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Neural Control of the Lower Urinary Tract: Peripheral and Spinal Mechanisms

L. Birder[1,2,*], **W. de Groat**[2], **I. Mills**[3], **J. Morrison**[4], **K. Thor**[5], and **M. Drake**[6]

[1]Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

[2]Department of Pharmacology and Chemical Biology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

[3]Pfizer Global Research and Development, Kent, UK

[4]Institute of Membrane and Systems Biology, University of Leeds, Leeds, UK

[5]Urogenix, Inc., Durham, North Carolina

[6]Bristol Urological Institute, Southmead Hospital, Bristol, UK

Abstract

This review deals with individual components regulating the neural control of the urinary bladder. This article will focus on factors and processes involved in the two modes of operation of the bladder: storage and elimination. Topics included in this review include: (1) The urothelium and its roles in sensor and transducer functions including interactions with other cell types within the bladder wall ("sensory web"), (2) The location and properties of bladder afferents including factors involved in regulating afferent sensitization, (3) The neural control of the pelvic floor muscle and pharmacology of urethral and anal sphincters (focusing on monoamine pathways), (4) Efferent pathways to the urinary bladder, and (5) Abnormalities in bladder function including mechanisms underlying comorbid disorders associated with bladder pain syndrome and incontinence.

Keywords

pelvic floor; sensory afferents; urothelium

THE UROTHELIUM

There is evidence that a number of functional pain syndromes are associated with changes in the epithelial layer. Alterations of bladder urothelium at the molecular and structural levels have been reported in both patients and animals modeled for various bladder disorders. Many therapies currently used in the treatment of bladder disease may actually target urothelial receptors and/or their release mechanisms.

Anatomy and Barrier Function of the Urothelium and Response to Injury

The urothelium is the epithelial lining of the lower urinary tract between the renal pelvis and the urinary bladder. Urothelium is composed of at least three layers: a basal cell layer

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*Correspondence to: Dr. L. Birder, A1207 Scaife Hall, Pittsburgh, PA 15213. lbirder@pitt.edu.

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attached to a basement membrane, an intermediate layer, and a superficial or apical layer composed of large hexagonal cells (diameters of 25–250 μm) known as "umbrella cells."[1,2] The umbrella cells are interconnected by tight junctions (which are composed of multiple proteins such as the claudins) and are covered on their apical surface (nearly 70–80%) by crystalline proteins called uroplakins that assemble into hexagonal plaques.[3-6] Uroplakins and other urothelial cellular differentiation markers, such as cytokeratin 20, are not expressed in the stratified epithelium of the urethra. In some species, the umbrella cells and perhaps also the intermediate cells have projections to the basement membrane.[1]

The ability of the bladder to maintain the barrier function, despite large alterations in urine volume and pressure during bladder filling and emptying, is dependent on several features of the umbrella cell layer. These features include tight junction complexes that reduce the movement of ions and solutes between cells and specialized lipid molecules and uroplakin proteins in the apical membrane, which reduce the permeability of the cells to small molecules (water, urea, and protons).[1,7] The apical surface of the urothelium is also covered with a sulfated polysaccharide glycosaminoglycan (GAG) or mucin layer that is thought to act as a nonspecific anti-adherence factor and as a defense mechanism against infection.[8-10] In addition, during bladder filling the umbrella cells become flat and squamous and this shape change is accompanied by vesicular trafficking (i.e., exocytosis/endocytosis) that adds membrane to the apical surface thereby increasing overall urinary bladder surface area.[3,11,12] There is evidence that this stretch-induced exocytosis is dependent on activation of epidermal growth factor receptor (EGFR).[13,14] These processes allow the bladder to accommodate increasing volumes of urine during filling without compromising the barrier function. Exocytosis/endocytosis (vesicular recycling) may also play an important role in modulating the release of a number of neurotransmitters/mediators as well as regulation of the function of many receptors and ion channels in urothelial cells.[15,16]

Though the urothelium maintains a tight barrier to ion and solute flux, a number of local factors such as tissue pH, mechanical or chemical trauma, or bacterial infection can modulate the barrier function of the urothelium.[3,17] When the barrier is compromised, water, urea, and toxic substances can pass into the underlying tissue (neural/muscle layers) resulting in urgency, frequency, and pain during bladder filling and voiding. Disruption of urothelial barrier integrity has also been linked to the expression of substances such as antiproliferative factor (APF), which also slows urothelial cell growth.[18-20] APF, a frizzled 8 protein detected in the urine of patients with bladder pain syndrome/interstitial cystitis (BPS/IC), is secreted by bladder epithelial cells obtained from these patients. Treatment of urothelial cells from normal patients with purified APF decreases the expression of adhesion and tight junction proteins. Other types of urothelial–neural interactions are also likely, based on the recent reports that various stimuli induce urothelial cells to release chemical mediators that can in turn modulate the activity of afferent nerves.[1,16] This has raised the possibility that the urothelium may have a role in sensory mechanisms in the urinary tract.

Roles for Urothelial Cells in Visceral Sensation

While urothelial cells are often viewed as bystanders in the process of visceral sensation, recent evidence has supported the view that these cells function as primary transducers of some physical and chemical stimuli and are able to communicate with underlying cells including bladder nerves, smooth muscle, myofibroblasts, and inflammatory cells (Fig. 1).

