Section 1
Chapter 1

Neurological control of pelvic organ functions

Neurological control of the bladder in health and disease

Derek J. Griffiths and Apostolos Apostolidis

Peripheral control of micturition

A dense network of nerves lies immediately below the bladder urothelium (in the "suburothelium"; Fig. 1.1), with occasional fibers penetrating the basal lamina. Afferent nerve endings in the bladder wall are important in conveying the sensations associated with various degrees of bladder fullness and also bladder pain to the spinal cord. Two main types of afferent axons are involved in this process: the myelinated Aδ-fibers and the unmyelinated C-fibers. Most Aδ-fibers are sensitive to mechanical stimuli, e.g. distension and stretch, whereas most C-fibers are not, due to a higher mechanical threshold. Thus, in conditions of health it is the Aδ-fibers which convey information about bladder filling, while C-fibers remain largely quiescent, responding only to noxious, chemical and cooling stimuli (Fig. 1.2).

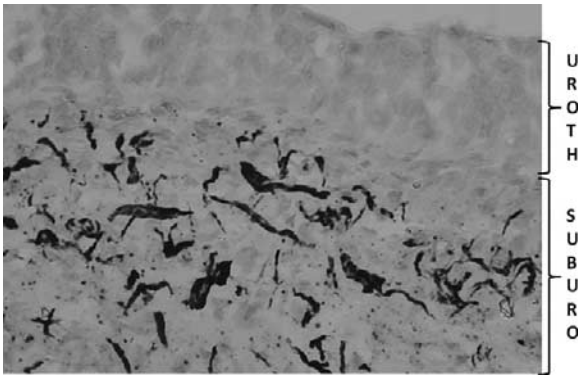

Fig. 1.1. Immunohistochemical staining of a human bladder specimen obtained via flexible cystoscopy with the pan-neuronal marker PGP9.5 depicts the dense network of suburothelial nerve fibers laying immediately below the basal lamina of the urothelium. Abbreviations: UROTH = urothelium, SUBURO = suburothelium. See plate section for color version.

Excitatory input to the bladder is conveyed by efferent parasympathetic nerves, whose axons originate in the S_2–S_4 intermediolateral column of the spinal cord. The S_2–S_4 roots contain the preganglionic parasympathetic fibers destined for ganglia in the pelvis, from which short postganglionic fibers originate to innervate the detrusor smooth muscle (Fig. 1.2).

The latter release acetylcholine (ACh), which acts on muscarinic receptors in the detrusor muscle and results in its contraction (see Fig. 1.3 and "Spinal control" below) [1]. A smaller contribution to detrusor contraction comes from the purinergic pathway, via release of adenosine triphosphate (ATP) by parasympathetic postganglionic terminals, which in health only achieves a fast, short-lived bladder contraction.

Important for continence is the contraction of the striated element of the urethral sphincter and the pelvic floor muscles, due to activation of nicotinic receptors by ACh released by somatic efferents originating at Onuf's nucleus in the anterior horn of the S_2–S_4 spinal cord. Afferent activity which increases as the bladder fills enhances efferent output to the sphincter, the basis of the "guarding reflex" (see Fig. 1.4 and "Spinal control" below).

A further contribution to storage and voiding comes from the sympathetic innervation. The bladder base and the urethral smooth muscle are innervated by sympathetic neurons originating at the intermediolateral cell column of the T_{11}–L_2 spinal cord (Fig. 1.5). The main sympathetic neurotransmitter is norepinephrine, which acts on α-adrenoreceptors resulting in contraction of the bladder base and urethral smooth muscle to

Pelvic Organ Dysfunction in Neurological Disease: Clinical Management and Rehabilitation, ed. Clare J. Fowler, Jalesh N. Panicker & Anton Emmanuel. Published by Cambridge University Press.

