptors located in the sensory receiving areas of the dorsal horn of the spinal cord may modulate input from the bladder, and norepinephrine released from descending pathways regulates bladder function [144]. Although they have not been tested clinically, these observations suggest that α_1-blockers may have a role in the treatment of urge-type symptoms or detrusor instability in women.

Because there are more adrenergic receptors at the bladder neck and proximal urethra than in the rest of the bladder [77,78,108], sympathomimetics have been used to increase the bladder neck and urethral tone to prevent stress urinary incontinence. Again, one major drawback in the pharmacological use of these agents is cardiovascular side effects.

There is increased nerve density in the suburothelial and detrusor muscle layers in the bladders of female patients with interstitial cystitis (IC) [145,146]. Since the submucosa is putatively where the bladder sensory nerves are located, it is theorized that the increased suprapubic pain in patients with IC is due to nerve proliferation. There is altered metabolism of the neurotransmitters neuropeptide Y and calcitonin gene-related peptide, leading to speculation that the phenomenon of neurogenic inflammation plays a role in IC similar to what has been described in rheumatoid arthritis and neurogenic inflammation of the airways [147,148]. The notion of altered sensory innervation in IC is also supported by the fact that transcutaneous electrical nerve stimulation (TENS) is an effective form of therapy in controlling pain [149]. The theory of TENS is that stimulation of myelinated afferents causes subsequent activation of segmental inhibitory outflow (gate theory) [150], thereby diminishing pain. In addition, TENS may decrease bladder hyperactivity associated with IC in a way similar to IVS.

Conclusion

Micturition and continence require switching from activation of the 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. These mechanisms make it somewhat difficult to initiate a bladder contraction, but once a micturition reflex is activated it is difficult to abort. Drugs used to treat voiding disorders work by affecting these pathways. Since 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.

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