There are at least three lines of evidence that suggest that urothelial cells participate in the detection of both physical and chemical stimuli. First, bladder nerves (afferent and efferent) are localized in close proximity, and some within, the urothelium.[16,21-23] In addition, a network of cells with morphologic characteristics similar to those of myofibroblasts or interstitial cells is also detected in the suburothelial space of the bladder in both humans and

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animals.[24-26] These cells, which are extensively linked by gap junctions and have close contacts with nerves, can respond to neurotransmitters, such as ATP released from nerves or urothelial cells, suggesting that they could act as intermediaries in urothelial–nerve interactions.[25-27]

A second line of evidence suggesting that urothelial cells play a role in sensory function is the expression of numerous receptors/ion channels similar to those found in both nociceptive and mechanoreceptive afferent nerves. Examples of neuronal "sensor molecules" (receptors/ion channels) that have been identified in urothelium include receptors for purines ($P2X_{1–7}$ and $P2Y_{1,2,4}$) adenosine (A_1, A_{2a}, A_{2b}, and A_3), norepinephrine (α and β), acetylcholine (muscarinic and nicotinic), protease-activated receptors (PARs), amiloride and mechanosensitive epithelial sodium channels (ENaC), bradykinin (B1 and B2), neurotrophins (p75, trkA, epidermal growth factor (EGF) family ErbB1-3), corticotrophin releasing factor (CRF), estrogens (Erα and ERβ), endothelins, and various TRP channels (TRPV1, TRPV2, TRPV4, TRPM8, and TRPA1).[21,28-36] The expression of various receptors enables the urothelium to respond to a number of "sensory inputs" from a variety of sources. These inputs include increased stretch during bladder filling, soluble factors (many found in the urine) such as EGF or chemical mediators/peptides/transmitters such as substance P (SP), calcitonin gene-related peptide (CGRP), CRF, acetylcholine, adenosine, or norepinephrine released from nerves, inflammatory cells, and even blood vessels.[1,15,16,37,38]

And finally, these cells secrete a number of transmitters or mediators capable of altering the excitability of sensory neurons including neurotrophins, peptides, ATP, acetylcholine, prostaglandins, prostacyclin, nitric oxide (NO), and cytokines.[15,16] For example, urothelial-derived NO can be released in response to mechanical as well as chemical stimulation and may inhibit the activity of bladder afferent nerves.[16,39] Release of various factors from the urothelium can also modulate the spontaneous activity of the underlying smooth muscle.[27,40]

The mechanisms underlying release of chemical mediators from the urothelium, for example, whether all sensory "inputs" stimulate membrane turnover (i.e., vesicular exocytosis) is not well understood. What little is known about the roles and dynamics of membrane-bound cytoplasmic vesicles in urothelial cell physiology is derived from measurements of membrane capacitance and microscopy of fixed tissues and cells. There is evidence that once released, ATP can act as an important autocrine mediator, which can induce membrane turnover as well as enhance both stretch-induced exocytosis and endocytosis.[41] Alterations in membrane turnover can not only increase apical surface area but also regulate the number and function of receptors and channels at the cell surface.

Clinical Significance of the Sensory Web

Defects in urothelial sensor molecules and urothelial-cell signaling are likely to contribute to the pathophysiology of bladder diseases. For example, a number of bladder conditions (BPS/IC, spinal cord injury (SCI), chemically induced cystitis) are associated with augmented release of urothelial-derived ATP, which is likely to result in altered sensations or changes in bladder reflexes induced by excitation of purinergic receptors on nearby sensory fibers.[5,6,32] ATP can also act in an autocrine manner that would facilitate its own release from urothelial cells.[6] Once released, ATP can alter the threshold for activation of ion channels such as TRPV1. This novel mechanism, which likely reflects activation of intracellular protein kinases and phosphorylation of the TRPV1 channel, represents a means by which large amounts of ATP released from damaged or sensitized cells, in response to injury or inflammation, could trigger the sensation of pain. Changes in epithelial signaling/barrier function would not be unique to the urinary bladder because airway epithelia in asthmatic patients as well as keratinocytes in certain types of skin diseases also exhibit a number of

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similar abnormalities and compromised repair processes.[42-44] This is particularly relevant given the high incidence of diseases that include both visceral and somatic dysfunctions, many of which exhibit a decrease in epithelial barrier properties. Taken together, epithelial cells can respond to a number of challenges (including environmental pollutants and mediators released from nerves or nearby inflammatory cells) resulting in altered expression and/or sensitivity of various receptor/channels as well as changes in release of mediators, all of which could impact function.

AFFERENT NEURONS

Properties of Bladder Afferent Neurons

Afferent axons in the pelvic, hypogastric (lumbar splanchnic), and pudendal nerves transmit information from the lower urinary tract to the lumbosacral spinal cord[45-47] and studies in several species including cats, rats, and mice have shown some similarities in properties.

The most sensitive afferents are excited by a physiological increase in volume and by detrusor contractions. It is believed that these low threshold afferents have small myelinated axons (A-delta fibers which are larger in diameter and conduct action potentials more rapidly than C-fibers) and that their endings are located in the detrusor smooth muscle. Neurons with this range of conduction velocities are less likely to contain peptides. They have been called “in series tension receptors”[48] because they are excited by bladder wall tension caused either by distension or by contraction.

There have been a number of systematic studies recently in mice and guinea pigs that have provided detailed information about the classes of receptors in the pelvic and hypogastric nerves. In the mouse, there are at least four classes of mechanosensitive afferents, which include myelinated and unmyelinated fibers that are distributed in the serosa, muscle, and urothelial layers of the organ. One class has mechanosensitive endings in both the muscle and urothelial layers. The lumbar splanchnic nerves contain principally serosal and muscular afferents whereas all four classes of afferents are present in the pelvic nerve (63% of which are muscular afferents).[49] The small myelinated afferents are involved in two processes: (a) sensing bladder volume and (b) reinforcing reflex function by monitoring the contractile state of the detrusor. In particular these afferents, which form the most sensitive distension receptors, are most probably responsible for the sensation of fullness and mediate the normal micturition reflex that involves a spinobulbospinal pathway that passes through the brainstem.