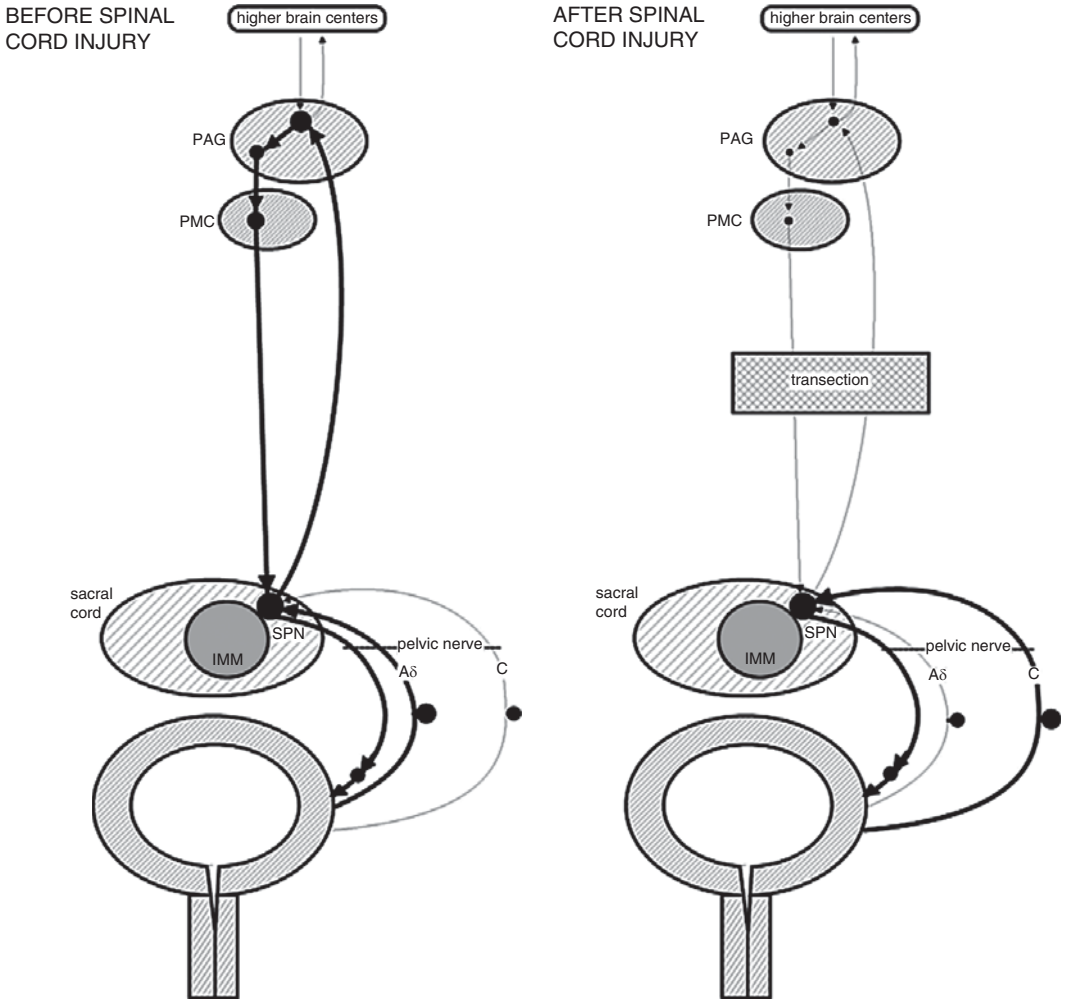

Fig. 1.2. These cartoon representations of simplified micturition pathways in health (left) and spinal cord lesions (right) aim to demonstrate the role of the types of bladder afferents in micturition reflexes. In conditions of health, Aδ-fibers convey information about bladder filling, whereas C-fibers remain largely quiescent. Both types of afferents run via the pelvic nerve. Sensory input to the spinal cord ascends to the PAG, where stimuli are filtered under the influence of higher brain centers to provide input to the PMC. Excitatory input descends via the spinal cord and the peripheral parasympathetic efferent nerve fibers running through the pelvic nerve to the detrusor. Thus a bladder contraction begins. Following a suprasacral spinal lesion, the formerly quiescent C-fiber afferents change their properties and hypertrophy and become highly excitable by mechanical stimuli. Consequently, they respond with increased afferent firing to the spinal cord at low urine volumes during bladder distension. This, in turn, produces increased parasympathetic input to the bladder and results in detrusor overactivity. Abbreviations: PAG = periaqueductal gray; PMC = pontine micturition center; SPN = sacral parasympathetic nucleus; IMM = sacral intermediomedial cell group.

contribute to continence during urine storage, and on β-adrenoreceptors resulting in relaxation of the detrusor muscle. The urethral smooth muscle also receives sacral parasympathetic efferents releasing nitric oxide (NO), which exerts an inhibitory effect on the muscle; this achieves urethral relaxation during contraction of the bladder (see Fig. 1.3 and "Spinal control" below) [1].

Cellular signaling pathways in normal bladder function

The detrusor muscle

The abundance of intercellular mechanical adhesions, known as "adherens" junctions, in detrusor muscle cells [2, 3] probably underlies the mechanical cell

coupling between those cells and contributes to the generation of both spontaneous and normal detrusor contractions. The actions of ACh, the main neurotransmitter of detrusor contractions in health, are mediated by five subtypes of muscarinic ACh receptors in the detrusor muscle (M_1–M_5). Although the M_2 subtype is predominant in density, it is the M_3 subtype which mediates detrusor contraction in health in all species [4]. However, the M_2 receptor may also have a supportive role in detrusor contraction and efficient voiding via inhibition of the cyclic adenosine monophosphate (cAMP)-mediated smooth muscle relaxation as well as via opposition of the sympathetic activation of β-adrenoreceptors [4]. In addition, M_1 receptors expressed in prejunctional cholinergic nerves appear to have a facilitatory role in the release of ACh, thus enhancing detrusor contraction and assisting efficient voiding function [4]. ATP, a co-transmitter with ACh in parasympathetic nerve terminals, is responsible for the atropine-resistant component of detrusor contraction in conditions of health [5]. Urine storage, on the other hand, is facilitated by the detrusor muscle relaxation via activation of a subpopulation of β-adrenoreceptors (β_3) [6].

The urothelium and suburothelium

Both ACh and ATP are released by the bladder urothelium during urine storage, in increasing concentrations as the bladder wall distends [7, 8]. Muscarinic, nicotinic and purinergic receptors have been identified in the bladder urothelium and/or suburothelium in human or animal studies [9–13] (Fig. 1.6). It has been proposed that ACh released from the urothelium during bladder storage acts on muscarinic receptors in the suburothelium and the detrusor to stimulate a constant muscle tone [14] and an additional autocrine role for urothelially released ACh cannot be excluded. Stimulation of urothelial muscarinic receptors has been shown to be associated with the release of an as yet unidentified urothelium-derived inhibitory factor with a relaxing effect on the detrusor [15]. Moreover, ACh released by the urothelium appears to activate two opposing nicotinic signaling pathways mediated by type α_7 (inhibitory) and type α_3 (excitatory) nicotinic receptors, which facilitate urine storage and bladder emptying respectively (Fig. 1.6) [13].

A role in bladder mechanosensation has been identified for the ATP-gated purinergic receptor $P2X_3$ [16]. It is thought that ATP released from the urothelium during bladder stretch activates $P2X_3$ receptors on suburothelial afferent nerve fibers to stimulate afferent firing to the spinal cord (Fig. 1.6) [17]. Recent studies have also confirmed the presence of the sensory receptor Transient Receptor Potential Vanilloid 1 (TRPV1, formerly known as the capsaicin or vanilloid receptor VR1) in urothelial cells [18] and suburothelial nerves (presumably C-fiber afferents) (Figs. 1.6 and 1.7) [19]. TRPV1 is necessary for the release of ATP and NO from the urothelium, and its gene depletion in a knockout mouse resulted in a number of changes in normal bladder function, supporting its role in normal bladder mechanosensation [20].