The unmyelinated afferents contain peptides and most appear to terminate within the lamina propria and within the transitional epithelium itself. Many of these afferents discharge within the higher range of physiological bladder volumes and are not usually sensitive to detrusor contraction, possibly because only the former causes stretch of the urinary epithelium. The C-fibers in the urothelium and lamina propria contain peptides such as SP and CGRP, which is a characteristic of one subgroup of afferent C-fibers. These and other C-fiber afferents may mediate the spinal C-fiber micturition reflex seen following cord transection in the cat.[50] It is not clear whether they also contribute to normal voiding in this species, but there is increasing evidence that they may be involved in normal bladder control in rats and mice.

Another group of unmyelinated bladder afferent axons does not respond to normal distending volumes but only become active during chemical irritation of the bladder, including high osmolality and high potassium solutions and during inflammation, when they behave like the high volume sensing C-fibers. These have been demonstrated in cats and rats, and are usually called “silent afferents” (meaning that they do not respond to normal

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distensions, but can become mechanosensitive in inflamed or over-distended tissues). Thus it would be unwise to infer function simply on the basis of conduction velocity. This group of afferents also appears to be sensitive to ATP.

Ultrastructural studies of nerves in the human bladder have found only unmyelinated nerves in the urothelial and immediate suburothelial layer. The small myelinated nerves appear only close to the smooth muscle layers.[51] Whether or not the suburothelial nerves become myelinated as they pass toward the serosal surface cannot be ascertained from this study but it would be inadvisable to make deductions about the relative number of C and A-delta fibers in the human based on these observations. Table I shows the properties of afferent fibers classified according to their volume thresholds.

Urothelial Afferents

The plexus of afferent nerves is thickest in the neck of the bladder and in the initial portion of the urethra, and it becomes progressively less dense in the adjacent regions. It does not extend beyond the equatorial region, and therefore the lamina propria of the cranial region of the bladder has no afferent axons. In contrast, the afferent innervation of the musculature is more diffuse, and appears uniform throughout the bladder. CGRP-immunofluorescence in urothelial afferent axons is enhanced in the surviving axons 5 days after contralateral denervation, a change which may be an early sign of regeneration of these axons.[52] In the human bladder, CGRP together with SP and NKA occur only infrequently in nerves in the muscle but are moderately frequent in the suburothelial layer. Also in the human there appears to be another population of CGRP-containing fibers that colocalize with neuropeptide Y (NPY) and galanin (Gal) and some of these synapse on intramural ganglia within the bladder.[53-56] There is also recent evidence that nerves cross the basal lamina and enter the basal layers of the human urothelium.[52]

Sensitivity of Afferent Endings

The term afferent sensitivity refers to the gain of the afferent signal, i.e., the number of impulses that are fired by an afferent ending at any level of distension. Sensitizing mediators are able to increase the size of the sensory signal (the frequency of impulse traffic) at a given level of distension, so the sensations that occur at a particular rate of firing in an afferent occur at lower bladder volumes if the afferent endings have been sensitized.

The sensitivity of afferent endings may be influenced by the release of mediators from different cell types, including possibly the urothelium, myofibroblasts, nerve endings, smooth muscle, mast cells, and other connective tissue cells. It is likely that many or all of these can release ATP, and some may release other mediators including NO, tachykinins (SP, neurokinin A, neurokinin B), growth factors (nerve growth factor [NGF], brain-derived-neurotrophic factor [BDNF], and others) and other endogenous mediators such as nociceptin. The similarity of the properties of the urothelial cells and the C-fiber afferents suggests that the most likely contender for a sensory cell may be a urothelial cell, but it is clear that the afferent endings themselves respond to a variety of stimuli, and that surrounding cells may simply enhance the gain of the transducer.

NGF and TTX-Resistant Na^+ Channels

Sensitization of afferents appears to be an important mechanism that leads to reflex hyperexcitability. A number of studies have linked the tetrodotoxin (TTX) resistant sodium channel, sometimes known as Nav1.8 to this process. Sensitizing agents including NGF are known to induce increased expression of this membrane channel; and this appears to be sufficient to change the properties of afferents to lower the threshold for firing and in turn lower the volume threshold for reflex voiding and induce overactive bladder contractions

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and urgency.[57] TTX-resistant Na^+ channels ($Na_V1.8$ and $Na_V1.9$) are expressed in SP/CGRP immunoreactive small, C-fiber DRG neurons supplying the bladder.[58,59] These neurons also express the trkA receptor, which binds NGF and is necessary for its action. Plasticity of Na^+ channels occurs in these neurons after SCI, including an increase in TTX-sensitive Na^+ currents, a decrease in TTX-resistant Na^+ currents, decreased expression of $Na_V1.8$ channel immunoreactivity, and a small increase in Na 1.9 channel immunoreactivity.[60,61]

The dependence of bladder afferent neuron sensitization on NGF and on changes in $Na_V1.8$ channel has been shown in experiments using immunoneutralization of NGF or anti-sense oligonucleotide treatment to reduce the expression of these channels in sensory neurons.[58,62] More recently in studies of ralfinamide, a drug that interferes with TTX-resistant sodium channels, indicate that this drug reduces inflammatory and neuropathic pain as well as bladder overactivity in rats. The ability of ralfinamide to reduce capsaicin-induced hyperexcitability and tonic activity of rat afferent neurons appears to be due to its action as a sodium channel antagonist.[63]

In clinical studies the local anesthetic lidocaine and the oral Na^+ channel blocker, mexiletine, which operate by reducing excitability in sensitized neurons have been used to treat urge incontinence and hyper-reflexic conditions[64-69] with variable degrees of success.

Afferents From the Urethra, Bowel, and Genital Organs

The micturition reflex can be influenced by activation of other sacral afferent pathways,[70] including those innervating the urethra, urethral sphincter, colon–rectum, anal canal, and reproductive organs. Facilitatory effects can be elicited in response to electrical stimulation of urethral afferents or by fluid flowing through the urethra; however, contraction of the urethral sphincter reflexly inhibits bladder motility.[71] Electrical stimulation of urethral afferent fibers when the bladder is full can evoke strong detrusor contractions sufficient for voiding in spinal intact cats[72,73] as well as acute spinalized cats.[74] Similarly, using minimally invasive methods to apply electrical stimulation within the proximal urethra via a catheter-mounted electrode, it has been shown that reflex bladder contractions can be generated in humans with complete paraplegia but these do not seem to produce efficient voiding. In chronic SCI cats voiding can be induced by 30–40 Hz electrical stimulation of afferents in the pudendal nerve.[75] This type of voiding can be enhanced by blocking the efferent pathways to the external urethral sphincter using very high frequency electrical stimulation of the pudendal nerve. On the other hand low frequency electrical stimulation of the pudendal nerve increases bladder capacity and inhibits reflex micturition. Inhibitory effects are also elicited in response to stimulation of the dorsal nerve of the clitoris.[76]

Excitability of spinal neurons receiving afferent input from the bladder can also be modulated by input from other pelvic structures such as the colon.[77-79] This convergence of sensory information from a number of pelvic organs can occur at the level of the spinal cord. In addition, the expansion of primary axon terminals within the spinal cord can also play a role in altering bladder reflexes.

Bladder afferent neurons contain a number of peptidergic neurotransmitters, and the central distribution of bladder afferent terminals and peptidergic immunoreactive fibers is quite similar. Expression of a number of peptides including CGRP, vasoactive intestinal polypeptide (VIP) as well as pituitary adenylate cyclase activating peptide (PACAP) is altered in primary afferent terminals and may correlate with changes in bladder function following SCI.[80-82] There has been considerable interest in the role of tachykinins in the micturition reflex[83] and in nociception. Intrathecal treatment of adult rats with intrathecal capsaicin can result in a reversible block of the micturition reflex.[84] Further, while normal

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micturition is not altered following ablation of NK1-R expressing SC neurons using SSP-saporin, the response to a nociceptive stimulus was significantly reduced. These and other studies[84,85] suggest that SP and its receptors may play a part in transmission of bladder nociceptive responses at the first synapse in the micturition reflex.

EFFERENT PATHWAYS TO THE BLADDER

Preganglionic Neurons

Parasympathetic preganglionic neurons (PPGN) are located in the lateral part of the sacral intermediolateral gray matter which send dendrites into lateral lamina I of the dorsal horn, the lateral funiculus, and medially into the dorsal gray commissure (DGC). PPGN, which are divided functionally into tonic and phasic types, are cholinergic but also contain opioid peptides and express nitric oxide synthase (NOS).[86] PACAP, a peptide present in visceral afferent neurons, enhances the firing of PPGN.[87] The DGC contains a group of interneurons, which are likely to be active during micturition[88,89] and may influence the function of the PPGN.[88-90]

At spinal levels L1–L2, both the intermediolateral horn and the DGC contain sympathetic preganglionic neurons whose axons project to the major pelvic ganglion. With ageing, there is selective attrition of these neurons, with reductions in the extent of the dendritic arbors of remaining cells.[91,92]

In man the preganglionic parasympathetic motor nerves to the bladder and other pelvic organs exit the sacral spinal cord in the anterior roots S2–S4 and course through the pelvic nerves. Stimulating the S3 roots with implanted electrodes designed principally for bladder emptying after SCI[93] elicits two principal responses; at low levels of stimulation, the external urethral sphincter, external anal sphincter, and pelvic floor muscles are contracted. At high levels of stimulation, parasympathetic activation contracts the detrusor muscle, leading to efficient emptying of the bladder when the sphincter muscle relaxes.[94] Attempts to use extracorporeal magnetic stimulation to achieve the same effect[95] have shown insufficient power to activate the small parasympathetic axons at the level of the lumbar-sacral roots.[96]

Ganglia

The postganglionic autonomic innervation to the lower urinary tract and reproductive organs, along with a substantial part of the extrinsic motor innervation of the lower bowel arises in the pelvic ganglia. There are substantial species differences in organization and neurochemistry of pelvic ganglion cells and their spinal inputs. Within the pelvic plexus there is topographical representation of the pelvic organs. In the female dog, neurons supplying different pelvic organs are located in separate ganglia, which possess a distinctive composition of neuron types and different preganglionic supply.[97] Neurons retrogradely labeled from the urinary bladder mainly occur in ganglia located at the vesico-ureteric junction. Autonomic ganglia are also found in the vicinity of the bladder neck, trigone, proximal urethra, and prostate. They receive noradrenergic and cholinergic excitatory innervation and noncholinergic, nonadrenergic inhibitory innervation.[98] Knowledge of this distribution allows strategic planning for surgical dissection.