C-fiber afferents are also thought to be responsible for thermal perceptions; TRPV1 is activated by temperatures higher than 43°C. From the same family of transient receptor potential channels, the "menthol" TRPM8 receptor is sensitive to low temperatures and menthol [21], is expressed in suburothelial fiber-like structures in the human [22], and appears to mediate the bladder cooling reflex which emerges following a spinal injury [23].

Sensory neuropeptides, namely substance P (SP) and calcitonin gene-related peptide (CGRP), are also abundantly found in suburothelial afferents (Fig. 1.7) [24, 25]. Although primarily associated with neurogenic inflammation and pain, both SP and CGRP appear to also be involved in lower urinary tract neuromodulation via complex interactions (Fig. 1.6). In brief, SP and CGRP may induce the expression of the neurotrophic growth factor (NGF) [26], regulate the expression of TRPV1 and $P2X_3$ [27], activate non-selective cation channels in afferent neurons [28], and sensitize P2X receptors to the action of ATP [29]. In turn, activation of TRPV1 promotes the release of SP and CGRP from afferent nerves via an ATP-mediated pathway [30]. In the rat bladder, SP levels were found to inversely correlate to the micturition threshold [31].

Recently, functional cannabinoid CB1 and CB2 receptors were identified in the human bladder [32, 33]. CB2 receptors were identified in sensory suburothelial nerves, and also in cholinergic neurons in the detrusor. Their activation decreased the nerve-evoked contractions of the bladder and increased the micturition intervals and bladder pressure, suggesting a modulatory role of CB2 in both afferent signaling and cholinergic nerve activity [33].

As the bladder urothelium expresses a large range of receptors and neurotrophic factors, and releases tachykinins, prostaglandins, NO, ACh and ATP, the

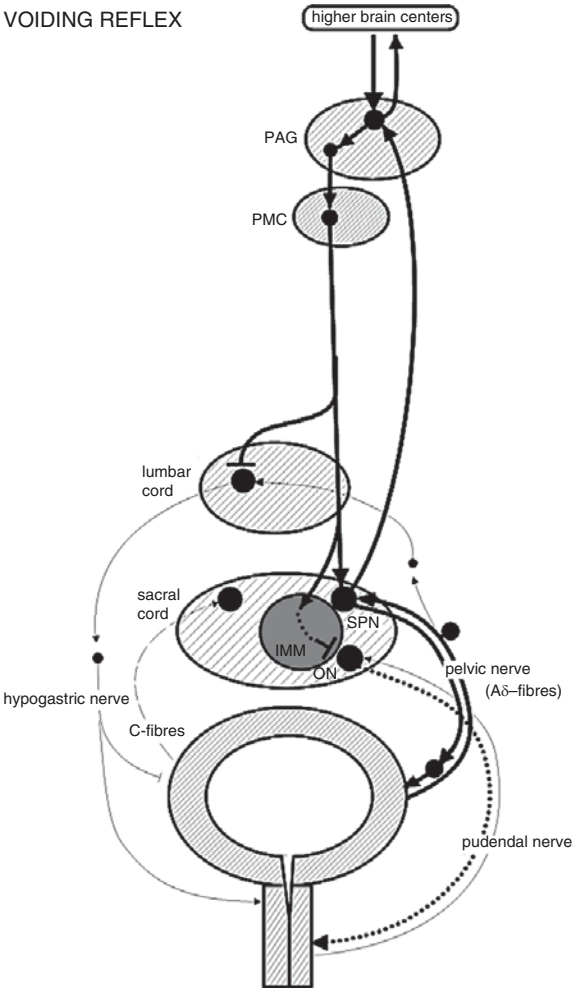

Fig. 1.3. Voiding depends on a bladder-to-bladder excitatory reflex, whereby increasing wall tension or detrusor pressure stimulates bladder afferents which synapse at the SPN. From there, afferent stimuli travel via the spinal cord to brain centers – the PAG and the PMC. From the latter, excitatory stimuli descend via the spinal cord. One branch inhibits the sympathetically mediated storage reflex (shown in Fig. 1.5) and another descends to the SPN and then via the pelvic nerve to the bladder wall, inducing detrusor contraction. At the same time, it excites an inhibitory interneuronal connection at sacral level and thus relaxes the striated urethral sphincter, so that voiding can occur. During the storage phase, excitation of this voiding reflex is blocked by inhibition of the PAG by higher centers (Fig. 1.10). When voiding is appropriate the inhibition is lifted so that the voiding reflex is excited, emptying the bladder.

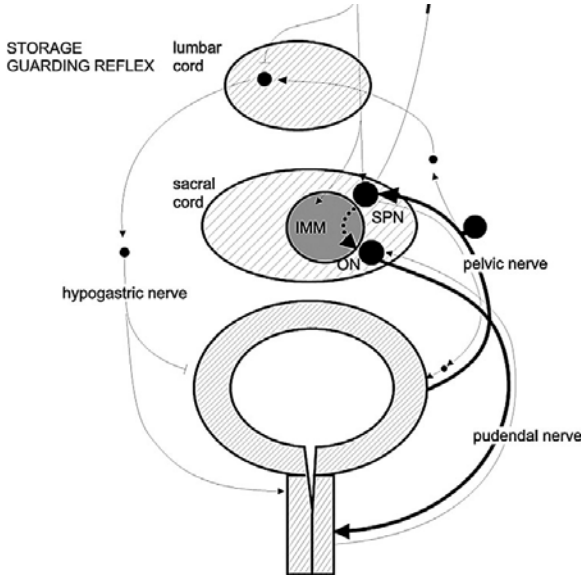

Fig. 1.4. During the storage phase somatic efferents originating from Onuf's nucleus (ON) in the anterior horn of S_2–S_4 spinal cord and running in the pudendal nerve are being stimulated by afferent firing from the bladder via a synapse with sacral interneurons.