The bladder wall itself contains intramural ganglia, and small clusters of autonomic ganglion cells are present in the adventitial connective tissue and among the detrusor muscle bundles. There is species variation in the extent of intramural innervation of the bladder; ganglia are present in many species such as the guinea pig,[99] while the rat bladder contains the postsynaptic innervation alone.[100] The ganglia are found throughout the bladder wall and vary considerably in size.[54,101] They show immunoreactivity to VIP, NOS, NPY, and Gal in

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varying amounts. However, they do not contain enkephalin (ENK), SP, CGRP, or somatostatin (Som),[53] suggesting that cell bodies of sensory neurons are not located in the intramural ganglia. Postganglionic sympathetic nerves, identified with antibodies to TH and NPY, also synapse on these neurons. Nicotinic receptors have been identified on intramural nerve cell bodies within the bladder.[102] α1-Adrenergic facilitatory receptors are present in bladder parasympathetic ganglia.[103]

Terminal Nerve Fibers

The majority of nerves running in the detrusor stain positively for acetylcholinesterase and for vesicular acetylcholine transferase (VAChT)[101,104] and are thought to be parasympathetic. Putative postganglionic sympathetic fibers immunoreactive for TH or NPY are rare in the detrusor, although they are moderately frequent in the suburothelium.[55] Nonetheless, presynaptic α1-adrenergic facilitatory receptors are present on efferent parasympathetic nerve terminals in the bladder wall.[105,106] The parasympathetic efferents release acetylcholine to stimulate muscarinic receptors. However, the presence of additional substances allows immunohistochemical subclassification of nerve fibers, and raises the question as to whether additional transmitters other than ACh have a role in normal micturition function or disease pathophysiology.

Pelvic Organ Interactions at the Efferent Neural Level

Bladder and Outlet—Neural coordination of physiological and behavioral functions depends on convergence within the nervous system of information from relevant areas, and convergence could result in collateral effects of pathology in one organ affecting function elsewhere. There is extensive convergence of pelvic organ input[107,108] at the levels of the spinal cord, dorsal column nuclei, solitary nucleus, medullary reticular formation, and thalamus.[109] Convergent processing underpins the coherent functioning of systems controlled by efferent outflows diverging from a common starting point, as exemplified by the synergic coordination of bladder and urethra required for normal voiding. The fundamental role of supraspinal mechanisms in lower urinary tract synergy is well recognized. However, synergic lower urinary tract function may also be a feature of the peripheral innervation, independent of central nervous system (CNS) coordination. In the female minipig, preganglionic pelvic nerve stimulation evokes a pressure increase in the bladder and a pressure decrease in the urethra.[110] It remains to be determined whether this observation reflects coherent activation of separate motoneurons (excitatory to the bladder, inhibitory to the outlet), or whether postganglionic motoneurons send branches which supply both bladder and urethra.

Bladder and Bowel/Uterus—Clinicians are familiar with the detrimental effect of bowel disorders on lower urinary tract activity. Physiologically, the efferent limb of the micturition reflex is inhibited by afferent input from the rectum;[111] thus, rectal distension inhibits bladder activity via glycinergic and GABAergic mechanisms in rats.[112] Dual labeling studies show that many neurons in Barrington's nucleus supply both colon and bladder, with smaller populations supplying the two organs separately. At the level of the major pelvic ganglion, double-labeled cells are relatively infrequent, but processes of colonic-retrograde-labeled cells often surround cell bodies of equivalent cells for the bladder. Dual-labeled cells in the spinal cord are rare.[113]

In addition to efferent input, local reflexes may contribute to the inhibition of detrusor activity, probably driven by interstitial cells,[114] so that peripheral autonomous activity increases as a result of bladder distension.[115,116] This has been proposed to signify the presence of a regional regulatory influence[117] and a peripheral "pacemaker"[118] and various mechanisms for the propagation of activity within the bladder wall.[119] In the clinical

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context, processes affecting peripheral innervation would then predispose to emergence of inappropriate detrusor activity during urine storage (through loss of inhibitory fibers), associated with inefficient bladder emptying (through loss of excitatory fibers).

NEURAL CONTROL OF FEMALE PELVIC FLOOR MUSCLES AND RHABDOSPHINCTERS

Structural Elements of the Pelvic Floor

The pelvic floor[120] in women is a bowl-shaped structure comprised of bone, muscle, and connective tissue. The rim of the bowl is formed by the bones of the pelvic girdle (sacrum, ileum, ischium, and pubis). The “inside and bottom” of the bowl is lined with striated muscle: the iliococcygeus and pubococcygeus (which together comprise the levator ani) as well as the coccygeus, and puborectalis muscles. The muscles are attached to the bone and to each other with various connective tissue supports. These three components, bone, muscle, and connective tissue provide support of the pelvic viscera (i.e., rectum, vagina, and bladder) but also allow for excretory and sexual functions.

Innervation of the Female Levator Ani Muscles

The levator ani muscle of the pelvic floor is innervated by the levator ani nerve in human,[121] squirrel monkey,[122-124] dog,[125] cat (Karicheti and Thor, unpublished observations), and rat.[126] The levator ani nerve primarily arises from sacral spinal roots (e.g., S3–S5 in humans) and travels along the intrapelvic face of the levator ani muscle with a high degree of variability in branching patterns.[121] In humans, there is some controversy whether or not the pudendal nerve also innervates the levator ani muscle.[127,128] This is not the case in other species (rat, cat, dog, squirrel monkey) where hodological studies show: (1) a marked loss of levator ani muscle mass and a decrease in levator ani myocyte diameter following transection of the levator ani nerve[124,126] but no change in levator ani muscle mass or myocyte diameter following pudendal neurectomy,[124,126] (2) the existence of only a single motor endplate zone at the point of levator ani nerve insertion into the levator ani muscles,[124,126] (3) absence of contractions of levator ani muscles upon electrical stimulation of pudendal nerve efferent fibers (Thor and Karicheti, unpublished observations), and (4) phenotypically distinctive motor neuron labeling following application of nerve tracers to the pudendal and levator ani nerves.[125,129-134]

Role of the Levator Ani Innervation in Pelvic Organ Prolapse in Monkeys

Because the pelvic floor is responsible for providing support of the viscera, and because one might expect contraction of pelvic floor muscles to be necessary for adequate support, damage to the levator ani innervation and subsequent muscle flaccidity might be expected to promote pelvic organ prolapse (POP). To test this expectation, the levator ani muscles were bilaterally denervated in squirrel monkeys,[122] which is a species that shows age and parity correlated POP similar to humans.[135] Surprisingly, these monkeys showed no POP following this procedure for 2–3 years after surgery, despite showing statistically significant decreases in levator ani muscle mass and myocyte diameter. However, a slight increase in bladder and cervical descent with abdominal pressure was seen on MRI evaluation compared to nulliparous controls. Of possible significance was the finding that, after a single birth, 2 of 4 bilateral levator ani neurectomy animals showed POP, which is unusual. Thus, these experiments indicate that, in the absence of childbirth, the pelvic floor muscle plays a minor role in providing visceral support and suggests that the connective tissue plays the major role.

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Innervation of Urethral and Anal Rhabdosphincters

At the level of the pelvic floor, the urethra and rectum are surrounded by intimately associated bands of striated muscle fibers; the urethral and anal rhabdosphincters, respectively. The muscles do not have “dedicated” attachments to skeletal structures and thus act as a true sphincters (i.e., contraction produces virtually no movement except constriction of the lumen). Extensive studies of the urethral rhabdosphincter, anal rhabdosphincter, bulbocavernosus, and ischiocavernosus muscles have shown that these muscles are innervated by the pudendal nerve,[121,129,131-134,136,137] which originates from the sacral roots and passes along the lateral surface of the internal obturator and coccygeus muscles, through Alcock’s canal, to eventually approach these muscles laterally from the extrapelvic surface of the pelvic floor.

Segmental Activation of Urethral and Anal Rhabdosphincters

Rhabdosphincter motor neurons can be activated via segmental[138-142] and descending pathways.[139,143,144] The segmental inputs can be activated by stretch receptors and nociceptors in the bladder or urethra or genitalia.[145-148] Electrophysiological studies[138,140-142,149,150] show that stimulation of either pelvic nerve or pudendal nerve afferent fibers can activate polysynaptic spinal segmental reflexes that can be recorded at a latency of about 10 msec from electrodes placed on pudendal nerve efferent fibers or inserted directly into the urethral or anal rhabdosphincter muscles.

Previously, the afferent inputs from the urinary bladder were emphasized as being of primary importance for activation of the segmental reflex by pelvic nerve stimulation and is often referred to as the “guarding reflex” or “continence reflex.” However, recent studies are placing greater emphasis on urethral afferent fibers[146,148,151] mediating spinal reflex activation of the urethral rhabdosphincter.

Supraspinal Activation of Rhabdosphincters and Pelvic Floor Muscles

Supraspinal activation of urethral and anal rhabdosphincter motor neurons includes voluntary inputs (i.e., corticospinal),[152] as well as involuntary reflexic inputs (e.g., during coughing, sneezing, vomiting) presumably from nucleus retroambiguus in the caudal medulla.[144,153-157]

Rhabdosphincter motor neurons are unique among somatic motor neurons in receiving input from the paraventricular hypothalamus,[143] although the function of this input has not been determined. In addition, their input from brainstem serotonergic and noradrenergic neurons is among the densest in the spinal cord.[158-161] Finally, rhabdosphincter motor neurons also receive input from the “L region” of the pons that might be important for maintaining continence, since a lesion in this area produced continuous incontinence in a cat.[162]

Pharmacology of Urethral and Anal Rhabdosphincters

The preferential association of norepinephrine and serotonin terminals[158-161] led to extensive studies of noradrenergic and serotonergic control of rhabdosphincter function and eventual clinical studies of duloxetine, a norepinephrine and serotonin reuptake inhibitor, as a treatment for stress urinary incontinence (SUI).[147,163-167] Elegant studies in humans using magnetic stimulation of brain and sacral nerve roots[168] have indicated that duloxetine increases the excitability of rhabdosphincter motor neurons to both supraspinal and segmental inputs and to double urethral pressure responses to sacral nerve root magnetic stimulation. Importantly, duloxetine’s ability to increase urethral rhabdosphincter activity did not interfere with the inhibition of sphincter activity during voiding (i.e., bladder–sphincter synergy was well-maintained). Similar clinical results have been seen with S,S-reboxetine, a selective norepinephrine reuptake inhibitor.[169,170] More recent data on the

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effect of the selective noradrenergic reuptake inhibitor, [S,S]-reboxetine in the treatment of SUI, indicate that the serotonergic activity of duloxetine may be redundant and that effects are dependent solely on noradrenergic reuptake inhibition.[169,170] This approach of increasing synaptic levels of serotonin and/or norepinephrine is logical since, it has been shown that noradrenergic and serotonergic terminals associated with rhabdosphincter motor neurons show an age-dependent decrease in density in rats.[171]