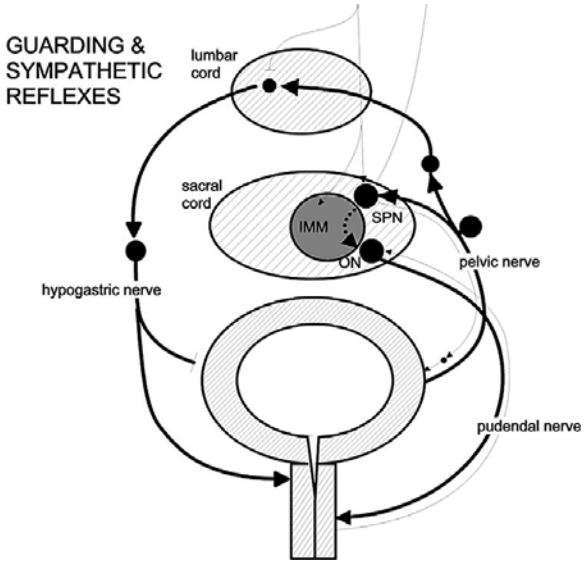

Fig. 1.5. During the storage phase, in addition to the guarding reflex (Fig. 1.4), sympathetic neurons originating at the intermediolateral cell column of the T_{11}–L_2 spinal cord and running through the hypogastric nerve convey efferent stimuli to the bladder and the smooth muscle of the urethra. These stimulate α-adrenoreceptors in the bladder base and urethral smooth muscle resulting in contraction and thus contributing to continence during urine storage, whilst other efferent stimuli act on β-adrenoreceptors in the body of the bladder resulting in relaxation of the detrusor muscle.

older notion that it serves as a plain protective barrier has now been superseded by the view that it is a sensory organ [34]. Its functional properties robustly support a complex interaction with the suburothelial space (Fig. 1.6). A recently identified cell entity, the suburothelial "myofibroblast" or interstitial cell, has become the focus of attention as an integral part of

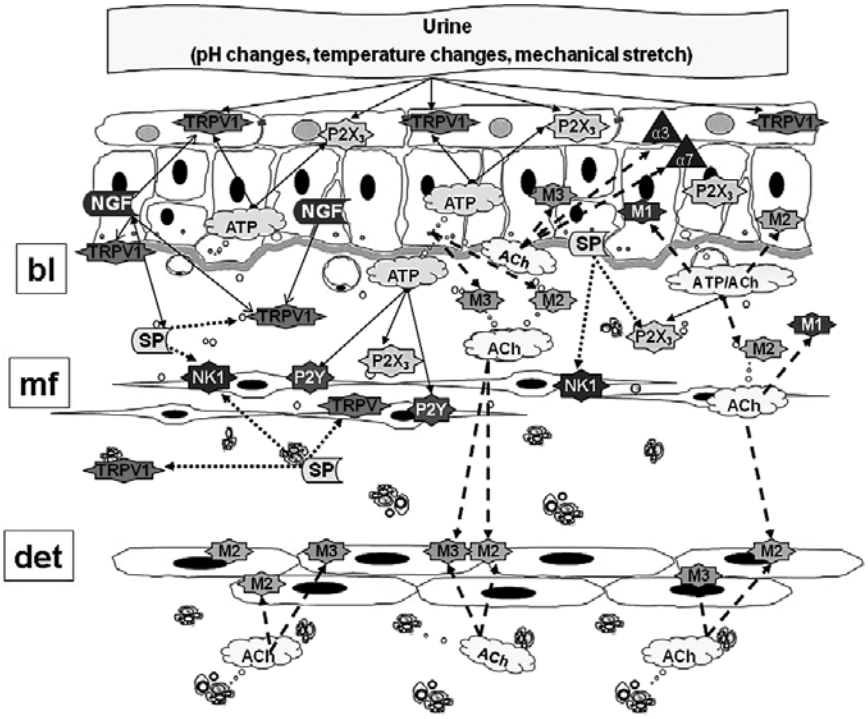

Fig. 1.6. In this cartoon representation of the ultrastructural components of the human bladder wall, the known or proposed location of receptors and sites of release of neuropeptides, neurotransmitters and growth factors thought to be involved in bladder mechanosensation are shown (updated from figure in [117]). A complex system of interactions has been proposed between the neurotransmitters and neuropeptides released and their respective receptors, which are thought to be up-regulated in DO. Fine-line arrows refer to the proposed activation of urothelial and suburothelial purinergic receptors and potentiation of the response of TRPV1 to irritative stimuli by urothelially released ATP. Dotted arrows refer to the proposed activation of suburothelial and detrusor muscarinic receptors by ACh released from the urothelium and suburothelial nerves. Dashed arrows refer to proposed activation of NK1 receptors on myofibroblasts and potentiation of suburothelial TRPV1 and $P2X_3$ receptors by SP. A reciprocal relationship appears to exist between SP and NGF, also identified by such arrows. Finally, thick-line arrows refer to the known effect of NGF on the expression of TRPV1. Abbreviations: bl = basal lamina of urothelium; mf = myofibroblast layer; det = detrusor muscle; TRPV1 = transient receptor potential vanilloid 1; $P2X_3$ = ionotropic purinergic receptor type 3; P2Y = metabotropic purinergic receptors types 2, 4 and 6; M2/M3 = muscarinic acetylcholine receptors types 2 and 3; α_3/α_7 = nicotinic acetylcholine receptors types 3 and 7; NK1 = neurokinin receptor type 1 (SP receptor); SP = substance P; NGF = nerve growth factor; ACh = acetylcholine; ATP = adenosine triphosphate. See plate section for color version.

the urothelio-suburothelial functional syncitium. In the human bladder, myofibroblasts were found to attach to each other and lay in close apposition to vesicle-packed unmyelinated nerve fibers [35] (Fig. 1.6). It has been shown that suburothelial myofibroblast-like cells are extensively linked by connexin-43-containing gap junctions [36], have high membrane capacitance, show spontaneous spikes of electrical activity and respond to ATP by an increase in intracellular Ca^{2+} sufficient to activate contractile proteins and generation of an inward current [37]. Further studies suggest the presence of muscarinic [11], purinergic [38] and TRP channel receptors [39] in myofibroblasts as well as expression of neuronal nitric oxide synthase (nNOS) [39]. It was thus hypothesized that the myofibroblasts and the closely associated nerve axons could collectively function as a bladder stretch receptor, where intracellular electrical signaling could pass from cell to cell, while contraction of that cell layer could exert stretch-dependent activation of the sensory nerves [37].