Multiple adrenergic receptor subtypes play a role in control of the rhabdosphincter, and the results with norepinephrine reuptake inhibitors indicate that these receptors can be activated by endogenous norepinephrine in anesthetized cats.[149] Strong evidence exists that α_1 adrenoceptors excite rhabdosphincter motor neurons.[149,172-174] On the other hand, strong evidence exists that α_2 adrenoceptor stimulation has the opposite effect, i.e., inhibition of rhabdosphincter activity.[149,175] Importantly, the innervation of the urethral and anal smooth muscle (i.e., the hypogastric nerve) shows similar adrenergic pharmacology—an enhancement of activity by α_1 adrenoceptors[149,172,176] and inhibition of activity by α_2 adrenoceptors.[149,172,177]

Multiple subtypes of serotonin (5-hydroxytryptamine, 5-HT) receptors are also involved in modulating rhabdosphincter motor neuron excitability. Strong evidence exists that 5-HT_2 receptors can excite sphincter motor neurons.[178] Indeed duloxetine's facilitatory effects on rhabdosphincter activity in anesthetized cats are mediated in part through activation of 5-HT_2 receptors.[147] Both 5-HT_{2A} and 5-HT_{2C} receptor agonists increase rhabdosphincter EMG activity in dogs, guinea pigs, and rats.[179,180] Recent in vitro rat spinal cord slice patch clamp studies show that part of this effect may be directly on rhabdosphincter motor neurons, as opposed to interneurons,[174] since 5-HT induces a direct depolarization of rhabdosphincter motor neurons. Interestingly, SP, a peptide transmitter that is colocalized with 5-HT in raphe spinal nerve terminals, also produces direct depolarization of rhabdosphincter motor neurons in rat spinal cord slices,[181] and thyrotropin releasing hormone (TRH), another peptide transmitter colocalized with 5-HT in nerve terminals, induces excitation of rat sphincter activity[182,183] in vivo.

Abnormal Lower Urinary Tract Function

Dysfunction of neural control may underpin a wide range of clinical urinary tract problems. On the afferent side, neural dysfunction will alter reflex activity and influence sensation, which can be enhanced, reduced, or altered (e.g., with the emergence of pain instead of usual bladder filling sensations). Although no consensus has been reached on the fundamental causes of BPS/IC, existing data suggest pathophysiological mechanisms including epithelial dysfunction, mast cell activation, and/or neurogenic inflammation.[184]

On the efferent side, motor activity within the components of the lower urinary tract (bladder and outlet) can be increased, reduced, or uncoordinated. For example, detrusor overactivity can arise in neuropathic conditions, secondary to bladder outlet obstruction. Several observations on structural and functional properties of the bladder have been made in individuals with detrusor overactivity. These can include patchy denervation within the bladder wall, exaggerated spontaneous myogenic activity, or changes in smooth muscle ultrastructure. A common ultrastructural feature of the overactive detrusor is the emergence of protrusion junctions and ultraclose abutments between the smooth muscle cells.[185] Preclinical studies in animal models of OAB/detrusor overactivity contribute further to our understanding of the importance of neural control in this condition. The main models relevant to OAB include (i) instillation of irritative agents into the bladder during cystometry, (ii) partial bladder outflow obstruction, (iii) the spontaneously hypertensive rat, (iv) SCI, and (v) other CNS lesions similar to those responsible for bladder dysfunction in humans.[186]

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SUI is characterized by a reduction in outflow resistance during urinary storage due to weakness in the urethral sphincter mechanism. It is often associated with weakness of the pelvic floor and urethral musculature, but peripheral nerve dysfunction is also implicated, in particular pudendal nerve damage following childbirth in women.[187] Animal models have contributed to understanding of the importance of the peripheral innervation of the urethra in SUI, with development of disease models associated with pudendal nerve crush and vaginal distension initiating neuropathic nerve injury in rats[188] and mice.[189] The role of pharmacological neuromodulation in the treatment of SUI has shown that urethral function and incontinence can be improved by augmenting somatic neuronal discharge using the serotonergic (5HT) and the noradrenergic (NE) reuptake inhibitor duloxetine or SS-reboxetine (discussed above).[163,190]

The significance of neural control mechanism in lower urinary tract dysfunction is further implied by a number of comorbid conditions that have been associated with BPS/IC and incontinence. Patients with BPS/IC and SUI are more likely to report depressive symptoms. BPS/IC has also been associated with other chronic pain conditions, especially fibromyalgia.[191-194] Based on recent improvements in understanding of pain processing pathways in the CNS, and in particular the role of limbic structures, especially the anterior cingulate cortex, hippocampus and amygdala, in chronic and affective pain perception, a condition termed limbic associated pelvic pain has been proposed to explain the concurrence of these various chronic pain conditions. This limbic dysfunction is manifest both as an increased sensitivity to nociceptive afferents from pelvic organs, and as an abnormal efferent innervation of pelvic musculature, which undergoes tonic contraction as a result of limbic efferent stimulation, generating a further sensation of pain. The nociceptive afferents from these pelvic organs then follow the medial pain pathway back to the sensitized, hypervigilant limbic system. Chronic stimulation of the limbic system by pelvic pain afferents again produces an efferent contraction of the pelvic muscles, thus perpetuating the cycle.