Changes in peripheral control of micturition in bladder disease states

Detrusor overactivity

Afferent pathway changes: the vanilloid and purinergic pathways

In animal models of suprasacral spinal lesions, a series of changes, including body hypertrophy and increased excitability, render the C-fiber

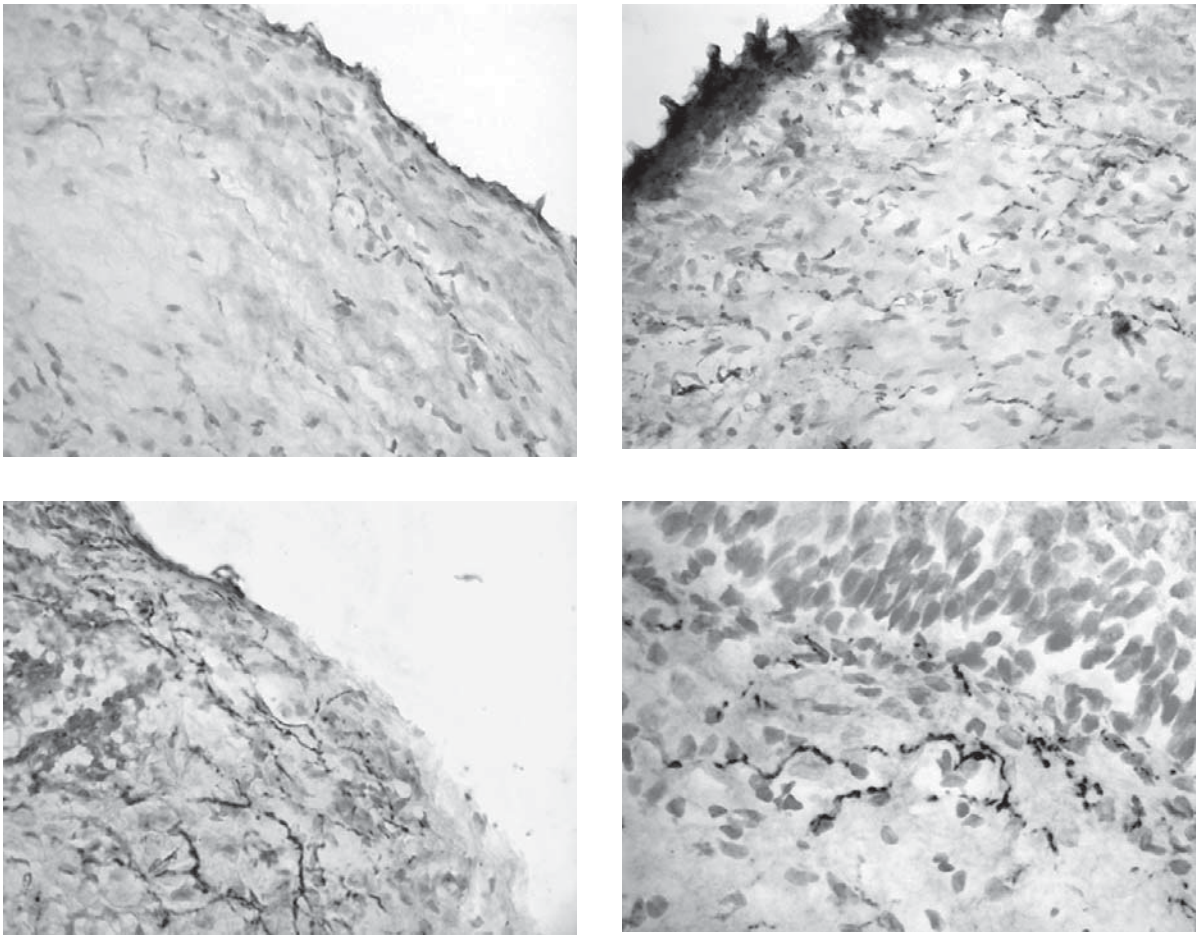

Fig. 1.7. Immunohistochemical staining of human bladder specimens obtained via flexible cystoscopy with specific antibodies to the vanilloid receptor TRPV1 (top left – suburothelial fiber-like staining, magnification x20), substance P (top right – urothelial cell and suburothelial fiber-like staining, magnification x20), vesicular acetylcholine transporter VAChT (bottom left – suburothelial fiber-like staining, magnification x20) and CGRP (bottom right – suburothelial fiber-like staining, magnification x40). See plate section for color version.

afferents in the bladder wall sensitive to mechanical stimuli (mechanosensitive) [1]. Consequently, the C-fibers become excited at low urine volumes in the bladder and respond with increased afferent firing to the spinal cord during bladder distension. This, in turn, induces increased parasympathetic input to the bladder, which results in detrusor overactivity (DO) [40] (Fig. 1.2).

Evidence exists for a similarly augmented afferent limb of the micturition reflex in humans with DO due to spinal lesions [1, 40] and is thought to be associated with the symptoms of urgency (defined as "a sudden, compelling desire to void, which is difficult to defer" [41]), urgency incontinence and also in part increased daytime micturition frequency and nocturia (the symptom of waking up at least once to pass urine). Increased density of suburothelial innervation and, in particular, sensory nerve fibers expressing TRPV1 and $P2X_3$ was found in patients with MS or suprasacral injury and was greatly reduced following intravesical instillations of C-fiber toxins, such as capsaicin and resiniferatoxin (RTX), in patients who benefited from treatment, but not in those who failed to respond [42–44].

Although increased daytime frequency and incontinence can be largely explained as consequences of the reflex detrusor contractions, the pathophysiology of urgency and nocturia remains to be elucidated. The sensation of urgency, which is distinct from the normal sensation of even strong desire to void, is thought to occur when a barrage of afferent activity, deriving from pathologically sensitive bladder

stretch-sensing receptors which increase in number, ascends via a sufficiently preserved spinal cord to consciousness. This should imminently precede the reflex detrusor contraction. To support this notion, peripheral afferent neuromodulation could suppress the sensation of urgency and associated incontinence [45]. Levels of suburothelial nerve $P2X_3$ receptors were decreased in parallel with the number of urgency episodes following successful treatment of DO [19]. Urgency and associated incontinence showed an earlier response to treatment than frequency (Fig. 1.8), [46] suggesting different pathophysiological mechanisms for the symptoms of the overactive bladder (OAB) syndrome [41]. Treatment of DO also improves nocturia but the pattern of post-treatment changes in nocturia is more unpredictable compared to other OAB symptoms. This implies that neural changes leading to DO may only partly contribute to the pathophysiology of nocturia.

The role of the urothelium in the dysfunction of the proposed urothelio-suburothelial functional syncitium appears crucial in bladder pathophysiology. Urothelial cell TRVP1 levels followed similar changes to suburothelial TRPV1 in patients with neurogenic DO (NDO) [47]. Similarly, an increase in urothelial cell $P2X_3$ was found in patients with DO in comparison with controls [19]. The function of urothelial $P2X_3$ is not known, but implies there may be an autocrine role for ATP released from the urothelium. The latter was found to be significantly increased in conditions of spinal NDO [48], but also via interactions with ACh [49].

Cholinergic pathway changes

Recent findings support the hypothesis that DO could be partly due to an increased urothelial release of ACh during bladder filling, which may excite afferent nerves in the suburothelium and within the detrusor and increase detrusor smooth muscle tone [14]. The evidence includes:

- an increase of distension-evoked urothelial ACh release with age [7] and the increased prevalence of DO in the elderly
- an effect of anticholinergic drugs on the bladder afferents [50, 51], which may explain why they reduce urgency and increase bladder capacity
- suppression of the muscarinically mediated inhibitory influence of the urothelium on the detrusor in patients with DO [15].

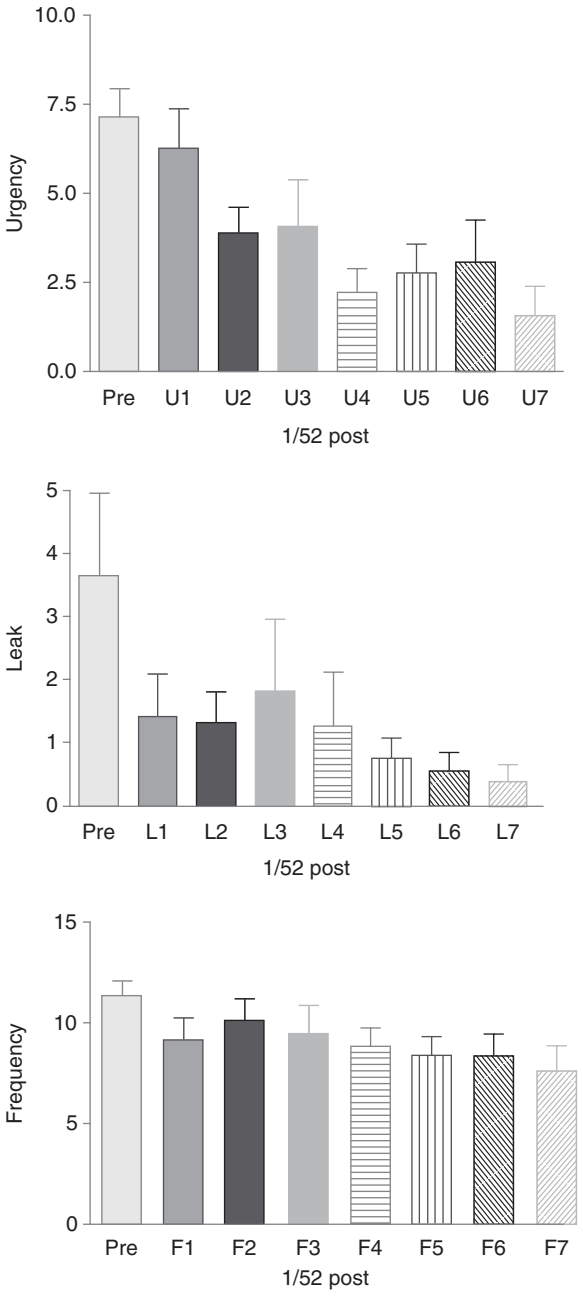

Fig. 1.8. Day-by-day changes in overactive bladder symptoms during the first week after treatment with intravesical BoNT/A injections. A more rapid onset of the therapeutic effect noted for urgency and incontinence episodes compared to micturition frequency implies differences in the pathogenesis of those symptoms.

Reports, however, on the changes of urothelial and suburothelial muscarinic receptors in bladder disease states have been conflicting [4, 11, 52], but suggest a possible role of the M_2 receptor.

A number of changes have been identified in the detrusor of ageing or obstructed human bladders, including:

- an age-related decrease in M_3 receptor mRNA
- a decrease in detrusor contractility with ageing [10]
- a decrease in the cholinergic component of bladder contraction as opposed to an increase in the atropine-resistant (purinergic) component in the ageing human detrusor [7] and the obstructed human bladder [56]
- denervation accompanied by hypersensitivity of the detrusor to ACh in obstructed bladders [56].

Such findings became the basis of the myogenic theory of overactive bladder pathophysiology, where local denervation of bladder smooth muscle leads to increased excitability of ACh receptors and facilitates signal transmission between smooth muscle cells, thus stimulating the propagation of coordinated contractions [57] or micromotions. This hypothesis is contradicted by studies showing no difference in response to ACh between detrusors with and without overactivity [58].