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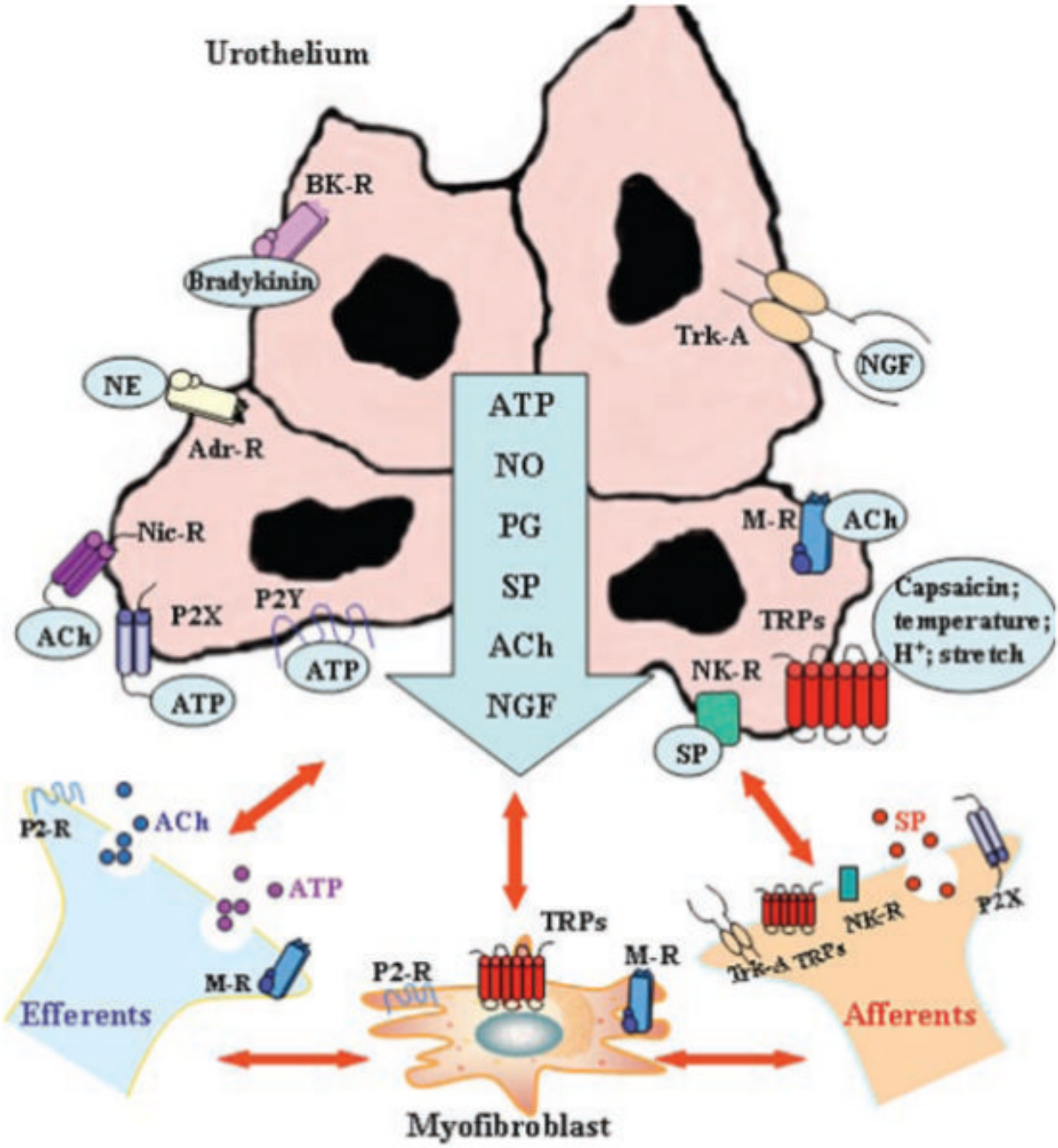

Fig. 1.

Hypothetical model depicting possible interactions between bladder afferent and efferent nerves, urothelial cells, smooth muscle, and myofibroblasts. Stimulation of urothelial receptors and channels can release mediators that target bladder nerves and other cell types; urothelial cells can also be targets for neurotransmitters released from nerves or other cell types. Urothelial cells can be activated by either autocrine (i.e., autoregulation) or paracrine (release from nearby nerves or other cells) mechanisms. Abbreviations: ACh, acetylcholine; AdR, adrenergic receptor; BR, bradykinin receptor; H^+, proton; MR, muscarinic receptor; NE, norepinephrine; NGF, nerve growth factor; NR, neurokinin receptor; NicR, nicotinic receptor; NO, nitric oxide; P2R, purinergic 2 receptor unidentified subtype; P2X and P2Y,

purinergic receptors; PG, prostaglandin; SP, substance P; Trk-A, receptor tyrosine kinase A, high affinity receptor for nerve growth factor; TRPs, transient potential channels.

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TABLE I

Properties of afferents classed according to volume thresholds

Sensitivity to distension (cat and rat)	Natural stimuli	Conduction velocity in cat and rat	Peptides	Experimental stimuli	Species	Inflammatory mediators	P2X3 agonist	Role of TRPV1	Pathway
Low threshold (LT)	Distension and contraction	Mainly A-delta (finely myelinated)	Peptides are relatively sparse	Distension (D), probing (P), tension (T), stroke (S), chemical (C)	Cat (D), rat (D,C), mouse (P,T,S,C), guinea pig (P,T,S,C)	Sensitization (M,R)	Increased firing rate	Normal bladder filling	Hypogastric pelvic
High threshold (HT)	Distension; some also respond to contraction	Mainly C (unmyelinated)	Many peptides	Distension (D), probing (P), tension (T), stroke (S), chemical (C)	Cat (D), rat (D), mouse (P,T,S,C), guinea pig (P,T,S)	Sensitization	Increased firing rate, lower threshold	Nociception	Hypogastric nerve
Silent (including nociceptive) (SIL)	Insensitive to distension unless inflamed	Mainly C (unmyelinated)	Many peptides	Distension (D)	Cat (D), rat (D), guinea pig (S,C)	Appearance of mechanosensitivity (R)	Appearance of mechanosensitivity	Nociception	Pelvic