The role of cell junctions

It has been shown that suburothelial myofibroblasts and detrusor smooth muscle cells are electrically coupled via gap junctions [37, 59]. Increased expression of the gap junction protein connexin-43 was found in suburothelial myofibroblasts [60] and in the detrusor [61] of patients with DO. In addition, there is evidence that cadherin, one of the proteins constituting the adherens junction complex, mediates cell-to-cell interactions between suburothelial myofibroblasts as between detrusor smooth muscle cells [62]. Cadherin-11 expression was found to be upregulated in the suburothelium, but was unchanged . in the detrusor of patients with DO [63]. Co-localization of cadherin-11 and connexin-43 implied that gap and adherens junctions may form a functional unit. Animal studies have linked both normal detrusor function and DO with the modulation of spontaneous activity by myofibroblasts [64]; inappropriate activation was proposed to result in pathological localized contractions and "sensory urgency" [65]. However, human detrusor cells are also known to possess properties that allow the development of spontaneous activity which may affect adjacent cells and thus produce a stronger myogenic response [59].

Bladder pain

Recent findings support a neurogenic basis for the "bladder pain syndrome" (BPS), especially its most studied form, interstitial cystitis (IC). In feline IC, bladder afferents exhibit increased firing in response to intravesical pressure, suggesting increased mechanoreceptor sensitivity [66]. Stretch-evoked urothelial ATP release and urothelial $P2X_3$ expression are increased in patients with IC [67, 68]. In support of neuroplastic changes, NGF levels and suburothelial SP-expressing fibers were found to be increased in IC bladders [69, 70]. Significant attenuation of pain and urgency in IC patients treated with intravesical instillation of lidocaine, which in addition to its known local anesthetic effect is also known to have an inhibitory effect on neurite regeneration and synapse formation, further supports a role of bladder afferents in the pathophysiology [71].

Detrusor underactivity

The least studied of bladder dysfunctions may have a variety of neural etiological associations, including sacral and infrasacral spinal lesions. However, the neurological concept of "upper and lower motor neuron" lesions, which is fundamental for understanding neurogenic skeletal muscle weakness, is not directly applicable to neurogenic bladder disorders because, although damage to an anterior horn cell in the cord or its motor axon in ventral root or peripheral nerve will result in denervated striated muscle and flaccid paralysis, a sacral root lesion does not produce detrusor denervation. This is because the S_2–S_4 roots contain the preganglionic parasympathetic fibers destined for ganglia in the pelvis, from which short postganglionic fibers originate to innervate the detrusor smooth muscle (Fig. 1.2). The bladder is innervated by both extramural and intramural ganglion cells [72] although the relative proportions of each type of ganglia are not known. Following loss of the parasympathetic innervation, it was shown in cats that preganglionic sympathetic nerves reinnervated the parasympathetic ganglion cells [73]. Subsequent bladder contractile activity was then demonstrated following hypogastric nerve stimulation so that it was proposed that the "autonomous hyperactive bladder" [74] seen following sacral root injury was due to plasticity in adrenergic innervation of the ganglia changes [73]. It seems likely that

intrinsic activity of the smooth muscle driven by urothelial-detrusor mediated reflexes may also contribute.

So it is that infrasacral cord or cauda equina lesions (Chapter 17) may produce an insensate "decentralized" bladder, with poor compliance or detrusor overactivity, presumably due to the mechanisms outlined above, as well as an underactive detrusor and urinary retention [75]. Retention can result from damage to the ganglia as may occur in the condition of pure autonomic failure with ganglionic autoantibodies, or surgical damage to the ganglia and postganglionic fibers during radical pelvic surgery (Chapter 18). Detrusor under activity expressed with incomplete bladder emptying or complete retention, reduced bladder sensation, increased bladder capacity, reduced micturition frequency and voiding difficulty can also result from the small fiber involvement of diabetic or amyloid neuropathy, which affect both the pre- and postganglionic innervations (Chapter 18).

Detrusor underactivity may also be associated with chronic bladder outlet obstruction; in men it is usually represented by the "decompensated" detrusor caused by benign prostatic enlargement. In women it has been described as part of Fowler's syndrome, characterized by a primary disorder of external urethral sphincter relaxation, possibly due to a hormonal channelopathy (Chapter 19) [76].

"Idiopathic" detrusor overactivity/overactive bladder

Although the term "idiopathic" is used in cases where detrusor overactivity cannot be associated with obvious neurology or bladder outlet obstruction, changes in the neural control of micturition have been identified, both in the afferent bladder pathways and the detrusor in IDO. IDO is the commonest cause of the OAB syndrome, in which urgency is considered the driving symptom for frequency, incontinence and (in part) nocturia. Up-regulation of sensory receptors [19] and neuropeptides [25] as well as increased release of excitatory neurotransmitters occurs in both neurogenic and idiopathic DO/OAB. Neural plasticity in idiopathic DO can be presumed from the successful regulation of bladder symptoms via both electrical neurostimulation of the afferents and chemical neuromodulation with the use of botulinum toxins and resiniferatoxin [45, 19, 46, 77]. The properties of suburothelial cell junctions are also affected, with changes in the expression of muscarinic receptors [11] and gap [60] and adherens junction proteins [63]. Further to evidence for the augmentation of the peripheral part of the afferent limb in idiopathic DO, assumptions about concurrent alteration of spinal reflexes can be drawn from the improvements made in urgency and urgency incontinence by peripheral and sacral nerve stimulation [45, 78]. Thus there is abundant evidence of various types of demonstrable peripheral pathologies in different types of IDO. Reconciliation of the view that IDO has peripheral causes with the view that the condition has its cause in the brain (see pp. 14–15) is difficult and the matter is as yet unresolved, with the "centralist" arguing that detrusor overactivity represents a loss of voluntary control of the bladder and control is exercised from the brain. The solution may lie with the more precise definition of different types of IDO.

Spinal control of bladder function

A series of spinal reflex mechanisms are involved in the control of the urethro-vesical unit. These promote urine storage and micturition via sympathetic, parasympathetic and somatic nerves mediating efferent and inhibitory input to the urethral sphincter and the bladder accordingly [1].

A bladder-to-urethral sphincter reflex, named the "guarding reflex," has a central role during bladder filling; pudendal urethral efferents are stimulated by afferent firing from the bladder via a synapse with sacral interneurons during the storage phase (Fig. 1.4). An increase in urethral electromyographic activity as the bladder progressively fills during urodynamic investigations provides evidence for the presence of this reflex in humans [79]. The low detrusor pressure achieved until micturition threshold is reached is maintained via an additional, *sympathetically mediated reflex* which inhibits detrusor contraction while promoting urethral smooth muscle contraction during bladder filling (Fig. 1.5) [78, 80].

When the bladder is full, activation of a *bladder-to-urethral sphincter inhibitory reflex* interrupts urethral sphincter activity, an event timely followed by a rise in detrusor pressure (detrusor contraction), which is promoted by a *bladder-to-bladder excitatory reflex* [78, 80]. Thus, voiding begins. In healthy adults these reflexes form part of the spinobulbospinal voiding reflex, with connections to the brainstem

and midbrain as shown in Fig. 1.3. This enables higher brain centers to exert control of the voiding phase, as discussed in the section on central control which follows.

The emerging role of interneurons

Interneurons at various levels of the spinal cord may represent a crucial element in the regulation of reflex activity, serving as integrating areas of afferent projections from both the bladder and the urethra [78, 80]. Urine storage is facilitated by the activation of a *bladder-sphincter-bladder reflex* pathway in which the *bladder-to-external urethral sphincter excitatory reflex* (Fig. 1.5) activates the *urethral sphincter-to-bladder inhibitory reflex* (Fig. 1.9) via interneuronal synapses. Suppression of bladder activity and urine storage are additionally facilitated by inhibition of excitatory interneurons and preganglionic parasympathetic neurons [80].

During the voiding phase, activation of excitatory interneurons and preganglionic parasympathetic neurons promotes detrusor contraction until the bladder empties (Fig. 1.9). Pudendal afferent activity from urogenital sites can inhibit the excitatory parasympathetic outflow to the bladder via interneuronal pathways (Fig. 1.9). At the same time, activation of interneurons by bladder afferents stimulates parasympathetic efferent inhibitory activity to the urethral smooth muscle.

Spinal reflexes and bladder pathophysiology

It is now proposed that augmented "excitatory" or "inhibitory" function of spinal interneurons could be etiologically involved in conditions of either bladder overactivity or urinary retention. Supporting evidence comes from the successful use of peripheral and central neurostimulation in the treatment of human bladder dysfunction: sacral nerve stimulation (SNS) can be effective in the treatment of both intractable DO [78] and urinary retention [81]. In the former, it is believed that SNS suppresses detrusor contraction via activation of the bladder-sphincter-bladder reflex pathway mentioned above (Fig. 1.3) [78, 80]. In the latter, SNS has been proposed to suppress inhibitory interneurons and release the bladder from an augmented sphincter-bladder reflex (Fig. 1.9). Finally, stimulation of pudendal afferents can suppress urgency and alter bladder function in patients with idiopathic DO (Fig. 1.9) [45].

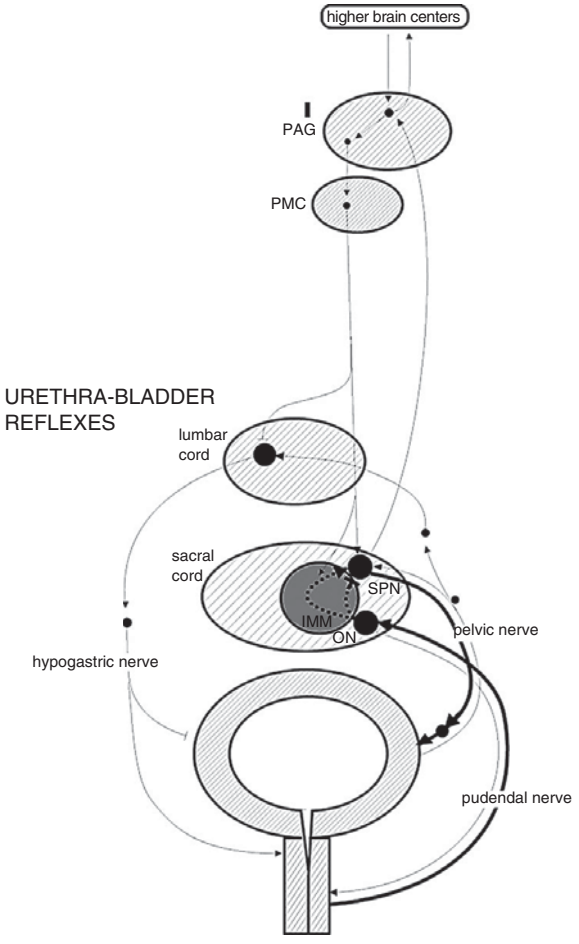

Fig. 1.9. A number of reflexes depending on urethral afferent signals utilize sacral interneurons to help regulate the coordination between the bladder and the urethra. Further to the "guarding reflex," urine storage is facilitated by the activation of a *urethral sphincter-to-bladder inhibitory reflex*, where pudendal afferents terminating at the ON synapse via inhibitory interneurons with parasympathetic efferents at the SPN. The latter activate β-adrenoreceptors in the bladder wall, resulting in detrusor relaxation. In contrast, during voiding, stimulation of urethral afferents by the urine passing through the urethra stimulates excitatory interneurons and preganglionic parasympathetic neurones, which in turn act on muscarinic acetylcholine receptors in the bladder wall to further promote detrusor contraction until the bladder empties completely.

The peripheral elements of the segmental bladder-sacral spinal cord-bladder reflex, which emerges following suprasacral spinal lesions, have been discussed in detail in a previous section. Further to DO, which develops as a result of this augmented reflex after the initial phase of spinal shock and results in reflex voiding (Fig. 1.2), the striated urethral sphincter becomes dyssynergic, i.e. it contracts